2015 International Conference on Diabetes & Metabolism

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2014 International Conference on Diabetes and Metabolism

Korean Diabetes Association

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2014 International Conference on Diabetes and Metabolism

16~18 October 2014

KINTEX Exhibition Center II, Gyeonggido, Korea

Plenary lectures

Symposia

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2014 International Conference on Diabetes & Metabolism

Date
16-18 October 2014

Venue
KINTEX Exhibition Center II, Gyeonggido, Korea

Invitation

Dear Diabetes researchers,

It is our great honor to invite you to the ICDM 2014 on behalf of the Korean Diabetes Association. This autumn symposium will be held in Kintex in Ilsan from Thursday 16 to Saturday 18, October 2014.

After starting off as an international symposium in 2011, the 4th anniversary of this symposium will be accompanied by more than 1500 distinguished researchers from 20 different countries, creating a much more productive and active environment.

The plenary lectures will be given by Dr. Jay H. Chung from NIH, Professor Steven Kliewer from the University of Texas, Southwestern and Professor Paolo Sassone-Corsi from University of California, Irvine. The main symposium consists of 14 sessions comprising basic and clinical researches on diabetes and metabolism. Various topics were selected by the organizing committee to cover diverse interests of the attendees.

The Korean Diabetes Association will endeavor to provide all attendees of the symposium with vast academic information and accommodate an environment for researchers to build up new relationships. In addition, travel grants are provided for young researchers from all over the world, to help them join this attractive meeting.

Lastly, we would like to thank you all for your attention and interest in ICDM 2014 and we dearly wish that you could spare some of your precious time to attend this symposium and honor us with your presence. We look forward to seeing you in Korea during this refreshing autumn.

Sincerely yours,

Moon-Gi Choi, M.D., Ph.D.
President
Korean Diabetes Association

Ki-Up Lee, M.D., Ph.D.
Chairman, Board of Directors
Korean Diabetes Association

Timetable

1st day (Thursday 16 October, 2014)				
	Room 1 (1F)	Room 2 (3F)	Room 3 (3F)	Room 4 (4F)
15:00 ~ 17:00				
17:00 ~ 17:30		Sulwon lecture		
17:30 ~ 18:00		Satellite symposium 1	Satellite symposium 2	
18:00 ~				
2nd day (Friday 17 October, 2014)				
07:00 ~ 08:00		Breakfast symposium 1 (MVL Hotel)	Breakfast symposium 2 (MVL Hotel)	
08:30 ~ 10:30		**S1 Clinical diabetes & therapeutics 1**	**S2 Epidemiology & genetics**	**S3 Insulin action**
10:30 ~ 11:00				
11:00 ~ 11:10	Opening address			
11:10 ~ 11:50	Plenary lecture 1			
11:50 ~ 13:00		Luncheon symposium 1	Luncheon symposium 2	Luncheon symposium 3
13:00 ~ 14:00				
14:00 ~ 15:00				
15:00 ~ 15:20				
15:20 ~ 16:00	Plenary lecture 2			
16:10 ~ 18:10		**S5 Clinical diabetes & therapeutics 2**	**S6 Diabetic complications 1**	**S7 Aging and metabolism**
18:20 ~				
3rd day (Saturday 18 October, 2014)				
07:30 ~ 08:30		Breakfast symposium 3 (MVL Hotel)	Breakfast symposium 4 (MVL Hotel)	
09:00 ~ 11:00		**S10 Clinical diabetes & therapeutics 3**	**S11 Diabetic complications 2**	**S12 Inflammation and metabolism**
11:00 ~ 11:30				
11:30 ~ 12:10	Plenary lecture 3			
12:10 ~ 13:30		Luncheon symposium 5	Luncheon symposium 6	Luncheon symposium 7
13:30 ~ 14:30				
14:30 ~	Closing ceremony			

Room 5 (4F)	Room 6 (3F)	Room 7 (3F)	Room 8 (3F)	Room 9 (3F)
	KDA research group on diabetic vascular cell biology	KDA research group on diabetic neuropathy	KDA research group on diabetes in old age	KDA research group on exercise (K)
Welcome reception (6 Hall-C)				
S4 Behavioral medicine/education (K)		Committee of clinical practice guideline session		
Coffee break (6 Hall Lobby)				
Luncheon symposium 4				
	Oral presentation 1	Oral presentation 2	Oral presentation 3	Committee of publication session
	Oral presentation 4	Oral presentation 5	Oral presentation 6	
Coffee break (6 Hall Lobby)				
S8 Clinical nutrition	Committee of the health insurance and legislation (K)	Commitee of international liaison	**S9 Integrated physiology/obesity**	
Dinner and art performance (Grand Ballroom, MVL Hotel)				
S13 Self care (K)	Committee of education session (K)	Committee of camp (K)	**S14 Islet biology**	
Coffee break (6 Hall Lobby)				
	Oral presentation 7	Oral presentation 8	Oral presentation 9	Oral presentation 10

*K: Korean session

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*K: Korean session

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Friday 17 October, 13:00~14:00 / Room 8

Oral Presentation 3 — Chairman: Yong Soo Park

Islet biology & insulin secretion **/ 129**

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Poster presentation

Friday 17~Saturday 18 October, 2014
6 Hall A, Exhibition Center II, KINTEX

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Thursday 16 October

Pil Han Kim

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➤Educational background & professional experience

2000	Seoul National University, Electrical Engineering / B.S.
2005	Seoul National University, Electrical Engineering / Ph.D.
2005-2010	Harvard Medical School, Massachussets General Hospital / Research Fellow
2010-present	Korea Advanced Institute of Science and Technology (KAIST) / Assistant Professor

➤Research interests

Advanced In Vivo Cellular Imaging System
Systemic Cellular Visualization of Animal Model for Human Disease
High-speed, Nano-scale Visualization of Organic and Inorganic Materials

➤Brief list of publications

1. Y Hwang, J Ahn, et al. In vivo analysis of THz wave irradiation induced acute inflammatory response in skin by laser-scanning confocal microscopy. Optics Express 22(10):11465-11475, 2014
2. K Jung, P Kim, et al. Endoscopic Time-Lapse Imaging of Immence Cells in Infarcted Mouse Hearts. Circulation Research 112(6):891-899, 2013
3. K Choe, Y Hwang, et al. In Vivo High Spatiotemporal Resolution Visualization of Circulating T Lymphocytes in High Endothelial Venules of Lymph Node. Journal of Biomedical Optics 18(3):036005, 2013
4. JK Kim, WM Lee, et al. Fabrication and operation of GRIN probes for in vivofluorescence cellular imaging of internal organs in small animals. Nature Protocols 7(8):1456-1469, 2012
5. P Kim, E Chung, et al. In vivo wide-area cellular imaging by side-view endomicroscopy. Nature Methods 7(4):303-305, 2010

Intravital laser-scanning microscopy for cellular imaging of vascular system

In this talk, recent *in vivo* 3D fluorescence cellular imaging studies utilizing custom-design ultrafast laser-scanning intravital microscopy system will be introduced. First, *in vivo* visualization of fast circulating T lymphocyte in lymph node will be demonstrated. Individual endothelial cell of high endothelial venule (HEV) in LN can be clearly identified with its distinctive cuboidal morphology. By visualizing the adaptively transferred T lymphocytes, we successfully analyzed dynamic flowing behaviors of T lymphocytes and their transendothelial migration while interacting with the endothelial cells in HEV *in vivo*. Second, *in vivo* visualization of dynamic process for the absorption and transport of lipids and drug molecule in small intestinal villi will be described. By utilizing lymphatic vessel reporter (Prox-1-GFP) mouse, we successfully visualized the lacteals and the absorption and transport dynamics of fluorescence-tagged fatty acids (FAs) in the villi at cellular level in real time, which consisted of transepithelial absorption via enterocytes, diffusive distribution over the lamina propria, and subsequent transport through lacteals. We also discovered that the apical and basolateral membranes of enterocytes had different permeable characteristics, acting as a regulatory barrier to allow only the properly processed lipids into the lamina propria. Third, novel *in vivo* quantitation technique for blood circulating tumor cells (CTC) will be introduced. Direct *in vivo* visualization of fast circulating cells in great saphenous vein (GSV) was achieved by the custom video-rate intravital microscopy system. By extracting a calibration factor through hemocytometric analysis of intravenously injected red blood cells, we could relatively quantitate of circulating cells including CTC in whole body blood *in vivo*. By repetitively monitoring the number of CTC at the GSV of various types of tumor bearing mouse model up to 6 weeks, a longitudinal variation of CTC number along with primary tumor growth and distant organ metastasis was analyzed *in vivo*.

Kyu-Tae Kang

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➤**Educational background & professional experience**

1995-1999	College of Pharmacy, Chung-Ang University / Pharmacy student
1999-2001	College of Pharmacy, Seoul National University / M.S. student
2002-2007	Medical College of Georgia / Ph.D. student
2008-2013	Boston Children's Hospital/Harvard Medical School / Postdoctoral research fellow
2013-present	College of Pharmacy, Duksung Women's University / Assistant Professor

➤**Research interests**

Cell-based therapy for tissue regeneration

➤**Brief list of publications**

1. Kang KT, Coggins M, Xiao C, Rosenzweig A, Bischoff J. Human vasculogenic cells form functional blood vessels and mitigate adverse remodeling after ischemia reperfusion injury in rats. Angiogenesis 16(4):773-784, 2013
2. Allen P, Kang KT, Bischoff J. ECFCs and MPCs trigger perfused blood vessels in collagen, fibrin, and PuraMatrix provisional matrices after 1 day in vivo. J Tissue Eng Regen Med 2013 [Epub ahead of print]
3. Kang KT, Allen P, Bischoff J. Bioengineered human vascular networks transplanted into secondary mice reconnect with the host vasculature and re-establish perfusion. Blood 118(25): 6718-6721, 2011. [covered by the research report of The Wall Street Journal, November 29, 2011]
4. Kang KT, Sullivan JC, Spradley FT, d'Uscio LV, Katusic ZS, Pollock JS. Anti-hypertensive therapy increases BH4 levels and NO/cGMP signaling in small arteries of angiotensin II-infused hypertensive rats. Am J Physiol Heart Circ Physiol 300(3): H718-724, 2011.
5. Kang KT, Sullivan JC, Sasser JM, Imig JD, Pollock JS. Novel nitric oxide synthase-dependent mechanism of vasorelaxation in small arteries from hypertensive rats. Hypertension 49(4):893-901, 2007.

Building blood vessels using human vasculogenic cells: clinical application

It is important to understand blood vessel regeneration process to treat ischemic diseases, to create vascularized bioengineered organs, and to find therapeutic target against vascular abnormality such as cancer. We showed previously that human endothelial colony forming cells (ECFC) combined with mesenchymal progenitor cells (MPC) form perfused human blood vessels. ECFC+MPC generate more blood vessels compared to the ECFC or MPC alone injection.

Using in vivo labeling with a systemically injected mixture of human- and murine-specific lectins, we demonstrated the ability of ECFC+MPC-blood vessels to reconnect with host vessels after transplantation. ECFC+MPC-blood vessels formed in donor mouse reconnect and are perfused at day 3 after transplanted into the secondary mouse. Furthermore, we quantified the longitudinal change in perfusion volume in the same implants before and after transplantation using contrast-enhanced micro-ultrasonic imaging. Perfusion was restored at day 3 after transplantation and increased with time. These results suggest that two cell system (ECFC+MPC) can provide vascular network where blood perfusion is needed or can be applied to generate vascularized engineered constructs and organ transplantation.

To prove the possibility of clinical application of two cell system, ECFC+MPC were injected into the ischemic tissues such as ischemic myocardium and ischemic hindlimb muscle. In both ischemic tissues, injected cells were retained and formed perfused blood vessels. In ischemic myocardium, ECFC+MPC injection reduced LV hypertrophy and restored cardiac function compared to PBS. Ischemic hindlimbs injected with ECFC+MPC showed faster and greater blood flow recovery compared with ECFC or MPC alone. Interestingly, systemic myeloid cell depletion with anti-Gr-1 administration blocked the improved blood flow recovery observed with ECFC+MPC in ischemic hindlimbs, suggesting that vasculogenic process of ECFC+MPC may be enhanced by coordination with host myeloid cells. Our data support that ECFC+MPC delivery could be used to reestablish blood flow and restore functions of ischemic tissues by neovascularization.

Yeon-Kyung Choi

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➤Educational background & professional experience

2000-2006	Kyungpook National University College of medicine / M.D.
2008-2012	Kyungpook National University / Residency, Internal medicine
2008-2010	Postgraduate School, Kyungpook National University College of Medicine / Internal medicine / Master degree
2012-2014	Postgraduate School, Kyungpook National University College of Medicine / Internal medicine / Ph.D.
2014-present	Kyungpook National University / Clinical professor

➤Research interests

Endocrinology and metabolism
Vascular complications of diabetes
Cancer metabolism

➤Brief list of publications

1. Min AK, Jeong JY, Go Y, Choi YK, Kim YD, Lee IK, Park KG. cAMP response element binding protein H mediates fenofibrate-induced suppression of hepatic lipogenesis. Diabetologia 2013 Feb;56(2):412-22
2. Min AK, Bae KH, Jung YA, Choi YK, Kim MJ, Kim JH, Jeon JH, Kim JG, Lee IK, Park KG. Orphan nuclear receptor Nur77 mediates fasting-induced hepatic fibroblast growth factor 21 expression. Endocrinology 2014 Jun 2
3. Jung YA, Choi YK, Jung GS, Seo HY, Kim HS, Jang BK, Kim JG, Lee IK, Kim MK, Park KG. Sitagliptin attenuates methionine/choline-deficient diet-induced steatohepatitis. Diabetes Res Clin Pract 2014 Jul;105(1)47-57
4. Choi YK, Park KG. Metabolic roles of AMPK and metformin in cancer cells. Mol Cells 2013 Oct;36(4):279-87
5. Choi YK, Kim MK,Bae KH, Seo HA, Jeong JY, Lee WK, Kim JG, Lee IK, Park KG. Serum irisin levels in new-onset type 2 diabetes. Diabetes Res Clin Pract 2013 Apr;100(1):96-101

In vivo and in vitro vascular calcification models

Vascular calcification is a major contributing factor of morbidity and mortality in patients with atherosclerosis, chronic kidney disease and diabetes. Vascular calcification is an active, cell-regulated process of matrix mineral metabolism resulting in the deposition of calcium phosphate in the arterial wall which has many similarities to bone formation. This phenomenon includes the dedifferentiation or transform of vascular smooth muscle cells (VSMCs) to a phenotypic switch with osteogenic characteristics in the setting of chronic kidney disease, diabetes, aging or inflammation. Once the osteogenic phenotype is induced, cells of the vascular wall increase levels of osteogenic markers including runt-related transcription factor 2 (Runx2), Msx2 or osterix, while loss endogenous inhibitors of mineralization, such as matrix γ-carboxyglutamic acidprotein (MGP) and fetuin.

To induce vascular calcification, vascular smooth muscle cells (Human, Mice, or Rat aorta smooth muscle cell, VSMC) are cultured with calcification medium containing inorganic phosphate or β-Glyccerophosphate. Calcification medium-induced VSMC calcification is confirmed by morphological changes and increased intracellular of calcium content using von kossa stain or Alizarin Red S stain. The expression of osteogenic markers including BMP2, Runx2, Msx2 can be evaluated.

Animal lacking gene that regulate bone formation including MGP, OPG and, smad6 gene product develop varying extents of arterial calcification. Atherogenic high-fat diet in murine knockout models of genes (ApoE or LDL), nephrectomy or Vitamin D toxicity animal model also have used commonly for vascular calcification.

In this talk, I will discuss the current knowledge about pathogenesis of vascular calcification and reviews the new insight into the more physiologic vascular calcification models.

Hyun Min Kim

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➤Educational background & professional experience

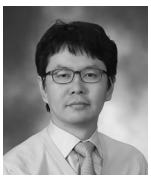
2006	College of Medicine, Yonsei University / M.D.
2012-2013	Yonsei University College of Medicine / Clinical Research / Assistant Professor
2013-2014	Chung-Ang University College of Medicine / Clinical assistant professor
2014-present	Chung-Ang University College of Medicine / Assistant Professor

➤Brief list of publications

1. Kang SB, Kim HM, Kim HJ, Seok H, Huh JH, Lee BW, Kang ES, Lee HC, Cha BS. Rosiglitazone attenuates casein-induced hepatic endoplasmic reticulum stress in Sprague-Dawley rats: a novel model of endoplasmic reticulum stress. Endocr J 2013;60(11):1231-40.
2. Kim HM, Lee BW, Song YM, Kim WJ, Chang HJ, Choi DH, Yu HT, Kang E, Cha BS, Lee HC. Potential association between coronary artery disease and the inflammatory biomarker YKL-40 in asymptomatic patients with type 2 diabetes mellitus. Cardiovasc Diabetol 2012 Jul 18;11(1):84.
3. Kim HM, Kim KJ, Lee HJ, Yu HT, Moon JH, Kang ES, Cha BS, Lee HC, Lee BW, Kim YJ. Epicardial adipose tissue thickness is an indicator for coronary artery stenosis in asymptomatic type 2 diabetic patients: its assessment by cardiac magnetic resonance. Cardiovasc Diabetol 2012 Jul 18;11:83.
4. Kim HM, Kim KJ, Moon JH, Lee HJ, Chae MK, Chang HJ, Kang ES, Cha BS, Lee HC, Kim YJ, Lee BW. Association between EPCs count and rate of coronary revascularization in asymptomatic type 2 diabetic patients Acta Diabetol. 2012 Dec;49(6):413-20.

Review of the clinical trials on vascular complications of diabetes

The incidence of diabetes is increasing, and as a consequence the incidence of diabetes-associated micro- and macrovascular complications is also increasing. Diabetic vascular complications are the leading causes of end-stage renal failure, acquired blindness, a variety of neuropathies, and accelerated atherosclerosis, which could account for the disabilities and high mortality rates found in diabetic patients. The precise mechanisms leading to the development of vascular complications in diabetes remain to be fully determined. Various hyperglycemia-induced metabolic and hemodynamic derangements, including increased formation of advanced glycation end products (AGEs), enhanced reactive oxygen species (ROS) generation, activation of protein kinase C (PKC), and stimulation of renin-angiotensin -aldosterone system (RAAS), are thought to contribute to vascular complications in diabetes. Current therapies, such as optimization of glucose and BP control as well as targeted intervention of the RAAS are effective in slowing the progression of vascular complications, however, they could not prevent them completely. Therefore, continuous basic research activities are under way to define the detailed mechanism and identify novel target. This presentation will review the recent evidences for the novel therapeutic targets and ongoing clinical trials of new agents for diabetic vascular complications.



Sang Soo Kim

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➤Educational background & professional experience

1999	Pusan National University / M.D.
2000-2004	Pusan National University Hospital, Department of Internal Medicine / Internal Medicine, resident
2008	Pusan National University Hospital, Department of Internal Medicine / Clinical fellow
2009-present	Pusan National University Hospital, Department of Internal Medicine / Assistant professor

➤Research interests

Diabetic complication

➤Brief list of publications

1. Soluble α-klotho as a novel biomarker in the early stage of nephropathy in patients with type 2 diabetes. PLoS One. 2014[In press]
2. Nonalbuminuric proteinuria as a biomarker for tubular damage in early development of nephropathy with type 2 diabetic patients. Diabetes/Metabolism Research and Reviews. 2014 Mar [Epub ahead print]
3. Duration of diabetes and effectiveness of insulin in the management of insulin-naïve Korean patients uncontrolled on oral antidiabetic drugs: a sub-analysis of the MOdaliTy of Insulin treatment eValuation (MOTIV) registry results. Acta Diabetologica 2014 Feb [Epub ahead print]
4. Prevalence and clinical implications of painful diabetic peripheral neuropathy in type 2 diabetes: Results from a nationwide hospital-based study of diabetic neuropathy in Korea. Diabetes Res Clin Pract 2014;103:522-529.
5. Urinary cystatin C and tubular proteinuria predict progression of diabetic nephropathy. Diabetes Care 2013;36:656-661.

Overview of painful and painless diabetic neuropathy - epidemiology and QOL

Diabetic peripheral neuropathy (DPN) is the most common complications of long-standing diabetes and is a risk factor for foot ulceration and lower extremity amputation. DPN is a paradoxical condition as up to half of all patients with that may have painful symptoms, whereas the remaining may be asymptomatic but have significant deficits on neurological examination. Some patients may have more confusing conditions, with painful symptoms and simultaneous marked loss of pain sensation. Pain is a very personal experience, and there is marked variation in the description of symptoms among patients with similar pathological lesions. In addition, sociocultural and ethnic differences influence pain perception and responses. Among the patients with type 2 diabetes, the prevalence of DPN ranges from 40% to 50%, and the prevalence of PDPN ranges from 10% to 20% according to the literature. Painful DPN is associated with diabetic micro- and macrovascular complications and negatively influences a patient's quality of life. In addition, patients with painful DPN have significantly poorer quality of life compared with patients with non-neuropathic pain. Western population based study reported that patients with PDPN had significantly poorer quality of life compared with the patients with type 2 diabetes mellitus without pain. Recently, we reported that painful DPN compared with non-painful DPN had greater effects on daily activities, sleep, and quality of life as assessed by patient-reported outcome measure questionnaires in Korean nationwide hospital-based study. As well as painful DPN, non-painful or insensate DPN also puts patients at risk for foot ulceration and the late sequelae of neuropathy, including Chartcot neuro-pathy; however, painful symptoms in DPN lead to a substantial disease burden and decreased quality of life.

Chong Hwa Kim

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➤**Educational background & professional experience**

1988-1994	College of Medicine, Chonbuk national university
1999-2001	Master course of medical science, Graduate school, Chonbuk national university
2002-2003	Endocrinology & Metabolism, Medical college of Chonbuk national university hospital / Fellow
2002-2007	Ph.D. course of medical science, Graduate school, Chonbuk national university, Majored in diabetology
2003-present	Endocrinology & Metabolism, Sejong general hospital / Director

➤**Research interests**

Diabetes, Diabetic neuropathy

➤**Brief list of publications**

1. Autoimmune Hypoglycemia in a Type 2 Diabetic Patient With Anti-Insulin and Insulin Receptor Antibodies. Diabetes Care 27: 288-289,2005
2. Autoimmune Hypoglycemia in a Type 2 Diabetic Patient With Anti-Insulin and Insulin Receptor Antibodies: Response to Sahin, Tutuncu, and Guvener. Diabetes Care 27: 1247,2005
3. Comparison of the efficacy and safety of tramadol/acetaminophen combination therapy and gabapentin in the treatment of painful diabetic neuropathy. Diabet Med 2010 Sep;27(9):1033-40
4. Prevalence and clinical characteristics of diabetic peripheral neuropathy in hospital patients with Type 2 diabetes in Korea. Diabet Med 2012 Sep;29(9):e290-e296
5. Prevalence and clinical implications of painful diabetic peripheral neuropathy in type 2 diabetes: Results from a nationwide hospital-based study of diabetic neuropathy in Korea. Diabetes Res Clin Pract 2013 Dec 25. pii: S0168-8227(13)00436-1

Painful and painless diabetic neuropathy: one disease or two?

The diabetic neuropathies are heterogeneous, affecting different parts of the nervous system that present with diverse clinical manifestations such as painful diabetic polyneuropathy (PDPN), painless DPN and autonomic neuropathy. PDNP is generally considered a variant of diabetic polyneuropathy (DPN) but the identification of distinctive aspects that characterize painful compared with painless DPN has however been addressed in many studies, mainly with the purpose of better understanding the mechanisms of neuropathic pain in the scenario of peripheral nerve damage of DPN, of determining risk markers for pain development, and also of recognizing who might respond to treatments. This lecture is aimed at examining available data dealing with the issue of similarities and differences between painful and painless DPN in an attempt to respond to the question of whether painful and painless DPN are the same disease or not and to address the conundrum of why some people develop the insensate variety of DPN whilst others experience distressing pain. Thus, I considers the clinical correlates of PDPN, its distinctive framework of symptoms, signs, and nerve functional and structural abnormalities, the question of large and small fiber involvement, the peripheral pain mechanisms, the central processing of pain and some new insights into the pathogenesis of pain in peripheral polyneuropathies and PDPN.

Miroslav Backonja

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➤Educational background & professional experience

1980	University of Zagreb Medical Faculty / MD
1984-1987	University of Wisconsin - Madison, Neurology / Neurology resident
1988	University of Wisconsin - Madison / Pain Fellow
1988-2011	University of Wisconsin - Madison / Professor
2011-present	CRILifetree part of PRAHS / Medical Director

➤Research interests

Neuropathic pain, Pain measurement, Translational pain medicine

➤Brief list of publications

1. Backonja MM, Attal N, Baron R, et al. Value of quantitative sensory testing in neurological and pain disorders: NeuPSIG consensus. Pain 2013;154(9):1807-19
2. Jones RC 3rd, Backonja MM. Review of neuropathic pain screening and assessment tools. Curr Pain Headache Rep. 2013,17(9):363. doi: 10.1007/s11916-013-0363-6
3. Backonja MM, Walk D, Edwards RR, Sehgal N, Moeller-Bertram T, Wasan A, Irving G, Argoff CE, Wallace MS,: Quantitative Sensory Testing (QST) in measurement of neuropathic pain phenomena and other sensory abnormalities. Clinical Journal of Pain, 2009:25(7):641-647
4. Backonja M, Beydoun A, Edwards KR et al: Gabapentin monotherapy for the symptomatic treatment of painful neuropathy: a multicenter, double blind, placebo-controlled trial in patients with diabetes mellitus. JAMA 280(21):1831-1836, Dec. 2, 1998.

Advances in the treatment of painful and painless diabetic neuropathy

Neuropathy is one of common manifestations of diabetes mellitus (DM) and it increases in incidence and severity as DM progresses, in particular if not well controlled. Neuropathy affects all nerve fiber types and in individual patients manifests with different severity leading to a range of symptoms from painless loss of sensation to severe pain or combination of both. The foundation of control of neuropathy and associated pain is blood sugar control and disease management. Influence of other metabolic and hormonal factors is now recognized as ones that could contribute to progression of neuropathy. In addition to disease management, pharmacotherapy is an important component of treatment for diabetic neuropathy (DN), in particular for painful. Number of therapies for DN is very limited and effects are small and not easy to reproduce. In contrast a few therapies have been investigated and a couple of them, pregabalin and duloxetine, are approved for treatment of pain in DN. Recent studies point to the fact that combination therapy is more effective than individual drugs. Certainly this approach needs to be weighed against side effects of the combination.

▌Panel Discussion ▐

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Jong Chul Won

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Sung Wan Chun

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➤Educational background & professional experience

1999	Yonsei University College of Medicine / MD
2002-2009	Severance Hospital Intern, Resident, Fellow
2005	Yonsei University Graduate School / MPH
2013	Yonsei University Graduate School / PhD
2010-present	Soonchunhyang University Cheonan Hospital / Assistant professor

➤Research interests

Diabetic neuropathy, Nutritional therapy

➤Brief list of publications

1. Lithospermic acid B protects beta-1 cells from cytokine-induced apoptosis by alleviating apoptotic pathways and activating anti-apoptotic pathways of Nrf2-HO-1 and Sirt1
2. Predictive characteristics of patients achieving glycaemic control with insulin after sulfonylurea failure
3. Effect of 17-beta Estradiol on Adipocyte Lipin-1 Expression in OLETF Rat
4. Summary of the Update to the Diabetic Neuropathy Management Guidebook
5. A polymorphism in the zinc transporter gene SLC30A8 confers resistance against posttransplantation diabetes mellitus in renal allograft recipients

Current state in the management of older adults with diabetes

Aging could be typically characterized by a general decline in physical function, a reduction in social relationships, and decreased socioeconomic status. The prevalence of diabetes in old age group was reported up to 3 times higher than that of fifth decades in Korea. Hospital admissions lasted twice as long for older patients with diabetes compared with age-matched control groups without diabetes. Improved life expectancy would be projected to continue to increase the incidence and prevalence of diabetes. Physiological changes due to aging, degeneration of glucose metabolism, diet changes, life-style changes could also explain the high prevalence and ongoing incidence of diabetes in the old age group.

The older people with diabetes, particularly those who were housebound or institutionalized, had special needs. The management of T2DM and its common co-morbidity of macrovascular disease was complicated in elderly subjects because of the added effects of aging on metabolism and renal function, the use of potentially diabetogenic drugs and low levels of physical activity. Cardiovascular risk was particularly high because many risk factors of the metabolic syndrome could be present for up to a decade before T2DM was diagnosed. Logistic regression demonstrated a significant rise in the prevalence of retinopathy with aging, independent of the effects of metabolic control, duration of disease and other risk variables. Impaired cognitive function and depression should be borne in mind when treating elderly subjects with diabetes. Chronic diabetic complications would often cause considerable disability in older people.

Despite their numerous problems, about two-thirds of older people with diabetes were thought to be suitable for strategies to improve or optimize glycemic control. Identifying "frail" patients and structured diabetes care were particularly important for older people. However, with the poor economic conditions, we could estimate that many elderly diabetic patients in Korea stand aside from the systematic management and education.

Jae Min Lee

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➤**Educational background & professional experience**

1999	Chungnam National University / MD
2006	Eulji University Hospital / Fellow
2011-present	Eulji University Hospital / Assistant professor

➤**Research interests**

Diabetes and gerontology

➤**Brief list of publications**

1. The clinical study to evaluate the safety and efficacy of D-chiro-inositol in patients with type 2 diabetes The Korean Journal of Medicine
2. The Effects of D-Chiro-Inositol on Glucose Metabolism in 3T3-L1 Cells KOREAN DIABETES J

Oral anti-diabetic drugs in older adults with diabetes

Recently the older population, persons 65 years or older, is rapidly growing. This phenomenon brings about many problems in socio-economic and medical aspects. Prevalence of diabetes mellitus in the old population is also increasing. There is some difference in treating elderly diabetic patients when compared to young or middle aged diabetic patients. Although anti-diabetics agents are not different, we have to consider many things, such as, age, comorbidity, polypharmacy, health and socioeconomic status. Factors of geriatric syndrome needs to be considered. Physicians must recognize that these factors affect glycemic control and it is closely correlated with mortality. The target of glycemic control should be individualized in elderly diabetic patients according to their situation. In patients with multiple comorbidities or short life expectancy, avoiding hypoglycemia and less stringent glycemic control may be appropriate rather than intensive glycemic control. Recent trials with intensive glycemic control have failed to demonstrate decreased mortality with glycemic control and severe hypoglycemia was associated with increased mortality. In conclusion, most appropriate treatment should be determined by considering characteristics and side effects of anti-diabetic agents and individualized target goals in elderly diabetic patients.

Sung Hoon Yu

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➤Educational background & professional experience

2002	Hanyang University College of Medicine / M.D
2002-2007	Samsung Cheil Hospital, Department of Internal Medcine / Residency
2007-2009	Seoul National University / Fellowship
2009-2012	Hallym University College of Medicine / Instructor
2012	Hanyang University College of Medicine / Ph.D.
2012-present	Hallym University College of Medicine / Assistant professor

➤Research interests

Diabetes complications, Geriatric medicine, Endocrine oncology

➤Brief list of publications

1. Cheng Ji Jin, Sung Hoon Yu, Xiao-Mei Wang, Se Joon Woo, Hyo Jin Park, Hyun Chul Lee, Sung Hee Choi, Kyoung Min Kim, Jung Hee Kim, Kyong Soo Park, Hak Chul Jang, Soo Lim. The effect of lithospermic acid, an antioxidant, on development of diabetic retinopathy in spontaneously obese diabetic rats. PLoS One. 2014 Jun 6;9(6):e98232.
2. Y.-C. Hwang, H.-Y. Ahn, S.-H. Yu, S.-W. Park and C.-Y. Park. Atherogenic dyslipidaemic profiles associated with the development of Type 2 diabetes: a 3.1-year longitudinal study. Diabet. Med. 2014 Jan;31(1) :24-30.
3. Chang Won Won, Hyung Joon Yoo, Sung Hoon Yu, Chang Oh Kim, Lourdes Carolina I. Dumlao, Esthika Dewiasty, Jeffrey Rowland, Hao-Hsiang Chang, Jintang Wang, Masahiro Akishita, Tan Thai Lian, Christopher Lum, Om Prakahsh. Lists of geriatric syndromes in the Asian-Pacific geriatric societies. Eur Geriatr Med. 2013:4:335-338.
4. Sung Hoon Yu, Jun Goo Kang, Yoo-Cheol Hwang, Kyu Jeung Ahn, Hyung Joon Yoo, Hong Yup Ahn, Sung Woo Park, Cheol-Young Park. Increasing achievement of the target goals for glycemic, blood pressure and lipid control for adults with diagnosed diabetes in Korea. J Diabetes Invest, 2013:4:460-465.
5. Chan Soo Shin, Min Joo Kim, Sang Mi Shim, Jin Taek Kim, Sung Hoon Yu, Bo Kyung Koo, Hwa Young Cho, Hyung Jin Choi, Sun Wook Cho, Sang Wan Kim, Seong Yeon Kim, Seung-O Yang, Nam H. Cho. The prevalence and risk factors of vertebral fractures in Korea. J Bone Miner Metab. 2012;30:183–192.

Comprehensive geriatric assessment in elderly adults with diabetes

Diabetes mellitus is common in the elderly population. The treatment of diabetes mellitus in the elderly population is often difficult because of impaired physical, psychological and cognitive functions, and the lack of social support. Elderly diabetic patients may have increased risk for functional dependency and frailty. Therefore, a comprehensive geriatric assessment may be necessary in the treatment of elderly diabetes. Diabetes mellitus is considered to lead to accelerated aging and atherosclerotic disease compared with non-diabetic population. The diabetes population has a high prevalence of geriatric syndrome such as functional disabilities, depression, fall, urinary incontinence, pain and dementia, which occur due to aging and diabetic complications. The geriatric symptoms lead to frailty, loss of independence and low quality of life. Importantly, these geriatric symptoms are major obstacles in the treatment and care of diabetic people.

The comprehensive geriatric assessment consists of a few dimensions: physical, psychological, cognitive function, socio-economic conditions, and patient's preference. The function in assessment can be used as predictors for disease prognosis, a tool for early diagnosis of complicated diseases like dementia. The comprehensive geriatric assessment is also useful in performing an individualized approach to improve physical, psychological, and mental functions as well as to achieve treatment goal of glucose in elderly patients with diabetes mellitus.

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➤**Educational background & professional experience**

2001-2004	Korea University / Assistant Professor
2004-2009	Korea University / Associate Professor
2005-2006	University of Texas / Research Fellow
2009-present	Korea University / Professor

➤**Research interests**

Adipokines & hepatokines, Sarcopenic obesity, Vascular inflammation

➤**Brief list of publications**

1. Hong HC, Hwang SY, Choi HY, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. The relationship between sarcopenia and non-alcoholic fatty liver disease (NAFLD): The Korean Sarcopenic Obesity Study (KSOS). Hepatology 2014 May;59(5):1772-8
2. Choi HY, Park JW, Lee N, Hwang SY, Cho GJ, Hong HC, Yoo HJ, Hwang TG, Kim SM, Baik SH, Park KS, Yoon B-S, Choi KM. Effects of a combined aerobic and resistance exercise program on C1q/TNF-related protein-3 (CTRP-3) and CTRP-5 levels. Diabetes Care 2013 Oct;36(10):3321-7
3. Choi KM, Hwang SY, Hong HC, Yang SJ, Choi HY, Yoo HJ, Lee KW, Nam MS, Park YS, Woo JT, Kim YS, Choi DS, Youn BS, Baik SH. C1q/TNF-related Protein-3 (CTRP-3) and Pigment Epithelium-Derived Factor (PEDF) Concentrations in Patients with Type 2 Diabetes and Metabolic Syndrome. Diabetes 2012 Nov;61(11):2932-6
4. Choi HY, Kim S, Yang SJ, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Association between adiponectin, resistin and vascular inflammation: Analysis with 18F-Fludorodeoxyglucose Positron Emission Tomography. Arterioscler Thromb Vasc Biol 2011 Apr;31(4):944-9
5. Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Care; 2010 Jul;33(7):1497-1499

Exercise training in patients with type 2 diabetes

Exercise has been shown to improve glycemic control in patients with type 2 diabetes as assessed by glycated hemoglobin. Furthermore, exercise is an effective treatment for type 2 diabetes, resulting in improvement in body composition, insulin resistance, and stabilization of plasma glucose. However, the most appropriate exercise protocol for type 2 diabetes has not been yet established, resulting from insufficient evidence to determine the optimal intensity, duration, and frequency of exercise training. In addition, patient engagement is suboptimal and there are several reasons; one possible factor may be a tendency in medical experts to prioritize the role of diet and medication over exercise in usual clinical practice. Moreover, published treatment guidelines are different in their approach to exercise training. Usually, most guidelines suggest that patients with type 2 diabetes should engage in 150 min of moderate to vigorous exercise per week. This recommendation is similar to the guidelines for the prevention of cardiovascular disease in the general population. Further studies may be needed to establish physiological mechanism of benefits of exercise training and the use of individualized prescription to optimize the beneficial effects of exercise.

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➤Educational background & professional experience

2013-2014 York University / Visiting professor
2009-present Kangbuk Samsung Hospital, Sungkyunkwan University / Associate professor

➤Research interests

Clinical diabetes, Lipid metabolism

➤Brief list of publications

1. Yang SJ, Choi JM, Chang EJ, Park SW, Park CY Sirt1 and Sirt6 Are Not Synergistic but Compensatory Factors that Improve Hepatocyte Steatosis. PLoS ONE (in press)
2. Park SE, Lee NS, Park JW, Rhee EJ, Lee WY, Oh KW, Park SW, Park CY, Youn BS. Urinary RBP4 as a Marker of Insulin Resistance, Inflammation, and Microalbuminuria. Eur J Endocrinol 2014 Jul 3. pii: EJE-14-0247
3. Hwang YC, Jung CH, Ahn HY, Jeon WS, Jin SM, Kim JH, Park CY, Lee BW. Optimal glycated albumin cutoff value to diagnose diabetes in Korean adults: A study based on the oral glucose tolerance test Clin Chim Acta 2014 Jul 4;437C:1-5 [Epub ahead of print]
4. Hwang YC, Ahn HY, Park SW, Park CY. Apolipoprotein B and non-HDL cholesterol are more powerful predictors for incident type 2 diabetes than fasting glucose or glycated hemoglobin in subjects with normal glucose tolerance: A 3.3-year retrospective longitudinal study. Acta Diabetol 2014 May 11. [Epub ahead of print]
5. Kim JD, Park CY, Ahn KJ, Cho JH, Choi KM, Kang JG, Kim JH, Lee KY, Lee BW , Mok JO, Moon MK, Park JY, Park SW. Non-HDL cholesterol is an independent risk factor for aspirin resistance especially in obese type 2 diabetes. Atherosclerosis 2014 Feb 12;234(1):146-151

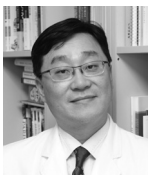
Debate session: benefits of exercise with or without weight loss - exercise decreases diabetes risk independent of weight

As everyone knows, regular physical activity is essential to manage the glucose, lipid, blood pressure.

American diabetes association recommends effective ongoing support program targeting weight loss of 7% of body weight and increasing physical activity to at least 150min/week of moderate activity for the prevention or delay of type 2 diabetes.

Some studies show structured exercise interventions of at least 8 weeks' duration have been shown to lower A1C in patients with type 2 diabetes, even with no significant change in BMI.

Regular exercise has been shown to improve blood glucose control, reduce cardiovascular risk factors, and contribute to weight loss. Although exercise is a part of weight loss program, exercise itself has a numerous benefit independent of weight loss.



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➤Educational background & professional experience

1987-1993	Yonsei University College of Medicine / M.D.
1997-2001	Internal Medicine, Severance Hospital / Resident
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2001-2002	Yonsei University College of Medicine / Clinical Fellow(endocrinology)
2013-present	Endocrinology, Ajou University School of Medicine / Professor

➤Research interests

Epidemiology of diabetes, Obesity and metabolic syndrome

➤Brief list of publications

1. Jeon JY, Kim DJ, Ko SH, Kwon HS, Lim S, Choi SH, Kim CS, An JH, Kim NH, Won JC, Kim JH, Cha BY, Song KH; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Current Status of Glycemic Control of Patients with Diabetes in Korea: The Fifth Korea National Health and Nutrition Examination Survey. Diabetes Metab J. 2014 Jun;38(3):197-203.
2. Park YM, Ko SH, Lee JM, Kim DJ, Kim DJ, Han K, Bower JK, Ahn YB; Committee of Clinical Practice Guideline, Korean Diabetes Association. Glycaemic and haemoglobin A1c thresholds for detecting diabetic retinopathy: The fifth Korea National Health and Nutrition Examination Survey (2011). Diabetes Res Clin Pract. 2014 Jun;104(3):435-42.
3. Choi YJ, Kim DJ, Lee Y, Chung YS. Insulin is inversely associated with bone mass, especially in the insulin-resistant population: the Korea and U.S. National Health and Nutrition Examination Surveys. J Clin Endocrinol Metab. 2014 Apr;99(4):1433-41.
4. Jeon JY, Ko SH, Kwon HS, Kim NH, Kim JH, Kim CS, Song KH, Won JC, Lim S, Choi SH, Jang MJ, Kim Y, Oh K, Kim DJ, Cha BY; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Prevalence of Diabetes and Prediabetes according to Fasting Plasma Glucose and HbA1c. Diabetes Metab J. 2013 Oct;37(5):349-57.
5. Lee YH, Bang H, Kim HC, Kim HM, Park SW, Kim DJ. A Simple Screening Score for Diabetes for the Korean Population: Development, validation, and comparison with other scores. Diabetes Care. 2012 Aug;35(8):1723-30.

Debate session: benefits of exercise with or without weight loss - weight plays a more dominant role in diabetes risk

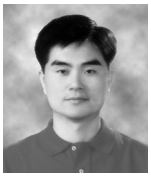
Obesity is an established risk factor for cardiometabolic disorders, including type 2 diabetes, cardiovascular disease, and mortality. There are many prospective studies and clinical trials shown the independent effects of cardiorespiratory fitness (CRF) and obesity (fatness) on the risk of type 2 diabetes. However, we don't know which one is more important to delay and/or prevent type 2 diabetes.

In this debate session, I would like to focus on the effect of fatness and weight reduction on diabetes risk. In the Diabetes Prevention Program (DPP), weight loss was the most important contributor to prevention of diabetes even though reduction of calories and increased physical activity were intensively introduced. This finding was also seen in the follow-up study of the DPP. In the Finnish Diabetes Prevention Study (DPS), the only significant association was shown between weight reduction and diabetes risk.

Interestingly, the degree of weight loss and maintenance are very important things. Weight regain is very common in clinical trial and real practice. According to the Hammen et al., every kilogram of weight loss in the DPP resulted in a 16% reduction in diabetes risk. However, weight loss of at least 3-4% is necessary to achieve significant reduction of diabetes. In the beginning of the DPPOS study, there are about 3-4% difference of weight between the lifestyle arm and control arm. There was no difference of incidence of diabetes between two arms.

In conclusion, both fitness and fatness are associated with higher risk of diabetes. However, fatness and weight reduction is more important determinant to prevent the diabetes.

▌Panel Discussion ▐



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➤Educational background & professional experience

1981	Seoul National University / M.D.
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1995	Scripps Research Institute / Research Associate
1997	Sungkyunkwan University / Associate Professor
2003-present	Sungkyunkwan University / Professor

➤Research interests

Autophagy, Apoptosis, Innate immunity, Microbiota, Mitochondria

➤Brief list of publications

1. Kim KH, Lee M-S. Autophagy- a key player in cellular and body metabolism. Nature Rev Endocrinol 10: 322-337, 2014
2. Kim J, Cheon H, Jeong YT, Quan W, Kim KH, Cho JM, Lim Y-M, Oh SH, Jin S-M, Kim JH, Lee M-K, Kim S, Komatsu M, Kang S-W, Lee M-S. Amyloidogenic peptide oligomer accumulation in autophagy-deficient β-cells leads to diabetes. J Clin Invest 124-3311, 2014
3. Kim KH, Jeong YT, Oh H, Kim S-H, Cho JM, Kim Y-N, Kim SS, Kim D-H, Hur KY, Kim HK, Koh T, Han J, Kim H, Kim J, Back SH, Komatsu M, Chen H, Chan DC, Konishi M, Itoh N, Choi CS, Lee M-S. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing FGF21, a 'mitokine'. Nature Medicine 19:83-92, 2013
4. Jung H-S, Chung KW, Kim JW, Kim J, Komatsu M, Tanaka K, Nguyen YH, Kang TM, Yoon K-H, Kim J-W, Jeong YT, Han MS, Lee M-K, Kim K-W, Shin J, Lee M-S. Loss of Autophagy Diminishes Pancreatic β-Cell Mass and Function with Resultant Hyperglycemia. Cell Metab 8:318-324, 2008
5. Kim HS, Han MS, Chung KW, Kim S, Kim E, Kim MJ, Jang E, Lee HA, Youn J, Akira S, Lee M-S. Toll-like receptor 2 senses b-cell death and contributes to the initiation of autoimmune diabetes. Immunity 27:321-333, 2007

β-cell autophagy deficiency leads to amyloidogenic peptide oligomer accumulation and diabetes

Islet amyloid is a hallmark of human type 2 diabetes (T2D), due to the amyloidogenic propensity of human IAPP (hIAPP) in contrast to mouse IAPP (mIAPP). Because autophagy is important in the clearance of amyloid-like proteins, we studied the role of autophagy in the pathogenesis of human T2D employing transgenic mice expressing *hIAPP* in β-cells. β-cell-specific autophagy-deficient mice expressing *hIAPP* (*hIAPP*$^{+}$*Atg7*$^{\Delta\beta\text{-cell}}$ mice) developed overt diabetes, while *hIAPP*$^{+}$ or *Atg7*$^{\Delta\beta\text{-cell}}$ mice never did. hIAPP oligomer and IAPP amyloid accumulated in islets of *hIAPP*$^{+}$*Atg7*$^{\Delta\beta\text{-cell}}$ mice, leading to increased death and decreased mass of β-cells. When *prepro-hIAPP* was expressed in vitro, the pro-hIAPP dimer was formed, which was absent or dramatically reduced when nonamyloidogenic *prepro-mIAPP* or mutant *prepro-hIAPP* was expressed. When autophagy was deficient, accumulation of the pro-hIAPP dimer markedly increased, and the pro-hIAPP trimer was additionally observed in the detergent-insoluble fraction. Trehalose, an autophagy enhancer, improved metabolic profile of *hIAPP*$^{+}$ mice fed high-fat diet. These results suggest that autophagy is critical for the clearance of amyloidogenic hIAPP and autophagy deficiency due to genetic predisposition or aging could play a role in the pathogenesis of human T2D. Autophagy enhancers could be therapeutic agents against human T2D characterized by islet amyloid accumulation.

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➤Educational background & professional experience

1987-1993	The Catholic University of Korea / M.D.
1995-1997	The Catholic University of Korea / MSc
2002-2005	The Catholic University of Korea / Ph.D.
2007-2008	Emory University, United States / Visiting Scholar
2014-present	The Catholic University of Korea / Professor

➤Research interests

Pathogenesis and risk factors of diabetic vascular complications
Pathogenesis and risk factors of the metabolic syndrome and diabetes mellitus

➤Brief list of publications

1. Choi JA, Han K, Kwon HS*. Association between Urinary Albumin Excretion and Intraocular Pressure in Type 2 Diabetic Patients without Renal Impairment. PLoS One. 2014 May 2;9(5):e96335. doi: 10.1371/journal.pone.0096335. eCollection 2014. [IF 3.534]
2. Lee SH, Han K, Yang HK, Kim MK, Yoon KH, Kwon HS*, Park YM. Identifying subgroups of obesity using the product of triglycerides and glucose: the Korea National Health and Nutrition Examination Survey, 2008-2010. Clin Endocrinol (Oxf). 2014 May 19. doi: 10.1111/cen.12502. [Epub ahead of print] [IF 3.353]
3. Jang EH, Park YM, Hur J, Kim MK, Ko SH, Baek KH, Song KH, Lee KW, Kwon HS*. Higher levels of small dense low-density lipoprotein (LDL) are associated with cardiac autonomic neuropathy in patients with Type 2 diabetes. Diabet Med. 2013 Jun;30(6):694-701. [IF 3.064]
4. Kim MK, Jang EH, Hong OK, Chun HJ, Yoo SJ, Baek KH, Kim W, Kim EK, Song KH, Kwon HS*. Changes in Serum Levels of Bone Morphogenic Protein 4 and Inflammatory Cytokines after Bariatric Surgery in Severely Obese Korean Patients with Type 2 Diabetes. Int J Endocrinol, vol. 2013, Article ID 681205, 5 pages, 2013. doi:10.1155/2013/681205 [IF 1.515]
5. Son JW, Jang EH, Kim MK, Kim HL, Baek KH, Song KH, Yoo SJ, Yoon KH, Cha BY, Lee KW, Son HY, Kwon HS*. Usefulness of Albuminuria as Predictor for Coronary Artery Stenosis, Regardless of Estimated Glomerular Filtration Rate, in Patients With Type 2 Diabetes Mellitus. Am J Cardiol. 2012 Nov 15;110(10):1434-9. [IF 3.425]

The new solution to T2DM: human GLP-1 analogue, liraglutide

Liraglutide is the first once-daily human GLP-1 analogue. Other GLP-1 receptor agonists are available but, unlike liraglutide, they are not analogues of native human GLP-1. Instead, they are based on the exendin-4 molecule found in the saliva of a lizard. In contrast to the up to 53% similarity between human GLP-1 and exendin-based therapies, liraglutide shares 97% sequence identity with human GLP-1. The high level of similarity between liraglutide and native human GLP-1 may explain the low incidence of anti-liraglutide antibodies observed in patients treated with liraglutide. In clinical trials, less than 9% of patients treated with liraglutide developed anti-liraglutide antibodies. By contrast, the lower level of similarity between exendin-based therapies and native GLP-1 may explain the comparatively high incidence of anti-exendin antibodies observed in patients treated with exendin-based therapies. In clinical trials, up to 57% of patients developed antibodies against exendin-based therapies. With some exendin-based therapies, high anti-exendin antibody titres may compromise glycaemic efficacy in a small proportion of patients. Antibody formation has not been associated with reduced efficacy of liraglutide.

When used in combination, treatment with liraglutide after first-line drugs (such as metformin) showed non-inferiority to glimepiride (sulphonylurea) and provided significantly more effective control of blood sugar levels compared to other commonly used antidiabetic agents such as insulin glargine as well as exenatide twice daily, sitagliptin and exenatide once weekly.

More patients with T2D treated with liraglutide achieve target blood sugar levels (HbA1c) of 〈7% than other commonly used antidiabetic agents, sitagliptin, glimepiride, exenatide once weekly.

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➤Educational background & professional experience

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2007-2009	Yonsei University, Internal Medicine, Endocrinology / fellow
2009-2011	Eulji university, Internal Medicine, Endocrinology / Assistant professor
2011-2013	Gwandong University, Internal Medicine, Endocrinology / Assistant professor
2013-present	Myongji Hospital, Internal Medicine, Endocrinology / Head of endocrinology

➤Research interests

Diabetes, Diabetic dyslipidemia, NAFLD

➤Brief list of publications

1. Small rice bowl-based meal plan for energy and marcronutrient intake in korean men with type 2 diabetes: a pilot study. 35(3):273-81 2011. diabetes & metabolism journal
2. Effects of aerobic exercise intensity on abdominal and thigh adipose tissue and skeletal muscle attenuation in overweight women with type 2 diabetes mellitus, 36(3):211-21, 2012 diabetes & metabolism journal
3. Balsamic Vinegar Improves High Fat-Induced Beta Cell Dysfunction via Beta Cell ABCA1.. 36(4):275-9. 2012. DIabetes & metabolism journal
4. The association of serum 25-hydroxyvitamin D and vertebral fractures in patients with type 2 diabetes., 60(2):179-84 ,2013. Endocrinology journal

The role of pre-mixed insulin for patients with T2DM comparing with basal insulin treatment

Glucotoxicity and lipotoxicity have long been recognized as having a deleterious effect on both β-cell function and insulin action. The rapid reversal of glucolipotoxicity by insulin therapy is one of the justifications for early insulin treatment. Despite the above justification, insulin initiation is frequently delayed in real clinical practice.

Ideally, an insulin treatment should be individualized to match patient's physiological response to glucose. International Diabetes Federation (IDF) recommends several different regimens, including basal insulin once daily, twice-daily premixed insulin, or a multi-injection (basal-bolus) regimen. ADA/EASD position statement in 2012 supports twice-daily premixed insulin as an initial insulin for patients willing to take more than one injection and who have higher HbA1c levels ($\geq$ 9.0%). Also, 2013 KDA treatment guideline recommends starting premixed insulin for patients with HbA1c higher than 8.5%.

Because premixed insulin addresses both the prandial and fasting glucose, it offers the advantage of being a more physiological regimen compared to basal insulin which primarily addresses fasting glucose. There is mounting evidence that it is important to control all aspects of the glucose triad — HbA_{1c}, fasting, and postprandial glucose. In a large observational study, impaired 2-h glucose tolerance was associated with increased mortality from cardiovascular disease. Thus, addition of mealtime insulin should be considered when significant postprandial glucose excursions (e.g., 〉180 mg/dL) occur. A logical intensification to control postprandial hyperglycemia would be to convert the regimen to a basal-bolus regimen. However, many patients refuse it because of the perceived treatment complexity and lifestyle burden. More readily accepted option is to switch the regimen to 3 doses of premixed insulin. Thus, it could be argued that premixed insulin, by virtue of their ability to control postprandial glucose in addition to its convenience, may offer significant prognostic advantages over basal insulin for patients with type 2 diabetic patients.

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1. International Diabetes Federation. Global Guidelines for type 2 Diabetes;2011
2. Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach Position Statement of the ADA/EASD. Diabetes Care 35;1364-1379, 2012
3. European Journal of Internal Medicine 18;56-62.
4. DECODE study group, on behalf of European Diabetes Epidemiology Group. Glucose and cardiovascular mortality Arch Intern Med 161;397-404, 2001
5. Korean Diabetes Association Treatment Guideline 2013

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➤Educational background & professional experience

1996	University of Ulsan College of Medicine / M.D.
2005	University of Ulsan College of Medicine / Ph.D.
2006-2009	Inje University, Dep. of Internal Medicine / Assistant Professor
2012-2014	University of Washington, Dep. of Internal Medicine / Visiting Scholar
2009-present	University of Ulsan, Asan Medical Center, Dep. of Internal Medidine / Assistant & Associate Professor

➤Research interests

Diabetes / Obesity and endothelial dysfunction
Diabetes / Obesity and vascular inflammation

➤Brief list of publications

1. Jung CH, Lee WJ, Hwang JY, Seol SM, Kim YM, Lee YL, Park JY. Vaspin protects vascular endothelial cells against free fatty acid-induced apoptosis through a phosphatidylinositol 3-kinase/Akt pathway. Biochem Biophys Res Commun. 413(2):264-9, 2011
2. Jung CH, Hwang JY, Yu JH, Shin MS, Bae SJ, Park JY, Kim HK, Lee WJ. The value of apolipoprotein B/A1 ratio in the diagnosis of metabolic syndrome in a Korean population. Clin Endocrinol (Oxf). 77(5):699-706, 2012
3. Jung CH, Lee WJ, Hwang JY, Yu JH, Shin MS, Lee MJ, Jang JE, Leem J, Park JY, Kim HK. Assessment of the fatty liver index as an indicator of hepatic steatosis for predicting incident diabetes independently of insulin resistance in a Korean population. Diabet Med. 30(4):428-35, 2013
4. Jung CH, Lee MJ, Hwang JY, Jang JE, Leem J, Park JY, Kim HK, Lee WJ. Elevated serum ferritin level is associated with the development of diabetes in healthy Korean men: a 4 year retrospective longitudinal study. PLoS One. 8(9):e75250, 2013
5. Jung CH, Lee MJ, Kang YM, Lee YL, Yoon HK, Kang SW, Lee WJ, Park JY. Vaspin inhibits cytokine-induced nuclear factor-kappa B activation and adhesion molecule expression via AMP-activated protein kinase activation in vascular endothelial cells. Cardiovascular Diabetology. 13(1):41, 2014

Importance of awareness about hypoglycemia risk and prevention of cardiovascular complications in T2DM

Hypoglycemia is an important obstacle in the treatment of diabetes. Hypoglycemia triggers activation of sympathoadrenal system and creates electrophysiologic alterations. Recent studies suggest a possible link between hypoglycemia and cardiovascular morbidity and mortality in patients with type 2 diabetes.

American Diabetes Association (ADA) recommends that a reasonable A1C goal for many non-pregnant adults is 〈 7%. ADA further suggests that more stringent A1C goal (〈6.5%) might be reasonable for selected patients if this can be achieved without significant hypoglycemia. However, the effort for rigorous glycemic control can lead to an increased risk of hypoglycemia.

Various therapeutic agents are available for the treatment of type 2 diabetes. They act on different pathways to control hyperglycemia. Among them, dipeptidyl peptidase-4 (DPP-4) inhibitors increase insulin release and decrease glucagon levels in a glucose-dependent manner. Because DPP-4 inhibitors increase insulin secretion in a glucose-dependent manner, they have an advantage regarding hypoglycemia.

In this presentation, my talk will focus on the data of sitagliptinin terms of hypoglycemia and cardiovascular safety.

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➤Educational background & professional experience

1991-1997	Ewha Women's University School of Medicine / Medicine
1999-2003	Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine / Internal Medicine
2007-2011	Endocrinology and Metabolism, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine / Assistant professor
2010-2011	Visiting professor in Cardiovascular Division, Brigham and Women's Hospital, Harvard University, Boston, MA, USA / Visiting Professor
2011-present	Endocrinology and Metabolism, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine / Associate professor

➤Research interests

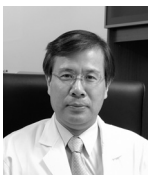
Diabetes, Endocrinology and metabolism, Vascular complications of diabetes

➤Brief list of publications

1. Rhee EJ, Lee MK, Kim JD, Jeon WS, Bae JC, Park SE, Park CY, Oh KW, Park SW, Lee WY. Metabolic health is a more important determinant for diabetes development than simple obesity: a 4-year retrospective longitudinal study. PLoS One. 2014 May 28;9(5):e98369.
2. Yu JH, Yim SH, Yu SH, Lee JY, Kim JD, Seo MH, Jeon WS, Park SE, Park CY, Lee WY, Oh KW, Park SW, Rhee EJ. The relationship of body composition and coronary artery calcification in apparently healthy korean adults. Endocrinol Metab (Seoul). 2013 Mar;28(1):33-40.
3. Rhee EJ, Seo MH, Kim JD, Jeon WS, Park SE, Park CY, Oh KW, Park SW, Lee WY. Metabolic health is more closely associated with coronary artery calcification than obesity. PLoS One. 2013 Sep 11;8(9):e74564.
4. Rhee EJ, Kim MK, Park SE, Park CY, Baek KH, Lee WY, Kang MI, Park SW, Kim SW, Oh KW. High serum vitamin D levels reduce the risk for nonalcoholic fatty liver disease in healthy men independent of metabolic syndrome. Endocr J. 2013;60(6):743-52.
5. Rhee EJ, Lee WY, Min KW, Shivane VK, Sosale AR, Jang HC, Chung CH, Nam-Goong IS, Kim JA, Kim SW; Gemigliptin Study 006 Group. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor gemigliptin compared with sitagliptin added to ongoing metformin therapy in patients with type 2 diabetes inadequately controlled with metformin alone. Diabetes Obes Metab. 2013 Jun;15(6):523-30.

Efficacy and durability: it's time to think of 10-year plan for our patients

Insulin secretory defect and insulin resistance are the two main pathophysiological mechanisms for the development of type 2 diabetes. As the prevalence of diabetes is markedly increasing, not only the treatment for diabetes itself and its complications, but also the preservation of pancreatic beta cell function is important in the maintenance of glucose control. Although numerous hypoglycemic agents have been developed and being developed at this moment, the choice for the optimal treatment agent for individual patient is still a source of trouble for a diabetologist.Once a hypoglycemic agent is chosen for an individual patient, it is not easy to change the treatment regimen. In addition, the selection of right agent to the right patient is one of the mostly important strategy not only for good glucose control, but also for the preservation of pancreatic beta cell function. Therefore, it is time to think of a long-term treatment plan for our patients newly diagnosed with diabetes, since our choice could affect the 10- or 20-year lives of our patients with diabetes. In this talk, I will discuss about the choice for the right agent and combination for glucose control and prevention of complications of diabetes regarding efficacy and durability.



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➤Educational background & professional experience

1981	Seoul National University / MD
1984	Seoul National University / MS
1991	Seoul National University / Ph.D
1991-1994	UC San Diego / Postdoctoral fellow
1994-present	Sungkyunkwan University School of Medicine / Professor

➤Research interests

Metabolic syndrome, Clinical trials, Beta cell biology, Incretin physiology

➤Brief list of publications

1. Kim MH, Jee J-W, Park S, Lee M-S, Kim K-W, Lee M-K. Metformin enhances glucagon-like peptide 1 via cooperation between insulin and Wnt signaling. J Endocrinol 2014;220:1-13
2. Suh S, Lee M-K. Metablic syndrome and cardiovascular diseases in Korea. J Atheroscl Thromb 2014:21(Suppl 1):S31-35
3. Chung HS, Suh S, Kim MY, Kim SK, Kim HK, Lee JI, Hur KY, Kim JH, Min YK, Lee MS, Kim KW, Kim SW, Chung JH, Lee M-K. Predictive factors of durability to sitagliptin: slower reduction HbA1c, older age, and higher baseline HbA1c. J Diab Invest 2014;5:doi:10.1111/jdi.12127
4. Jin SM, Choi SH, Choi DW, Heo JS, Suh S, Bae JC, Kim JH, Lee MS, Kim KW, Lee M-K. Glucaon/insulin ratio in preoperative screening before pancreatic surgery: correlation with hemoglobin A1c in subjects with and without pancreatic cancer. Endocrine 2014 Jan 23 (epub ahead of print)
5. Kim MH, Hong SH, Lee MK. Insulin receptor-overexpressing β-cells ameliorate hyperglycemia in diabetic rats through Wnt signaling activation. PLoS ONE 2013 Jul 9;8(7):e67802.

SGLT2 inhibitors in the treatment of type 2 diabetes mellitus

Sodium-glucose cotransporter 2 (SGLT2), located in the renal proximal convoluted tubule, is responsible for the glucose reabsorption by the kidney, and SGLT2 inhibitors are new class of glucose-lowering drugs that reduce renal glucose reabsorption and lead to increased urinary glucose excretion. SGLT2 is a low-affinity, high-capacity transporter and is overexpressed in patients with type 2 diabetes mellitus and is responsible for over 80% of renal glucose reabsorption. The mechanism of action is independent of insulin secretion or action. Several SGLT2 inhibitors had been developed and some of them are recently approved for the treatment of type 2 diabetes by US FDA and EMA. They effectively improve glycemic control in patients with type 2 diabetes when used as monotherapy, or added to other oral hypoglycemic agents and/or insulin. They are well tolerated and showed a low risk of hypoglycaemia. Other favorable effects associated with SGLT2 inhibitors include decreased body weight and reductions in systolic blood pressure. Adverse effects associated with SGLT2 inhibitors included genital and urinary tract infections. As SGLT2 inhibitors directly target the kidney, and is expected to be effective regardless of the degree of beta-cell dysfunction, they might be a promising antidiabetic drug both as monotherapy or in combination with any other diabetic medications.

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➤Educational background & professional experience

1990-1996	Premedical Course, Seoul National University College of Natural Science & Seoul National University College of Medicine
1996-2003	Department of Internal Medicine, Seoul National University Hospital / Intern, resident, fellow
1998-2004	Graduate School, Seoul National University
2009-2010	Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, B.C., Canada / Visiting Professor
2003-present	Department of Internal Medicine, Seoul National University Hospital and Seoul National University College of Medicine / Clinical Assistant Professor & Assistant Professor

➤Research interests

Role of the gastrointestinal tract in diabetes and obesity

➤Brief list of publications

1. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab. 2014 Mar 21. [Epub ahead of print]
2. Oh TJ, Kim MY, Shin JY, Lee JC, Kim S, Park KS, Cho YM. The incretin effect in Korean subjects with normal glucose tolerance or type 2 diabetes. Clin Endocrinol (Oxf). 2014 Feb;80(2):221-7.
3. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia. 2013 Apr;56(4):696-708
4. Oh TJ, Shin JY, Kang GH, Park KS, Cho YM. Effect of the combination of metformin and fenofibrate on glucose homeostasis in diabetic Goto-Kakizaki rats. Exp Mol Med. 2013 Jul 5;45:e30.
5. Cho YM, Fujita Y, Kieffer TJ. Glucagon-like peptide-1: glucose homeostasis and beyond. Annu Rev Physiol. 2014;76:535-59.

What's new in the incretin-based therapy?

Incretin hormones are secreted in response to meal ingestion to promote glucose-dependent insulin secretion from pancreatic beta cells. As of yet, we have two incretin hormones: GLP-1 and GIP, which are readily degraded into inactive metabolites by the enzymatic action of DPP-4. Hence, to exploit the glucose lowering effect of the incretin hormones, small molecule inhibitors that block the action of DPP-4 are used in the form of monotherapy or in combination of other anti-diabetes drugs. Because GIP contributes little in insulin secretion in patients with type 2 diabetes but GLP-1 still exerts its insulinotropic action in patients with type 2 diabetes, several GLP-1 analogs have been developed and some of them are currently approved for clinical application. Recently, combination of incretin therapies with insulin therapy has been or is being tested in clinical trials. DPP-4 inhibitors effectively and safely lower blood glucose levels in patients with type 2 diabetes who exhibit poor glycemic control with insulin. GLP-1 receptor analogues also effectively and safely reduce HbA1c levels in patients with poorly controlled type 2 diabetes with basal insulin therapy. The latter combination showed benefits in terms of body weight and needs of prandial insulin injection. In this symposium, current clinical data on the combination of insulin and incretin therapy will be reviewed.

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➤Educational background & professional experience

1990-1996	Pusan National University, college of medicine / MD
1997-2001	Asan medical center, internal medicine / Resident
2001-2002	Asan medical center, department of endocrinology / Fellow
2002-2005	Ulsan University, college of medicine / PhD
2011-present	Lilly Korea / Medical advisor

➤Research interests

Diabetes, Obesity, Gestational diabetes

➤Brief list of publications

1. 2000 The role of preoperative and postoperative thyroglobulin measurements in the detection of well differenciated thyroid carcinoma's recurrence. The Journal of Korean Endocrinology Society
2. 2001 The effects of uncoupling protein3 overexpression on glucose metabolism in OLETF rats in vivo and cultured skeletal muscle cells in vitro. Diabetes and Metabolism Journal.
3. 2009 Adipokine concentrations in pregnant Korean women with normal glucose tolerance and gestational diabetes mellitus. Diabetes and Metabolism Journal
4. 2013 Longitudinal evaluation of thyroid autoimmunity and function in pregnant Korean women. Clinical Chemistry and Laboratory Medicine

Fibroblast growth factor 21 as an emerging metabolic regulator

FGF21 is a non-mitogenic member of the FGF ligand family similar to FGF19 and FGF23. Together, these molecules form a unique subfamily of "hormone-like" FGFs. FGF21 is a soluble, secreted protein that is expressed primarily in liver and pancreas and acts via FGF receptors in tissues (liver, pancreas, and adipose). FGF21 is thought to contribute through these actions to regulate both glucose and lipid metabolism. In vivo, the administration of wild type FGF21 normalizes hyperglycemia via amelioration of total and hepatic insulin resistance, without causing hypoglycemia, improves dyslipidemia through concerted attenuation of lipogenesis and activation of lipid oxidation, and decreases body weight through an increase in energy expenditure in animal models of diabetes and obesity, such as the db/db, ob/ob, and diet-induced obese mouse, Zucker Diabetic Fatty rat, and obese/diabetic rhesus monkey. A novel FGF21 variant, LY2405319, was developed to maintain physical stability of the protein. LY2405319 was selected for further testing in early stage clinical trials. The results of the clinical development for LY2405319 will be discussed.

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➤**Educational background & professional experience**

2005-2014	Kyung Hee University Hospital, Department of Endocrinolgy and Metabolism / Chief
2008-present	Kyung Hee University School of Medicine, Department of Endocrinology and Metabolism / Chair Professor
2009-present	Kyung Hee University Hospital, Clinical Research Center / Director
2013-2014	Korean Society for the Study of Obesity / Chair, Board of Directors
2014-2014	Korean Diabetes Association / Vice President

➤**Research interests**

Clinical research,

➤**Brief list of publications**

1. Chang Hee Jung , You-Cheol Hwang , Kwang Joon Kim, Bong Soo Cha, Cheol-Young Park, Won Seon Jeon, Jae Hyeon Kim, Sang-Man Jin, Sang Youl Rhee, Jeong-taek Woo , Byung-Wan Lee, Development of an HbA1c-Based Conversion Equation for Estimating Glycated Albumin in a Korean Population with a Wide Range of Glucose Intolerance PloS One 2014, 9:e95729
2. Jung Il Son, Sang Youl Rhee, Jeong-taek Woo, Jin Kyung Hwang, Sang Ouk Chin, Suk Chon, Seungjoon Oh, Sung Woon Kim, Young Seol Kim. Hemoglobin A1c May Be an Inadequate Diagnostic Tool for Diabetes Mellitus in Anemic Subjects, Diabetes Metab J 2013, 37:342-348
3. Sang Youl Rhee, You-Cheol Hwang, Jeong-taek Woo, Sang Ouk Chin, Suk Chon, and Young Seol Kim Arsenic Exposure and Prevalence of Diabetes Mellitus in Korean Adults. J Korean Med Sci 2013, 28: 861-868
4. Suk Chon, Yun Jung Lee, Gemma Fraterrigo, Paolo Pozzilli, Moon Chan Choi, Mi-Kwang Kwon, Sang Ouk Chin, Sang Youl Rhee, Seungjoon Oh, Young-Seol Kim, and Jeong-Taek Woo, Evaluation of Glycemic Variability in Well-Controlled Type 2 Diabetes Mellitus. Diabetes Technol Ther 2013, 15:455-460
5. Sang Youl Rhee, You-Cheol Hwang, Jeong-taek Woo, Dong Hyun Sinn, Sang Ouk Chin, Suk Chon and Young Seol Kim, Blood lead is significantly associated with metabolic syndrome in Korean adults: an analysis based on the Korea National Health and Nutrition Examination Survey (KNHANES), 2008. Cardiovasc Diabetol 2013, 12:9

The effect of early intensive diabetes treatment on long-term glycaemic control in newly diagnosed type 2 diabetes: multicentre randomised parallel trial

Background and aims: Early intensive insulin therapy in newly diagnosed type 2 diabetes has been reported to improve pancreatic beta-cell function and facilitate long-term glycaemic control. However, it is unclear whether those results are by virtue of the effect of elimination of glucotoxicity or of insulin therapy itself. We performed a multicenter randomized trial to compare the long-term effects of early short-term intensive diabetes treatment modalities: intensive insulin therapy (IIT) versus combined oral antidiabetic therapy (COAD).

Materials and methods: Eligible newly diagnosed 97 patients (aged 25-70 years, HbA1c 8-12%, drug naïve) were randomised to IIT group (50, multiple daily insulin therapy with glargine and glulisine) or COAD group (47, glimepiride and metformin) for early intensive diabetes treatment in eight diabetes centers of Korea between 2007 and 2009. Early intensive treatment was performed in outpatient clinic setting according to the protocols and was stopped after achieving HbA1c 〈 7% or total inulin requirement 〈 10 U/day or 12 weeks of treatment duration. Patients were then followed-up every 1-3 months for 2 years on diet/exercise alone or rescue drug therapy as a protocol in case of HbA1c more than 8%. Primary endpoint was long-term glycaemic control and remission (HbA1c 〈 7% without drug) rate at 2 year after early intensive therapy. Analysis was per protocol.

Results: After early intensive treatment, the mean HbA1c significantly decreased from 10.1 ± 1.0 to 6.8 ± 0.7% in IIT and 10.0 ± 1.2 to 6.6 ± 0.6 % in COAD group with no significant difference between two groups. In IIT group, mean HbA1c was reduced below 7% at 8 weeks but at 12 weeks in COAD group. During the 104 weeks of follow-up period, both groups maintained good glycemic control with mean HbA1c around 7% (P = 0.093, linear mixed model analysis IIT vs. COAD), but the proportion of patients with HbA1c 〈 7% was significantly higher in IIT groups through the follow-up period (68.1%-88.6% in IIT vs. 47.1-65.0% in COAD). In IIT group, 58.1% at 1 year and 51.4% at 2 year maintained glycaemic control with diet/exercise alone, but 33.3% and 21.4%, respectively in COAD group. Remission rate at 104 weeks was significantly higher in IIT groups than in COAD group (P = 0.022).

Conclusion: Early intensive diabetes treatments with IIT or COAD in newly diagnosed type 2 diabetes were effective on long glycaemic control, but IIT was more favorable on the remission rate and maintenance of optimal glycaemic control than COAD.

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➤Educational background & professional experience

2009-present Yong Loo Lin School of Medicine, Department of Medicine / Associate Professor
2009-present Saw Swee Hock School of Medicine / Associate Professor
2009-present Yong Loo Lin School of Medicine, Cardiovascular and Metabolic Program / Associate Professor

➤Research interests

Type 2 diabetes mellitus, Lipids, Obesity, Genetics

➤Brief list of publications

1. DIAbetes Genetics Replication And Meta-analysis (DIAGRAM) Consortium; Asian Genetic Epidemiology Network Type 2 Diabetes (AGEN-T2D) Consortium; South Asian Type 2 Diabetes (SAT2D) Consortium; Mexican American Type 2 Diabetes (MAT2D) Consortium; Type 2 Diabetes Genetic Exploration by Nex-generation sequencing in muylti-Ethnic Samples (T2D-GENES) Conrortium. Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nat Genet. 2014 Mar;46(3):234-44. doi: 10.1038/ng.2897. Epub 2014. Feb 9. PubMed PMID: 24509480; PubMed Central PMCID: PMC3969612.
2. Okada Y, Sim X, Go MJ, Wu JY, Gu D, Takeuchi F, et al. Meta-analysis identifies multiple loci associated with kidney function-related traits in east Asian populations. Nat Genet. 2012 Jul 15;44(8):904-9. doi: 10.1038/ng.2352. PubMed PMID: 22797727.
3. Wen W, Cho YS, Zheng W, Dorajoo R, Kato N, Qi L, Chen CH, et al. Meta-analysis identifies common variants associated with body mass index in east Asians. Nat Genet. 2012 Feb 19;44(3):307-11. doi: 10.1038/ng.1087. PubMed PMID: 22344219; PubMed Central PMCID: PMC3288728.
4. Cho YS, Chen CH, Hu C, Long J, Ong RT, Sim X, et al. Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians. Nat Genet. 2011 Dec 11;44(1):67-72. doi: 10.1038/ng.1019. PubMed PMID: 22158537; PubMed Central PMCID: PMC3582398.
5. Kooner JS, Saleheen D, Sim X, Sehmi J, Zhang W, Frossard P, et al. Genome-wide association study in individuals of South Asian ancestry identifies six new type 2 diabetes susceptibility loci. Nat Genet. 2011 Aug 28;43(10):984-9. doi: 10.1038/ng.921. PubMed PMID: 21874001; PubMed Central PMCID: PMC3773920.

The genetics of type 2 diabetes in multi-ethnic populations - challenges and opportunities

Over the past decade, genome-wide association studies have identified numerous genetic variants associated with type 2 diabetes. While many of the initial studies were carried out in populations of European ancestry, increasing numbers of studies have been carried out in populations of differing ancestry. The ability of carry out studies in different ethnic groups provides novel opportunities. Firstly, for common variants with similar effects across ethnic groups, differences in patterns of linkage disequilibrium can help narrow the genomic region that harbors the functional variant. Secondly, differences in population history may also result in differing allele frequencies between populations. For some variants, this provides for greater power to identify these variants in some ethnic groups and not in others. Finally, if we intend to use human genetics to validate therapeutic targets for T2D, we need to identify functional variants. These variants tend to occur at low allele frequencies and are often ancestry specific. As such, access to large collections of multi-ethnic populations is required to identify variants that would facilitate such target validation studies.

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➤Educational background & professional experience

1996-2002	Seoul National University College of Medicine / M.D.
2003-2007	Seoul National University Hospital / Resident
2009-2012	Graduate School, Seoul National University / Ph.D.
2010-2011	Seoul National University Hospital, Department of Internal Medicine / Fellow
2011-present	Seoul National University Hospital, Department of Internal Medicine / Assistant Professor

➤Research interests

Diabetes, Gestational diabetes, Genetics

➤Brief list of publications

1. Kwak SH, Park YJ, Go MJ, Lee KE, Kim SJ, Choi HS, Kim TH, Choi SH, Lim S, Kim KW, Park DJ, Kim SS, Lee JY, Park KS, Jang HC, Cho NH. A genome-wide association study on thyroid function and anti-thyroid peroxidase antibodies in Koreans. Hum Mol Genet. 2014 Apr 17. [Epub ahead of print].
2. Kwak SH, Choi SH, Kim K, Jung HS, Cho YM, Lim S, Cho NH, Kim SY, Park KS, Jang HC. Prediction of type 2 diabetes in women with a history of gestational diabetes using a genetic risk score. Diabetologia. 2013 Dec;56(12):2556-63
3. Kwak SH, Choi SH, Jung HS, Cho YM, Lim S, Cho NH, Kim SY, Park KS, Jang HC. Clinical and Genetic Risk Factors for Type 2 Diabetes at Early or Late Post Partum After Gestational Diabetes Mellitus. J Clin Endocrinol Metab. 2013 Apr;98(4):744-52.
4. Kwak SH, Kim SH, Cho YM, Go MJ, Cho YS, Choi SH, Moon MK, Jung HS, Shin HD, Kang HM, Cho NH, Lee IK, Kim SY, Han BG, Jang HC, Park KS. A genome-wide association study of gestational diabetes mellitus in Korean women. Diabetes. 2012 Feb;61(2):531-41.
5. Cho YS, Chen CH, Hu C, Long J, Ong RT, Sim X, Takeuchi F, Wu Y, Go MJ, Yamauchi T, Chang YC, Kwak SH, Ma RC, Yamamoto K, Adair LS, Aung T, Cai Q, Chang LC, Chen YT, Gao Y, Hu FB, Kim HL, et al. Meta-analysis of genome-wide association studies identifies eight new loci for type 2 diabetes in east Asians. Nat Genet. 2011 Dec 11;44(1):67-72.

Genetic variants associated with lipid metabolism in Koreans

Dyslipidemia is a well known risk factor for cardiovascular disease and stroke. It is a complex trait that is affected by both genetic and environmental factors. It is estimated that as much as 30-60% of the variation is determined by genetic factors. Recent progress in genome-wide association studies have identified more than 150 genetic loci associated with lipid level. Genes that were annotated by the variants includes those that play important role in lipogenesis, lipid transport, and lipolysis. However, these variants had small effect size and only explained a limited portion of heritability. The advent of next generation sequencing enabled us to identify rare functional variants that have higher effect size. We have sequenced 917 type 2 diabetes case control subjects in whole exome scale and examined genetic variants associated with lipid levels of total cholesterol, triacylglyceride, high density lipoprotein (HDL) cholesterol, and low density lipoprotein (LDL) cholesterol. Medication status was adjusted for the LDL cholesterol level. Whole exome capture was prepared using Agilent SureSelect version 4 + UTR and sequencing was performed by Illumina HiSeq 2000. Sequence alignment was done using BWA and Picard software and variant identification was done using GATK software. Variant Tools software was used for rare variant association testing. Nonsynonymous variants that were associated LDL cholesterol level were located in APOE and PCSK9. A nonsynonumous variant in APOB gene was associated with total cholesterol level. A nonsynonymous variant in APOA5 was associated with triacyglycerol level. Finally, a nonsynonymous variant in CETP was associated with HDL cholesterol level. Further replication study to confirm our preliminary findings are currently underway.

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➤Educational background & professional experience

1994-1998	Yonsei University, Chemistry Department / BS
2001-2005	University of Chicago, Chemistry Department / Ph.D
2006-2009	Harvard Medical School, Genetics Department / Post Doc
2009-present	Yonsei University, Chemistry Department / Associate Professor

➤Research interests

Medical genomics, Synthetic genomics

➤Brief list of publications

1. Jin Woo Ahn, Han Sang Kim, Jung-Ki Yoon, … Byoung Chul Cho, Ji Hyun Lee, Duhee Bang, Genome Medicine, 2014, Identification of Somatic Mutations in EGFR/KRAS/ALK-negative Lung Adenocarcinoma in Never-Smokers.
2. Hwangbeom Kim, Hyojun Han, Jinwoo Ahn, Joongoo Lee, Namjin Cho, Hoon Jang, Hyoki Kim, Sunghoon Kwon, and Duhee Bang. High-throughput Construction of Large DNA Molecules, Nucleic Acids Research, 2012, 40, e140
3. Wang HH, Kim H, Cong L, Jeong J, Duhee Bang, Church GM, Genome-scale Promoter Engineering by Co-Selection MAGE Nature Methods, 2012, 9, 591-593, Cover Article of the June 2012 issue
4. Isaacs FJ, et al, Precise Manipulation of Chromosomes in vivo Enables Genome-wide Codon Replacement, Science, 2011, 333, 348-53. (New York Times article)
5. Duhee Bang, G. M. Church, Gene Synthesis by Circular Assembly Amplification, Nature Methods, 2008, 5, 37-39

Development of efficient target capture technologies for medical genomics

Although recently developed NGS technologies are adopted for clinical genomics, whole genome sequencing and exome sequencing are not as effective for calling mutations with high confidence compared to target capture sequencing. Thus, several diagnostic platforms have been emerged as target capture based diagnostic methods that are fine-tuned for the applications in mutation characterizations. These include Ampliseq-based target capture panel, Ilumina's target panel, and Agilent's SureSelect panel. However, all of these panels are fixed in terms of number of genes, and custom-designed panels are hard to be implemented in terms of turn-around time, and cost. In this seminar, we present our approaches for custom design and applications in clinical genomics. We particularly will emphasize our approach is also efficient and helpful for the applications in genetic studies on diabetes and metabolism.

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➤**Educational background & professional experience**

2001-2004	University of Pennsylvania / Postdoctoral fellow
2004-2006	Hanyang University / Research professor
2006-2009	Korea National Institute of Health / Principal researcher
2009-2012	Korea National Institute of Health / Deputy scientific director
2011-present	Hallym University / Professor

➤**Research interests**

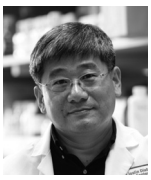
Disease genomics

➤**Brief list of publications**

1. Morris A.....Yoon Shin Cho.....DIAGRAM (2014) Genome-wide trans-ancestry meta-analysis provides insight into the genetic architecture of type 2 diabetes susceptibility. Nature Genetics 46, 234-244.
2. Wanqing Wen, Yoon Shin Cho, et al. (2012) Meta-analysis identifies common variants associated with body mass index in east Asians. Nature Genetics 44, 307-311.
3. Yoon Shin Cho, et al. (2012) Meta-analysis of genome-wide association studies identifies 8 new loci for type 2 diabetes in east Asians. Nature Genetics 44, 67-72.
4. Young Jin Kim ·····Yoon Shin Cho. (2011) Large-scale genome-wide association study in East Asians identify new genetic loci influencing metabolic traits. Nature Genetics 43, 990-995.
5. Yoon Shin Cho, et al. (2009) A large scale genome-wide association study of Asian populations uncovers genetic factors influencing eight quantitative traits. Nature Genetics 41, 527-534.

Identification of low frequency variants influencing body mass index

Advances in technologies and analytic methods in the genome research area greatly contribute to identifying numerous genetic factors influencing complex traits. Indeed Genome-Wide Association Study (GWAS) has been emerged as the major method and largely conducted to identify genetic factors for diverse complex diseases including type 2 diabetes, obesity, cardiovascular diseases and many types of cancers. Obesity is a medical condition in which excess body fat has accumulated to the extent that it may have a negative effect on health, leading to reduced life expectancy and increased health problems. To date, more than 40 loci for body mass index (BMI), an indicator of human body fatness, were identified mainly by GWAS. However, these GWAS loci (mostly common variants) could not fully explain the heritability for BMI. Moreover, most GWAS genes for BMI reported were not necessarily causal. In the hope to gain insight into the complete heritability as well as the genetic causality of BMI, we performed association analyses to identify low frequency and rare variants influencing BMI using exome sequencing data from 917 individuals. Highly promising BMI variants identified from the first stage of exome sequencing data will be further tested by de novo genotyping from about 10,000 individuals. Combining together, current progress will be discussed in this presentation.



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➤Educational background & professional experience

1983	Seoul National University / BS
1993	Boston University, School of Medicine / Ph.D.
1995-1999	Joslin Diabetes Center/Harvard Medical School / Research Fellow
2006-present	Joslin Diabetes Center / Assistant Investigator
2009-present	Harvard Medical School / Assistant Professor

➤Research interests

Immunometabolism

➤Brief list of publications

1. Cipolletta D, Feuerer M, Li A, Kamei N, Lee J, Shoelson SE, Benoist C, Mathis D. (2012) PPAR-gamma is a major driver of the accumulation and phenotype of adipose tissue Treg cells. Nature. 486, 549-553.
2. Lee J. (2013) Adipose tissue macrophages in the development of obesity-induced inflammation, insulin resistance and type 2 Diabetes. Arch. Pharm. Res. 36, 208-222.
3. Kim MS, Yamamoto Y, Kim KJ, Kamei N, Shimada T, Liu L, Moore K, Woo JR, Shoelson SE, Lee J. (2013) Regulation of Diet-induced Adipose Tissue and Systemic Inflammation by Salicylates and Pioglitazone. PLoS One. 8, e82847.
4. Lee BC, Lee J. (2014) Cellular and molecular players in adipose tissue inflammation in the development of obesity-induced insulin resistance. Biochim. Biophys. Acta. 1842, 446-462.
5. Lee J, Miyazaki M, Romeo GR, Shoelson SE. (2014) Insulin Receptor Activation with Transmembrane Domain Ligands. J. Biol. Chem. 289, 19769-19777.

Cross-talk between adipose immune cells and adipocytes in the regulation of insulin action

It has been well supported now that obesity-induced inflammation contributes the development of insulin resistance and Type 2 Diabetes. Recent studies have further shown that immune cells at the local tissues, in particular at adipose tissues, play a major role in the regulation of obesity-induced inflammation. On the other hand, insulin resistance is caused by the impairment of insulin signaling in insulin responsive cells including adipocytes, hepatocytes and myocytes. Hence, this strongly suggests that regulation of obesity-induced insulin resistance by inflammation requires cross-talk between two cellular compartments, namely tissue immune cells that regulate local inflammation and insulin responsive cells that regulate glucose homeostasis. This has been most studied in adipose tissue. In adipose tissue, obesity activates inflammatory immune cells including adipose tissue macrophages (ATMs), while it suppresses anti-inflammatory immune cells such as regulatory T cells (Treg). Then, this accordingly regulates insulin signaling in adipocytes by modulating several steps in the insulin signaling pathway including increases in inhibitory Ser/Thr phosphorylations of IRS-1 and 2. In this presentation, interrelationship between adipose tissue immune cells and adipocytes and the role of Ser phosphorylations of IRS-1 in insulin signaling will be discussed.

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➤Educational background & professional experience

1994	Sungkyunkwan University, Dept. of Pharmacy / B.Pharmacy
1996	Sungkyunkwan University, Dept. of Pharmacy / M. Pharmacy
2004	Friedrich Miescher Institute for Biomedical Research, University of Basel, Switzerland / Ph.D
2004-2009	University of Cincinnati, College of Medicine, U.S.A / Postdoctoral fellow
2009-present	Dept. of Molecular Cell Biology,. Sungkyunkwan University, School of Medicine, Korea / Associate professor

➤Research interests

Diabetes, obesity, Nutrient-sensitive signaling, Metabolism

➤Brief list of publications

1. Kim SH, Chau GC, Jang YH, Lee SI, Pyo S and Um SH*, Clinicopathologic significance and function of mTOR activation in esophageal squamous cell carcinoma, Human Pathology 2013, 44(2):226-36
2. Kim SH, Jang YH, Chau GC, Pyo S and Um SH*, Prognostic significance and function of phosphorylated ribosomal protein S6 in esophageal squamous cell carcinoma. Modern Pathology 2013, 26, 327–335
3. Kim KJ, Pyo S, Um SH*, S6K2 deficiency enhances ketone body production and increases PPARα activity in the liver. Hepatology 2012, 55(6):1727-37
4. Um SH, D'Alessio D, Thomas G, Nutrient overload, insulin resistance, and ribosomal protein S6 kinase 1, S6K1. Cell Metabolism 2006, 3(6):393-402.
5. Um SH, Frigerio F, Watanabe M, Picard F, Joaquin M, Sticker M, Fumagalli S, Allegrini P, Kozma SC, Auwerx J and Thomas G, Absence of S6K1 Protects Against Age and Diet-Induced Obesity While Enhancing Insulin Sensitivity. Nature 2004, 431, 200-205

The roles of nutrient-sensitive signaling pathways in insulin action and metabolism

Insulin resistance is an important pathogenic consequence of obesity and it also plays a central role in the development of type 2 diabetes and the onset of cardiovascular diseases. These two diseases are, in fact, major causes of the rising death rates and health care costs which are prevalent in western societies. Thus, nutrient overload, in conjunction with genetic predispositions, may have a significant influence on the development of insulin resistance. Furthermore, in insulin resistant states of obesity, plasma concentrations of amino acids, particularly of the branched-chain amino acids, are elevated. These findings expand the roles of excess dietary proteins and nutrient-sensitive signaling pathways in metabolic disease. Therefore, the molecular mechanisms by which nutrient-sensitive signaling components lead to the regulation of insulin sensitivity have important implications for the treatment of metabolic disorders. Here, we present our recent findings demonstrating how nutrient-sensitive ribosomal protein S6 Kinase 1 (S6K1), and S6K2 as downstream components of mTOR signaling, mediate insulin action and regulate nutrient homeostasis. Understanding the mechanisms of how nutrient-sensitive signaling pathways affect insulin action and insulin sensitivity may introduce novel strategies for the treatment of type 2 diabetes.

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➤Educational background & professional experience

1994	Yonsei University, Biology / BS
1996	Yonsei University, Biology / MS
2006	Univ. of Texas Southwestern Medical Center / Ph.D.
2009-2014	Salk Institute / Postdoctoral Fellow
2014-present	KAIST / Assistant Professor

➤Research interests

Adipose biology, Obesity, Diabetes, Nuclear receptors

➤Brief list of publications

1. Suh JM, Jonker JW, Ahmadian MA, Goetz R, Lackey D, Huang Z, Osborn O, van Dijk T, Yoshihara E, Liu W, Havinga R, Fan W, Yin Y, Yu RT, Liddle C, Atkins AR, Olefsky JM, Mohammadi M, Downes M, Evans RM. (2014) Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer. Nature, accepted.
2. Stenesen D, Suh JM, Seo J, Yu K, Lee KS, Kim JS, Min KJ, Graff JM. (2012) Adenosine nucleotide biosynthesis and AMPK regulate adult life span and mediate the longevity benefit of caloric restriction in flies. Cell Metab, 17, 101-12.
3. Jonker JW, Suh JM, Atkins AR, Ahmadian M, Li P, Whyte J, He MX, Juguilon H, Yin Y, Phillips CT, Yu RT, Olefsky JM, Henry RR, Downes M, Evans RM. (2012) A PPARγ-FGF1 axis is required for adaptive adipose remodeling and metabolic homeostasis. Nature, 485, 391-394
4. Zeve D, Seo J, Suh JM, Stenesen D, Tang W, Berglund ED, Wan Y, Williams LJ, Lim A, Martinez MJ, McKay RM, Millay DP, Olson EN, Graff JM. (2012) Wnt signaling controls an insulin-independent mechanism to regulate glucose uptake. Cell Metab, 15, 492-504.
5. Suh JM, Zeve D, McKay R, Seo J, Salo Z, Li R, Wang M, Graff JM.(2007) Adipose is a conserved dosage-sensitive anti-obesity gene. Cell Metab 6, 195-207.

Endocrinization of FGF1 produces a neomorphic and potent insulin sensitizer

Fibroblast Growth Factor 1 (FGF1) is an autocrine/paracrine regulator whose binding to heparan sulfate proteoglycans effectively precludes its circulation. Though originally described as a mitogenic factor, our recent studies revealed an indispensable role for FGF1 in metabolic homeostasis as FGF1 knockout mice develop severe insulin resistance when stressed by a high fat diet. Here we show that parenteral delivery of a single dose of recombinant FGF1 (rFGF1) results in potent, insulin-dependent glucose lowering in diabetic mice that is dose-dependent, but does not lead to hypoglycemia. Chronic pharmacological rFGF1 treatment increases insulin-dependent glucose uptake in skeletal muscle and suppresses hepatic glucose production to achieve whole-body insulin sensitization. The sustained glucose lowering and insulin sensitization attributed to rFGF1 are not accompanied by the side effects of weight gain, liver steatosis and bone loss associated with current insulin sensitizing therapies. Furthermore, we demonstrate that the glucose lowering activity of FGF1 can be dissociated from its mitogenic activity and is mediated predominantly via FGF receptor 1 (FGFR1) signaling. In summary, we have uncovered an unexpected, neomorphic insulin sensitizing action for exogenous non-mitogenic human FGF1 with therapeutic potential for treatment of insulin resistance and type 2 diabetes.

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➤Educational background & professional experience

1984-1990	Jichi Medical University, School of Medicine, Tochigi, Japan / M.D.
1995-1999	Kumamoto University, Graduate School of Medicine, Kumamoto, Japan / Ph.D.
2002-2005	Keio University School of Medicine, Department of Cell Differentiation, Tokyo, Japan / Assistant Professor
2006-2007	Keio University School of Medicine, Laboratory of Vascular Biology & Metabolism, Center for Integrated Medical Research, Tokyo, Japan / Associate Professor
2007-present	Kumamoto University, Graduate School of Medical Sciences, Department of Molecular Genetics, Kumamoto, Japan / Professor and Chairman

➤Research interests

Cardiovascular disease, Metabolic syndrome, Obesity

➤Brief list of publications

1. Oike Y, Akao M, Yasunaga K, Yamauchi T, Morisada T, Ito Y, Urano T, Kimura Y, Kubota Y, Maekawa H, Miyamoto T, Miyata K, Matsumoto S, Sakai J, Nakagata N, Takeya M, Koseki H, Ogawa Y, Kadowaki T & Suda T. Angiopoietin-related growth factor (AGF) antagonizes obesity and related insulin resistance. Nat Med 11:400-408, 2005
2. Oike Y, Akao M, Kubota Y & Suda T. Angiopoietin-like proteins: potential new targets for metabolic syndrome therapy. Trends Mol Med 11:473-479, 2005
3. Tabata M, Kadomatsu T, Fukuhara S, Miyata K, Ito Y, Endo M, Urano T, Zhu HJ, Tsukano H, Tazume H, Kaikita K, Miyashita K, Iwawaki T, Shimabukuro M, Sakaguchi K, Ito T, Ando Y, Ogawa H, Mochizuki N, Itoh H, Suda T & Oike Y. Angiopoietin-like protein 2 promotes chronic adipose tissue inflammation formation and obesity-related systemic insulin resistance. Cell Metab 10:178-188, 2009
4. Doi Y, Ninomiya T, Ninomiya T, Hirakawa Y, Takahashi O, Mukai N, Hata J, Iwase M, Kitazono T, Oike Y, & Kiyohara Y. Angiopoietin-like protein 2 and risk of diabetes in a general Japanese population: the Hisayama study. Diabetes Care 36:98-100, 2013
5. Kadomatsu T, Endo M, Miyata K, & Oike Y. Diverse roles of ANGPTL2 in physiology and pathophysiology. Trends Endocrinol Metab 25:245-254, 2014

Role of ANGPTL2 in obesity and insulin resistance

Stresses based on aging and lifestyle cause tissue damage. Repair of the damage by tissue remodeling is usually meditated by tissue homeostasis. However, a breakdown of tissue homeostasis leads to development of various lifestyle-related diseases. Angiopoietin-like protein 2 (ANGPTL2) maintains tissue homeostasis by promoting adaptive inflammation and subsequent tissue reconstruction, whereas excess ANGPTL2 activation induced by prolonged stress promotes a breakdown of tissue homeostasis due to chronic inflammation and irreversible tissue remodeling, promoting development of various lifestyle-related diseases. Thus, it is important to define how ANGPTL2 signaling is regulated in order to understand the mechanisms underlying disease development.

In mice, ANGPTL2 expression in adipose tissues increases under obese conditions. In the early phase of obesity, increased ANGPTL2 secretion from adipose tissues promotes MMP activation and induces angiogenesis and ECM remodeling, leading to adipogenesis and adipocyte hypertrophy, which function to store excess energy in adipose tissue. Lifestyle changes, such as overnutrition or inactivity, induce severe obesity and lead to excess ANGPTL2 secretion and pathologic adipose tissue remodeling, resulting in obesity-related insulin resistance and type 2 diabetes.

In obese human subjects, circulating ANGPTL2 concentrations increase and correlate with systemic insulin resistance. A 7-year follow-up of an epidemiological study of a general population with no history of diabetes shows that elevated serum ANGPTL2 levels are positively associated with future *de novo* development of type 2 diabetes, independent of other risk factors. Moreover, changes in serum ANGPTL2 levels reflect positive effects of lifestyle intervention in terms of weight loss and improved metabolic parameters, such as TG, insulin, and homeostasis model assessment-insulin resistance (HOMA-IR) index in overweight subjects. These findings suggest that alterations in circulating ANGPTL2 levels could serve as a biomarker to assess these disease conditions.

Thus, excess ANGPTL2 signaling in adipose tissues contributes to development of obesity-related insulin resistance and type 2 diabetes.

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➤Educational background & professional experience

2003-2005	Severance Hospital, Seoul, Korea / Clinical Fellow
2005-2006	Yonsei University College of Medicine, Seoul, Korea / Instructor
2006-2010	Yonsei University College of Medicine, Seoul, Korea / Assistant Prof.
2009-2011	Harvard Medical School, Beth Israel Deaconess Medical Center, Boston MA / Visiting Professor
2010-Present	Yonsei University College of Medicine, Seoul, Korea / Associate Prof.

➤Research interests

Posttransplantation diabetes (New onset diabetes after transplantation)
Pancreatic zinc transporter
Metabolic effect of HMG CoA reductase inhibitors
Type 2 diabetes genetics and pharmacogenetics

➤Brief list of publications

1. HMG CoA Reductase Inhibitor Treatment Induces Dysglycemia in Renal Allograft Patients. Transplantation 97(4):419-425, 2014
2. Statin Therapy is associated with Development of New Onset Diabetes after Transplantation in Liver Recipients with High Fasting Plasma Glucose. Liver Transplantation 20(5):557-563, 2014
3. Variants of the Adiponectin and Adiponectin Receptor 1 Genes and Posttransplantation Diabetes Mellitus in Renal Allograft Recipients. JCEM 97:E129-E135, 2012
4. Low-risk ZnT-8 allele (W325) for PTDM is protective against cyclosporin A-induced impairment of Beta-cell insulin secretion capacity. Pharmacogenomics J 11:191-198, 2011
5. Association of Common type 2 Diabetes Risk Gene Variants and PTDM in Renal Allograft Recipients in Korea. Transplantation 88:693-698, 2009

Molecular mechanism of diabetogenic effect of statin

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➤**Educational background & professional experience**

2009-present Baekseok University, Counseling Department / Associate Professor

➤**Research interests**

Motivational interviewing

➤**Brief list of publications**

1. SH Cho. (2013) Motivational Interviewing in psychosomatic medicine, Chapter 19, 261-272, in Somatization and Psychosomatic Symptoms (K. B. Koh, ed..) Springer.
2. SH Cho. (In print) Addiction and Motivational Interviewing. Sigma Press.
3. SH Cho. (In print) Motivational Interveiwing Principles and Applications. Hakjisa.

Why motivational interviewing?

Motivational Interviewing was introduced by Dr. William Miller in 1983 as a communication style that clinicians should apply in the process of helping patients explore their ambivalence about behavior change and resolve the ambivalence. Motivational Interviewing has been widely utilized and found as an evidence-based practice in the field of health care as well as addiction field. In comparison with traditional interventions for weight loss, medication adherence, diet, exercises for diabetes patients, Motivational Interviewing has been found more effective in increasing motivation to keep self-care behavior so that a hemoglobin A1c (HbA1c) level may be controlled. The efficacy of Motivational Interviewing has found for blood sugar control for both adolescents and adults with diabetes. Motivational Interviewing emphasizes the importance of building partnership between clinician and patient, evoking inner motivation for change, accepting patient and having compassion for patient, which is referred to as the spirit of Motivational Interviewing. Core skills of Motivational Interviewing include asking open-ended questions, affirming, reflective listening and summarizing, all of which are used to elicit change talk from patient. The more change talk patient states, the higher the likelihood of change patient has. Why Motivational Interviewing? It is because it helps patient reduce resistance about treatment, and rather retain treatment.

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➤Educational background & professional experience

1997	Hanyang university, School of medicine / M.D.
2001-2004	Hangyang University Hospital, department of Psychiatry / Resident
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2007-present	Seongnam addiction management center / Head

➤Research interests

Addiction psychiatry

➤Brief list of publications

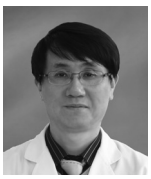
1. The biology and the pharmacological treatment in alcoholism. Yong-In Psychiatry Bull 2008;15:25-33.
2. Differential pattern of heart rate variability in patients with schizophrenia, Prog Neuropsychopharmacol Biol Psychiatry. 2009 Aug 31;33(6):991-5
3. Korean Addiction Treatment Guidelines Series (I) : Development of Korean Guidelines for the Treatment of Alcohol Use Disorde, J Korean Neuropsychiatr Assoc (2013. 3)
4. Korean Addiction Treatment Guidelines Series (II): Pharmacological Treatment of Alcohol Withdrawa, J Korean Neuropsychiatr Assoc (2013. 7)
5. Evidence-Based, Non-Pharmacological Treatment Guideline for Depression in Korea, J Korean Med Sci (2014. 1)

Motivational interviewing and psychiatry: use in addiction treatment

Motivational interviewing (MI) has many applications within psychiatry, as it is particularly helpful for use in settings where there is resistance to change. The core principle of MI is negotiation rather than conflict.

This approach is very useful for treating addictions, and for helping psychiatric patients with many other health-related adverse behaviors (e.g., smoking, exercise, poor eating habits, and others). MI can also help psychiatrists address common problems of nonadherence in pharmacotherapy and follow-up care and can function as an adjunct to a variety of most other psychotherapies.

In this symposium I review the available evidence on usefulness of MI in addiction treatment, and discuss practical details of its implementation and the skills of good motivational therapist. I hope that the principles and skills discussed in this symposium will help clinicians better understand MI and facilitate their further application them in clinical practice to promote patients self-awareness and instill a motivation to change health behaviors.



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➤Educational background & professional experience

1987	Chungnam National University, school of Medicine / M.D
1999	Chungnam National University, school of Medicine / Master of Medicine
2003	Chungnam National University, school of Medicine / Ph.D
2008-present	Eulji University, School of Medicine, Department of Internal Medicine/Endocrinology / Professor
	Eulji University Hospital, Department of Diabetes & Endocrinology Center / Medical Director

➤Research interests

Diabetes treatment & Clinical trial

➤Brief list of publications

1. Circulating levels of monocyte chemoattractant protein-1 are associated with menopause status in Korean women. Clinica Chimica Acta 403
2. Serum ferritin is inversely correlated with serum adiponectin level: Population-based cross-sectional study. Disease Markers Volume 27, Number 6 / 2009
3. Novel ERBB receptor feedback inhibitor 1 (ERRFI1) + 808 T/G polymorphism confers protective effect on diabetic nephropathy in a Korean population. Disease Markers Volume 34, Number 2
4. PINITOL AS AN INSULIN SENSITIZING AGENT. Frontiers in Clinical Drug Research-Diabetes & Obesity
5. The value of red blood cell distribution width in subclinical hypothyroidism. Arq Bras Endocrinologia Metabologia June /25/2013

Treatment motivation in diabetes patients

Diabetes mellitus is one of the most demanding chronic illnesses, in both the physical and psychological sense. To live with a chronic incurable illness is to live in a state of constant uncertainty. The treatment motivation is an important factor in the success of diabetes management. The most important factor of treatment motivation in diabetic patients is resolving illness uncertainty. Diabetic patients with greater uncertainty feel less motivated toward treatment, especially those with greater uncertainty toward prognosis and treatment, who feel less intrinsically motivated to adhere to treatment. The intrinsic and extrinsic motivational factors are related to treatment motivation and intrinsic than extrinsic factors are known to be more important. The good life style modification and action plan have played an important role in treatment motivation. Primary, the goal of diabetes treatment is control of HbA1c and preprandial, postprandial blood glucose level and the prevention of acute and chronic complications, especially cardiovascular disease. First of all, diabetes educator team "Glycemic Control" must be oriented to focus on. Removal of negative thoughts about insulin and drug treatment is the starting point for success. If patients do not have an optimal blood sugar control, their treatment motivation is exacerbated by the frustration and depression. Poorly controlled blood glucose levels is a big obstacle to maintain treatment motivation. In order to overcome the illness uncertainty , it is important to target goal will be set. Through diabetic education , to reduce illness uncertainty and maintain therapy and adaptation to the illness. thus adopting a life style appropriate to the disease, with a view to improving quality of life and adding years to one's life and life to one's years.

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➤Educational background & professional experience

2005	Seoul National University Hospital, Social Work Department / Medical Social Worker, Intern
2006-2007	SMG-SNU Boramae Medical Center, Social Work Department / Medical Social Worker
2007-2010	Soongsil University, Department of Social Welfare / Master of Social Work(MSW)
2008-present	Kyung-Hee University Medical Center, Social Work Department / Medical Social Worker & Diabetes Educator

➤Research interests

Motivational interviewing, Behavior medicine & Stress, Mindfulness-based therapy

➤Brief list of publications

[Translation Book]

Motivational Interviewing in Social Work Practice. 2014, Hakjisa.

[Article]

1. Diabetes Self-care and Mindfulness Meditation. The Journal of Korean Diabetes, 2014; 14(1), 41-45.
2. Motivational Interviewing for People with Diabetes Mellitus. The Journal of Korean Diabetes, 2011; 12(2), 109-113.
3. Parent-child Communication and Self-management of Adolescents with Type 1 Diabetes : The Mediating Effect of Diabetes-related Family Support. Korean Journal of Family Social Work, 2011; 32(6), 235-260.
4. Measuring Family Support of Adolescents with Type 1 Diabetes: An Application of the DSSQ-Family in Korea. Korean Journal of Social Work Practice in Healthcare, 2010; 3(1), 27-46.

The practice of motivational interviewing

Motivational interviewing is directive, client-centered conversation style. Motivational Interviewing provides health care professionals with the appropriate tools to treat individuals who are resistant to change and can help with lifestyle and behavioral change. Motivational Interviewing has been incorporated into health care settings to treat a variety of health conditions. The purpose of this presentation is to provide health care professionals how to actually adapt motivational interviewing in everyday practice.

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➤Educational background & professional experience

1995-2001	Korea University
2002-2005	Korea University, Preventive Medicine
2010-present	National Evidence-based Healthcare Collaborating Agency / Director / Associate research fellow

➤Research interests

Methodology for the development of guidelines

➤Brief list of publications

1. Tool for Assessment of Quality of Adapted Guidelines (TAAD). NSCR. 2012 (Korean)
2. Manual for guideline Adaptation ver. 2. NECA. 2011 (Korean)
3. Guidance for development of clinical practice guidelines. NECA. 2011 (Korean)
4. Standard Reporting Items for clinical practice guidelines (STARIGs). NECA. 2011 (Korean)

How to develop clinical practice guidelines

The number of research studies published is constantly increasing. Furthermore, there is insistence that much of the material may be biased and not applicable to important target populations. In these circumstances, clinicians and patients have difficulty in determining and following specific medical procedures. Clinical practice guidelines (CPGs) provide good solution to these problems.

There are instances, however, where CPGs are not always trustworthy, because the current state of CPG development has yet to meet quality standards. Furthermore, systematic review of evidence and assessment of the benefits and harms of alternatives has not been conducted. Hence the quality of CPGs differs greatly, and at the moment, is particularly low in Korea.

To ensure greater confidence, CPGs require a more rigorous development process, control for conflict of interest, and balancing of the benefits and harms, while at the same time, considering cost and patients' preferences.

In my view we need to discuss the development processes of CPGs and the challenges associated with them.

* Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by systematic review of evidence and assessment of the benefits and harms of alternative care options (Institute of medicine, 2011).

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➤Educational background & professional experience

1988-1994	College of Medicine, The Catholic University of Korea / M.D.
1999-2003	Division of Endocrinology & Metabolism, Department of Internal Medicine, The Catholic University of Korea / Instructor
2000-2003	College of Medicine, The Catholic University of Korea / Ph.D.
2008-2009	Division of Endocrinology, University of Virginia / Visiting Professor
2010-present	Division of Endocrinology & Metabolism, Department of Internal Medicine, The Catholic University of Korea / Associate Professor

➤Research interests

Type 2 diabetes, Complication, Beta cell biology

➤Brief list of publications

1. Park YM, Ko SH, et al. Committee of Clinical Practice Guideline, Korean Diabetes Association. Glycaemic and haemoglobin A1c thresholds for detecting diabetic retinopathy: the fifth Korea NHANES (2011). Diabetes Res Clin Pract. 2014;104(3):435-42.
2. Ko SH, et al. Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Higher prevalence and awareness, but lower control rate of hypertension in patients with diabetes than general population: the fifth korean NHANES in 2011. Diabetes Metab J. 2014;38(1):51-7
3. Yun JS, Ko SH. Cardiovascular autonomic dysfunction predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. Diabetes Care. 2014;37(1):235-41.
4. Yun JS, Ko SH, Presence of macroalbuminuria predicts severe hypoglycemia in patients with type 2 diabetes: a 10-year follow-up study. Diabetes Care. 2013;36(5):1283-9.
5. Ko SH et al. Long-term changes of the prevalence and control rate of hypertension among Korean adults with diagnosed diabetes: 1998-2008 Korean NHANES. Diabetes Res Clin Pract. 2012;97(1):151-7.

Clinical practice guideline for type 2 diabetes in Korea

The Committee of Clinical Practice Guideline of Korean Diabetes Association (KDA) was founded in 2010 to develop a "Clinical Practice Guideline" for patients with type 2 diabetes that would be best suitable in Korea. Based on many clinical evidences, international clinical recommendations, and clinical trials performed in Korea, the Committee published 'Clinical Practice Guideline (4th edition) for patients with type 2 diabetes' at the end of 2010. During this development, the Committee reviewed extensive references, held public hearings and obtained opinions from government and associated societies. This guideline was mainly targeted for general physicians in Korea.

In 2012-2013, the Committee revised and updated the guideline. This revised edition consisted of 32 subtitles and an appendix. In the KDA guideline, we emphasized on active screenings of high risk individuals to detect early type 2 diabetes and strengthened the appendix; this was for a more practical approach based on clinical studies performed in Korea. We also developed an algorithm for oral hypoglycemic agents and insulin treatments according to the patient's HbA1C levels. The updated guideline for 2013 has been widely distributed to KDA members as booklets, and is freely accessible to both healthcare professionals and the general public by KDA website. Also KDA has made various education materials for patients and diabetes educators using this updated guideline.

Dramatically increased prevalence of type 2 diabetes which is accompanied by its acute or chronic complications is major health concerns in Korea. Screening of high risk individuals to discover early detection as well as proper management of type 2 diabetes is urgently needed. Although clinical trials should be undertaken and more evidence found, appropriate clinical practice guidelines characterized by Korean people with type 2 diabetes has been persistently developed and updated to provide better glycemic control and favorable clinical outcomes.

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➤**Educational background & professional experience**

1995	Seoul National University, College of Medicine / M.D.
2005	Seoul National University, College of Medicine / Ph. D.
2005-2008	Boramae Hospital, Department of Internal Medicine / Assistant Professor
2012-2013	University of California, San Diego, Division of Biological Sciences / Research Scientist
2010-present	Samsung Seoul Hospital, Sungkyunkwan University School of Medicine, Department of Medicine / Associate Professor

➤**Research interests**

Diabetes, Islet transplantation, Adrenal disease

➤**Brief list of publications**

1. Clinical factors associated with absolute and relative measures of glycemic variability determined by continuous glucose monitoring: An analysis of 480 subjects. Diabetes Res Clin Pract. 2014 May;104(2):266-72.
2. Co-transplantation of bone marrow-derived endothelial progenitor cells improves revascularization and organization in islet grafts. Am J Transplant. 2013 Jun;13(6):1429-40.
3. Non-HDL-cholesterol/HDL-cholesterol is a better predictor of metabolic syndrome and insulin resistance than apolipoprotein B/apolipoprotein A1. Int J Cardiol. 2013 Oct 3;168(3):2678-83.
4. Counting small hypointense spots confounds the quantification of functional islet mass based on islet MRI. Am J Transplant. 2012 May;12(5):1303-12
5. Coagulation abnormalities in deceased donors are associated with unsuccessful human islet cell isolation. Diabetes Res Clin Pract. 2012 Mar;95(3):e45-8

Treatment guideline for adult patients with type 1 diabetes

The number of type 1 diabetes (T1D) is increasing worldwide including many part of Asia. Tight glycemic control with intensive insulin therapy reduces microvascular and macrovascular complication in patients with T1D, but it accompanies increasing severe hypoglycemia. In addition, despite efforts to optimize glycemic control, there have been individuals with T1D who experience frequent and severe hypoglycemia and/or severe glycemic lability. Compared to patients with T1D in Western Countries, Korean patients with T1D showed lower hypoglycemic risk, but greater glycemic variability in a multicenter study. In addition, the glycemic variability were negatively correlated with fasting C-peptide level, and hypoglycemic risk were positively correlated with duration of diabetes. Recent studies showed that real-time continuous glucose monitoring (CGM) is a useful tool to lower A1C in patients with T1D. We also reported that the 3-day (CGM) appears to be clinically useful for rapidly assessing the risk of hypoglycemic events and glycemic variability in patients with T1D. Recent study of almost 27,000 patients with type 1 diabetes in USA showed that increased daily frequency of SMBG was significantly associated with lower A1C (0.2% per additional test per day, leveling off at 10 tests per day). Since 2011, Korean national health insurance service (KNHIS) has started reimbursing the cost of 4 strips per day to patients with T1D. After then we enrolled over 8 hundred Korean patients with T1D from 5 tertiary hospitals. We found that Korean patients with T1D performed their SMBG less frequently, and had higher A1C levels and higher prevalence of nephropathy compared to those in USA. It suggests that there are still unmet needs for optimal management of Korean adult patients with T1D. In this lecture, we will discuss how to manage Korean adult patients with T1D.

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➤Educational background & professional experience

1986-1992	Korea University, College of Medicine / MD
1997-1999	Korea University, College of Medicine / Ph.D.
2005-2011	Korea University, College of Medicine / Associate professor
2006-2008	NIDDK, NIH, USA / Research Fellow
2011-present	Korea University, College of Medicine / Professor

➤Research interests

Epidemiology, NAFLD, Diabetic nephropathy

➤Brief list of publications

1. Kim NH, Park J, Kim SH, Kim YH, Kim DH, Cho GY, Baik I, Lim HE, Kim EJ, Na JO, Lee JB, Lee SK, Shin C. Non-alcoholic fatty liver disease, metabolic syndrome and subclinical cardiovascular changes in the general population. Heart 2014 Jun;100(12):938-43
2. Yoo W, Noh KH, Ahn JH, Yu JH, Seo JA, Kim SG, Choi KM, Baik SH, Choi DS, Kim TW, Kim HJ, Kim NH. HIF-1α Expression as a Protective Strategy of HepG2 Cells Against Fatty Acid-Induced Toxicity. J Cell Biochem 2014 Jan 9
3. Kim NH, Cho NH, Yun CH, Lee SK, Yoon DW, Cho HJ, Ahn JH, Seo JA, Kim SG, Choi KM, Baik SH, Choi DS, Shin C. Association of obstructive sleep apnea and glucose metabolism in subjects with or without obesity. Diabetes Care 2013 Oct 7
4. Seo JA, Eun CR, Cho HJ, Lee SK, Yoo HJ, Kim SG, Choi KM, Baik SH, Choi DS, Yim HJ, Shin C, Kim NH. Low vitamin D status is associated with nonalcoholic fatty liver disease independent of visceral obesity in Korean adults. Plos One 2013 Oct 9;8(10):e75197
5. Kim NH, Eun CR, Seo JA, Cho H, Kim SG, Choi KM, Baik SH, Choi DS, Yun CH, Kim NH, Shin C. Short Sleep Duration Combined with Obstructive Sleep Apnea is Associated with Visceral Obesity in Korean Adults. Sleep 2013 May 1;36(5):723-9.

Mortality from diabetes in Korea

Diabetes increases mortality, with this excess mainly being attributable to cardiovascular disease (CVD). However, patterns of mortality may be changing. Marked declines in mortality among the general population, primarily from CVD, have been noted in the past decades, with some evidence that mortality in type 2 diabetes may be approaching that of the general population. On the contrary, there is increasing concern about the role of diabetes as a risk factor for certain types of cancers, such as pancreas, liver, and colon, rectum, and for cancer mortality in several populations.

Compared to western countries, the proportion of people with diabetes has dramatically increased throughout Asia. People in Asia tend to develop diabetes with a lesser degree of obesity at a younger age, suffer more from complications diabetes, and die sooner than people in other regions. On behalf of the Committee on the Epidemiology of Diabetes Mellitus in KDA, we had analyzed the mortality data from the three pooled community-based cohort study. They showed that diabetes was associated with higher risk of death from all causes and cancer. I will talk about the extension analysis of this pooled studies, and other epidemiologic evidences to show the trends of mortality and causes of death in patients with diabetes in Korea.

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➤**Educational background & professional experience**

1976-1980	M.I.T. (Electrical Engineering, Biology) / B.S.
1980-1988	Harvard Medical School / MD, PhD
1988-1990	Brigham and Womens Hospital, Boston / Internship/residency
1990-1994	NIH / Endocrinology Fellow
1994-present	NIH / Principal Investigator

➤**Research interests**

1. Mechanisms of aging and type 2 diabetes.
2. Molecular mechanism of abdominal fat accumulation.
3. Understanding the link between aging and Alzheimer's disease

➤**Brief list of publications**

1. Metabolic sensor AMPK directly phosphorylates RAG1 protein and regulates V(D)J recombination. Um JH, Brown AL, Singh SK, Chen Y, Gucek M, Lee BS, Luckey MA, Kim MK, Park JH, Sleckman BP, Gellert M, Chung JH. Proc Natl Acad Sci U S A 110(24):9873-8. (2013).
2. Resveratrol ameliorates aging-related metabolic phenotypes by inhibiting cAMP phosphodiesterases. Park SJ, Ahmad F, Philp A, Baar K, Williams T, Luo H, Ke H, Rehmann H, Taussig R, Brown AL, Kim MK, Beaven MA, Burgin AB, Manganiello V, Chung JH. Cell. 2012 Feb 3;148(3):421-33.
3. Peptide switch is essential for Sirt1 deacetylase activity. Kang H, Suh JY, Jung YS, Jung JW, Kim MK, Chung JH. Mol. Cell. 2011 Oct 21;44(2):203-13
4. AMP-activated protein kinase-deficient mice are resistant to the metabolic effects of resveratrol. Um JH, Park SJ, Kang H, Yang S, Foretz M, McBurney MW, Kim MK, Viollet B, Chung JH. Diabetes. 2010 Mar;59(3):554-63.

Aging and metabolic decline

One of the strongest risk factors for type 2 diabetes is old age. In the US, almost 40% of individuals above age 70 are either prediabetic or diabetic. Understanding the mechanism by which aging increases the risk for type 2 diabetes is not only crucial for understanding the disease itself but also for developing an effective treatment for it. We have been interested in understanding how aging causes a decline in mitochondrial content and function. AMP-activated protein kinase (AMPK), which lowers glucose production and increases glucose uptake, is known to increase mitochondrial biogenesis and function. Aging leads to a decline in AMPK activity by an unknown mechanism. One strategy that increases AMPK activity is treatment with resveratrol, a polyphenol present in red wine and in other plant-based foods. We find that the metabolic benefits of resveratrol are largely mediated by inhibiting cAMP phosphodiesterases (PDEs), which degrade cAMP. Inhibiting PDE4 with a small molecule inhibitor protects against diet-induced obesity and glucose intolerance by increasing cAMP levels and thereby activating AMPK.

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➤Educational background & professional experience

2013-2014 York University / Visiting professor
2009-present Kangbuk Samsung Hospital, Sungkyunkwan University / Associate professor

➤Research interests

Clinical diabetes, Lipid metabolism

➤Brief list of publications

1. Yang SJ, Choi JM, Chang EJ, Park SW, Park CY Sirt1 and Sirt6 Are Not Synergistic but Compensatory Factors that Improve Hepatocyte Steatosis. PLoS ONE (in press)
2. Park SE, Lee NS, Park JW, Rhee EJ, Lee WY, Oh KW, Park SW, Park CY, Youn BS. Urinary RBP4 as a Marker of Insulin Resistance, Inflammation, and Microalbuminuria. Eur J Endocrinol 2014 Jul 3. pii: EJE-14-0247
3. Hwang YC, Jung CH, Ahn HY, Jeon WS, Jin SM, Kim JH, Park CY, Lee BW. Optimal glycated albumin cutoff value to diagnose diabetes in Korean adults: A study based on the oral glucose tolerance test Clin Chim Acta 2014 Jul 4;437C:1-5 [Epub ahead of print]
4. Hwang YC, Ahn HY, Park SW, Park CY. Apolipoprotein B and non-HDL cholesterol are more powerful predictors for incident type 2 diabetes than fasting glucose or glycated hemoglobin in subjects with normal glucose tolerance: A 3.3-year retrospective longitudinal study. Acta Diabetol 2014 May 11. [Epub ahead of print]
5. Kim JD, Park CY, Ahn KJ, Cho JH, Choi KM, Kang JG, Kim JH, Lee KY, Lee BW , Mok JO, Moon MK, Park JY, Park SW. Non-HDL cholesterol is an independent risk factor for aspirin resistance especially in obese type 2 diabetes. Atherosclerosis 2014 Feb 12;234(1):146-151

Comprehensive approach for diabetic dyslipidemia management

The Steno-2 study shows the comprehensive management of cardiovascular risk factors has additive effects for the prevention of vascular complication. Dyslipidemia management is one of the major treatment targets for cardiovascular disease in type 2 diabetes. Although pharmacological treatment especially statin for dyslipidemia recommended in most patient with type 2 diabetes, there are some limitation such as drug side effect and failure to achieving target goals. Insulin resistance in the gut is important in intestinal overproduction of highly atherogenic apoB48-containing lipoproteins in the type 2 diabetes. Therefore 'Ezetimibe', a cholesterol-absorption inhibitor is one of the candidates of diabetic dyslipidemia treatment with mono- or combination therapy.

1. Federico LM1, Naples M, Taylor D, Adeli K. Intestinal insulin resistance and aberrant production of apolipoprotein B48 lipoproteins in an animal model of insulin resistance and metabolic dyslipidemia: evidence for activation of protein tyrosine phosphatase-1B, extracellular signal-related kinase, and sterol regulatory element-binding protein-1c in the fructose-fed hamster intestine. Diabetes. 2006 May;55(5):1316-26.
2. Taskinen MR. Diabetic dyslipidemia. Atheroscler Suppl. 2002 May;3(1):47-51.
3. Park SW. Intestinal and hepatic niemann-pick c1-like 1. Diabetes Metab J. 2013 Aug;37(4):240-8. doi: 10.4093/dmj.2013.37.4.240.

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➤Educational background & professional experience

1990-1996	Premedical Course, Seoul National University College of Natural Science & Seoul National University College of Medicine
1996-2003	Department of Internal Medicine, Seoul National University Hospital / Intern, resident, fellow
1998-2004	Graduate School, Seoul National University
2009-2010	Department of Cellular and Physiological Sciences, University of British Columbia, Vancouver, B.C., Canada / Visiting Professor
2003-present	Department of Internal Medicine, Seoul National University Hospital and Seoul National University College of Medicine / Clinical Assistant Professor & Assistant Professor

➤Research interests

Role of the gastrointestinal tract in diabetes and obesity

➤Brief list of publications

1. Kim YG, Hahn S, Oh TJ, Park KS, Cho YM. Differences in the HbA1c-lowering efficacy of glucagon-like peptide-1 analogues between Asians and non-Asians: a systematic review and meta-analysis. Diabetes Obes Metab. 2014 Mar 21. [Epub ahead of print]
2. Oh TJ, Kim MY, Shin JY, Lee JC, Kim S, Park KS, Cho YM. The incretin effect in Korean subjects with normal glucose tolerance or type 2 diabetes. Clin Endocrinol (Oxf). 2014 Feb;80(2):221-7.
3. Kim YG, Hahn S, Oh TJ, Kwak SH, Park KS, Cho YM. Differences in the glucose-lowering efficacy of dipeptidyl peptidase-4 inhibitors between Asians and non-Asians: a systematic review and meta-analysis. Diabetologia. 2013 Apr;56(4):696-708
4. Oh TJ, Shin JY, Kang GH, Park KS, Cho YM. Effect of the combination of metformin and fenofibrate on glucose homeostasis in diabetic Goto-Kakizaki rats. Exp Mol Med. 2013 Jul 5;45:e30.
5. Cho YM, Fujita Y, Kieffer TJ. Glucagon-like peptide-1: glucose homeostasis and beyond. Annu Rev Physiol. 2014;76:535-59.

Update on emerging novel agents for the treatment of type 2 diabetes: focus on dapagliflozin

Diabetes mellitus, a Latin word, is literally translated as sweet urine or glycosuria. Excretion of glucose through the urine is once thought as a typical symptom or sign of diabetes mellitus. However, it turned into a very useful therapeutic option to treat patients with type 2 diabetes. Blood glucose is freely filtrated through the glomerulus to renal tubular space, but is reabsorbed nearly completely via the action of sodium-glucose cotransporters 1 and 2 (SGLT1 and SGLT2), where SGLT2 plays a major role and reabsorbs 90% of filtered glucose. Dapagliflozin, an SGLT2 inhibitor, specifically and reversibly inhibits SGLT2 in the renal tubule and promotes the renal glucose excretion about 70-90 g per day. Dapagliflozin effectively decreases HbA1c in patients with type 2 diabetes independent of insulin action and/or insulin secretion. Therefore, dapagliflozin exhibits its efficacy across the full spectrum of type 2 diabetes. In addition, dapagliflozin decreases blood pressure and causes a modest weight loss. Common adverse effects include urogenital infection and symptoms related to dehydration. However, dapagliflozin is generally well tolerated. An outcome study (DECLARE-TIMI58) to examine whether dapagliflozin decreases cardiovascular events in patients with type 2 diabetes is currently under way. In this lecture, mechanism of action and the results of pivotal studies of dapagliflozin will be reviewed.

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1991-1997	Yonsei University College of Medicine / MD
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2004-2007	Seoul National University, College of Medicine, Bundang Hospital / Instructor (Internal Medicine)
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2012-	Seoul National University, College of Medicine & Bundang SNU Hospital /Associate Professor (Internal Medicine)

➤Research interests

Adipokine, Insulin resistance, Lipid metabolism, Atherosclerosis, Diabetes, Metabolic syndrome

➤Brief list of publications

1. Kim SJ, Chae S, Kim H,,,,Hwang D, Choi SH (corresponding), Lee SW. A protein profile of visceral adipose tissues linked to early pathogenesis of type 2 diabetes mellitus. Mol Cell Proteomics 2014 Mar 13(3):811-822
2. Kim SJ, Chae S, Kim H,,,,Hwang D, Choi SH (corresponding), Lee SW. A protein profile of visceral adipose tissues linked to early pathogenesis of type 2 diabetes mellitus. Mol Cell Proteomics 2014 Jan 8
3. Lee Y, Lim S, Hong ES, Kim JH, Moon MK, Chun EJ, Choi SI, Kim YB, Park YJ, Park KS, Jang HC, Choi SH. Serum FGF21 Concentration is associated with hypertriglyceridemia, hyperinsulinemia and pericardial fat accumulation, indendently of obesity, but not with current coronary artery status. Clin Endocrinol 2014 Jan 80(1):57-64
4. Cho NH, Kim TH, Woo SJ, Park NH, Lim S, Cho YM, Park KS, Jang HC, Choi SH. Optimal HbA1c cutoff for detecting diabetic retinopathy. Acta Diabetol. 2013 Dec;50(6):837-842
5. Choi SH, Hong ES, Lim S. Clinical implications of adipocytokines and newly emerging metabolic factors with relation to insulin resistance and cardiovascular health, Front Endocrinol 2013 Aug 21:4:97

Management of hyperglycemia in patients with type 2 diabetes uncontrolled on a combination of sulfonylurea and metformin: results of MOHAS disease registry in Korea

Aim: To observe the glucose lowering effects according to changed prescription in patients with type 2 diabetes mellitus (T2DM) uncontrolled on sulfonylurea plus metformin.

Methods: This open-label, multicenter, non-interventional, prospective, observational study, conducted in 144 centers in Korea, from June 2008 to July 2010, included patients with T2DM who received sulfonylurea and metformin at least for 3 months and had HbA1c 〉7% in the last 1-month. Information on change in HbA1c, concomitant medications and laboratory results was collected for 6 months in 3 visits. This study classified groups by changed prescription patterns. Descriptive statistics was used to analyze results.

Results: Out of 2,995 patients enrolled, 2,870 patients were evaluated and classified to groups according to type of prescription. Mean decrease in HbA1c level from baseline to last visit was found to be highest in basal insulin + short-acting insulin ± oral hypoglycemic agents (OHAs) group (-2.61% ± 2.25%, p〈 0.0001). Marked decrease in fasting blood glucose (-67.90 ± 52.61 mg/dL; p〈 0.0001) was observed in the basal insulin ± OHA group.

Conclusions: Basal insulin add-on therapy resulted in greater glycemic control than OHAs alone. These findings suggest that early use of basal insulin will be an important option in better management of patients with T2DM in Korea.

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➤**Educational background & professional experience**

1992-1998	Pusan National University / MD
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2004-2012	Meryknoll Medical Center, Cariology / Faculty
2013	Brown University Rhod Island Hospital / Research fellow
2013-present	Kosin Univerity, Cardiology Department / Assistant professor

➤**Research interests**

Echocardiography, Carotid atherosclerosis, Stress and heart

➤**Brief list of publications**

1. Effects of inhaled iloprost on exercise capacity, quality of life, and cardiac function in patients with pulmonary arterial hypertension secondary to congenital heart disease (the Eisenmenger syndrome) (from the EIGER Study)2013.12. Am J Cardiol
2. Impact of cilostazol on the progression of carotid atherosclerosis in patients with retinal vascular occlusion 2013.12 Cardiovasc Ther
3. Peripheral Artery Questionnaire improves ankle brachial index screening in symptomatic patients with peripheral artery disease 2014.9. International J of clinical practice
4. The predictive value of retinal vascular findings for carotid artery atherosclerosis: are further recommendations with regard to carotid atherosclerosis screening needed? 2012.6. Heart and vessls
5. Carotid arterial stiffness in patients with rheumatoid arthritis assessed by speckle tracking strain imaging: its association with carotid atherosclerosis 2012.9 Clin Exp Rheumatology

Benefit of carotid ultrasonography and antiplatelet therapy for diabetic patients

Antiplatelet agents are widely reported to be effective in preventing the recurrence of cardiovascular events. Cilostazol, a selective phosphodiesterase 3 inhibitor, has antiplatelet and vasodilating effects and has been proposed to have beneficial effects in the prevention of atherosclerosis. In the retinal and choroidal vasculature, phosphodiesterase 3 appears to contribute to the regulation of intracellular cAMP levels because cilostazol elicits vasodilation of the retinal blood vessels and enhances the choroidal blood flow. In addition, cilostazol can be applied as a neuroprotective agent in optic nerve diseases such as glaucoma or ischemic optic neuropathy. Although ultrasound assessment of the carotid intima-media thickness (IMT) is generally accepted as an early indicator of generalized atherosclerosis, measuring the carotid plaque area adds to the arsenal of tools for identifying high-risk patients and has a higher diagnostic accuracy for the prediction of future coronary artery disease (CAD) events than the IMT. Considering the assessment of plaque regression, measuring plaque size as a continuous variable appears to be more powerful than simply detecting the presence or absence of plaque at extracoronary sites or counting the number of sites involved. Because the carotid IMT largely represents medial hypertrophy related to hypertension and a substantial proportion of strokes are due to hypertensive small-vessel disease, it is not surprising that the IMT predicts strokes more strongly than CAD, whereas the opposite is true for plaque area. We previously showed that there was a substantial regression in the mean CCA-IMT and ICA-IMT after 1 year of cilostazol treatment, suggesting that cilostazol has potent anti-atherosclerotic effects and can reverse the process of atherosclerosis in patients with retinal vascular occlusion, similar to the results for diabetic atherosclerosis in Asian patients.

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➤Educational background & professional experience

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2007-2010	Devision of Endocrinology and Metabolism, Department of internal medicine, Yonsei University, College of Medicine / Research fellow/ Clinical research assistant professor
2009-2012	Yonsei University, College of Medicine / PhD
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➤Research interests

Diabetes, Metabolic syndrome, Insulin resistance, Prediabetes

➤Brief list of publications

1. The association between pulse wave velocity and metabolic syndrome and adiponectin in patients with impaired fasting glucose: cardiovascular risks and adiponectin in IFG, Nam JS, Park JS, Cho MH, Jee SH, Lee HS, Ahn CW, Lowe WL Jr, Kim KR, Diabetes Res Clin Pract. 2009 May;84(2):145-51
2. The Effect of Rosiglitazone on Insulin Sensitivity and Midthigh Low Density Muscle in Patients with Type 2 Diabetes, Nam JS, Nam JY, Cho MH, Park JS, Ahn CW, Cha BS, Lee EJ, Lim SK, Kim KR, Lee HC, Diabetic Med 2010; 27(1): 30-6
3. Insulin resistance is independently associated with peripheral and autonomic neuropathy in Korean type 2 diabetic patients. Lee KO, Nam JS, Ahn CW, Hong JM, Kim SM, Sunwoo IN, Moon JS, Na SJ, Choi YC. Acta Diabetol; 2012 Apr;49(2):97-103.
4. The humoral immune response to the inactivated influenza A (H1N1) 2009 monovalent vaccine in patients with Type 2 diabetes mellitus in Korea. Nam JS, Kim AR, Yoon JC, Byun Y, Kim SA, Kim KR, Cho S, Seong BL, Ahn CW, Lee JM. Diabet Med. 2011 Jul;28(7):815-7
5. Transplantation of insulin-secreting cells differentiated from human adipose tissue-derived stem cells into type 2 diabetes mice. Nam JS, Kang HM, Kim J, Park S, Kim H, Ahn CW, Park JO, Kim KR. Biochem Biophys Res Commun. 2014; 443: 775-781.

Serum adiponectin and type 2 diabetes: a 6-year follow-up cohort study

Background: Studies on factors which may predict the risk of diabetes are scarce. This prospective cohort study was conducted to determine the association between adiponectin and type 2 diabetes among Korean men and women.

Methods: A total of 42,845 participants who visited one of seven health examination centers located in Seoul and Gyeonggi province, Republic of Korea between 2004 and 2008 were included in this study. The incidence rates of diabetes were determined through December 2011. To evaluate the effects of adiponectin on type 2 diabetes, the Cox proportional hazard model was used.

Results: Of the 40,005 participants, 959 developed type 2 diabetes during a 6-year follow-up. After the adjustment for age, body mass index (BMI), and waist circumference, the risks for type 2 diabetes in participants with normoglycemia had a 1.70-fold (95% confidence interval [CI], 1.21 to 2.38) increase in men and a 1.83-fold (95% CI, 1.17 to 2.86) increase in women with the lowest tertile of adiponectin when compared to the highest tertile of adiponectin. For participants with impaired fasting glucose (IFG), the risk for type 2 diabetes had a 1.46-fold (95% CI, 1.17 to 1.83) increase in men and a 2.52-fold (95% CI, 1.57 to 4.06) increase in women with the lowest tertile of adiponectin. Except for female participants with normoglycemia, all the risks remained significant after the adjustment for fasting glucose and other confounding variables. Surprisingly, BMI and waist circumference were not predictors of type 2 diabetes in men or women with IFG after adjustment for fasting glucose and other confounders.

Conclusion: A strong association between adiponectin and diabetes was observed. The use of adiponectin as a predictor of type 2 diabetes is considered to be useful.

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➤Educational background & professional experience

2006	College of Medicine, the Catholic University of Korea, Seoul, Korea / M.D.
2006-2007	Catholic Medical Center, Seoul, Korea / Internship
2007-2011	Catholic Medical Center, Seoul, Korea / Residency
2014-present	Division of Endocrinology and Metabolism, Department of Internal Medicine, The Catholic University of Korea / Clinical fellow

➤Research interests

Diabetes complications

➤Brief list of publications

1. Yun JS, Ko SH, Kim JH, Moon KW, Park YM, Yoo KD, Ahn YB. Diabetic retinopathy and endothelial dysfunction in patients with type 2 diabetes mellitus. Diabetes & metabolism journal 2013;37:262-9.
2. Yun JS, Ko SH, Ko SH, Song KH, Ahn YB, Yoon KH, Park YM, Ko SH. Presence of Macroalbuminuria Predicts Severe Hypoglycemia in Patients With Type 2 Diabetes Mellitus: A 10-year follow-up study. Diabetes care 2013;36:1283-1289
3. Yun JS, Kim JH, Song KH, Ahn YB, Yoon KH, Yoo KD, Park YM, Ko SH. Cardiovascular Autonomic Dysfunction Predicts Severe Hypoglycemia in Patients with Type 2 Diabetes Mellitus: A Ten-year Follow-up Study. Diabetes care 2014;37:235-241

Diabetic retinopathy and endothelial dysfunction in patients with type 2 diabetes mellitus

Endothelial dysfunction is important in the early pathophysiology of vascular complications. Beyond its role as simply a passive barrier for blood vessels, the endothelium has important physiological functions that are mediated by the release of vasoactive factors responsible for regulating vessel wall tone, cellular growth, homeostasis and inflammation. Broadly speaking, the term endothelial dysfunction refers to an impairment of the ability of the endothelium to properly maintain vascular homeostasis, and it may be an important determinant of altered vascular reactivity. Arguably, the most critical mediator of endothelium-derived molecules is nitric oxide (NO), and the earliest and most important marker of endothelial dysfunction is represented by a reduction in NO bioactivity. The most widely-used technique for assessing systemic endothelial function is called "flow-mediated vasodilatation" (FMD). This non-invasive method is based on the principle that physiological increases in blood flow and endothelial shear stress induce vasodilatation, which are mainly mediated by an increased endothelial NO release. FMD is known to be endothelium-dependent and gives a reliable measure of endothelial function in peripheral arteries.

Endothelial dysfunction is considered the first step in the progression of accelerated atherosclerosis. In addition to the relationship with macrovascular complications, endothelial dysfunction also has been associated with the development of microalbuminuria, which itself is strongly connected with retinopathy in patients with type 2 diabetes. This finding suggests that endothelial dysfunction might affect the development of diabetic microvascular complications. Development of microvascular complications and impaired vascular responses to reactive hyperemia have several underlying pathogenetic mechanisms in common. In this presentation, based on our data, we suggest that endothelial dysfunction is the independent predictor of diabetic retinopathy in patients with T2DM.

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➤Educational background & professional experience

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2014-present	Department of Internal Medicine, Jeju National University School of Medicine, Jeju, Korea / Clinical professor

➤Research interests

Pituitary disorder, Diabetes, Metabolism

➤Brief list of publications

1. Chin SO, Rhee SY, Chon S, Hwang YC, Jeong IK, Oh S, Kim SW. Investigation of Responsiveness to Thyrotropin-Releasing Hormone in Growth Hormone-Producing Pituitary Adenomas. Int J Endocrinol 2013, ID 159858.
2. Chin SO, Chon S, Hwang YC, Jeong IK, Oh S, Kim SW. Change in Somatostatinergic Tone of Acromegalic Patients According to the Size of Growth Hormone-Producing Pituitary Tumors. J Korean Med Sci 2013;28(12):1774-1780.
3. Chin SO, Rhee SY, Chon S, Hwang YC, Jeong IK, Oh S, Ahn KJ, Chung HY, Woo JT, Kim SW, Kim JW, Kim YS, Ahn HY. Sarcopenia is independently associated with cardiovascular disease in older Korean adults: the Korea National Health and Nutrition Examination Survey (KNHANES) from 2009. PLoS One. 2013;8(3):e60119.
4. Chin SO, Hwang JK, Rhee SY, Chon S, Hwang YC, Oh S, Ahn KJ, Chung HY, Woo JT, Kim SW, Kim YS, Kang JH, Jeong IK. Risk factors for the progression of intima-media thickness of carotid arteries: A two-year follow-up study in patients with newly diagnosed type 2 diabetes, Diabetes Metab J. 2013 Oct;37(5):358-364.
5. Chung HY, Chin SO, Kang MI, Koh JM, Moon SH, Yoon BK, Yoon HK, Chung YS, Park HM. Efficacy of risedronate with cholecalciferol on 25-hydroxyvitamin D level and bone turnover in Korean patients with osteoporosis. Clin Endocrinol (Oxf). 2011 Jun;74(6):699-704.

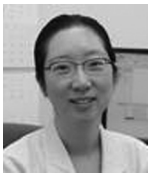
Risk factors for the progression of intima-media thickness of carotid arteries: a two-year follow-up study in patients with newly diagnosed type 2 diabetes

Background: Intima-media thickness (IMT) of the carotid arteries is known to have a positive correlation with the risk of cardiovascular disease. This study was designed to identify risk factors affecting the progression of carotid IMT in patients with type 2 diabetes mellitus (T2DM).

Method: Patients with newly diagnosed T2DM with carotid IMT measurements were enrolled, and their clinical data and carotid IMT results at baseline and two years later were compared.

Results: Of the 171 patients, 67.2% of males and 50.8% of females had abnormal baseline IMT of the left common carotid artery. At baseline, systolic blood pressure, body mass index and smoking in male participants, and fasting plasma glucose and HbA1c levels in females were significantly higher in patients with abnormal IMT than in those with normal IMT. Low-density lipoprotein cholesterol (LDL-C) levels in males and high-density lipoprotein cholesterol (HDL-C) levels in females at the two-year follow-up were significantly different between the non-progression and the progression groups. Reduction of the United Kingdom Prospective Diabetes Study (UKPDS) 10-year coronary heart disease (CHD) risk score after two years was generally higher in the non-progression group than the progression group.

Conclusions: LDL-C levels in males and HDL-C levels in females at the two-year follow-up were significantly different between participants with and without progression of carotid IMT. Furthermore, a reduction in the UKPDS 10-year CHD risk score appeared to delay the advancement of atherosclerosis. Therefore, the importance of establishing the therapeutic goal of lipid profiles should be emphasized to prevent the progression of carotid IMT in newly diagnosed T2DM patients.



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➤**Educational background & professional experience**

2001-2007	Korea University College of Medicine /M.D.
2009-2011	Graduate School, Korea University / M.S.
2012-present	Korea University, Department of Internal medicine, Division of Endocrinology and Metabolism / Cinical Instructor

➤**Research interests**

Diabetes mellitus

➤**Brief list of publications**

1. Ahn JH, Yu JH, Ko SH, Kwon HS, Kim DJ, Kim JH, Kim CS, Song KH, Won JC, Lim S, Choi SH, Han K, Cha BY, Kim NH. Prevalence and determinants of diabetic nephropathy in Korea: Korea national health and nutrition examination survey. Diabetes Metab J. 2014 Apr;38(2):109-19.
2. Yoo W, Noh KH, Ahn JH, Yu JH, Seo JA, Kim SG, Choi KM, Baik SH, Choi DS, Kim TW, Kim HJ, Kim NH. HIF-1α expression as a protective strategy of HepG2 cells against fatty acid-induced toxicity. J Cell Biochem. 2014 Jun;115(6):1147-58.
3. Kim NH, Cho NH, Yun CH, Lee SK, Yoon DW, Cho HJ, Ahn JH, Seo JA, Kim SG, Choi KM, Baik SH, Choi DS, Shin C. Association of obstructive sleep apnea and glucose metabolism in subjects with or without obesity. Diabetes Care. 2013 Dec;36(12):3909-15.
4. Ahn JH, Hong HC, Cho MJ, Kim YJ, Choi HY, Eun CR, Yang SJ, Yoo HJ, Kim HY, Seo JA, Kim SG, Choi KM, Baik SH, Choi DS, Kim NH. Effect of eplerenone, a selective aldosterone blocker, on the development of diabetic nephropathy in type 2 diabetic rats. Diabetes Metab J. 2012 Apr;36(2):128-35.
5. Ahn JH, Kim SY, Kim YJ, Lee SY, Lee JH, Kang SH, Hong HC, Yang SJ, Yoo HJ, Seo JA, Kim SG, Kim NH, Choi KM, Baik SH, Choi DS, Choi HY. Hyperprolactinemia-Associated Breast Uptake of Radioiodine Following 131I Postablation Scan in Differentiated Thyroid Cancer, Endocrinol Metab. 2011 Dec;26(4):345-347

Prevalence and determinants of diabetic nephropathy in Korea : Korea National Health and Nutrition examination survey

Background: Diabetic nephropathy is the leading cause of end stage renal disease, and is associated with increased risk of cardiovascular mortality. Diabetic nephropathy is manifested as albuminuria or impaired glomerular filtration rate (GFR). But the prevalence of diabetic nephopathy varies with ethnicity. In Korean adults, the prevalence of diabetic nephropathy and the determinants had not been studied at the national level. This cross sectional study was undertaken to ascertain the prevalence and determinant of albuminuria and chronic kidney disease (CKD) in Korean diabetic patients.

Methods: The Korea National Health and Nutrition Examination Survey (KNHANES) V, conducted in 2011, was used to define albuminuria (N=4,652), and the dataset of KNHANES IV-V from 2008 to 2011 was used to define CKD (N= 21,521). Selected samples were weighted to represent all civilian populations in Korea.

Results: In the adults with diabetes, 26.7% subjects had albuminuria and 8.6% subject had CKD. Only systolic blood pressure was significant risk factor of albuminuria, and old age, high serum triglyceride level and previous cardiovascular disease were risk factors of CKD in diabetic subjects. Diabetes was associated with about 2.5 fold increased risk of albuminuria, with virtually no difference between new-onset and known diabetes.

Conclusion: Korean subjects with diabetes had higher prevalence of albuminuria and CKD than those without diabetes. Using KNHANES, our analysis could be first comprehensive sample of diabetic nephropathy in the Korean population.

Key Words: diabetes, diabetic nephropathy, albuminuria, chronic renal disease, Korean

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2008–2009	Seoul National University Hospital / Intern
2009–2013	Seoul National University Hospital / Resident
2013-present	Seoul National University Hospital / Fellow

➤Research interests

Molecular mechanism of insulin resistance associated with obesity and type 2 diabetes

➤Brief list of publications

1. Counterintuitive Relationship Between Visceral Fat and All-cause Mortality in An Elderly Asian Population. Hong ES, Khang AR, Roh E, Ku EJ, Kim YA, Kim KM, Moon JH, Choi SH, Park KS, Kim KW, Jang HC, Lim S. Obesity. in press
2. A Case of MELAS Syndrome Presenting with Type 1 Diabetes Mellitus. Jung CH, Roh E, Ahn CH, Kim LK, Lim S, Jang HC, Choi SH. Korean J Med. in press
3. Prevalence and Management of Dyslipidemia in Korea: Korea National Health and Nutrition Examination Survey during 1998 to 2010. Roh E, Ko SH, Kwon HS, Kim NH, Kim JH, Kim CS, Song KH, Won JC, Kim DJ, Choi SH, Lim S, Cha BY; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Diabetes Metab J. 2013 Dec;37(6):433-49.
4. Two Cases of Methimazole-induced Insulin Autoimmune Syndrome in Graves' Disease. Roh E, Kim YA, Ku EJ, Bae JH, Kim HM, Cho YM, Park YJ, Park KS, Kim SY, Kwak SH. Endocrinol Metab. 2013 Mar;28(1):55-60.
5. A case of mediastinal ectopic thyroid presenting with a paratracheal mass. Roh E, Hong ES, Ahn HY, Park SY, Yoon HI, Park KS, Park YJ. Korean J Intern Med. 2013;28(3):361-364

Prevalence and management of dyslipidemia in Korea: Korea National Health and Nutrition examination survey during 1998 to 2010

Dyslipidemia is a major risk factor of cardiovascular disease. The aim of this study was to investigate the changing trends in the prevalence and management status of dyslipidemia among Korean adults. The prevalence of dyslipidemia and the rates of awareness, treatment, and control of dyslipidemia were investigated in adults aged ≥20 years from the Korea National Health and Nutrition Surveys (KNHANES) 1998 to 2010. The updated National Cholesterol Education Program criteria was used, which define dyslipidemia as having one or more of the following lipid abnormalities: hypercholesterolemia (total cholesterol ≥ 240 mg/dL or diagnosis of dyslipidemia or use of lipid-lowering drugs), hypertriglyceridemia (≥ 150 mg/dL), hyper-low density lipoprotein (LDL) cholesterolemia (≥ 160 mg/dL or diagnosis of dyslipidemia or use of lipid-lowering drugs), and hypo-high density lipoprotein (HDL)-cholesterolemia (〈 40 mg/dL in men and 〈 50 mg/dL in women). The number of participants was 6,921, 4,894, 5,312, 2,733, 6,295, 6,900, and 5,738 in KNHANES 1998, 2001, 2005, 2007, 2008, 2009, and 2010, respectively. Age-standardized prevalence rates of dyslipidemia were 54.0%, 65.8%, 66.5%, 60.6%, 58.7%, 58.9%, and 59.0% in 1998, 2001, 2005, 2007, 2008, 2009, and 2010, respectively. Hypertriglyceridemia and hypo-HDL-cholesterolemia were the two most frequent lipid abnormalities. The overall prevalence of hypercholesterolemia and hyper-LDL-cholesterolemia increased by 1.36- and 1.35-fold in 2010 compared with 2007, respectively. Awareness, treatment, and control rates of dyslipidemia improved over the period of surveys in both sexes. In 2010, about 30% of dyslipidemic patients who received lipid-lowering treatment reached target levels. Although the management status of dyslipidemia has improved during recent years, effective strategy is required for achieving better prevention, treatment, and control of dyslipidemia.

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➤Educational background & professional experience

1981	Seoul National University / M.D.
1990	Seoul National University / Ph.D.
1995	Scripps Research Institute / Research Associate
1997	Sungkyunkwan University / Associate Professor
2003-present	Sungkyunkwan University / Professor

➤Research interests

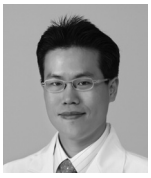
Autophagy, Apoptosis, Innate immunity, Microbiota, Mitochondria

➤Brief list of publications

1. Kim KH, Lee M-S. Autophagy- a key player in cellular and body metabolism. Nature Rev Endocrinol 10: 322-337, 2014
2. Kim J, Cheon H, Jeong YT, Quan W, Kim KH, Cho JM, Lim Y-M, Oh SH, Jin S-M, Kim JH, Lee M-K, Kim S, Komatsu M, Kang S-W, Lee M-S. Amyloidogenic peptide oligomer accumulation in autophagy-deficient β-cells leads to diabetes. J Clin Invest 124-3311, 2014
3. Kim KH, Jeong YT, Oh H, Kim S-H, Cho JM, Kim Y-N, Kim SS, Kim D-H, Hur KY, Kim HK, Koh T, Han J, Kim H, Kim J, Back SH, Komatsu M, Chen H, Chan DC, Konishi M, Itoh N, Choi CS, Lee M-S. Autophagy deficiency leads to protection from obesity and insulin resistance by inducing FGF21, a 'mitokine'. Nature Medicine 19:83-92, 2013
4. Jung H-S, Chung KW, Kim JW, Kim J, Komatsu M, Tanaka K, Nguyen YH, Kang TM, Yoon K-H, Kim J-W, Jeong YT, Han MS, Lee M-K, Kim K-W, Shin J, Lee M-S. Loss of Autophagy Diminishes Pancreatic β-Cell Mass and Function with Resultant Hyperglycemia. Cell Metab 8:318-324, 2008
5. Kim HS, Han MS, Chung KW, Kim S, Kim E, Kim MJ, Jang E, Lee HA, Youn J, Akira S, Lee M-S. Toll-like receptor 2 senses b-cell death and contributes to the initiation of autoimmune diabetes. Immunity 27:321-333, 2007

FGF21 as a stress hormone: the role of FGF21 in stress adaptation and in the treatment of metabolic diseases

Fibroblast growth factor 21 (FGF21) is an endocrine hormone that is primarily expressed in the liver and exerts beneficial effects on obesity and related metabolic diseases. In addition to its remarkable pharmacologic actions, the physiological roles of FGF21 include the maintenance of energy homeostasis in the body in conditions of metabolic or environmental stress. The expression of FGF21 is induced in multiple organs in response to diverse physiological or pathological stressors, such as starvation, nutrient excess, autophagy deficiency, mitochondrial stress, exercise, and cold exposure. Thus, the FGF21 induction caused by stress plays an important role in adaptive response to these stimuli. Here, we highlight our current understanding of the functional importance of the induction of FGF21 by diverse stressors as a feedback mechanism that prevents excessive stress.



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➤Educational background & professional experience

2006-2008	Kyung Hee University Hospital / Instructor
2008-2009	Ministry of National Defense / Physician
2009-2011	The Armed Forces Capital Hospital / Chief physician
2011-present	Kyung Hee University Hospital /Clinical Assistant Professor

➤Research interests

Early stage of type 2 diabetes mellitus, Metabolic syndrome, Obesity, Epidemiology, Genetics

➤Brief list of publications

1. Rhee SY et al. Arsenic exposure and prevalence of diabetes mellitus in Korean adults J Korean Med Sci 28: 861-848, 2013
2. Rhee SY et al. Blood lead is significantly associated with metabolic syndrome in Korean adults: an analysis based on the Korea National Health and Nutrition Examination Survey (KNHANES), 2008. Cardiovasc Diabetol 12: 9, 2013.
3. Rhee SY et al. Vitamin D and diabetes in Koreans: analyses based on the Fourth Korea National Health and Nutrition Examination Survey (KNHANES), 2008-2009. Diabetic Med 29: 1003-1010, 2012.
4. Rhee SY et al. A novel PRKAR1A mutation in Korean Carney complex family. Exp Clin Endocrinol Diabetes 120: 7-13, 2012.
5. Rhee SY et al. Characteristics of insulin resistance and insulin secretory capacity in Korean subjects with IFG and IGT. Diabetes Res Clin Pract 89: 250-255, 2010.

Heavy metal exposure and metabolic diseases in Korea: evidences based on the KNHANES

Although an association between low-level environmental heavy metal exposure and the incidence of various metabolic diseases has been hypothesized, little research on this topic has been conducted on a population-wide level.

With this background, we analyzed the correlation between blood heavy metal concentration and metabolic diseases using data from the Korea National Health and Nutrition Examination Survey (KNHANES), which is one of the most important epidemiologic data in Korea.

We investigated two studies. At first, we analyzed the association of glucose tolerance status and urinary creatinine adjusted total arsenic concentrations, and We also analyzed the metabolic syndrome status and whole blood lead, mercury, cadmium, manganese, and creatinine-adjusted urine arsenic concentrations in the other study.

In the result from the first study, urinary arsenic concentrations in subjects with DM were significantly higher than those in subjects with normal glucose tolerance and those with impaired fasting glucose. Furthermore, the urinary total arsenic concentration was inversely associated with the insulin secretion index. In the result from second study, blood lead was the only heavy metal that was significantly associated with MS after adjusting multiple variables.

These findings suggest that higher prevalence of metabolic diseases were closely associated with environmental exposure of heavy metal in the Korean population.

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➤Educational background & professional experience

1983-1988	Kyungpook National University, School of Medicine / M.D
1989-1995	Kyungpook National University, School of Medicine / M.S., Ph.D.
1990-1992	Kyungpook National University, School of Medicine, Department of Preventive Medicine / Resident
1993-2002	Kosin University, School of Medicine, Department of Preventive Medicine / Lecturer, Assistant professor
2003-present	Kyungpook National University, School of Medicine, Department of Preventive Medicine / Associate professor, professor

➤Research interests

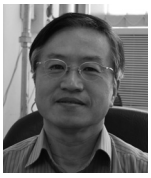
Health effects of chronic exposure to low dose persistent organic pollutants in human

➤Brief list of publications

1. Lee DH, Porta M, Jacobs DR Jr, Vandenberg LN. Chlorinated Persistent Organic Pollutants, Obesity, and Type 2 Diabetes. Endocr Rev. 2014 (in press)
2. Hong NS, Kim KS, Lee IK, Lind PM, Lind L, Jacobs DR, Lee DH. The association between obesity and mortality in the elderly differs by serum concentrations of persistent organic pollutants: a possible explanation for the obesity paradox. Int J Obes (Lond). 2012 Sep;36(9):1170-5.
3. Lee DH, Lind PM, Jacobs DR Jr, Salihovic S, van Bavel B, Lind L. Polychlorinated Biphenyls and Organochlorine Pesticides in Plasma Predict Development of Type 2 Diabetes in the Elderly: The Prospective Investigation of the Vasculature in Uppsala Seniors (PIVUS) study. Diabetes Care. 2011;34(8):1778-84.
4. Lee DH, Steffes MW, Sjödin A, Jones RS, Needham LL, Jacobs DR Jr. Low dose of some persistent organic pollutants predicts type 2 diabetes: a nested case-control study. Environ Health Perspect. 2010;118(9):1235-42.
5. Lee DH, Lee IK, Song K, Steffes M, Toscano W, Baker BA, Jacobs DR Jr. A strong dose-response relation between serum concentrations of persistent organic pollutants and diabetes: results from the National Health and Examination Survey 1999-2002. Diabetes Care. 2006;29(7):1638-44.

Low dose mixture of persistent organic pollutants, obesity, and type 2 diabetes: what can we do?

Persistent organic pollutants (POPs) is a general term for the mixture of several hundred chemicals with common properties like strong lipophilicity, resistance to biodegradation, and biomagnification in the food chain. Background exposure to POPs has recently been linked to type 2 diabetes and other components of metabolic syndrome. Possible molecular mechanisms include glutathione depletion and mitochondrial dysfunction. Although toxicological and epidemiological studies traditionally have tried to identify which specific POPs cause harm, the disease risk associated with POPs is better thought of as reflecting POP mixtures than any several specific compounds. If low dose exposure to POP mixtures is really problematic, how we can protect ourselves? Usually, the primary approach to protecting the public against chemical exposure is by avoiding them through regulation of individual chemicals, including banning, strict safety standards, and carefully controlled use. Unfortunately, however, this kind of approach may not work for POP mixtures. Importantly, glutathione status and mitochondrial function can improve at higher (but still below toxic) POP doses. This mode of dealing with xenobiotic chemicals is related to the concept of hormesis even though traditional hormesis signifies only low dose beneficial effects contrasting with high dose toxic effects, without any consideration of very low dose chronic exposure. Defined broadly, hormesis means mild stress-induced stimulation of cellular protective mechanisms, including increased glutathione synthesis and mitochondrial biogenesis. Diverse stressors can induce hormesis in experimental settings, but be classified into 3 categories depending on their possibility of application to pubic: (1) disadvantageous stressors: chemicals like POPs and radiation, but these could harm humans because of issues like chemical mixtures, endocrine disruption, and susceptible populations, (2) neutral stressors: cold, heat, and gravity which are appropriate for controlled human use, and (3) advantageous stressors: moderate exercise, phytochemical intake, and calorie restriction are active stressors that have wide human applicability.



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➤Educational background & professional experience

1985-1989	Neuropharmacology, Medical College of Wisconsin, Milwaukee, WI, USA / Ph.D.
2002-present	Department of Pharmacology, College of Medicine, Hallym University, Korea / Professor
2007-present	Institute of Natural Medicine, College of Medicine, Hallym University, Korea / Head

➤Research interests

1. Research on pain and blood glucose level regulation
2. Signal transduction mechanism involved in pain transmission and interaction with opioid system
3. Mechanism of hippocampal neuronal cell death in kainic acid-induced seizure model

➤Brief list of publications

1. Yun-Beom Sim, Soo-Hyun Park, Sung-Su Kim, Su-Min Lim, Jun-Sub Jung, Hong-Won Suh. Pertussis toxin administered spinally induces a hypoglycemic effect on normal and diabetic mice. Pharmacology. 2014.7. (In press)
2. Yun-Beom Sim, Soo-Hyun Park, Sung-Su Kim, Su-Min Lim, Jun-Sub Jung, Hong-Won Suh. The modulatory role of alpha-melanocyte stimulating hormone administered spinally in the regulation of blood glucose level in D-glucose-fed and restraint stress mouse models. Neuropeptides. 48:207-212, 2014.5.
3. Yun-Beom Sim, Soo-Hyun Park, Sung-Su Kim, Chea-Ha Kim, Su-Jin Kim, Su-Min Lim,Jun-Sub Jung, Hong-Won Suh. Ghrelin administered spinally increases the blood glucose level in mice. Peptides. 54:162-165, 2014.1.
4. Yun-Beom Sim, Soo-Hyun Park, Yu-Jung Kang, Jun-Sub Jung, Ohk-Hyun Ryu, Moon-Gi Choi, Seong-Soo Choi, Hong-Won Suh. Interleukin-1b (IL-1b) increases pain behavior and the blood glucose level: Possible involvement of glucocorticoid system. Cytokine. 64, 351-356, 2013.9
5. Yun-Beom Sim, Soo-Hyun Park, Yu-Jung Kang, Sung-Su Kim, Chea-Ha Kim, Su-Jin Kim, Jun-Sub Jung, Ohk-Hyun Ryu, Moon-Gi Choi & Hong-Won Suh. Effect of GABA Receptor Agonists or Antagonists Injected Spinally on the Blood Glucose Level in Mice. Neurochemical Research. 38(5):1055-1062, 2013.5.

The pharmacological study on the blood glucose regulation and its association with different types of diseases

In the first part, the roles of α2-adrenergic receptors located in the spinal cord in the regulation of blood glucose levels were studied in mice. Intrathecal (i.t.) injection with clonidine caused a pronounced elevation of the blood glucose level, whereas i.t. administration of yohimbine did not affect the blood glucose levels. Clonidine-induced hyperglycemic effect was dose-dependently attenuated by yohimbine. I.t. pretreatment with pertussis toxin (PTX) almost abolished the hyperglycemic effect induced by clonidine. Plasma insulin levels were reduced by clonidine, and PTX pretreatment reversed the clonidine-induced reduction of the insulin levels. In addition, i.t. pretreatment with N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) or intraperitoneal pretreatment with mifepristone (RU486), hexamethonium and 6-hydroxydopamine attenuated the hyperglycemic effect induced by clonidine. I.t. injected clonidine significantly increased the plasma corticosterone levels. The elevated blood glucose levels induced by clonidine were significantly decreased in adrenalectomized mice. Our results suggest that the α2-adrenergic receptors located in the spinal cord play important roles for the elevation of the blood glucose levels. Spinally located PTX-sensitive G-proteins appear to be involved in the hyperglycemic effect induced by clonidine. The hyperglycemic effect induced by clonidine appears to be mediated by a reduction of the blood insulin levels. In addition, glucocortioid system appears to be involved in clonidine-induced hyperglycemic effect. Furthermore, the clonidine-induced hyperglycemia appears to be mediated via activating the spinal nerves or peripheral sympathetic nervous system.

In the second part, the role of the hyperglycemia induced by clonidine for the regulation in animal sepsis model will be discussed. In addition, the effects of anti-diabetic drugs administered spinally or supraspinally on the regulation of the blood glucose level and their neuroprotective effect against kainic-acid (KA)-induced hippocampal neuronal cell death. Furthermore, the changes of the blood glucose levels in KA-induced seizure model and in the animal model of depression will be discussed.

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➤**Educational background & professional experience**

2003-2007	University of Antwerp / MSc
2007-2013	University of Antwerp Department: Biology Systemic Physiological and Ecotoxicological Research / PhD
2013-present	University of California, Irvine Department: Developmental and Cell Biology Blumberg-lab / Postdoctoral researcher

➤**Research interests**

The role of environmental endocrine disrupting compounds in the development of type 2 diabetes

➤**Brief list of publications**

1. Hectors TLM, Vanparys C, van der Ven K, Martens GA, Jorens PG, Van Gaal LF, Covaci A, De Coen W, Blust R. 2011. Environmental pollutants and type 2 diabetes: A review of mechanisms that can disrupt β-cell function. Diabetologia 54: 1273-1290
2. Hectors TLM, Vanparys C, Pereira-Fernandes A, Knapen D, Blust R. 2012. Mechanistic evaluation of the insulin response in H4IIE hepatoma cells: New endpoints for toxicity testing? Toxicology Letters 212: 180-189
3. Hectors TLM, Vanparys C, Pereira-Fernandes A, Martens GA, Blust R. 2013. Evaluation of the INS-1 832/13 cell line as a β-cell based screening system to assess pollutant effects on β-cell function. PLoS ONE 8: e60030
4. Hectors TLM, Vanparys C, Van Gaal LF, Jorens PG, Covaci A, Blust R. 2013. Insulin resistance and environmental pollutants: Experimental evidence and future perspectives. Environmental Health Perspectives 121: 1273-1281

Environmental pollutants and diabetes: where are we now and where are we heading?

Metabolic diseases have reached epidemic proportions worldwide and projections portend an even greater increase in prevalence in the future. Nowadays, obesity and diabetes are considered one of the greatest threats for human health in the 21st century and their socioeconomic impact is expected to be immense. To tackle further increases, the development of prevention strategies is a high research priority. Prevention is however based on knowledge of underlying risk factors and, as for a lot of other non-communicable diseases, the list of factors that need to be considered and are potentially harmful for metabolic disorders is not clear cut. Although energy-rich diets and a sedentary lifestyle are for sure major contributors in the recent metabolic disease pandemic, other non-traditional risk factors such as environmental chemicals, stress, altered gut microbiome, etc. have been implied as well. Especially the potential involvement of ubiquitous environmental pollutants, so-called "metabolic disruptors", has caught the interest of the scientific community and governmental and regulatory instances, and has been declared a high research priority.

The present research focuses on the link between environmental pollutants and diabetes, and handles two major questions. The first question that will be answered is "what is the evidence at hand for the existence of "diabetogenic metabolic disruptors?". Secondly, an overview will be given of what information is missing and what are potentially interesting research directions while discussing the question "how are we going to deal with diabetogens in the future?".

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➤Educational background & professional experience

1983	Kyushu University School of Medicine / MD
1990-1994	Harvard Medical School / Postdoctoral Fellow
1994-1998	University of Michigan / Assistant Professor
2004-2011	UMDNJ / Professor
2011-present	Rutgers New Kersey Medical School / Professor and Chair

➤Research interests

Signaling mechanism of heart failure and myocardial ischemia, the role of autophagy, oxidative stress and the hippo signaling pathway in the heart.

➤Brief list of publications

1. Del Re, D.P., Matsuda, T., Zhai, P., Maejima, Y., Jain, M.R., Liu, T., Li, H., Hsu, C.-P., Sadoshima, J. Mst1 promotes apoptosis through phosphorylation and inhibition of Bcl-xL in cardiomyocytes. Mol Cell 54, 639-650, 2014.
2. Shao, D., Oka, S., Liu, T., Zhai, P., Ago, T., Sciarretta, S., Li, H., Sadoshima, J., A Redox-Dependent Mechanism for Regulation of AMPK Activation by Thioredoxin1 during Energy Starvation. Cell Metab 19, 232-245, 2014.
3. Maejima, Y., Kyoi, S., Zhai, P., Liu, T., Li, H., Ivessa, A., Sciarretta, S., Del Re, D. P., Zablocki, D. P., Hsu, C.-P., Lim, D.-S., Isobe, M., Sadoshima, J., Mst1 inhibits autophagy by promoting Beclin-1Bcl-2 interaction. Nature Med: 19, 1478-1488, 2013.
4. Oka S, Alcendor RR, Zhai P, Park JY, Shao D, Cho J, Yamamoto T, Tian B, Sadoshima J. PPARa-Sirt1 complex mediates cardiac hypertrophy and failure through suppression of the ERR transcriptional pathway. Cell Metab: 14, 598-611, 2011.
5. Ago T, Liu T, Zhai P, Chen W, Li H, Molkentin JD, Vatner SF, Sadoshima J. A redox dependent pathway for regulating class II HDAC and cardiac hypertrophy. Cell: 133, 978-993, 2008.

Regulation of myocardial survival and death by autophagy during metabolic stress

Autophagy is an important mechanism of cell survival during energy stress such as myocardial ischemia. Cytosolic long-lived proteins and damaged intracellular organelles are sequestrated by autophagosomes and degraded in lysosomes. Amino acids and fatty acids extracted by autophagy are utilized for ATP synthesis and cell survival. We have previously shown that autophagy in the heart is positively regulated by FoxO-dependent mechanisms and negatively regulated by mammalian sterile 20-like kinase 1 (Mst1) and mTOR. Here we investigated how autophagy is affected during high-fat diet (HFD) feeding in mice and what its functional consequence is. Mice with HFD-induced obesity and metabolic syndrome exhibited deregulated cardiac activation of mTORC1, particularly during ischemia. HFD mice presented inhibition of cardiac autophagy and displayed increased ischemic injury. Pharmacological and genetic inhibition of mTORC1 restored autophagy and abrogated the increase in infarct size observed in HFD mice, yetfailed to protect HFD mice in the presence of genetic disruption of autophagy. Thus, mTORC1 may represent a therapeutic target to reduce myocardial damage during ischemia through stimulation of autophagy, particularly in patients with metabolic syndrome and obesity.

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➤Educational background & professional experience

1994-2003	Department of Internal Medicine and Molecular Science, Osaka University / Fellow
2003-2005	Molecular Cardiology, Boston University / Research Associate
2005-2010	Department of Medicine, Boston University / Assistant Professor
2010-2014	Department of Molecular Cardiology, Nagoya University / Professor
2014-present	Molecular Cardiovascular Medicine, Nagoya University / Professor

➤Research interests

To clarify the roles of fat-derived secreted factors, known as adipocytokines, in metabolic and cardiovascular diseases.

➤Brief list of publications

1. Maruyama S, Shibata R, Kikuchi R, Izumiya Y, Rokutanda T, Araki S, Kataoka Y, Ohashi K, Daida H, Kihara S, Ogawa H, Murohara T, Ouchi N. Fat-derived factor omentin stimulates endothelial cell function and ischemia-induced revascularization via an endothelial nitric oxide synthase-dependent mechanism. J Biol Chem. 2012;287:408-17.
2. Ogura Y, Ouchi N, Ohashi K, Shibata R, Kataoka Y, Kambara T, Kito T, Maruyama S, Yuasa D, Matsuo K, Enomoto T, Uemura Y, Miyabe M, Ishii M, Yamamoto T, Shimizu Y, Walsh K, Murohara T. Therapeutic impact of follistatin-like 1 on myocardial ischemic injury in preclinical animal models. Circulation. 2012;126:1728-38.
3. Kambara T, Ohashi K, Shibata R, Ogura Y, Maruyama S, Enomoto T, Uemura Y, Shimizu Y, Yuasa D, Matsuo K, Miyabe M, Kataoka Y, Murohara T, Ouchi N. CTRP9 protects against myocardial injury following ischemia-reperfusion through AMPK-dependent mechanism. J Biol Chem. 2012;287:18965-73.
4. Uemura Y, Shibata R, Ohashi K, Enomoto T, Kambara T, Yamamoto T, Ogura Y, Yuasa D, Joki Y, Matsuo K, Miyabe M, Kataoka Y, Murohara T, Ouchi N. Adipose-derived factor CTRP9 attenuates vascular smooth muscle cell proliferation and neointimal formation. FASEB J 2013;27:25-33.
5. Kataoka Y, Shibata R, Ohashi K, Kambara T, Enomoto T, Uemura Y, Ogura Y, Yuasa D, Matsuo K, Nagata T, Oba T, Yasukawa H, Numaguchi Y, Sone T, Murohara T, Ouchi N. Omentin prevents myocardial ischemic injury through AMPK- and Akt-dependent mechanisms. J Am Coll Cardiol. 2014;63:2722-33.

Role of adipocytokines in cardiovascular complication

Obesity, in particular, excessive visceral fat accumulation, is frequently accompanied by various metabolic disorders including type 2 diabetes, ultimately leading to the development of cardiovascular disease. It is well recognized that adipose tissue functions as an endocrine organ that secretes a variety of bioactive molecules, also referred to as adipocytokines or adipokines. Obese conditions typically lead to upregulation of various pro-inflammatory adipocytokines, which promote obesity-related disorders. In contrast, obesity induces downregulation of anti-inflammatory adipocytokine adiponectin that exerts favorable effects on obesity-linked cardiovascular diseases. C1q/TNF-related protein (CTRP) 9 is a recently identified adipocytokine, which is an adiponectin paralog. Circulating CTRP9 level is reported to associate positively with favorable glucose and metabolic phenotypes. Systemic administration of CTRP9 to mice improves acute cardiac injury and pathological vascular remodeling. Omentin is an adipocytokine that is expressed abundantly in human visceral adipose tissue. Plasma levels of omentin are decreased in association with obese complications including type 2 diabetes and coronary heart disease. Omentin promotes ischemia-induced revascularization and ameliorates myocardial ischemic injury in mice. Thus, it is conceivable that reduced production of these adipocytokines under conditions of obesity (e.g. type 2 diabetes) participates in the development of cardiovascular disorders. I will talk about our recent findings on the role of these adipocytokines in regulation of cardiovascular complication.

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➤Educational background & professional experience

1996	University of Ulsan College of Medicine / M.D.
2005	University of Ulsan College of Medicine / Ph.D.
2006-2009	Inje University, Dep. of Internal Medicine / Assistant Professor
2012-2014	University of Washington, Dep. of Internal Medicine / Visiting Scholar
2009-present	University of Ulsan, Asan Medical Center, Dep. of Internal Medidine / Assistant & Associate Professor

➤Research interests

Diabetes / Obesity and endothelial dysfunction
Diabetes / Obesity and vascular inflammation

➤Brief list of publications

1. Jung CH, Lee WJ, Hwang JY, Seol SM, Kim YM, Lee YL, Park JY. Vaspin protects vascular endothelial cells against free fatty acid-induced apoptosis through a phosphatidylinositol 3-kinase/Akt pathway. Biochem Biophys Res Commun. 413(2):264-9, 2011
2. Jung CH, Hwang JY, Yu JH, Shin MS, Bae SJ, Park JY, Kim HK, Lee WJ. The value of apolipoprotein B/A1 ratio in the diagnosis of metabolic syndrome in a Korean population. Clin Endocrinol (Oxf). 77(5):699-706, 2012
3. Jung CH*, Lee WJ*, Hwang JY, Yu JH, Shin MS, Lee MJ, Jang JE, Leem J, Park JY, Kim HK. Assessment of the fatty liver index as an indicator of hepatic steatosis for predicting incident diabetes independently of insulin resistance in a Korean population. Diabet Med. 30(4):428-35, 2013
4. Jung CH, Lee MJ, Hwang JY, Jang JE, Leem J, Park JY, Kim HK, Lee WJ. Elevated serum ferritin level is associated with the development of diabetes in healthy Korean men: a 4 year retrospective longitudinal study. PLoS One. 8(9):e75250, 2013
5. Jung CH, Lee MJ, Kang YM, Lee YL, Yoon HK, Kang SW, Lee WJ, Park JY. Vaspin inhibits cytokine-induced nuclear factor-kappa B activation and adhesion molecule expression via AMP-activated protein kinase activation in vascular endothelial cells. Cardiovascular Diabetology. 13(1):41, 2014

Endothelial nitric oxide/VASP signaling regulates macrophage activation

Accumulating evidence supports an important role of macrophage activation in a broad spectrum of inflammatory conditions including obesity-associated insulin resistance. Although endothelial nitric oxide (NO) signaling has anti-inflammatory functions in metabolic tissues, whether endothelial NO signaling mediates macrophage polarization is unknown. To determine whether endothelial NO signaling contributes to macrophage polarization, we examined the expression of inflammatory (M1) or anti-inflammatory (M2) genes in macrophages in the setting of suppressed or enhanced endothelial NO level. Increased endothelial NO level by eNOS overexpression in mice or administration of NO donor in macrophages inhibits M1 gene expression and enhances the expression of M2 genes, while reduction of endothelial NO increases M1 activation and decreases M2 activation of macrophages. To further determine whether the effect of NO involves vasodilatory-stimulated phosphoprotein (VASP) as a downstream mediator, we investigated the effect of VASP on macrophage polarization using VASP-deficient mice or VASP-overexpressed RAW cells. Overexpression and knockout of VASP reproduced the effect of NO overexpression and deficiency, respectively, implying that VASP is a downstream mediator of NO in macrophage polarization. These data collectively suggest that endothelial NO and VASP signaling contributes to the regulation of macrophage polarization.

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➤**Educational background & professional experience**

2001-2004	Korea University / Assistant Professor
2004-2009	Korea University / Associate Professor
2005-2006	University of Texas / Research Fellow
2009-present	Korea University / Professor

➤**Research interests**

Adipokines & hepatokines, Sarcopenic obesity, Vascular inflammation

➤**Brief list of publications**

1. Hong HC, Hwang SY, Choi HY, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. The relationship between sarcopenia and non-alcoholic fatty liver disease (NAFLD): The Korean Sarcopenic Obesity Study (KSOS). Hepatology 2014 May;59(5):1772-8
2. Choi HY, Park JW, Lee N, Hwang SY, Cho GJ, Hong HC, Yoo HJ, Hwang TG, Kim SM, Baik SH, Park KS, Yoon B-S, Choi KM. Effects of a combined aerobic and resistance exercise program on C1q/TNF-related protein-3 (CTRP-3) and CTRP-5 levels. Diabetes Care 2013 Oct;36(10):3321-7
3. Choi KM, Hwang SY, Hong HC, Yang SJ, Choi HY, Yoo HJ, Lee KW, Nam MS, Park YS, Woo JT, Kim YS, Choi DS, Youn BS, Baik SH. C1q/TNF-related Protein-3 (CTRP-3) and Pigment Epithelium-Derived Factor (PEDF) Concentrations in Patients with Type 2 Diabetes and Metabolic Syndrome. Diabetes 2012 Nov;61(11):2932-6
4. Choi HY, Kim S, Yang SJ, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Association between adiponectin, resistin and vascular inflammation: Analysis with 18F-Fludorodeoxyglucose Positron Emission Tomography. Arterioscler Thromb Vasc Biol 2011 Apr;31(4):944-9
5. Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Care; 2010 Jul;33(7):1497-1499

Novel diagnostic and therapeutic targets for cardiometabolic disorders

Over the last two decades, the prevalence of overweight or obesity in the world has increased at an accelerating and alarming rate. Obesity is a strong risk factor for metabolic syndrome, type 2 diabetes, and cardiovascular diseases. Adipose tissue, which used to be simply known as storage of surplus energy, is now regarded as an active endocrine organ. Adipose tissue releases a large number of bioactive mediators (adipokines) that signal to organs such as brain, liver, skeletal muscle, and the immune system, which lead to modulate lipid and glucose metabolism, inflammation, and atherosclerosis. Dysregulated production of adipokines has been found to participate in the development of metabolic and vascular diseases related to obesity. Moreover, dysregulation of adipokine production by excess adipose tissue promotes a state of low-grade systemic inflammation, implicated in the development of both atherosclerosis and subsequently cardiovascular diseases. Adipose tissue is composed of adipocytes embedded in a loose connective tissue meshwork containing adipocyte precursors, fibroblasts, immune cells, and various other cell types. With obesity, macrophages infiltrate adipose tissue, and numerous adipokines are released by both macrophages and adipocytes. The release of pro-inflammatory adipokines leads to a chronic low-grade inflammation that could play a pivotal role in the development of insulin resistance. In fact, insulin resistance plays a key role in the pathophysiology of obesity-related disorders such as metabolic syndrome, type 2 diabetes, and atherosclerosis. Analogous to adipokines, liver and muscle also regulate glucose homeostasis and insulin resistance by producing hepatokines and myokines, respectively. Lifestyle modification and pharmacological therapy can reduce obesity-related cardiometabolic risk, a benefit that may be partly due to their effects on these endogenous control substances.

In this session, I would like to summarize the recent research about novel diagnostic and therapeutic targets for cardiometabolic disorders.

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➤Educational background & professional experience

1984	Shiga University of Medical Science / M.D.
1992	Shiga University of Medical Science / Ph.D.
2005-present	Kanazawa Medical University / Prodessor

➤Research interests

Diabetes and its complications

➤Brief list of publications

1. Linagliptin-Mediated DPP-4 Inhibition Ameliorates Kidney Fibrosis in Streptozotocin-Induced Diabetic Mice by Inhibiting Endothelial-to-Mesenchymal Transition in a Therapeutic Regimen. Kanasaki K, Shi S, Kanasaki M, He J, Nagai T, Nakamura Y, Ishigaki Y, Kitada M, Srivastava SP, Koya D.Diabetes. 2014 Jun;63(6):2120-31
2. Calorie restriction in overweight males ameliorates obesity-related metabolic alterations and cellular adaptations through anti-aging effects, possibly including AMPK and SIRT1 activation. Kitada M, Kume S, Takeda-Watanabe A, Tsuda S, Kanasaki K, Koya D. Biochim Biophys Acta. 2013 Oct;1830(10):4820-7.
3. Ketogenic essential amino acids replacement diet ameliorated hepatosteatosis with altering autophagy-associated molecules. Xu L, Kanasaki M, He J, Kitada M, Nagao K, Jinzu H, Noguchi Y, Maegawa H, Kanasaki K, Koya D. Biochim Biophys Acta. 2013 Oct;1832(10):1605-12.
4. SIRT1 inactivation induces inflammation through the dysregulation of autophagy in human THP-1 cells. Takeda-Watanabe A, Kitada M, Kanasaki K, Koya D. Biochem Biophys Res Commun. 2012 Oct 12;427(1):191-6
5. Calorie restriction enhances cell adaptation to hypoxia through Sirt1-dependent mitochondrial autophagy in mouse aged kidney. Kume S, Uzu T, Horiike K, Chin-Kanasaki M, Isshiki K, Araki S, Sugimoto T, Haneda M, Kashiwagi A, Koya D. J Clin Invest. 2010 Apr;120(4):1043-55.

Nutrient sensing and metabolic health

To extend the length of healthy life span through keeping metabolic health, we have to understand and control the mechanisms that determine the rate of aging. The sirtuins, especially the mammalian SIRT1, are a family of deacetylases that are implicated in the regulation of aging and metabolic health. Ketogenic amino acid (KAA) replacement on high fat diet (HFD) showed increased AMP-activated protein kinase (AMPK) phosphorylation, enhanced liver kinase B1 (LKB1) expression compared to control HFD-fed mice. The KAA-HFD-induced activation of AMPK was associated with an increased protein expression of SIRT1, decreased forkhead box protein O3a (Foxo3a) level, and suppression of mammalian target of rapamycin (mTOR) phosphorylation compared with the HFD-fed mice. Treatment with Sirtinol, a chemical inhibitor of SIRT1, induced the overexpression of inflammation-related genes such as tumor necrosis factor (TNF)-α and interleukin (IL)-6 through nuclear factor (NF)-κB signaling activation, which was associated with autophagy dysfunction, as shown through p62/Sqstm1 accumulation and decreased expression of light chain (LC) 3 II in THP-1 cells. The autophagy inhibitor, 3-methyladenine, also induces inflammation-related NF-κ B activation. In p62/Sqstm1 knockdown cells, Sirtinol-induced inflammation through NF-κB activation was blocked. In addition, inhibition of SIRT1 was involved in the activation of the mammalian target of rapamycin (mTOR) pathway and decreased 5'-AMP activated kinase (AMPK) activation, leading to the impairment of autophagy. The mTOR inhibitor, rapamycin, abolished Sirtinol-induced inflammation and NF-κB activation associated with p62/Sqstm1 accumulation. In summary, SIRT1 regulates metabolic health and inflammation via nutrient-sensing pathways such as the mTOR and AMPK pathways.

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➤Educational background & professional experience

1988	Chiba University / M.D.
1992-1996	Ludwig Institute for Cancer Research / Guest researcher
1996	Uppsala University / PhD
2009-present	Chiba University, Department of Medicine / Professor
2011-present	Chiba University Hospital / Deputy Director

➤Research interests

Metabolic disorders and atherosclerosis, Progeroid syndrome

➤Brief list of publications

1. Kobayashi K, Yokote K et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin compared with α-glucosidase inhibitor in Japanese patients with type 2 diabetes inadequately controlled on sulfonylurea alone (SUCCESS-2): a multicenter, randomized, open-label, non-inferiority trial. Diabetes Obes Metab. 2014, Epub ahead of print.
2. Muto T, Yokote K et al. Concurrent loss of Ezh2 and Tet2 cooperates in the pathogenesis of myelodysplastic disorders. J Exp Med. 2013, 210(12): 2627.
3. Watanabe K, Yokote K et al. Sitagliptin improves postprandial hyperglycemia by inhibiting glucagon secretion in Werner syndrome with diabetes. Diabetes Care. 2013, 36(8): e119.
4. Teramoto T, Yokote K et al. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. J Atheroscler Thromb. 2013; 20(6):517.
5. Takemoto M, Yokote K et al. Diagnostic criteria for Werner syndrome based on Japanese nationwide epidemiological survey. Geriatr Gerontol Int. 2013, 13(2): 475.

Progeroid syndrome as a model of aging-related metabolic disorders

Some human diseases are known to show accelerated aging phenotypes. Among them, Werner syndrome (WS) is a rare autosomal recessive disorder caused by a mutation in the WRN DNA helicase. It is known for early aging symptoms including the graying and loss of hair, cataracts, skin atrophy, osteoporosis and insulin-resistant diabetes mellitus appearing after adolescence. The patients usually die in their forties due to premature atherosclerosis or malignant neoplasms. Total management of multiple metabolic and atherogenic risk factors in WS seems to be associated with improved prognosis of the patients. We have newly discovered ~400 WS patients in Japan, collected clinical information including metabolic characteristics and established diagnostic criteria/treatment guidelines. WS is known to be associated with genetic instability, and the fibroblasts derived from patients tend to show acceleration of replicative senescence. Recently, inducible pluripotent stem (iPS) cells were established from skin fibroblasts of Hutchinson-Gilford Progeria Syndrome (HGPS), a fatal disease occurring in childhood caused by a mutation in the lamin A gene, characterized by premature arteriosclerosis and degeneration of vascular smooth muscle cells. We generated iPS cells from WS skin fibroblasts, which acquired self-replicative capacity and pluripotency. The iPS cells derived from progeroid syndromes may be useful tool to elucidate the mechanism underlying premature aging phenotypes as well as aging-related disorders.

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➤Educational background & professional experience

1980	Pusan National University, Department of Pharmacy / B.S.
1982	Seoul National University, Graduate School / M.S
1988	Toyama Medical and Pharmaceutical University Graduated School (in Japan) / Ph.D
1995	University of Texas Health Science Center / Post-Doc

➤Research interests

Molecular mechanism of aging
Mechanism of vascular aging
Development of new drug for aging intervention

➤Brief list of publications

1. Kim DH, Park MH, Chung KW, Kim MJ, Jung YR, Bae HR, Jang EJ, Lee JS, Im DS, Yu BP, Chung HY: The essential role of FoxO6 phosphorylation in aging and calorie restriction. Age, 36(4):9679 (2014)
2. Jung KJ, Kim DH, Lee EK, Song CW, Yu BP, Chung HY: Oxidative stress induces inactivation of protein phosphatase 2A, promoting proinflammatory NF-κB in aged rat kidney. Free Radical Bio Med, 61:206-217(2013)
3. Park D, Lee EK, Jang EJ, Jeong HO, Kim BC, Ha YM, Hong SE, Yu BP, Chung HY: Identification of the dichotomous role of age-related LCK in calorie restriction revealed by integrative analysis of cDNA microarray and interactome. AGE, 35(4):1045-1060(2013)
4. Kim DH, Kim JM, Lee EK, Choi YJ, Kim CH, Choi JS, Kim ND, Yu BP, Chung HY: Modulation of FoxO1 phosphorylation/acetylation by baicalin during aging. J Nutr Biochem, 23 (2012) 1277–1284(2012)
5. Kim JM, Heo HS, Ha YM, Ye BH, Lee EK, Choi YJ, Yu BP, Chung HY: Mechanism of Ang II involvement in activation of NF-κB through phosphorylation of p65 during aging. AGE, 34(1):11-25(2012)

Insulin resistance and molecular inflammation as the underlying mechanism of aging and their intervention by MHY908

Insulin resistance is common with aging and is associated with the inflammatory response in both humans and rodents. A number of PPARα/γ dual agonists have been tested for their abilities to attenuate insulin resistance and type 2 diabetes. However, there is no study on the effects of PPARα/γ dual agonists on inflammation and insulin resistance during aging. In the present study, we investigated the ability of 2-[4-(5-chlorobenzothiazothiazol-2-yl) phenoxyl-2-methyl-propionic acid (MHY908), a newly synthesized novel PPARα/γ dual agonist, to suppress the inflammatory response and attenuate insulin resistance in aged rats.

Twenty month-old rats were divided into 4 groups: ad libitum fed, ad libitum fed supplemented with MHY908 (1 mg and 3 mg/kg/day for 4 weeks), and 40% calorie restricted (CR). Six-month-old ad libitum fed rats were used as an age control.

The aged rats supplemented with MHY908 showed reduced serum glucose, triglyceride (TG), and insulin levels, as well as reduced liver TG levels. MHY908 brought about a reduction in endoplasmic reticulum (ER) stress and activation of the c-Jun N-terminal kinase (JNK) in the livers of aged rats, which consequently improved insulin signaling. In the kidneys of aged rats, the efficacy of MHY908 as a potent anti-inflammatory agent was shown by its suppression of NF-κB activation through inhibition of the Akt/IKK signaling pathway.

Therefore, the major finding of this study is that MHY908 acts as a therapeutic agent against age-related inflammation associated with insulin resistance by activating PPARα and PPARγ, thus attenuating ER stress.

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➤Educational background & professional experience

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1987-1993	Chongqing Xinqiao Hospital, the Third Military Medical University / Attending Endocrinologist
1993-1996	Shanghai Second Medical University / PhD candidate
1998-2003	Baylor College of Medicine and McGill University / Postdoc., Research Associate
2003-present	Shanghai Institute of Endocrinology and Metaboism, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine / Professor

➤Research interests

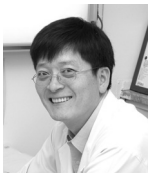
Obesity, diabetes and fatty liver

➤Brief list of publications

1. Lu Y, Liu X, Jiao Y, Xiong XL, Wang E, Wang XL, Zhang ZJ, Zhang HJ, Pan LL, Guan YF, Cai DS, Ning G, Li XY# Periostin promotes liver steatosis and hypertriglyceridemia through downregulation of PPARα. J Clin Invest 2014 accepted
2. Xiong XL, Wang XL, Lu Y, Wang E, Zhang ZJ, Yang J, Zhang HJ, Li XY# Hepatic steatosis exacerbated by endoplasmic reticulum stress-mediated downregulation of FXR in aging mice. J Hepatol 2014 Apr;60(4):847-54 (Corresponding author)
3. Lu Y, Ma ZM, Zhang ZJ, Xiong XL, Wang XL, Zhang HJ, Shi GJ, Xia XF, Ning G, Li XY#, Yin Yang 1 promotes hepatic steatosis through repression of farnesoid X receptor in obese mice. GUT 2014;63(1):170-8
4. Lu Y, Xiong XL, Wang XL, Zhang ZJ, Li J, Shi GJ, Yang J, Zhang HJ, Ning G, Li XY#. Yin Yang 1 promotes hepatic gluconeogenesis through upregulation of glucocorticoid receptor. Diabetes 2013;62(4):1064-73
5. Lu Y, Zhang Z, Xiong X, Wang X, Li J, Shi G, Yang J, Zhang X, Zhang H, Hong J, Xia X, Ning G, Li XY#. Glucocorticoids Promote Hepatic Cholestasis in Mice by Inhibiting the Transcriptional Activity of the Farnesoid X Receptor. Gastroenterology. 2012;143(6): 1630-1640

Hepatokine periostin and fatty liver

Hepatosteatosis is characterized by an aberrant accumulation of triglycerides in the liver. However, the molecular mechanisms of obesity-induced fatty liver remain largely unknown. Here, our data demonstrate that periostin, a secreted cell adhesion protein, is markedly upregulated in the liver in obese rodents and humans. Notably, overexpression of periostin in the liver leads to hepatic steatosis and hypertriglyceridemia. Conversely, ablation of periostin using genetic models and a neutralizing antibody dramatically improves hepatosteatosis and hypertriglyceridemia. With regard to the molecular mechanism, periostin downregulates peroxisome proliferator-activated receptor (PPAR) α expression through α6β4 integrin-mediated JNK signaling pathway. Therefore, our results identify an important role for periostin in obesity-induced hepatosteatosis.



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➤Educational background & professional experience

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1986-1989	Department of Internal Medicine, Pusan National University Hospital / Internal Medicine, Risidency
2006-	University of Toronto, ON, CANADA / Visiting Professor
1994-present	Department of Internal Medicine, Pusan National University Hospital / Professor

➤Research interests

Diabetic complication

➤Brief list of publications

1. Nonalbuminuric proteinuria as a biomarker for tubular damage in early development of nephropathy with type 2 diabetic patients. Diabetes Metab Res Rev 2014 Mar 28 [Epub ahead of print]
2. Duration of diabetes and effectiveness of insulin in the management of insulin-naïve Korean patients uncontrolled on oral antidiabetic drugs: a sub-analysis of the MOdaliTy of Insulin treatment eValuation (MOTIV) registry results. Acta Diabetol. 2014 Feb 28 [Epub ahead of print]
3. High-normal serum uric acid predicts the development of chronic kidney disease in patients with type 2 diabetes mellitus and preserved kidney function. J Diabetes Complications 2014;28:130-4
4. Urinary cystatin C and tubular proteinuria predict progression of diabetic nephropathy. Diabetes Care 2013;36:656-661
5. Clinical implication of plasma and urine YKL-40, as a proinflammatory biomarker, on early stage of nephropathy in type 2 diabetic patients. J Diabetes Complications 2012;26:308-12, 2012

Overview of inflammation and nutrition

Diet is an important regulatory factor on healthy immune balance. Whereas malnutrition is related to immunosuppression, nutritive overload also leads to immunoactivation due to a susceptibility to an inflammatory condition. Several studies have shown inflammatory effects of nutritive overload, even in the absence of weight gain. Obesity or/and adiposity, as a main result of nutritive overload, induces variable chronic metabolic disorders including type 2 diabetes mellitus. Adipose tissue is not merely an inert tissue related to energy storage but active endocrine organ in the regulation of physiological or/and pathological inflammatory process as well. Thus, adipose tissue produces a numerous adipokines and anti- or pro-inflammatory cytokines. High dietary carbohydrate, when it counted by glycemic load (GL) or/and glycemic index (GI), was significantly associated with high pro-inflammatory cytokines and low adiponectin. Although large observation studies had shown an association between high dietary GL/GI and inflammatory cytokines, interventional study such as the restriction of high GL had not shown this association. Different fatty acids including trans-, saturated and polyunsaturated fatty acid had been investigated for their different effects on inflammation. A number of studies had shown that high consumption of vegetables and fruits were negatively correlated with inflammatory markers, but others could not convincingly support this association. Some vitamins and minerals might have an association with levels of inflammatory markers with effect on oxidative stress. In conclusion, some nutritional component and overload might have an influence inflammation process associated with the development of metabolic disorders including diabetes.

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➤**Educational background & professional experience**

1958-1962	Iowa State University, Ames, Iowa / B.S. in Chemistry
1962-1965	Purdue University, Lafayette, Indiana / PhD in Biochemistry
1965-1970	University of Wisconsin, Madison, Wisconsin / Postdoctoral Fellow in Institute for Enzyme Research
2009-2014	Kyungpook National University School of Medicine, Daegu, South Korea / Visiting Professor of WCU Program
1970-present	Indiana University School of Medicine, Indianapolis, Indiana / Distinguished Professor

➤**Research interests**

Regulation of metabolic processes

➤**Brief list of publications**

1. Jeoung NH, Harris RA. Role of pyruvate dehydrogenase kinase 4 in regulation of blood glucose levels. Korean Diabetes Journal 34: 274-283 (2010).
2. Jeoung NH, Rahimi Y, Wu P, Lee WNP, Harris RA. Fasting induces ketoacidosis and hypothermia in PDHK2/PDHK4 double knockout mice. Biochemical J. 443: 829-839 ((2012).
3. Novarino G, El-Fishawy P, Kayserili H, Kara M, Schroth J, Silhavy JL, Gabriel S, Sweetman L, Rahimi Y, Harris RA, State MW, Gleeson JG. Mutations in the BCKD-kinase lead to a potentially treatable form of autism with epilepsy. Science 338: 394-397 (2012).
4. Jeoung NH, Harris CR, Harris RA. Regulation of pyruvate metabolism in metabolic-related diseases. Reviews in Endocrine and Metabolic Disorders 15: 99-110 (2014).

Tissue specific roles of PDK2 and 4 in regulation of blood glucose levels

The pyruvate dehydrogenase complex (PDC) is relatively active in the fed state to direct pyruvate into the citric acid cycle and lipid synthesis. In the starved state PDC is shut down by phosphorylation by pyruvate dehydrogenase kinases (PDKs) to conserve three carbon substrates for gluconeogenesis. This helps maintain blood glucose levels during starvation but contributes to hyperglycemia in insulin deficient and resistant states. Studies with PDK2 KO and PDK4 KO mice provide evidence for tissue specific roles for the PDKs in setting fasting blood glucose levels. Loss of control of PDC activity in PDK KO mice lowers the liver concentration of pyruvate which limits the synthesis of oxaloacetate by pyruvate carboxylase. In PDK4 KO mice the delivery of pyruvate to the liver is reduced by an increase in pyruvate oxidation in peripheral tissues as evidenced by reduced blood levels of lactate and pyruvate. In PDK2 KO mice, liver pyruvate concentration is reduced by an increase in hepatic pyruvate oxidation as evidenced by no reduction in blood levels of lactate and pyruvate. These findings indicate PDK2 is primarily responsible for regulation of PDC activity in the liver while PDK4 is primarily responsible in skeletal muscle. This study shows that tissue specific regulation of PDC activity by PDKs is important for pyruvate carboxylase activity which in turn is important in setting the rate of hepatic glucose synthesis and therefore the blood glucose level.

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➤Educational background & professional experience

1982	University of Minnesota (Nutrition) / Ph.D.
1985-1989	University of Nebraska Medical Center / Assistant Professor, Instructor,
1989-1994	Creighton University School of Medicine / Associate professor, Assistant professor
1994-present	Hallym University / Professor, Associate Professor

➤Research interests

The molecular mechanisms of tumor promotion by high-fat diet–induced obesity and cancer prevention with anti-inflammatory phytochemicals, with emphasis on cytokines/chemokines as prime targets.

➤Brief list of publications

1. Jung JI, Cho HJ, Jung YJ, Kwon SH, Her S, Choi SS, Shin SH, Lee KW, Park JHY: High-fat diet-induced obesity increases lymphangiogenesis and lymph node metastasis in the B16F10 melanoma allograft model: Roles of adipocytes and M2-macrophages. Int J Cancer, in press doi: 10.1002/ijc.28983
2. Kim M, Cho HJ, Kwon GT, Kang YH, Kwon SH, Her S, Park T, Kim Y, Kee Y, Park JHY: Benzyl isothiocyanate suppresses high-fat diet-stimulated mammary tumor progression via the alteration of tumor microenvironments in obesity-resistant BALB/c mice. Mol Carcinogen, in Press doi: 10.1002/mc.22159
3. Kwon SJ, Park SY, Kwon GT, Kwon Lee KW, Kang YH, Choi MS, Yun JW, Jeon JH, Jun JG, Park JHY: Licochalcone E present in licorice suppresses lung metastasis in the 4T1 mammary orthotopic cancer model. Cancer Prev Res, 6: 603-613, 2013
4. Cho HJ, Jung JI, Lim DY, Kwon GT, Her S, Park JH, Park JHY: Bone marrow-derived, alternatively-activated macrophages enhance solid tumor growth and lung metastasis of mammary carcinoma cells in a Balb/C mouse orthotopic model. Breast Cancer Res 14/3: R81, 2012
5. Kim EJ, Choi MR, Park H, Kim M, Hong JE, Lee JY, Chun HS, Lee KW, Park JHY: Dietary fat increases solid tumor growth and metastasis of 4T1 murine mammary carcinoma cells, and mortality in obesity-resistant BALB/c mice. Breast Cancer Res 11;13(4):R78, 2011

Stimulation of tumor progression by high-fat diet and its suppression by dietary phytochemicals

Obesity and overweight are major risk factors of a wide variety of cancers. Unfortunately, over the past several decades the prevalence of overweight and obesity has been rising at an alarming rate worldwide. In obesity the secretion of growth factors and cytokines by adipose tissues is deregulated, which may make a permissive environment for tumor cell growth and metastasis. Using several mouse tumor models, we have shown that the chronic consumption of a high-fat diet (HFD) stimulates solid tumor growth and metastasis and thereby reduces the survival rate. Angiogenesis and lymphangiogenesis in tumor tissues and lymph node (LN)s are markedly increased in HFD-fed mice. HFD feeding increases adipocytes and M2-macrophage (M2-MΦ)s as well as the concentrations of many cytokines including MCP-1 and M-CSF in tumor tissues. Results from in vivo and in vitro co-culture studies revealed that the crosstalk between adipocytes, tumor cells, M2-MΦs, and/or lymphatic endothelial cell (LEC)s stimulates the expression of several growth factors, cytokines, and receptors, which stimulates tumor cell/monocyte migration, angiogenesis, and lymphangiogenesis via endocrine and paracrine mechanisms. Our results indicate that increased adipocytes in HFD-fed mice play important roles in the recruitment of M2-MΦs in tumor tissues and lymphangiogenesis as well as tumor cell migration. We have also demonstrated that several phytochemicals inhibit solid tumor growth and metastasis. For example, β-caryophyllene (BCP), a natural bicyclic sesquiterpene found in many essential oils inhibits HFD-induced solid tumor growth and metastasis of B16F10 melanoma cells. Dietary BCP reduces adipocytes and M2-MΦs in tumor tissues and macrophages in adipose tissues surrounding the LN in HFD-fed mice. BCP suppresses HFD-induced increases in the levels of various cytokines including MCP-1 and M-CSF in tumor tissues.

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➤Educational background & professional experience

1985-1990	Rutgers University, UMDNJ Medical School / Joint Ph.D.
1990-1994	Harvard Medical School / Post-doc fellow
1995-1996	KRIBB / Foreign invited scientist
1996-present	Chonnam National University / professor
2011-present	National Creative Research Initiatives Center for Nuclear Receptor Signals / Director

➤Research interests

Nuclear receptor mediated regulation of liver diseases

➤Brief list of publications

1. Nat Med. 2014 Apr;20(4):419-24.
2. Diabetes. 2013 Sep;62(9):3093-102
3. Gut. 2013 Jul;62(7):1044-54.
4. Nat Immunol. 2011 Jul 3;12(8):742-51
5. Cell Metab. 2010 Apr 7;11(4):331-9

Orphan nuclear receptor ERRgamma and iron homeostasis

A defensin-like peptide hepcidin is an iron-regulatory hormone contributing to innate immunity and host defense. In response to inflammatory stimuli, hepcidin limits the vital iron, an essential nutrient for invading microorganisms, by reducing iron transfer and release from enterocytes and macrophages. Here, we report that nuclear receptor ERRγ is a novel transcriptional mediator of Salmonella-mediated regulation of hepcidin and iron metabolism, and demonstrate a beneficial impact of the inverse agonist GSK5182. Hepatic ERRγ gene expression was induced by Salmonella-stimulated interleuklin-6 (IL-6) signaling, and led to induction of hepcidin and hypoferremia in mice. Conversely, liver-specific ablation of ERRγ gene expression blocked Salmonella-mediated induction of hepcidin, and normalized the hypoferremia by Salmonella infection. An inverse agonist of ERRγ ameliorated Samonella-mediated hypoferremia through reduction of ERRγ-mediated hepcidin gene expression, and performed a potent antimicrobial function for the intracellular growth of Salmonella. Control of iron metabolism by an ERRγ-specific inverse agonist could be a novel therapeutic approach to host defense against intracellular bacteria.

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➤Educational background & professional experience

1987-1993	Yonsei University College of Medicine / M.D.
1999-2002	Yonsei University Graduate School of Medicine / M.Sc.
1997-2001	Internal Medicine, Severance Hospital / Resident
2001-2002	Yonsei University College of Medicine / Clinical Fellow(endocrinology)
2013-present	Endocrinology, Ajou University School of Medicine / professor

➤Research interests

Epidemiology of diabetes, obesity and metabolic syndrome

➤Brief list of publications

1. Jeon JY, Kim DJ, Ko SH, Kwon HS, Lim S, Choi SH, Kim CS, An JH, Kim NH, Won JC, Kim JH, Cha BY, Song KH; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Current Status of Glycemic Control of Patients with Diabetes in Korea: The Fifth Korea National Health and Nutrition Examination Survey. Diabetes Metab J. 2014 Jun;38(3):197-203.
2. Park YM, Ko SH, Lee JM, Kim DJ, Kim DJ, Han K, Bower JK, Ahn YB; Committee of Clinical Practice Guideline, Korean Diabetes Association. Glycaemic and haemoglobin A1c thresholds for detecting diabetic retinopathy: The fifth Korea National Health and Nutrition Examination Survey (2011). Diabetes Res Clin Pract. 2014 Jun;104(3):435-42.
3. Choi YJ, Kim DJ, Lee Y, Chung YS. Insulin is inversely associated with bone mass, especially in the insulin-resistant population: the Korea and U.S. National Health and Nutrition Examination Surveys. J Clin Endocrinol Metab. 2014 Apr;99(4):1433-41.
4. Jeon JY, Ko SH, Kwon HS, Kim NH, Kim JH, Kim CS, Song KH, Won JC, Lim S, Choi SH, Jang MJ, Kim Y, Oh K, Kim DJ, Cha BY; Taskforce Team of Diabetes Fact Sheet of the Korean Diabetes Association. Prevalence of Diabetes and Prediabetes according to Fasting Plasma Glucose and HbA1c. Diabetes Metab J. 2013 Oct;37(5):349-57.
5. Lee YH, Bang H, Kim HC, Kim HM, Park SW, Kim DJ. A Simple Screening Score for Diabetes for the Korean Population: Development, validation, and comparison with other scores. Diabetes Care. 2012 Aug;35(8):1723-30.

Policies for enhancing insurance coverage for diabetes care - focus on diabetes supplies

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Health insurance policy of the government

▌Panel Discussion ▐

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➤**Educational background & professional experience**

1981	MS University Baroda, India / MD
1981-1994	Pharma Industry / Medical Director
1994-2000	Novo Nordisk, India / Managing Director
2000-2006	Novo Nordisk A/S / Vice President
2006-2013	World Diabetes Foundation / Managing Director

➤**Research interests**

Diabetes, Clinical research, Public Health

➤**Brief list of publications**

1. The double burden of diabetes and tuberculosis - Public health implications. Kapur A, Harries AD. Diabetes Res Clin Pract. 2013 Jan 7. pii: S0168-8227(12)00497-4. doi: 10.1016/j.diabres.2012.12.001. [Epub ahead of print]
2. Effect of diabetes on treatment outcome of smear-positive pulmonary tuberculosis--a report from South India. Viswanathan V, Vigneswari A, Selvan K, Satyavani K, Rajeswari R, Kapur A. J Diabetes Complications. 2014 Mar-Apr;28(2):162-5. doi: 10.1016/j.jdiacomp.2013.12.003. Epub 2013 Dec 24.
3. Prevalence of type 2 diabetes among newly detected pulmonary tuberculosis patients in China: a community based cohort study. Wang Q, Ma A, Han X, Zhao S, Cai J, Ma Y, Zhao J, Wang Y, Dong H, Zhao Z, Wei L, Yu T, Chen P, Schouten EG, Kok FJ, Kapur A. PLoS One. 2013 Dec 18;8(12):e82660. doi: 10.1371/journal.pone.0082660. eCollection 2013.
4. The impact of diabetes on tuberculosis treatment outcomes: a systematic review. Baker MA, Harries AD, Jeon CY, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera SD, Murray MB. BMC Med. 2011 Jul 1;9:81. doi: 10.1186/1741-7015-9-81.
5. Bi-directional screening for tuberculosis and diabetes: a systematic review. Jeon CY, Harries AD, Baker MA, Hart JE, Kapur A, Lönnroth K, Ottmani SE, Goonesekera S, Murray MB. Trop Med Int Health. 2010 Nov;15(11):1300-14. doi: 10.1111/j.1365-3156.2010.02632.x. Epub 2010 Sep 24. Review.

The public health relevance of the deadly duet of diabetes and tuberculosis

Diabetes mellitus (DM) and tuberculosis (TB) have existed for thousands of years. In the past TB accounted for a large number of deaths amongst people with diabetes. The incidence of TB is declining slowly but it still remains a big problem in many large and populous, low and middle income countries. On the other hand the burden of diabetes is increasing very rapidly, particularly in the very same countries where TB is endemic. Undiagnosed, inadequately treated and poorly controlled diabetes mellitus is a much bigger threat to TB prevention and control in high TB burden countries than previously realized. The intersecting double burden is therefore ominous particularly as several recent studies and systematic reviews have indicated that DM increases the risk of TB disease, complicates the clinical presentation and results in poor treatment outcomes. People working in both TB and DM are either unaware of the association or do not play enough heed to the sound of this deadly duet. Continuing to ignore or underplay this association may undermine and undo decades of painstaking gains in TB control and prove disastrous both in terms of health and economics. To address the double burden, in 2011, WHO and the International Union against Tuberculosis and Lung Disease (The Union) with support from the World Diabetes Foundation launched a collaborative framework for the care and control of diabetes and tuberculosis, to encourage collaborative research and implement bidirectional screening of the two diseases in routine settings. This lecture will present some of the new evidence for the association between TB and DM, and will discuss issues with regard to clinical presentation and outcomes and present the arguments to support routine bidirectional screening based on field studies; as well as present strategies and challenges for implementing the framework. Finally it will present suggestions on how diabetes care delivery may benefit from the lessons of the public health principles used in TBDOTS approach to improve structured diabetes care delivery.

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➤Educational background & professional experience

1990-1996	Chung-Ang University / Student
1997-2001	Chung-Ang University Hospital / Resident
2004-2006	Samsung Medical Center / Research Fellow
2007-2009	Chung-Ang University Hospital / Assistant Professor
2009-present	Chung-Ang University Hospital / Associated Professor

➤Research interests

Tuberculosis, Non-tuberculous mycobacterial lung disease

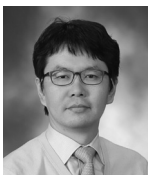
➤Brief list of publications

1. The effect of diabetic control status on the clinical features of pulmonary tuberculosis. Park SW, Shin JW, Kim JY, Park IW, Choi BW, Choi JC, Kim YS. European Journal of Clinical Microbiology & Infectious Diseases. 2012:31(7):1305-10
2. Risk factors for development of paradoxical response during anti-tuberculosis treatment in HIV-negative patients with pleural tuberculosis. Jung JW, Shin JW, Kim JY, Park IW, Choi BW, Seo JS, Choi JC. Tohoku J Exp Med. 2011;223(3):199-204.
3. The difference in clinical presentations between healthcare-associated and community-acquired pneumonia in university-affiliated hospital in Korea. Jeon EJ, Cho SG, Shin JW, Kim JY, Park IW, Choi BW, Choi JC. Yonsei Med J. 2011 Mar;52(2):282-7.
4. HRCT and whole-blood interferon-gamma assay for the rapid diagnosis of smear-negative pulmonary tuberculosis. Lee HM, Shin JW, Kim JY, Park IW, Choi BW, Choi JC, Seo JS, Kim CW. Respiration. 2010;79(6):454-60. Epub 2010 Jan 21.
5. The effect of previous tuberculin skin test on the follow-up examination of whole-blood interferon-gamma assay in the screening for latent tuberculosis infection. Choi JC, Shin JW, Kim JY, Park IW, Choi BW, Lee MK. Chest. 2008 Jun;133(6):1415-20. Epub 2008 Mar 17.

The effect of diabetes on tuberculosis

Tuberculosis (TB) and diabetes mellitus (DM) are major global health problem. Although the incidence of tuberculosis has declined in high-income countries, it remains still high in South Korea. At the same time, the prevalence of DM is increasing. Therefore, it is important to know about the relationship between DM and TB.

There is growing evidence that DM is an important risk factor for TB and might affect disease presentation and treatment response. A systematic review found a relative risk of 3.1 for TB disease among persons with DM compared with persons who did not have DM. In addition, diabetic populations show more severe presentations than non-diabetic populations. Several studies evaluated the manifestations and outcomes of TB in diabetic populations. And, they found that diabetic populations have higher smear positive rate, more cavities and higher rates of treatment failure than non-diabetics. Impairment of host defense plays an important role for these presentations and treatment outcome in diabetic patients. It is also reported that the severity of tuberculosis depends on the degree of hyperglycemia. Therefore, glucose control is also important for the TB control.



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➤Educational background & professional experience

1999	Pusan National University / M.D.
2000-2004	Pusan National University Hospital, Department of Internal Medicine / Internal Medicine, resident
2008	Pusan National University Hospital, Department of Internal Medicine / Clinical fellow
2009-present	Pusan National University Hospital, Department of Internal Medicine / Assistant professor

➤Research interests

Diabetic complication

➤Brief list of publications

1. Soluble α-klotho as a novel biomarker in the early stage of nephropathy in patients with type 2 diabetes. PLoS One. 2014 [In press]
2. Nonalbuminuric proteinuria as a biomarker for tubular damage in early development of nephropathy with type 2 diabetic patients. Diabetes/Metabolism Research and Reviews. 2014 Mar [Epub ahead print]
3. Duration of diabetes and effectiveness of insulin in the management of insulin-naïve Korean patients uncontrolled on oral antidiabetic drugs: a sub-analysis of the MOdaliTy of Insulin treatment eValuation (MOTIV) registry results. Acta Diabetologica. 2014 Feb [Epub ahead print]
4. Prevalence and clinical implications of painful diabetic peripheral neuropathy in type 2 diabetes: Results from a nationwide hospital-based study of diabetic neuropathy in Korea. Diabetes Res Clin Pract. 2014;103:522-529.
5. Urinary cystatin C and tubular proteinuria predict progression of diabetic nephropathy. Diabetes Care. 2013;36:656-661.

DM & tuberculosis - how to control and care

Tuberculosis (TB) is a representative communicable disease that is usually concentrated in low-income countries and is linked to poor sanitation, nutrition, and access to health services. Diabetes is a representative non-communicable disease that is generally more concentrated in high-income or developed countries and is related to the overnutrition and low activity that are associated with industrialization. Ironically, the comorbidity of these two diseases is common in both low-income and high-income countries. An increasing amount of evidence indicates that diabetes and TB often manifest together and complicate each other on many levels. Glycemic control in diabetic patients may affect one's risk for TB as well as disease severity and mortality. Similarly, infections such as TB can worsen glycemic control in known diabetic patients. Although it is unclear whether TB infection leads to diabetes in patients not previously known to be diabetic, numerous studies have demonstrated that TB patients have a higher rate of abnormal glucose tolerance than community control groups. Moreover, TB patients experience nutritional and pharmacological issues during the co-management of diabetes and TB. Because TB and diabetes are significantly influenced by social and economic conditions, the comorbidity of these disorders is not merely an individual issue but a public health issue as well. The bidirectional screening for TB in diabetic patients or for diabetes in TB patients could play an indispensable role in the routine health care system. Recently, the World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (The Union) have recognized the need for international guidelines regarding the co-management and control of TB and diabetes. As it is likely that the comorbidity of these diseases will increase in the coming future, a provisional collaborative framework is necessary for the care and control of both TB and diabetes.

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➤Educational background & professional experience

1993	Hanyang University / MD
1997	Seoul National University, School of Public Health / MPH
2002	Hanyang University / PhD
2004-2005	Division of HIV and TB Control, Korea Centers for Disease Control and Prevention / Vice Director
2005-2010	Division of VPD Control and NIP, Korea Centers for Disease Control and Prevention / Director
2010-2013	WHO/HQ/HSE, Geneva / Medical officer

➤Research interests

Epidemiology, Infectious diseases, Vaccine preventable diseases, HIV/AIDS, Tuberculosis

➤Brief list of publications

1. The comparative evaluation of expanded national immunization policies in Korea using ananalytic hierarchy process
2. Estimation of the incidence of sudden infant death syndrome in Korea: using the capture-recapture method
3. Sero-epidemiology of measles and mumps in Korea: impact of the catch-up campaign on measles immunity
4. Measurement Characteristic of anal cytology, histopathology and high-resolution anoscopic visual impression in an anal dysplasia screening program

Tuberculosis and latent tuberculosis infection control programme in Korea

The Government of Korea (GOK), through the Korea Center for Disease Control and Prevention (KCDC) has developed a 5 Year Plan for TB Elimination for the Republic of Korea(hereafter 5 year plan) in 2013 to address the stagnation in the decline of TB incidence in the country. The 5 year plan states as its goals to achieve by 2020 an incidence of TB less than 50 per 100,000 population, a treatment success rate of 95% and a TB mortality rate of less than 2.5/100,000.

The GOK intends to substantially scale up its TB control efforts to meet the ambitious goals. The TB incidence rate (all forms) in the Republic of Korea is still high, estimated 108 per 100,000 in 2012, and some 2,466 TB deaths in 2012. These are the highest figures among OECD countries. MDR-TB is estimated at 2.6% of new cases.

The strategic plan to achieve the 5 year plan aims to prevent TB incidence and infection through management of cases with TB and Latent TB Infection (LTBI), establish an integrated TB information system to monitor and evaluate the TB management and refine the basic infrastructure for a successful implementation of the Plan for TB elimination.

Through the international consultation held in 2011, experts from WHO, US CDC and Korea recommended the following action plan:

(1) Expansion of contact investigation and LTBI treatment
(2) Expansion of private-public cooperation projects
(3) Establishment of a TB management system for vulnerable groups including homeless people
(4) Improvement of diagnostic system for early case detection
(5) Research and development for TB management
(6) Private-government development of TB standard guidelines
(7) Support for improving the efficiency of treatment for intractable MDR-TB patients
(8) Establishment of an integrated TB information system for monitoring and evaluating the TB programme, including patient management.

From 2011, the GOK scaled up the programmes and strengthened the infrastructures, special focus on private-public collaborative TB case management. In 2013, the incidence of TB decreased 9% compare than 2012, and it would be resulted from the intensified control programme from 2011.

To expand the contact investigation and LTBI treatment, in 2013, a total of 1,200 contact investigations performed. 769(64%) investigations performed at schools and other educational institutions, 201(16.7%) investigations performed at shelters or prisons, 127(10.6%) investigations performed at military settings. LTBI rate among middle school students, high school students were 5.9%, 6.1% respectively.

To achieve the 5 year plan states as its goals to achieve by 2020 an incidence of TB less than 50 per 100,000 population, a more comprehensive control and management programme for latent tuberculosis infection will be essential.

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➤Educational background & professional experience

1998-2002	Biochemistry, Kangwon National University, Republic of Korea / Ph. D.
2002-2007	National Institutes of Health, USA / Postdoctoral fellow
2007-2009	Nuclear Receptor Biology Section, Clinical Endocrinology Branch NIDDK, NIH, USA / Research fellow
2009-2012	Department of Medicine, University of California, San Diego, USA / Assistant Project Scientist
2012-present	Korea Basic Science Institute (KBSI) / Senior Researcher

➤Research interests

1. Epigenetic modification
2. non-alcoholic fatty liver disease (NAFLD)
3. Anti-obesity
4. brown adipocyte

➤Brief list of publications

1. Ji-Eun Lee, Chaochen Wang, Shiliyang Xu, Young-Wook Cho, Lifeng Wang, Xuesong Feng, Anne Baldridge, Vittorio Sartorelli, Lenan Zhuang, Weiqun Peng, Kai Ge (2013) H3K4 mono- and di-methyltransferase MLL4 is required for enhancer activation during cell differentiation. eLife 2:e0150301 (eLife will not promote the Impact Factor)
2. Jeremy A. Daniel, Margarida Almeida Santos, Zhibin Wang, ChongzhiZang, Kristopher R. Schwab, Mila Jankovic, Darius Filsuf, Hua-Tang Chen, Anna Gazumyan, Arito Yamane, Young-Wook Cho, Hong-Wei Sun, Kai Ge, WeiqunPeng, Michel C. Nussenzweig, Rafael Casellas, Gregory R. Dressler, Keji Zhao, André Nussenzweig (2010) PTIP promotes chromatin changes critical for immunoglobulin class switch recombination. Science 329, 917-923
3. Young-Wook Cho, SunHwa Hong, Qihuang Jin, Lifeng Wang, Ji-Eun Lee, Oksana Gavrilova and Kai Ge (2009) Histone methylation regulator PTIP is required for PPARγ and C/EBPα expression and adipogenesis. Cell Metabolism 10, 27-39.
4. Sunhwa Hong*, Young-Wook Cho*, Li-Rong Yu, Hong Yu, Timothy D. Veenstraand Kai Ge (2007) Identification of JmjC domain-containing UTX and JMJD3 as histone H3 lysine 27 demethylases. Proc Natl Acad Sci USA104, 18439-18444.
5. Young-Wook Cho, Teresa Hong, SunHwa Hong, Hong Guo, Hong Yu, Doyeob Kim, Tad Guszczynski, Gregory R. Dressler, Terry D. Copeland, Markus Kalkum and Kai Ge (2007) PTIP associates with MLL3- and MLL4-containing histone H3 lysine 4 methyltransferase complex. Journal of Biological Chemistry 282, 20395 - 20406. (JBC Paper of the Week)

Epigenetic regulation of adipogenesis by MLL3/MLL4 complex

Adipogenesis, or the development of fat cells from preadipocytes, has been one of the most intensely studied models of cellular differentiation. Histone methylation is implicated in both gene activation and repression, depending on the specific lysine residue that gets methylated. We showed the histone H3K4 and H3K27 modifying complex is required for adipogenesis. MLL3/MLL4 complex is composed of 10 subunits which are common subunits (ASH2L, RBBP5, WDR5, DPY30), unique subunits (NCOA6 and C16ORF53 named PA1), Set-domain-containing histone methyltransferases (MLL3 and MLL4), and substoichiometric amount of JmjC domain-containing histone H3K27 demethylase UTX (PNAS, 2007) in a Set1-like complex that carried robust histone H3 lysine-4 (H3K4) methyltransferase activity. Among the epigenetic modifications, methylation at histone H3 lysine 27 is associated with gene repression, while di- and tri-methylations at histone H3 lysine 4 are associated with gene activation. In this complex, two histone H3 K4 methyltransferases (MLL3 and MLL4) and a histone demethylase (UTX) cooperate to activate gene expression because they are in the same complex. It is called "histone crosstalk". PTIP deletion in MEFs (mouse embryonic fibroblasts) leads to marked decreases of PPARγ expression and PPARγ -stimulated C/EBPα expression. PTIP is essential for induction of PPARγ and C/EBPα expression during preadipocyte differentiation. Deletion of PTIP impairs the enrichment of H3K4 trimethylation and RNA polymerase II on PPARγ and C/EBP α promoters. Rescue of the adipogenesis defect in PTIP-/- MEFs requires coexpression of PPARγ and C/EBPα. Finally, deletion of PTIP in brown adipose tissue significantly reduces tissue weight and the KO mice were cold intolerant. Thus, by regulating PPARγ and C/EBPα expression, PTIP plays a critical role in adipogenesis (Cell Metabolism, 2009).

Further studies are expected to shed light on the process of adipogenesis, as well as obesity by elucidating the molecular mechanisms.

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➤Educational background & professional experience

1976-1980	Seoul National University, Electronic Engineering / B.S.
1980-1982	Seoul National University, Computer Engineering / M.S.
1983-1987	University of Southern California, Physiology / Ph.D.
1989-1990	Washington University, St. Louis, Medicine / Postdoc
1990-present	University of Southern California, Physiology / Associate Professor

➤Research interests

Mechanisms of insulin resistance, pathogenesis of obesity and type 2 diabetes, roles of individual free fatty acids in energy homeostasis, regulation of renal potassium excretion, role of gene expression in metabolic regulation and drug effects.

➤Brief list of publications

1. YT Oh, J Kim, I Kang, JH Youn. Regulation of hypothalamic-pituitary-adrenal axis by circulating free fatty acids in male Wistar rats: role of individual free fatty acids. Endocrinology 155:923-931, 2014
2. JH Youn, AA McDonough. Need to quickly excrete K+? Turn off NCC. Kidney International 83:779-782, 2013
3. YT Oh, KS Oh, I Kang, JH Youn. A fall in plasma free fatty acid (FFA) level activates the hypothalamic-pituitary- adrenal axis independent of plasma glucose: evidence for brain sensing of circulating FFA. Endocrinology 153:3587-92, 2012
4. I Kang, SW Kim, JH Youn. Effects of nicotinic acid on gene expression: potential mechanisms and implications for wanted and unwanted effects of the lipid-lowering drug. J Clin Endocr Metab 96: 3048-3055, 2011
5. YT Oh, KS Oh, YM Choi, A Jokiaho, CM Donovan, S Choi, I Kang, JH Youn. Continuous 24-h nicotinic acid infusion in rats causes FFA rebound and insulin resistance by altering gene expression and basal lipolysis in adipose tissue. Am J Physiol Endocrinol Metab. 300:E1012-21, 2011

Distinct roles of circulating palmitate and oleate in energy homeostasis

Our recent study showed that a fall in plasma free fatty acid (FFA) level activates the hypothalamic-pituitary-adrenal (HPA) axis to increase plasma adrenocorticotropic hormone (ACTH) and corticosterone levels in rats. Because these hormones increase lipolysis in adipocytes, these responses may serve as a feedback mechanism for the maintenance of plasma FFA levels, consistent with the concept that the brain monitors and controls circulating FFA levels. Interestingly, this regulation appeared to be mediated by palmitate (C16:0), but not by other long-chain fatty acids, such as oleate (C18:1) or linoleate (C18:2). In contrast, our preliminary studies showed oleate-specific effects to reduce food intake in rats, consistent with previous findings that, when injected into the brain, oleate, but not other long-chain FFAs, was sensed by the brain to reduce food intake. Taken together, these data suggest the intriguing possibility that circulating FFAs, particularly oleate and palmitate, may have distinct roles in vivo in energy homeostasis; circulating oleate, which originates largely from food, may signal food intake for the brain to subsequently reduce food intake. In contrast, circulating palmitate, which can be produced from other major fuels, such as glucose and amino acids, may signal the amount of available fuels for the brain to regulate the mobilization of stored fat via the HPA axis. Thus, oleate and palmitate may serve not only as fuels but also as distinct signals for brain control of energy homeostasis, and there may be a "division of labor" between oleate- and palmitate-sensing mechanisms for separate regulation of energy balance (by oleate) and storage/mobilization (by palmitate).

Toshinari Takamura

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➤Educational background & professional experience

1988-1992	Kanazawa University Graduate School of Medical Sciences / MD, PhD
1993-1997	Department of Biochemistry, Tohoku University (Prof. Hiroshi Okamoto) / Special Researcher, Japan Society for the Promotion of Science
2001-2014	Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Sciences / Associate Professor
2014-present	Department of Comprehensive Metabology, Kanazawa University Graduate School of Medical Sciences / Professor
2014-present	Division of Endocrinology and Metabolism, Kanazawa University Hospital / Director

➤Research interests

Endocrinology and metabolism

➤Brief list of publications

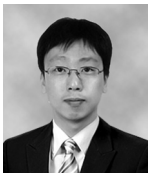
1. Ishikura K, Misu H, Kumazaki M, Takayama H, Matsuzawa-Nagata N, Tajima N, Chikamoto K, Lan F, Ando H, Ota T, Sakurai M, Takeshita Y, Kato K, Fujimura A, Miyamoto K, Saito Y, Kameo S, Okamoto Y, Takuwa Y, Takahashi K, Kidoya H, Takakura N, Kaneko S, Takamura T*. Selenoprotein P as a diabetes-associated hepatokine that impairs angiogenesis by inducing VEGF resistance in vascular endothelial cells. Diabetologia 57:1968-76, 2014
2. Lan F, Misu H, Chikamoto K, Takayama H, Kikuchi A, Mohri K, Takata N, Hayashi H, Matsuzawa-Nagata N, Takeshita Y, Noda H, Matsumoto Y, Ota T, Nagano T, Nakagen M, Miyamoto KI, Takatsuki K, Seo T, Iwayama K, Tokuyama K, Matsugo S, Tang H, Saito Y, Yamagoe S, Kaneko S, Takamura T*. LECT2 functions as a hepatokine that links obesity to skeletal muscle insulin resistance. Diabetes 63:1649-64, 2014
3. Otoda T, Takamura T*, Misu H, Ota T, Murata S, Hayashi H, Takayama H, Kikuchi A, Kanamori T, Shima KR, Lan F, Takeda T, Kurita S, Ishikura K, Kita Y, Iwayama K, Kato KI, Uno M, Takeshita Y, Yamamoto M, Tokuyama K, Iseki S, Tanaka K, Kaneko S. Proteasome Dysfunction Mediates Obesity-Induced Endoplasmic Reticulum Stress and Insulin Resistance in the Liver. Diabetes 62:811-24, 2013
4. Takamura T*, Misu H, Ota T, Kaneko S. Fatty liver as a consequence and cause of insulin resistance: Lessons from type 2 diabetic liver (Review). Endocr J 59:745-63, 2012
5. Misu H, Takamura T*, Takayama H, Hayashi H, Matsuzawa-Nagata N, Kurita S, Ishikura K, Ando H, Takeshita Y, Ota T, Sakurai M, Yamashita T, Mizukoshi E, Yamashita T, Honda M, Miyamoto K, Kubota T, Kubota N, Kadowaki T, Kim HJ, Lee IK, Minokoshi Y, Saito Y, Takahashi K, Yamada Y, Takakura N, Kaneko S. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. Cell Metab 12:483-95, 2010

Remodeling of nutrient homeostasis by obesity-associated proteasome dysfunction in the liver

Chronic endoplasmic reticulum (ER) stress is a major contributor to obesity-induced insulin resistance in the liver. However, the molecular link between obesity and ER stress remains to be identified. Proteasomes are important multicatalytic enzyme complexes that degrade misfolded and oxidized proteins. We have previously reported that the hepatic expression of genes involved in proteasomal degradation pathway including proteasome activator (PA) 28 subunit genes is coordinately up-regulated in people with obesity and type 2 diabetes (T2D) (Obesity 2008).

Here, we report that both mouse models of obesity and diabetes and proteasome activator 28 (PA28)-null mice showed 30-40% reduction in proteasome activity and accumulation of poly-ubiquitinated proteins in the liver. PA28-null mice also showed hepatic steatosis, decreased hepatic insulin signaling, and increased hepatic glucose production. The link between proteasome dysfunction and hepatic insulin resistance involves ER stress leading to hyperactivation of c-Jun N-terminal kinase in the liver. Administration of a chemical chaperon phenylbutyric acid (PBA) partially rescued the phenotypes of PA28-null mice. To confirm part of the results obtained from in vivo experiments, we pretreated rat hepatoma-derived H4IIEC3 cells with bortezomib, a selective inhibitor of the 26S proteasome. Bortezomib causes ER stress and insulin resistance in vitro, responses that are partly blocked by PBA.

Taken together, our data suggest that proteasome dysfunction mediates obesity-induced ER stress, leading to insulin resistance in the liver. Our model partly explains the paradox of 'selective insulin resistance' in the type 2 diabetic liver; insulin signaling is impaired in the gluconeogenic pathway, whereas it is enhanced in the lipid synthesis pathway. Possible cross-talk among protein, glucose and lipid metabolic pathways in the liver and its disruption in obesity will be discussed.



Tae Il Jeon

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➤Educational background & professional experience

2000-2004	Konkuk University, Applied Biology and Chemistry / PhD
2005-2010	University of California Irvine, Molecular Biology and Biochemistry / Postdoctoral Scholar
2010-2011	Sanford-Burnham Medical Research Institute, Metabolic Signaling and Disease Program / Staff Scientist
2011-2012	Korea Food Research Institute / Senior Scientist
2012-present	Chonnam National University, Animal Science / Assistant Professor

➤Research interests

Sterol Regulatory Element Binding Proteins (SREBPs) are master regulators of cellular lipid homeostasis. The research of my laboratory focuses on understanding the mechanistic links between SREBP and hormone- or nutrient-regulated signaling pathway in the control of metabolic homeostasis.

➤Brief list of publications

1. Jeon TI, Esquejo RM, Roqueta-Rivera M, Phelan PE, Moon YA, Govindarajan SS, Esau CC, Osborne TF. An SREBP-responsive microRNA operon contributes to a regulatory loop for intracellular lipid homeostasis. Cell Metabolism 2013, 18(1): 51-61.
2. Jeon TI, Osborne TF. (2012) SREBPs: metabolic integrators in physiology and metabolism. Trends in Endocrinology and Metabolism. 23(2):65-72.
3. Ahn J, Lee H, Jung CH, Jeon TI, Ha TY. MicroRNA-146b promotes adipogenesis by suppressing the SIRT1-FOXO1 cascade. EMBO Mol. Med. 2013, 5(10): 1602-1612.
4. Seo YK*, Jeon TI*, Chong HK, Biesinger J, Xie X, Osborne TF. (2011) Genome-wide localization of SREBP-2 in hepatic chromatin predicts a role in autophagy. Cell Metabolism. 13(4): 367-375. *co-first author
5. Jeon TI, Zhu B, Larson JL, Osborne TF. (2008) SREBP-2 regulates gut peptide secretion through intestinal bitter taste receptor signaling in mice. Journal of Clinical Investigation. 118(11):3693-3700.

New roles of SREBP-2 in lipid metabolism

Genome-wide approaches highlight new functions for sterol regulatory element binding proteins (SREBPs) in connecting lipid metabolism with other cellular processes where lipid pathway flux affects physiologic or pathophysiologic adaptation, such as cancer, steatosis, and innate immunity. Here, I present that a new mechanism for regulation of lipid metabolism that is mediated by (1) the SREBP-2 activation of genes responsible for autophagy that facilitates lipid mobilization and (2) the concerted action of a pair of miRs, miR-182, miR-183, and miR-96 that are expressed from the same SREBP-2 regulated miR locus and each targets a different protein of the multi-step pathway that regulates SREBP function.

Saturday 18 October

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➤Educational background & professional experience

2003-2005	Severance Hospital, Seoul, Korea / Clinical Fellow
2005-2006	Yonsei University College of Medicine, Seoul, Korea / Instructor
2006-2010	Yonsei University College of Medicine, Seoul, Korea / Assistant Prof.
2009-2011	Harvard Medical School, Beth Israel Deaconess Medical Center, Boston MA / Visiting Professor
2010-present	Yonsei University College of Medicine, Seoul, Korea / Associate Prof.

➤Research interests

Posttransplantation diabetes (New onset diabetes after transplantation)
Pancreatic zinc transporter
Metabolic effect of HMG CoA reductase inhibitors
Type 2 diabetes genetics and pharmacogenetics

➤Brief list of publications

1. HMG CoA Reductase Inhibitor Treatment Induces Dysglycemia in Renal Allograft Patients. Transplantation 97(4):419-425, 2014
2. Statin Therapy is associated with Development of New Onset Diabetes after Transplantation in Liver Recipients with High Fasting Plasma Glucose. Liver Transplantation 20(5):557-563, 2014
3. Variants of the Adiponectin and Adiponectin Receptor 1 Genes and Posttransplantation Diabetes Mellitus in Renal Allograft Recipients. JCEM 97:E129-E135, 2012
4. Low-risk ZnT-8 allele (W325) for PTDM is protective against cyclosporin A-induced impairment of Beta-cell insulin secretion capacity. Pharmacogenomics J 11:191-198, 2011
5. Association of Common type 2 Diabetes Risk Gene Variants and PTDM in Renal Allograft Recipients in Korea. Transplantation 88:693-698, 2009

DPP4 inhibitor, linagliptin, to simplify treatment for a broad range of T2DM patients (2014 ADA highlight)

Linagliptin is highly selective, xanthine-based DPP4 inhibitor. Linagliptin, given in a once-daily, single dose 5 mg regimen, is excreted mainly by non-renal pathways and any dose adjustment is not needed. This pharmacological profile suggests that linagliptin might be particularly useful for treatment for the broad range of T2DM patients. We explored oral glucose-lowering combination therapy in newly diagnosed (≤ 12 months) T2DM patients with marked hyperglycemia (n = 316) utilizing prespecified subgroup analyses from a randomized double-blind study of initial combination of linagliptin + metformin (Lina + Met) vs. linagliptin. Baseline mean ± SD age and HbA1c were 48.8 ± 11.0 years and 9.8 ± 1.1%, respectively. The primary endpoint was HbA1c change from baseline to week 24. Mean ± SE HbA1c reduction was -3.4 ± 0.2% vs. -2.5 ± 0.2% with Lina + Met and LINA, respectively, in patients with baseline HbA1c ≥ 9.5%, and -2.1 ± 0.2% vs. -1.4 ± 0.2% in patients with baseline HbA1c 〈 9.5%. Hypoglycemia was rare with no severe episodes. We pooled data from a global clinical trials program to further assess the safety, focusing on hypoglycemia of linagliptin. Adults with T2DM aged ≥ 65 years who participated in 11 randomized, placebo-controlled, Ph3 trials were included. Overall, 1489 patients were treated (LINA, n = 948; PBO, n = 541). Mean ± SD age was 70.9 ± 4.6 y. Incidence of confirmed hypoglycemia was 26.3% in the LINA group and 34.0% in the PBO group (RR: 0.77 [95% CI: 0.66, 0.91; p 〈 0.05]). Overall, incidence of severe hypoglycemia was low in both groups. Linagliptin was previously evaluated in two randomized 52-week clinical trials of T2DM patients with moderate to severe renal impairment. Data from these trials were pooled to evaluate long-term efficacy and safety of LINA. Efficacy was assessed (n = 359; LINA, 178; PBO/GLM, 181) by change in HbA1c from baseline to 12 weeks. At baseline, mean ± SD HbA1c was 8.1 ± 0.9% in both treatment groups. PBO-adjusted change from baseline in HbA1c at 12 weeks was −0.47 (P 〈 0.0001). Incidences of AEs, drug-related AEs and Investigator-defined hypoglycemia rates were similar between treatment groups.

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➤**Educational background & professional experience**

1992	College of Medicine, Ewha Womens University / B.S
2000	Ajou University, College of Medicine / Internal Medicine, M.S
2003	Ajou University, College of Medicine / Preventive Medicine, Ph.D
1992-1997	Hallym University, Kangnam Sacred Heart Hospital / Internship & Residency
1997-1998	Department of Internal Medicine, Sejong Hospital / Faculty
1998-2000	Ajou University School of Medicine / Clinical research fellow
2000-2002	Pochon CHA University, College of Medicine / Full-time Lecturer
2002-present	Hallym University, Kangnam Sacred Heart Hospital / Associate Professor

➤**Research interests**

1. Molecular signal pathway and metabolic changes in diabetic heart disease
2. Association between inflammatory or anti-inflammatory cytokines and insulin sensitivity

➤**Brief list of publications**

1. Ohn JH, Kwon IH, Park JR, Ryu OH, Lee SJ, Kim DM, Ihm SH, Choi MG, Yoo HJ, Hong EG. Unprotected daily sun exposure is differently associated with central adiposity and beta-cell dysfunction by gender: The Korean national health and nutrition examination survey (KNHANES) V. Environmental Research 13: 253-259, 2014
2. Hong EG, Kim BW, Jung DY, Lee EJ, Yu T, Da Silva WS, Friedline RH, Russell K, Larsen PR, Bianco AC, Kim JK: Cardiac Expression of Human Type 2 Iodothyronine Deiodinase Increases Glucose Metabolism and Protects Against Doxorubicin-Induced Cardiac Dysfunction in Male Mice. Endocrinology 154:3937-3946, 2013
3. Yew NS, Zhao H, Hong EG, Wu IH, Przybylska M, Siegel C, Shayman JA, Arbeeny CM, Kim JK, Jiang C, Cheng SH: Increased hepatic insulin action in diet-induced obese mice following inhibition of glucosylceramide synthase. PLoS One 5(6): e11239, 2010
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Metabolic karma - the essential solution in T2DM

Recently the concept of "Metabolic Karma" was introduced in 2014 ADA. This refers to the legacy effect of UKPDS which proved the correlation between early glycemic control and prevention of diabetes complications later in life. Since the landmark study, the early glycemic control has been standard of care in type 2 diabetes management. The updated KDA guideline as well as ADA recommends physicians to consider early combination therapy in order to reduce the time diabetes patients are exposed to hyperglycemia.

In achieving such intensive treatment goal, sulfonylurea (SU) is one of the most cost-effective treatment options in the market. Glimepiride, the 3rd generation SU, has distinguished itself as more intense and fast glucose lowering agent especially when added-on to other treatment regimen. The efficacy of glimepiride in lowering HbA1c level as combination therapy will be addressed.

In general, treatment with SU comes with common risk of hypoglycemia and weight gain. This may be true for general SUs but glimepiride has relatively safer profile: the weight gain is rather neutral and the danger of hypoglycemia is much improved in this 3rd generation SU. Also, due to SU's mechanism of action, there has been contemplation about SU and its negative influence on pancreatic beta-cells. Various clinical data will be addressed which defeat this assumption; beta-cell function decline over the course of type 2 diabetes as part of the natural disease progression and this is shown in not only SU but also in other treatment groups.

Overall, glimepiride can offer the fast and intense glucose control in diabetes patients when added on to early combination therapy regimen. In addition, unlike the new classes of treatment options, safety profile has been proved.

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➤Educational background & professional experience

2001	The Catholic University of Korea / M.D.
2006-2009	The Catholic University of Korea, Division of Endocrinology and Metabolism / Research fellow
2009-present	The Catholic University of Korea, Division of Endocrinology and Metabolism / Assistant professor

➤Research interests

Diabetes mellitus, Obesity

➤Brief list of publications

1. Kim MK, Han K, Kwon HS, Song KH, Yim HW, Lee WC, Park YM. Normal-weight obesity in Korean adults. Clin Endocrinol (Oxf). 2014 Feb;80(2):214-20.
2. Kim MK, Lee JW, Baek KH, Song KH, Kwon HS, Oh KW, Jang EH, Kang MI, Lee KW. Endocrinopathies in transfusion-associated iron overload. Clin Endocrinol (Oxf). 2013 Feb;78(2):271-7.
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Cognitive impairment in patients with diabetes mellitus

Several longitudinal epidemiological studies over the past two decades have linked diabetes mellitus, particularly type 2 diabetes mellitus, with an increased risk of cognitive impairment and dementia. However, there has been no consensus in regards to the incidence of all type dementia, Alzheimer's disease and vascular dementia in diabetes mellitus as compared with the general population. The recent meta-analysis of 28 observational studies showed a 73% increased risk of all type dementia, 56% increase in Alzheimer's disease and 127% increase in vascular dementia in patients with history of diabetes as compared with non-diabetic people.

I will present my topic focusing on the association and postulated mechanisms between diabetes mellitus and dementia.

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➤**Educational background & professional experience**

1986	Seoul National University, Neurology / M.D.
1989-1992	Seoul National University, Neurology / Residency
1998-1999	University of California, San Diego, Neurology / Clinical research associate
2007-present	University of Ulsan, Neurology / Professor

➤**Research interests**

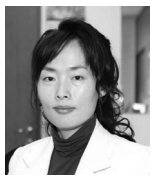
Alzheimer's disease & Vascular dementia

➤**Brief list of publications**

1. Jee Hoon Roh, Jae-Hong Lee. Recent updates on subcortical ischemic vascular dementia. JoS 2014:16(1):18-26.
2. Lee JH, Kim SH, Kim GH, Seo SW, Park HK, Oh SJ, Kim JS, Cheong HK, Na DL. Identification of pure subcortical vascular dementia using 11C-Pittsburgh compound B. Neurology 2011;77(1):18-25.
3. Lee JH, Sevigny J. Effects of body weight on tolerability of rivastigmine transdermal patch: A post-hoc analysis of a double-blind trial in patients with Alzheimer disease. Alzheimer Dis Assoc Disord 2011;25(1):58-62.
4. Lee JH, Olichney JM, Hansen LA, Hofstetter CR, Thal LJ: Small concomitant vascular lesions do not influence rates of cognitive decline in patients with Alzheimer disease. Arch Neurol 2000;57(10):1474-9.

Diabetes and Alzheimer's disease

Diabetes carries an increased risk of cognitive impairment and dementia. Late-onset Alzheimer's disease is a heterogeneous disorder resulting from the cumulative perturbation of multiple pathways. Type 2 diabetes is associated with global brain atrophy and an increased burden of cerebral small-vessel disease evidenced by brain MRI. Brain imaging studies show both degenerative and vascular brain damage which develops slowly over the course of many years. A cluster of interconnected factors, including hyperglycemia, dyslipidemia, and insulin resistance are considered major contributing mechanisms. Vascular damage is a key underlying process. The vascular unit dysfunction resulting from endothelial distubance and release of inflammatory mediators contributes to neuronal degeneration by inducing vascular-derived insults in Alzheimer's disease. Faulty clearance of the Abeta protein across the blood-brain-barrier determine Abeta retention in the brain, causing the promotion of cerebral amyloidosis. Glucose-mediated processes and other metabolic disturbances may also play a role. Oligomerized amylin which is produced in pancreatic islets in obese and insulin-resistant patients has been shown to accumulate in the cerebrovascular system and brain parenchyma of diabetic patients, serving as an another link between diabetes and Alzheimer's disease. Management of vascular risk factors and optimization of glycemic control could have therapeutic benefit. Alterations in brain insulin metabolism has recently gained much interest as a pathophysiologic factor underlying this neurodegenerative disorder. Improving central nervous system insulin signaling via intranasal insulin or insulin sensitizers could represent an effective strategy to prevent or treat Alzheimer's disease. A better understanding of the underlying mechanisms is necessary to establish interventions that will improve long-term cognitive outcomes for patients with type 2 diabetes.



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➤Educational background & professional experience

1987-1993	Yonsei University College of Medicine, Seoul, Korea / M.D
1994-1998	Dept. Neurology, Yonsei University Medical Center, Seoul / Residency
1997-2001	Dept. Biochemistry and Molecular Biology, Yonsei University Graduate School, Seoul / Ph.D.
2006-2008	Dept. Neuroscience, UCSD, USA / Postdoctoral Scholar
2002-present	Dept. Neurology, Soonchunhyang University Bucheon Hospital, Bucheon / Instructor through Professor

➤Research interests

Molecular mechanism Alzheimer's disease
Alzheimer's disease biomarkers

➤Brief list of publications

1. Jung HJ, Kim Y-J, Eggert S, Chung KC, Choi KS, Park SA. Age-dependent increases in tau phosphorylation in the brains of type 2 diabetic rats correlate with a reduced expression of p62. Exp Neurol 2013 Oct; 248: 441-450
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3. Woo JA, Jung AR, Lakshmana MK, Bedrossian A, Lim Y, Bu JH, Park SA, Koo EH, Mook0Jung I, Kang DE. Pivotal role of the RanBP9-cofilin pathway in Aβ-induced apoptosis and neurodegeneration. Cell Death Differ 2012;19(9):1413-1423.
4. HJ Jung; SS Park; JO Mok; TK Lee; CS Park, SA Park. Increased expression of three-repeat isoforms of tau contribute to tau pathology in a rat model of chronic type 2 diabetes. Exp Neurol. 2011;228:232-241.
5. SA Park. Pathogenic Mechanism Linking Type-2 Diabetes and Alzheimer's Disease: Evidence from Animal Models. J Clin Neurol 2011;7:10-18

Novel mechanism of age-dependent pathologic tau accumulations in type 2 diabetes

Tau pathology in brain is related to various neurodegenerative disorders including Alzheimer's disease (AD). The increase of tau phosphorylation is one of the most consistently identified AD-related pathology in diabetic brains. Alterations in kinase and phosphatase activities due to impaired insulin signaling have been demonstrated to be the main underlying mechanism. However, we recently identified the novel mechanism of increased levels of pathologic tau proteins in the brain of chronic type 2 diabetic rats. Increased tau phosphorylations at AD-related sites were accompanied by the loss of synaptic proteins. Although there was a significant decrease in protein phosphatase 2 activities in brain of aged rats, it was not enough to explain the extent of tau increase. Interestingly, accumulated tau proteins were identified highly polyubiquitinated in neurons. Despite of no significant alterations in autophagic pathway, the marked decline in p62 expression was identified with age. Accordingly, the level of p62 mRNA was also severely diminished. Taken together, these findings suggest that the decreased expression of p62 was intimately related with increased pathologic tau accumulations in chronic type 2 diabetic rats.

In this talk I will present the related data and discuss about its possible therapeutic applications.

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➤Educational background & professional experience

1982-1988	Yonsei University College of Medicine / M.D.
1993-1998	Yonsei University College of Medicine, Department of Internal Medicine / M.S., PhD., Instructor
1998-2000	University of Californis at San Diego, VA Hospital / Post-doc researcher
2000-2008	Yonsei University College of Medicine, Department of Internal Medicine / Assistant/Associate Professor
2009-present	Yonsei University College of Medicine, Department of Internal Medicine / Professor

➤Research interests

Diabetes Mellitus, Insulin resistance, Energy Metabolism, Regulation of PPARs, Thiazolidinediones

➤Brief list of publications

1. Moon JH, Kim HJ, Kim HM, Yang AH, Lee BW, Kang ES, Lee HC, Cha BS: The effect of rosiglitazone on LRP1 expression and amyloid β uptake in human brain microvascular endothelial cells: a possible role of low-dose thiazolidinedione for dementia treatment. Int J Neuropsychopharm 15:135-142, 2012.
2. Moon JH, Kim HJ, Kim HM, Yang AH, Lee BW, Kang ES, Lee HC, Cha BS: Upregulation of hepatic LRP1 by rosiglitazone: a possible novel mechanism of the beneficial effect of thiazolidinediones on atherogenic dyslipidemia. J Mol Endocrinol 49:165-174, 2012.
3. Moon JH, Kim HJ, Kim HM, Choi SH, Lim S, Park YJ, Jang HC, Cha BS: Decreased expression of hepatic low-density lipoprotein related protein 1 in hypothyroidism: a novel mechanism of atherogenic dyslipidemia in hypothyroidism. Thyroid 23:1057-1065, 2013.
4. Kang SB, Kim HM, Kim HJ, Seok H, Huh JH, Lee BW, Kang EK, Lee HC, Cha BS: Rosiglitazone attenuates casein-induced hepatic endoplasmic reticulum stress in SD rats: a novel model of ER stress. Endocrine J 60:1231-1240, 2013.
5. Kim HJ, Moon JH, Kim HM, Yun MR, Jeon BH, Lee BW, Kang ES, Lee HC, Cha BS: The hypolipidemic effect of cilostazol can be mediated by regulation of hepatic low-density lipoprotein receptor-related protein 1 (LRP 1) expression. Metabolism 63:112-119, 2014.

Possible therapeutic option of low-dose PPAR-γ agonist through LRP1 regulation in Alzheimer's disease

Alzheimer's disease (AD), the most frequent form of senile dementia, is characterized by extracellular senile plaques, neurofibrillary tangles, as well as vascular amyloid and progressive neurodegeneration. 'Amyloid hypothesis' is the most widely accepted explanation for the pathogenesis of AD. Over-production and/or impaired clearance of amyloid β (Aβ) peptide in human brain result in pathologic deposits observed in AD brain, serial neuronal dysfunction and loss, brain atrophy in involved area and finally, clinical symptoms. Aβ, a 38–43kDa peptide, is derived from the proteolytic cleavage of the amyloid precursor protein (APP) and forms the core of the senile plaque.

Low-density lipoprotein receptor-related protein 1 (LRP1) is one of the LDL receptor gene family, and a multifunctional scavenger and signaling receptor. In several studies, It has been revealed that LRP1 in brain capillaries mediates Aβ outward transport across the blood-brain barrier (BBB) and plays a key role in clearing Aβ from the brain to the blood circulation.

Rosiglitazone and pioglitazone, peroxisome proliferator-activated receptor-γ (PPARγ) agonists are oral hypoglycemic agents that improve insulin resistance. Recently, evidences of the epidemiological association between AD and diabetes have been reported and numerous studies investigating the mechanism linking AD and diabetes have been performed. Additionally, anti-diabetic agents including PPARγ agonist have attracted attention as a new therapeutic option of AD. Interestingly, PPARγ agonist has been reported to ameliorate memory and learning deficit in AD animal studies, as well as in clinical studies. But the molecular mechanism of the effect of PPARγ agonist in AD is not fully understood.

We investigated the effect of rosiglitazone and pioglitazone on the expression and function of LRP1 in endothelial cells derived from HBMEC and in senile senescence animal model. Our data could suggest potential therapeutic interest for the use of low-dose PPAR-γ agonists in the treatment of AD with safety.

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➤Educational background & professional experience

1996	Kyoto University / MD
2003	Kyoto University Graduate School of Medicine / PhD
2003-2007	RIKEN CDB, Laboratory for Stem Cell Biology / Research Scientist
2009-2014	Kobe University, Division of Vascular Biology / Assistant Professor
2014-present	Nagoya City University, Department of Retinal Vascular Biology / Professor

➤Research interests

Molecular pathology of diabetic retinopathy

➤Brief list of publications

1. Kim C, Yang H, Fukushima Y, Saw PE, Lee J, Park JS, Park I, Jung J, Kataoka H, Lee D, Heo WD, Kim I, Jon S, Adams RH, Nishikawa S, Uemura A, Koh GY. Vascular RhoJ is an effective and selective target for tumor angiogenesis and vascular disruption. Cancer Cell. 25:102-117, 2014.
2. Uemura A. Identification of novel drug targets for the treatment of diabetic retinopathy. Diabetes Metab J. 37:217-224, 2013.
3. Fukushima Y, Okada M, Kataoka H, Hirashima M, Yoshida Y, Mann F, Gomi F, Nishida K, Nishikawa S, Uemura A. Sema3E-PlexinD1 signaling selectively suppresses disoriented angiogenesis in ischemic retinopathy in mice. J Clin Invest. 121:1974-1985, 2011.
4. Uemura A, Kusuhara S, Wiegand SJ, Yu RT, Nishikawa S. Tlx acts as a pro-angiogenic switch by regulating extracellular assembly of fibronectin matrices in retinal astrocytes. J Clin Invest. 116:369-377, 2006.
5. Uemura A, Ogawa M, Hirashima M, Fujiwara T, Koyama S, Takagi H, Honda Y, Wiegand SJ, Yancopoulos GD, Nishikawa S. Recombinant angiopoietin-1 restores higher-order architecture of growing blood vessels in mice in the absence of mural cells. J Clin Invest. 110:1619-1628, 2002.

Novel molecular targets for the treatment of diabetic retinopathy

In diabetic retinopathy, dropout of pericytes from retinal capillary walls has been assumed to be an initial trigger for the subsequent vascular disorders including elevated vascular leakage and neovascularization. However, because of the lack of diabetic animal models that recapitulate human retinopathy, the pathophysiology underlying the onset and progression of diabetic retinopathy remains elusive. To tackle this obstacle, we aimed to reproduce retinal vascular abnormalities resulting from pericyte dropout by injecting neonatal mice with anti-PDGFRβ antibody that inhibit recruitment of pericytes to developing retinal vessels. Consequently, mouse retinas devoid of pericytes displayed vessel dilation and tortuosity, and progressive hemorrhage and edema, all of which are characteristic features in human diabetic retinopathy. Of interest, comprehensive gene expression analysis in pericyte-free endothelial cells demonstrated that pericyte dropout directly induced inflammatory responses in retinal vessels. Given that high blood glucose can also induce inflammation in retinal vessels, it is plausible that high glucose, pericyte dropout, and inflammation synergistically exacerbate the disease conditions in diabetic retinopathy. In order to break this vicious circle, we are seeking for distinct molecular targets including cytokines and chemokines which are requisite for leukocyte adhesion and infiltration in pericyte-free retinal vessels. We believe that these experimental works will contribute to developing new therapeutic modalities that can halt the progression of diabetic retinopathy.

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➤**Educational background & professional experience**

2001-2004	Kyungpook National University Hospital, Ophthalmology / Resident
2008-2011	Kyungpook National University Hospital, Ophthalmology / Clinical fellow
2012-present	Kyungpook National University Hospital, Ophthalmology / Assistant professor

➤**Research interests**

Retina, Genetic study of age-related macular degeneration, Angiogenesis retinal diseases

➤**Brief list of publications**

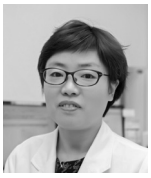
1. "One Year Follow-up of Macular Ganglion Cell Layer and Peripapillary Retinal Nerve Fiber Layer Thickness Changes after Panretinal Photocoagulation" BJO 2014 Feb, 98(2):213-217
2. "Association of Plasma Malondialdehyde with ARMS2 Genetic Variants and Phenotypes in Polypoidal Choroidal Vasculopathy and Age-related Macular Degeneration" Retina 2014 June, 34(6):1167-1176
3. "Association of ARMS2/HTRA1 Variants with Polypoidal Choroidal Vasculopathy Phenotype in a Korean population" Japanese Journal of Ophthalmology 2012 Jan;56(1):60-67
4. "LOC387715/HTRA1 Variants and the Response to Combined Photodynamic Therapy with Intravitreal Bevacizumab for Polypoidal Choroidal Vasculopathy" Retina 2012 Feb;32(2): 299-307
5. "Polymorphism in Vascular Endothelial Growth Factor Gene in Polypoidal Choroidal Vasculopathy in a Korean Population" Japanese Journal of Ophthalmology 2012 Mar;56(2):145-151

Bullseye for diabetic retinopathy

Macular edema (ME) in patients with ischemic retinopathies, including diabetic retinopathy (DR), remains the leading cause of vision loss in working-age populations.

In progression of DR, a variety of proangiogenic factors are implicated in pathogenesis including ME and retinal neovascularization. The antiangiogenic factors are also important to maintain normal vascular structure and restrict abnormal angiogenesis. In ischemic retinopathies, sustained hypoxia exacerbates extraretinal vascular outgrowth, which can cause vision-imparing hemorrhage and retinal detachment. The balance of proangiogenic and antiangiogenic factors is believed to be essential for maintain the normal vasculature in retina.

Proangiogenic factor, such as vascular endothelial growth factor (VEGF), is a potent inducer of vasopermeability and ME. The recent treatments using anti-VEGF agents result in improvement of visual acuity in patients with DR. However despite the clinically significant benefits of intravitreal injection of anti-VEGF agents, some patients remained low visual acuity with persistent ME, emphasizing the need to identify alternative therapeutic targets. Several reports have suggested that VEGF is a survival factor of endothelium, and the neutralization of VEGF could worsen of retinal ischemia. The authors investigated the concentration of other biomarkers in the aqueous humor from patients with DR. Also the authors evaluated the potential implications of these factors in the pathogenesis of retinal ischemia and macular edema in DR.



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➤Educational background & professional experience

1993-1999	College of Medicine, Inje University / M.D.
2003-2005	Graduate School, University of Ulsan / M.S.
2005-2007	Graduate School, University of Ulsan / Ph.D.
2009-2014	Department of Endocrinology and Metabolism, Asan MeMedical Center / Clinical Assistant Professor
2014-present	Internal Medicine, College of Medicine, University of Ulsan / Associate Professor

➤Research interests

Diabetic nephropathy, non-alcholic steatohepatitis

➤Brief list of publications

1. Kim SY, Hong SW, Kim MO, Kim HS, Jang JE, Leem J, Park IS, Lee KU, Koh EH. S-adenosyl methionine prevents endothelial dysfunction by inducing heme oxygenase-1 in vascular endothelial cells. Mol Cells. 2013;36(4):376-84
2. Jeon MJ, Leem J, Ko MS, Jang JE, Park HS, Kim HS, Kim M, Kim EH, Yoo HJ, Lee CH, Park IS, Lee KU, Koh EH. Mitochondrial dysfunction and activation of iNOS are responsible for the palmitate-induced decrease in adiponectin synthesis in 3T3L1 adipocytes. Exp Mol Med. 2012 ;44(9):562-70 (Park HS, Jeon BH, Woo SH, Leem J, Jang JE, Cho MS, Park IS, Lee KU, Koh EH. Time-dependent changes in lipid metabolism in mice with methionine choline deficiency-induced fatty liver disease. Mol Cells. 2011;32(6):571-7. (Correspondent author)
3. Koh EH, Lee WJ, Lee SA, Kim EH, Cho EH, Jeong E, Kim DW, Kim MS, Park JY, Park KG, Lee HJ, Lee IK, Lim S, Jang HC, Lee KH, Lee KU. Effects of alpha-lipoic Acid on body weight in obese subjects. Am J Med. 2011;124(1):85.e1-8.
4. Koh EH, Kim M, K C R, Kim H, Park HS, Oh KS, Park IS, Lee WJ, Kim MS, Park JY, Youn JH, Lee KU. eNOS plays a major role in adiponectin synthesis in adipocytes. Am J Physiol Endocrinol Metab. 2010; 30, E846-853.

Effect of lipid metabolites from high fat diet-induced renal injury

In addition to obesity is recognized as a major risk factor for the cardiovascular disease and for type 2 diabetes, there is evidence that obesity is recognized as a major and independent risk factor for the development of kidney disease [1].

Administration of high fat diet (HFD) is well known to induce obesity, insulin resistance and diabetes. Similarly, HFD administration to mice induces renal injury that in many aspects resembles diabetes- and obesity-related kidney disease in human [2]. Recent studies have suggested that non-TG metabolites of free fatty acids (FFAs) cause insulin resistance and lipotoxic tissue injury. Ectopic deposition of lipids into nonadipose tissues, such as the kidney, often occurs in obesity [3]. Sphingolipids, including ceramide and its derivatives, are recognized as important signal mediators in the regulation of inflammation, apoptosis, proliferation, and differentiation [4]. Lines of evidence have shown that abnormal ceramide metabolism is involved in the pathogenesis of obesity and obesity-induced metabolic diseases [4]. Ceramide can be produced by de novo synthesis or via the hydrolysis of sphingomyelin by sphingomyelinases. Serine palmitoyltransferase (SPT) is the initial, rate-limiting enzyme of de novo ceramide synthesis. Recently, we found that administration of myriocin, a well-known inhibitor of SPT, was shown to prevent HFD-induced obesity and glomerular injury.

In this session, the role of lipid metabolites in the HFD-induced renal injury will be discussed.

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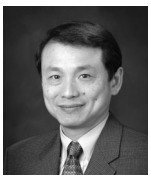
1. Hall ME, et al., Obesity, hypertension, and chronic kidney disease. Int J Nephrol Renovasc Dis. 2014;7:75-88.
2. Deji N et al., Structural and functional changes in the kidneys of high-fat diet-induced obese mice. Am J Physiol Renal Physiol. 2009;296:F118-26
3. Unger RH, Scherer PE. Gluttony, sloth and the metabolic syndrome: a roadmap to lipotoxicity. Trends Endocrinol Metab. 2010;21: 345–352.
4. Kang SC et al., Sphingolipid metabolism and obesity-induced inflammation. Front Endocrinol (Lausanne). 2013;4:67.



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➤Educational background & professional experience

1984	Kaohsiung Medical College, Taiwan / MD
1985	Harvard University / SM
1985	Joslin Diabetes Center, Boston / Research Fellow
1991	Harvard Longwood Endocrinology Fellowship / Clinical Fellow
1994	University of California, Irvine / Assistant Professor
2006	University of California, Irvine / Professor
2003	University of California, Irvine Medical Center / Chief, Endocrinology
2004-present	UCI Diabetes Center / Director

➤Research interests

Diabetes and its complications, Hormone actions, Stem cell biology

➤Brief list of publications

1. Wang PH, Lau J, Chalmers TC. Meta-analyses of effects of intensive blood glucose control on late complications of type I diabetes. Lancet 1993;341:1306-1309.
2. Pedrini M, Lau J, Levey A, Chalmers TC, Wang PH. The effect of Dietary protein restriction on the progression of diabetic and non-diabetic renal disease: meta-analysis. Annals of Internal Medicine 1996;124:627-32.
3. Chen H, Shan Y, Yang T, Lin H, Chen J, Lin, S, Wang PH. Insulin Deficiency Down-Regulated Hsp60 and IGF-1 Receptor Signaling in Diabetic Myocardium. Diabetes 2005;54(1):175-81.
4. Yang J, Deng W, Chen Y, Fan W, Baldwin KM, Jope RJ, Wallace DC, Wang PH. Impaired Translocation and Activation of Mitochondrial Akt1 Mitigated Mitochondria Oxidative Phosphorylation Complex V Activity in Diabetic Myocardium. Journal of Molecular and Cellular Cardiology 2013;59:167-75.
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Akt1 translocation to mitochondria - a novel mechanism underlying energy dysregulation in diabetic cardiomyopathy

Metabolic dysregulation plays a critical role during the development of heart failure, and diabetes aggravates heart failure. Mitochondria are the major source of ATP production in the heart, via glycolysis and β-oxidation. Glycolytic Oxidative phosphorylation is significantly reduced in the diabetic myocardium, thereby creating a metabolic switch to selectively relying on β-oxidation, which is associated with lipotoxicity and inefficient energy conversion. While mitochondria play a pivotal role in the dysregulation of bioenergetics and oxidative stress, the exact molecular mechanisms underlying diabetic mitochondria dysfunction is not completely understood. Our studies showed that insulin stimulated Akt1 translocation to mitochondria and modulated oxidative phosphorylation complex V in cardiac muscle, thus raised the possibility that mitochondrial Akt1 may regulate glycolytic oxidative phosphorylation and mitochondria function in cardiac muscle cells. Mitochondrial Akt1 signaling played a protective role against apoptosis and necrosis during ischemia-reperfusion stress, and suppressed mitochondrial calcium overload and mitochondrial membrane depolarization. Activation of Akt1 signaling in mitochondria increased glucose uptake, enhanced respiration efficiency, reduced superoxide generation, and increased ATP production in the cardiomyocytes. Insulin regulation of ATP production required mitochondrial Akt1 signaling because inhibition of mitochondrial Akt attenuated insulin response. To identify the protein targets of Akt1 signaling in mitochondria, proteomic approach revealed 15 novel targets of Akt1 signaling in mitochondria, including pyruvate dehydrogenase complex (PDC). We have confirmed and characterized the association of Akt1 and PDC subunits, and verified stimulatory effect of mitochondrial Akt1 on the enzymatic activity of PDC. Akt1 interacted with the E3 subunit of PDC through an interface enriched with positively and negatively charged amino acid side chains, by forming salt bridges. These findings suggested that Akt1 formed protein complexes with multiple mitochondria proteins and improved mitochondria function in stressed cardiomyocytes. The novel Akt1 signaling targets in mitochondria may become a resource for future metabolism research and drug discovery.

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➤Educational background & professional experience

1992-1999	College of Veterinary Medicine, Kyungpook National University / D.V.M (Doctor of Veterinary Medicine)
1999-2004	College of Veterinary Medicine, Department of Pathology, Kyungpook National University / M.S. & Ph.D.
2005-2008	NIAAA/National Institute of Health, USA / Post-Doc fellow
2009-2012	Graduate School of Medical Science and Engineering, KAIST / Assistant Professor
2012-present	Graduate School of Medical Science and Engineering, KAIST / Associate Professor

➤Research interests

Broad spectrum of liver disease including fatty liver, hepatitis, fibrosis and tumor.
Metabolic disorders (steatosis, inflammation and insulin resistance)

➤Brief list of publications

1. Alcohol dehydrogenase III Exacerbates Liver Fibrosis by Enhancing Stellate Cell Activation and Suppressing Natural Killer Cells in Mice. Hepatology 2014 (Accepted)
2. Activation of toll-like receptor 3 attenuates alcoholic liver injury by stimulating Kupffer cells and stellate cells to produce interleukin-10 in mice. Journal of Hepatology, 2013, 58, p.342-349.
3. CD11b+Gr1+ bone marrow cells ameliorate liver fibrosis by producing interleukin-10 in mice. Hepatology, 2012, 56(5), p1902-1912.
4. Suppression of innate immunity (natural killer cell/interferon-γ) in the advanced stages of liver fibrosis in mice. Hepatology, 2011, 53(4), p.1342-1351.
5. Paracrine Activation of Hepatic CB1 Receptors by Stellate Cell-Derived Endocannabinoids Mediates Alcoholic Fatty Liver. Cell Metabolism, 2008, 7(3), p. 227-235.

Role of NADPH oxidase 2 in hepatic steatosis and insulin resistance

Background & Aim: Generation of reactive oxygen species (ROS) is one of major causes in hepatic steatosis and insulin resistance during inflammatory responses, in which infiltrated immune cells may generate ROS by multiple sources including mitochondrial respiratory chain, peroxisomes and nicotinamide adenine dinucleotide phosphate (NADPH) oxidases. Particularly, infiltrated macrophages and neutrophils in hepatic steatosis express NADPH oxidase 2 (NOX2) highly. Therefore, we explored the role of NOX2 in hepatic steatosis and insulin resistance.

Methods: Wild-type (WT) and NOX2-deficient (NOX2-/-) mice or chimeric mice with reciprocal bone marrow transplantation were maintained with regular chow or a high-fat diet (HFD) for 12 weeks. Hepatocytes and non-parenchymal cells including hepatic stellate cells (HSCs) and liver mononuclear cells (MNCs) were isolated for the cellular mechanism analyses.

Results: The HFD feeding induced hepatic steatosis and insulin resistance in WT mice but not in NOX2-/- mice. Moreover, WT mice showed increased expression of endocannabinoid receptor 1, sterol regulatory element-binding protein 1c and fatty acid synthase in hepatocytes, and that of phospholipase D and diacylglycerol lipase α, specific genes for the production of endocannabinoid, in HSCs compared with those of NOX2-/- mice. Furthermore, isolated liver MNCs of NOX2-/- mice showed higher expression of interleukin-10 (IL-10) and IL-6 than that of WT mice. Accordingly, chimeric WT and NOX2-/- mice transplanted with NOX2-/- bone marrow showed less steatosis and insulin resistance or higher expression of IL-10 and IL-6 than those of WT and NOX2-/- mice transplanted with WT bone marrow.

Conclusion: NOX2 deficiency in infiltrated immune cells attenuates HFD-induced steatosis and insulin resistance in mice. Probably, increased production of IL-10 and IL-6 in liver MNCs might inhibit endocannabinoid signaling pathway and hepatic lipogenesis in HSCs and hepatocytes, respectively.

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1993-1997	Korea University, Seoul, Korea / B.S
2001-2006	Purdue University, West Lafayette, IN, USA / Ph.D
2006-2014	University of Michigan Medical School, Ann Arbor, MI, USA / Research Fellow
2014-present	SoonChunHyang University, Cheonan, Korea / Assistant Professor

➤**Research interests**

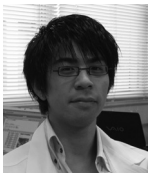
Adipose tissue inflammation and insulin resistance

➤**Brief list of publications**

1. Cho KW, Morris DL, DelProposto JL, Geletka LM, Zamarron B, Meyer KA, Singer K, O'Rourke RW, Lumeng CN. (2014) An MHC Class II Dependent Activation Loop Between Adipose Tissue Macrophages and CD4+ T cells Controls Obesity-Induced Inflammation. Cell reports, in press
2. Wang G-X, Cho KW, Uhm M, Hu C-R, Li S, Cozacov Z, Xu AE, Cheng J-X, Saltiel AR, Lumeng CN, Lin JD (2014) Otopetrin 1 protects mice from obesity-associated metabolic dysfunction through attenuating adipose tissue inflammation. Diabetes 63 (4): 1340-52
3. Morris DL, Cho KW, Delproposto JL, Oatment KE, Geletka LM, Marinez-Santibanez G, Singer K, Lumeng CN (2013) Adipose tissue macrophages function as antigen presenting cells and regulate adipose tissue CD4+ T cells in mice. Diabetes 62 (8): 2762-72
4. Cho KW, Zhou Y, Liang S, Rui L (2011) Lipocalin-13 regulates glucose metabolism by both insulin-dependent and –independent mechanisms. Mol Cell Biol. 31(3):450-7
5. Cho KW, Lee OH, Banz WJ, Moustaid-Moussa N, Shay NF, Kim YC (2010) Daidzein and the daizein metabolite, equol, enhance adipocyte differentiation and PPARgamma transcriptional activity. J Nutr Biochem. 21(9): 841-7

Adipose tissue macrophages and metabolic syndrome

It is established that chronic inflammation leads to metabolic syndrome and associated disease including cardiovascular disease and type 2 diabetes. Obesity induces chronic local inflammation in adipose tissue and a network of adipose tissue leukocytes participates in the innate and adaptive immune response to obesity. Adipose tissue macrophages (ATMs), major innate immune cell in adipose tissue, are crucially involved in adipose inflammation and systemic metabolic abnormalities. Recently, the involvement of CD4+ T cells in adipose tissue inflammation has been also identified. However, it has been unknown how ATMs interact with CD4+ T cells and the importance in generating adipose tissue inflammation. In this presentation, the complexity and dynamic alteration of ATMs during obesity will be introduced. Furthermore, the novel function of ATMs as the regulator for CD4+ T cells will be discussed. I provide several in vivo and in vitro experimental evidences to evaluate communication between ATMs and T cells and underlying mechanism to regulate adipose tissue inflammation and insulin resistance. Overall, I provide integrative perspective regarding how ATM and obesity interact to regulate the metabolic syndrome.



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➤Educational background & professional experience

1999	Department of medicine, Shiga University of Medical Science / M.D.
2003	Shiga University of Medical Science (Got a Ph.D. in 2007) / Doctoral student
2007	Research Fellow of the Japan Society for the Promotion / Research fellow
2011-present	Department of medicine, Shiga University of Medical Science / Assistant professor

➤Research interests

Diabetes, Diabetic nephropathy, Aging

➤Brief list of publications

1. Kume S, Yamahara K, Yasuda M, Maegawa H, Koya D. Autophagy: emerging therapeutic target for diabetic nephropathy. Semin Nephrol. 2014 Jan;34(1):9-16.
2. Yasuda M, Tanaka Y, Kume S, Morita Y, Chin-Kanasaki M, Araki H, Isshiki K, Araki SI, Koya D, Haneda M, Kashiwagi A, Maegawa H, Uzu T. Fatty acids are novel nutrient factors to regulate mTORC1 lysosomal localization and apoptosis in podocytes. Biochim Biophys Acta. 2014 Apr 13;1842(7):1097-1108.
3. Yamahara K, Kume S, Koya D, Tanaka Y, Morita Y, Chin-Kanasaki M, Araki H, Isshiki K, Araki S, Haneda M, Matsusaka T, Kashiwagi A, Maegawa H, Uzu T. Obesity-mediated autophagy insufficiency exacerbates proteinuria-induced tubulointerstitial lesions. J Am Soc Nephrol. 2013 Nov;24(11):1769-81.
4. Kume S, Thomas MC, Koya D. Nutrient sensing, autophagy, and diabetic nephropathy. Diabetes. 2012 Jan;61(1):23-9.
5. Kume S, Uzu T, Horiike K, Chin-Kanasaki M, Isshiki K, Araki S, Sugimoto T, Haneda M, Kashiwagi A, Koya D. Calorie restriction enhances cell adaptation to hypoxia through Sirt1-dependent mitochondrial autophagy in mouse aged kidney. J Clin Invest. 2010 Apr 1;120(4):1043-55.

Role of autophagy in diabetic nephropathy

The study of autophagy in mammalian systems in homeostasis and disease states is advancing rapidly, and many investigators are entering this new and exciting field. Autophagy is a major catabolic pathway by which mammalian cells degrade and recycle macromolecules and organelles. It plays a critical role in removing protein aggregates, as well as damaged or excess organelles, to maintain intracellular homeostasis and to keep the cell healthy. Autophagy is activated by starvation and some environmental stress conditions in proximal tubular cells, and constitutively occurs under normal conditions in podocytes. The functional role of autophagy in the kidney is currently under intense investigation, indicating that autophagy in both podocytes and proximal tubular cells may play a pivotal role in maintaining cell homeostasis in various renal diseases. We have previously reported that the normal aging process suppresses autophagy activity in proximal tubular cells. This suppression is associated with the development of age-related nephropathy in a mouse model. Thus, accumulating evidence has shown the pathophysiological importance of autophagy in the kidney. We have recently investigated the role of autophagy in the pathogenesis of podocyte damage and proteinuria-induced proximal tubular cell damage in diabetic nephropathy. The results from our studies using autophagy-deficient mouse models have suggested that autophagy is essential to protect both podocytes and proximal tubular cells from various toxic stimuli in diabetic nephropathy. Here, we present new experimental evidence regarding the role of autophagy in the pathogenesis of diabetic nephropathy to help advance future investigations in this field.

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➤Educational background & professional experience

1988-1992	Kanazawa University Graduate School of Medical Sciences / MD, PhD
1993-1997	Department of Biochemistry, Tohoku University (Prof. Hiroshi Okamoto) / Special Researcher, Japan Society for the Promotion of Science
2001-2014	Department of Disease Control and Homeostasis, Kanazawa University Graduate School of Medical Sciences / Associate Professor
2014-present	Department of Comprehensive Metabology, Kanazawa University Graduate School of Medical Sciences / Professor
2014-present	Division of Endocrinology and Metabolism, Kanazawa University Hospital / Director

➤Research interests

Endocrinology and metabolism

➤Brief list of publications

1. Ishikura K, Misu H, Kumazaki M, Takayama H, Matsuzawa-Nagata N, Tajima N, Chikamoto K, Lan F, Ando H, Ota T, Sakurai M, Takeshita Y, Kato K, Fujimura A, Miyamoto K, Saito Y, Kameo S, Okamoto Y, Takuwa Y, Takahashi K, Kidoya H, Takakura N, Kaneko S, Takamura T*. Selenoprotein P as a diabetes-associated hepatokine that impairs angiogenesis by inducing VEGF resistance in vascular endothelial cells. Diabetologia 57:1968-76, 2014
2. Lan F, Misu H, Chikamoto K, Takayama H, Kikuchi A, Mohri K, Takata N, Hayashi H, Matsuzawa-Nagata N, Takeshita Y, Noda H, Matsumoto Y, Ota T, Nagano T, Nakagen M, Miyamoto KI, Takatsuki K, Seo T, Iwayama K, Tokuyama K, Matsugo S, Tang H, Saito Y, Yamagoe S, Kaneko S, Takamura T*. LECT2 functions as a hepatokine that links obesity to skeletal muscle insulin resistance. Diabetes 63:1649-64, 2014
3. Otoda T, Takamura T*, Misu H, Ota T, Murata S, Hayashi H, Takayama H, Kikuchi A, Kanamori T, Shima KR, Lan F, Takeda T, Kurita S, Ishikura K, Kita Y, Iwayama K, Kato KI, Uno M, Takeshita Y, Yamamoto M, Tokuyama K, Iseki S, Tanaka K, Kaneko S. Proteasome Dysfunction Mediates Obesity-Induced Endoplasmic Reticulum Stress and Insulin Resistance in the Liver. Diabetes 62:811-24, 2013
4. Takamura T*, Misu H, Ota T, Kaneko S. Fatty liver as a consequence and cause of insulin resistance: Lessons from type 2 diabetic liver (Review). Endocr J 59:745-63, 2012
5. Misu H, Takamura T*, Takayama H, Hayashi H, Matsuzawa-Nagata N, Kurita S, Ishikura K, Ando H, Takeshita Y, Ota T, Sakurai M, Yamashita T, Mizukoshi E, Yamashita T, Honda M, Miyamoto K, Kubota T, Kubota N, Kadowaki T, Kim HJ, Lee IK, Minokoshi Y, Saito Y, Takahashi K, Yamada Y, Takakura N, Kaneko S. A liver-derived secretory protein, selenoprotein P, causes insulin resistance. Cell Metab 12:483-95, 2010

A satiety-induced hepatokine LECT2 causes skeletal muscle insulin resistance via JNK activation

We previously examined the association between ectopic fat and organ-specific insulin resistance in insulin-target organs in patients with nonalcoholic fatty liver disease (PLOS ONE 2014). Unexpectedly, fat accumulation in the skeletal muscle and adipose tissue was not associated with organ-specific insulin resistance. Instead, liver fat was associated not only with hepatic insulin resistance, but also with skeletal muscle insulin resistance, supporting a central role of fatty liver in systemic insulin resistance. The findings also suggest a network exists between the liver and skeletal muscle, but the causal relationship remains unclear.

The liver may contribute to muscle insulin resistance by releasing secretory proteins, termed hepatokines. Here, we demonstrate that leukocyte cell-derived chemotaxin 2 (LECT2), as an energy-sensing hepatokine, is a link between obesity and skeletal muscle insulin resistance. Circulating LECT2 positively correlated with the severity of both obesity and insulin resistance in humans. Hepatic expression of LECT2 was upregulated on high fat diet feeding and physical inactivity in mice. LECT2 expression was negatively regulated by starvation-sensing kinase adenosine monophosphate-activated protein kinase (AMPK) in H4IIEC hepatocytes. Genetic deletion of LECT2 in mice increased insulin sensitivity in the skeletal muscle. Treatment with recombinant LECT2 protein impaired insulin signaling via phosphorylation of JNK in C2C12 myocytes. These results demonstrate the involvement of LECT2 in fatty liver-associated skeletal muscle insulin resistance, and suggest that LECT2 may be a therapeutic target for obesity-associated insulin resistance.

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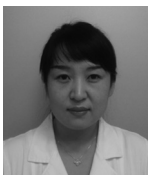
➤**Educational background & professional experience**
2003-present Dankook University Hospital, Diabetes & Endocrinology Center / Diabetes education nurse

➤**Research interests**
Diabetes education & behavior change

➤**Brief list of publications**

Management of patient with diabetes mellitus and cerebral - cardiovascular disease

Cerebral · cardiovascular disease is a more common cause of death than microvascular complications in populations with diabetes. Also diabetes mellitus is one of the major causes of cardiovascular morbidity and mortality, and its prevalence is increasing. In the DCCT, there was a trend toward lower risk of CVD events with intensive control. In the 9-year post-DCCT follow-up of the EDIC cohort, participants previously randomized to the intensive arm had a significant 57% reduction in the risk of nonfatal myocardial infarction (MI), stroke, or CVD death compared with those previously in the standard arm. In type 2 diabetes, there is evidence that more intensive treatment of glycemia in newly diagnosed patients may reduce long-term CVD rates. During the UKPDS trial, there was a 16% reduction in CVD events in the intensive glycemic control arm that did not reach statistical significance (P 5 0.052), and there was no suggestion of benefit on other CVD outcomes (e.g., stroke). However, after 10 years of follow-up, those originally randomized to intensive glycemic control had significant long-term reductions in MI and in all-cause mortality. ACCORD, ADVANCE, and VADT studies suggested no significant reduction in CVD outcomes with intensive glycemic control in participants who had more advanced type 2 diabetes than UKPDS participants. All three trials were conducted in participants with more long-standing diabetes (mean duration 8–11 years) and either known CVD or multiple cardiovascular risk factors. Diabetes mellitus a with cerebral · cardiovascular disease often goes unrecognized and unmanaged. However, once risk reduction through improved control of risk factors and therapeutic lifestyle changes is a central strategy for preventing CHD. Nurses play an important role in primary care such as assessing risk factors and CHD risk as well as providing behavioral interventions and education. In this section, I will review about cerebral · cardiovascular disease with diabetese diagnosis, prevention, management and education for lifestyle modification.



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➤Educational background & professional experience

1995	Gachon University of Medicine and Science The Science of Nursing / Bachelor's degree
1995-2007	Sanggye paik hospital ICU / RN
2007-	Sanggye paik hospital Diabetes center / Education Nurse
2014-	Inje Institute of Advanced Studies / Master of Public Health
2014-	Korean Association of Diabetes Nurse Education / Co-Director

➤Research interests

The effect of follow-up counselling care program in DM patient.

➤Brief list of publications

1. A comparison of doctor-patient communication method in type 2 diabetes mellitus: OTDMS system versus patient diary.2012.
2. Complementary Role of Rapid Current Perception Threshold Test adding to Michigan Neuropathy Screening Instrument in the Diagnosis of Diabetic Peripheral Neuropathy.2012.
3. A case of Human Insulin Allergy by Human Recombination Insulin.2013.

Management of diabetes mellitus in demented patient

As age grows, the risk of diabetes, stroke and dementia increases and diabetes patients suffer from difficulty in blood glucose control and complications. According to the 2005 Delphi Consensus study on the world dementia prevalence rate, 4.6 million new dementia patients occur over the world each year and the study expected the number of dementia patients to grow up to about 38.1 million in 2008. The dementia prevalence rate in the Korean elderly population of ages over 65 will continuously increase in the future due to rapid aging.

Diabetes is closely related to changes of cognitive functions and a main risk factor for vascular dementia and Alzheimer's disease of nerve cells. Diabetes patients' risk of vascular dementia is 2~3 times higher than ordinary persons and the risk of Alzheimer's disease is 1.5~2 times higher. Vascular dementia is one of the serious complications, and as patients' ability to control glucose decrease, losing memory or judgment, they are more easily exposed to the risks of hypoglycemia or hyperglycemia. Diabetes patients have 2~3 times higher risk of blood vessel cognitive disorder, and one out of 10~15 dementia patients is a diabetes patient. Therefore, care of diabetes patients with dementia should be based on functional maintenance through possible improvement of dementia and place priorities on, first, prevention of emergencies such as hypoglycemic coma and hyperosmolar ketotic coma and, second, maintenance and improvement of quality of life (QOL).

Therefore, educators should make education plans on the premise of overall understanding of dementia diabetes patients, sociocultural characteristics and sufficient consideration of pre-education patients. For effective management of diabetes, target should be put on individual and realistic control of diabetes, depending on degree of cognitive impairments and dementia, by establishing and performing education plans including individual and realistic set-up of diabetes control target taking consideration of gerontology, individualized education on diabetes considering the state of physical functions, induction of family involvement in diabetes control, plan to make use of community social institutions/services, strengthening of team access for integrated control, introduction to social welfare systems/services and development of educational tools making use of strengths of patients and resources.

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➤Educational background & professional experience

1995-present	Wonju Severance Christian Hospital / RN
2009-present	Wonju Severance Christian Hospital Diabetes Center / Diabetes Nursing Educator
2011	Younsei University Wonju College of Nursing / BSN

➤Research interests

Diabetic education

The management of diabetes in patients with cancer

According to data provided by the Statistics Korea, the most common cause of death for population over 65 years old in recent 10 years is cancers, cerebroascular diseases, cardiovascular diseases and diabetes. This represents that cancer and diabetes are the major causes of death for adults.

Cancers have been occurred independently for many of patients with diabetes during the treatment periods, leading them to have significant financial burden for medical treatment expenses and higher mortalities.

According to recent studies, approximately 4.7% of patients with diabetes have cancers, and this implies that the diabetes patients have 1.6 fold higher chances of having cancers than normal population.

Diabetes is associated with increased cancer risk for the tumors in various parts such as breast, bladder, pancreas, liver and colorectal cancer and it is reported that these cancers have 40~80% of mortality rate than normal people.

Since active diabetes management significantly influences in health condition outcome of the patients with diabetes the management must be considered important, however, due to the fear for cancer itself the diabetes management has been easily neglected.

Unlike simple diabetes management for patients who solely have diabetes alone, there are several factors which should be considered for the diabetes management for diabetes patients accompanied with cancer.

At first , blood glucose control goal should be set according to stages and symptoms of cancer.

At second, when medications for treatment of diabetes and cancer are determined, detailed information of the medications must be provided to prevent hyperglycemia and hypoglycemia.

At third, customized dietary plan and exercise plan depending on patient's physical status should be provided and trained.

At fourth, social welfare programs and supports should be assisted for patients to appropriately react against crisis and change of life caused by cancer accompanied with diabetes.

At fifth, precise information for various attempts for complementary and alternative medicine must be provided to prevent exacerbation and complications for diabetes.

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➤Educational background & professional experience

2002	Graduate school of Nursing, Chosun University / M.D
1995-2007	Chosun University Hospital, medical ward / Nurse
2008-present	Chosun University Hospital, Diabetes Center / Diabetes Nurse Educator
2012	Graduate school of Health Sciences, Chosun University / Ph.D

➤Research interests

Diabetes education

➤Brief list of publications

1. Hae-Jeong Lee, Yun-Ju Ha. The effect of the horticultural activities program on loneliness and life satisfaction of the disabled female. J of Korean Acad psychiatr Ment Health Nurs Vol. 20, No.4. 386-394, December, 2011
2. Jin-Hwa Kim, Ji-Hye Shin, Hae-Jeong Lee, Sang-yong Kim, Hak-Yeon Bae. Discordance between HbA1c and fasting plasma glucose criteria for diabetes screening is associated with obesity and old age in Korean individuals. Diabetes Res Clin Pract. 10 August 2011
3. Quality of life is associated with stress, sleeping time, and fasting plasma glucose in Korean Diabetic adults. IDF abstract poster display. 2011

Management of post-transplantation diabetes mellitus

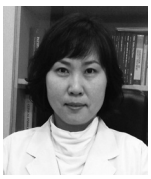
Post-transplantation diabetes mellitus (PTDM) has been recognized as a major com-plications of solid organ transplantation. Both patient and graft survival is significantly reduced in recipients affected by PTDM. The main clinical aspects of transplant recipients with PTDM are patient and graft survival rate, infections, cardiovascular complications, and late complications of diabetes that include nephropathy, neuropathy, retinopathy, micro-macroangiopathy, and bone disease. Although its incidence has decreased with efforts to lower the dose of steroid used, PTDM continues to be prevalent in solid organ transplantation.

Its pathogenesis is complex, with interaction between intrinsic factors (older age, body mass index, individual and family history, hepatitis C virus infection), and graft related factors (immunosuppressive regimen, HLA status). PTDM can compromise the transplanted patients' follow-up as it increase health events and hospitalizations and affects the patients' quality of life.

The incidence rates of PTDM vary by organ transplanted and post-transplant interval. The estimated incidence rates at 12 months post-transplant are 2~52% for kidney transplants, 9~21% for liver transplants, and approximately 20% for lung transplants.

Early detection is crucial in the management and control of PTDM which can be achieved through pre-transplant screening there by identifying high risk patients and implementing the measures to reduce the development of PTDM. The classical risk factors for diabetes (such as family history, age, obesity, ethnicity, inactivity, prediabetes status) breed true in the post-transplant population. In addition, exposure to immunosuppressive agents, including glucocorticoids and calcineurin inhibitors (tacrolimus and cyclosporine), is a frequent antecedent to the development of PTDM. Although PTDM management is similar to type 2 diabetes management in the general population, there are some specific considerations in PTDM management, including the immunosuppressive agent, more individualized treatment to set important goals.

Here, we have a discussion with the prevalence, risk factors, influences on outcomes, diagnosis, and individualized management of post-transplantation diabetes mellitus.



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➤Educational background & professional experience

1994	Yeungnam University / M.D
2000-2002	Yeungnam University / FELLOWSHIP
2002-2005	Sooncheonhyang University / Assistant Professor,
2005-present	Yeungnam University / Professor
2007-2008	Diabetes Endocrinology Research Center, University of Washington,Seattle, USA / Visiting Scholarship

➤Research interests

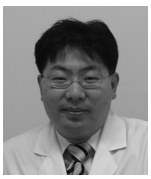
Diabetic complications and atherosclerosis

➤Brief list of publications

1. JS Moon, KS Ha, JS Yoon, HW Lee, HC Lee, KC Won, BETA study group. The effect of glargine versus glimepiride on pancreatic b-cell function in patients with type 2 diabetes uncontrolled on metformin monotherapy: open-label, randomized, controlled study. Acta Diabetol 2014;51:277–285
2. BS Park, JS Yoon. Relative Skeletal Muscle Mass Is Associated with Development of Metabolic Syndrome. Diabetes Metab J 2013;37:458-464
3. JS Yoon, HW Lee. Diabetogenic Effect of Statins: A Double-Edged Sword? Diabetes Metab J 2013;37:415-422
4. BS Park, JS Moon, KC W, HW Lee, JS Yoon. Predicting Mortality of Critically Ill Patients by Blood Glucose Levels. Diabetes Metab J 2013;37:385-390
5. JS Moon, JE Lee, JS Yoon. Variation in Serum Creatinine Level Is Correlated to Risk of Type 2 Diabetes. Endocrinol Metab 2013;28:207-213.

Diabetic microvascular complications: prevention and management (advanced)

People with diabetes have an increased risk of developing microvascular complications which encompass long-term complications of diabetes affecting small blood vessels. These classically have included retinopathy, nephropathy, and neuropathy, which, if undetected or left untreated, can have an unfavorable impact on quality of life and land a significant burden on health care costs with reducing life expectancy. Diabetic retinopathy is the leading cause of blindness in adults and divided into two main categories: nonproliferative retinopathy and proliferative retinopathy. Nonproliferative retinopathy can be recognized by development of soft and hard exudates, microaneurysms, venous beading and retinal dot blot hemorrhages. Proliferative retinopathy is defined as presence of new blood vessels with or without vitreous hemorrhage. Diabetic nephropathy represents the major cause of end stage renal disease. Clinically, it is characterized by the development of proteinuria with a subsequent decline in glomerular filtration rate, which progresses over a long period of time, often over 10–20 years. Neuropathy is a group of conditions characterized by nerve dysfunction. More than half of patients with diabetes eventually develop neuropathy, with a lifetime risk of one or more lower extremity amputations. It is classified according to the nerves affected and includes focal, diffuse, sensory, motor and autonomic neuropathy. The strongest risk factors of diabetic microvascular complications are glycemic control and duration of diabetes. Other modifiable risk factors such as hypertension, dyslipidemia and smoking, and unmodifiable risk factors such as age and genetic factors may also play a part. Along with risk factors, diabetic microvascular complications share similar pathogenetic mechanisms and some associations have been presented between diabetic microvascular complications themselves. As the incidence of diabetes continues to rise, the burden of diabetic microvascular complications will increase in future, hence the need for early detection and treatment as early as possible in order to further reduce morbidity and mortality.



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➤Educational background & professional experience

1998	College of Medicine, Hanyang University / M.D
2003-2004	Seoul National University Hospital / Fellow
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2006	Graduate School, Hanyang University / Ph.D
2013-present	Hallym University Sacred Heart Hospital / Associate Professor

➤Research interests

Obesity & Clinical diabetes

➤Brief list of publications

1. Comparison between the therapeutic effect of metformin, glimepiride and their combination as an add-on treatment to insulin glargine in uncontrolled patients with type 2 diabetes. PLoS One. 2014 Mar 10;9(3):e87799. doi: 10.1371/journal.pone.0087799. eCollection 2014.
2. Non-HDL cholesterol is an independent risk factor for aspirin resistance in obese patients with type 2 diabetes. Atherosclerosis. 2014 May;234(1):146-51. doi: 10.1016/j.atherosclerosis.2014.01.015. Epub 2014 Feb 12.
3. Increasing Achievement of the Target Goals for Glycemic, Blood Pressure, and Lipid Control for Adults with Diagnosed Diabetes in Korea. J Diabetes Invest 2013 Sep;4(5):460-465
4. Gender and age differences in obesity among Korean adults. Korean J Intern Med 2013 Jan 2013;28:19-21
5. Anti-Obesity Drugs: A Review about Their Effects and Safety. Diabetes Metab J 2012 Feb;36(1):13-25

Diabetes educator training module-hyperglycemic crises [HHS & DKA]

The Diabetes Educator Training Module (DETM), which was developed in 2011, contained more than 900 slides. The purpose of the DETM is to help Korean diabetes educators develop programs for diabetic patients and health professionals. Separating DETM into two tracks was the development principle of the DETM. There was a quite large difference in the level of knowledge among diabetes educators and preparatory educators participating in ICDM held each year and therefore, there were opinions that the lectures did not bring real values to certain participants and this led to developing basic and advanced module separating.

This presentation is about hyperglycemic crises (HHS and DKA) within advanced module. DKA and HHS are the two most serious acute metabolic complications of uncontrolled diabetes and economic burden of these treatment continue to rise. However, mortality associated with hyperglycemic crises has reduced significantly over the years due to better understanding of the pathogenesis of hyperglycemic emergencies and the application of evidence-based guidelines which incorporates low-dose insulin and appropriate fluid and electrolyte repletion therapy. I will present the pathogenesis and important precipitating factors in DKA and HHS which are provided as a necessary condition for understanding the rationale for the effective management. The protocols for the management, patient monitoring and prognostic factors of patients with HHS and DKA are also discussed.

I hope that this advanced module will be a useful tool for helping diabetic patients to understand their disease and to improve their glycemic control and treatment adherence.

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➤Educational background & professional experience

2001	Dankook University, Sports Science Department / BS.
2001-2003	Dankook University, Sports Medicine Department, Special Graduate School / MS.
2006-2013	Dankook University, graduate school / PhD.
2001-present	Inje University Ilsan Paik Hospital Sports Medical Center / Exercise Specialist

➤Research interests

Exercise prescription for patients, Sports medicine

➤Brief list of publications

1. Comparison of balance ability between patients with type 2 diabetes and with and without peripheral neuropathy. PM R. 2014 Mar;6(3):209-14.
2. Comparison of Cardiopulmonary Endurance among Positions in Middle School Soccer Players and Their Sports Injuries, The Korean Journal of Sports Medicine, 2013, 31(2): 63-68.
3. The Effect of 12 Week Exercise Training on Cardiopulmonary and Muscular Function in Chronic Obstructed Pulmonary Disease Patients, HEALTH & SPORTS MEDICINE, 2013, 15(1): 97-108.
4. Effect of exercise Rehabilitation on the Muscular Function and Sense of Balance in Patient with after Cervical Fixation, HEALTH & SPORTS MEDICINE, 2010, 12(3):75-87.

Exercise for patients with diabetes

The benefits of regular exercise in patients with type 2 diabetes mellitus include improved glucose tolerance, increased insulin sensitivity, decreased HbA1c, and insulin requirements. Additional exercise benefits for people with type 1 and type 2 diabetes mellitus include improvement in CVD risk factors and wellbeing.

People with diabetes mellitus with ≥ 10% risk of a cardiac event over a 10 year period and who want to begin a vigorous intensity exercise program should undergo medically supervised graded exercise test (GXT) with electrographic (ECG) monitoring.

Exercise program may differ among those with type 1 and type 2 diabetes mellitus. A primary purpose for a person with type 1 diabetes mellitus to undertake an exercise program is often cardiovascular health related; whereas for a person with type 2 diabetes mellitus, the primary purposes are often healthy weight loss and improved glucose disposal. The aerobic exercise training recommendations for those with diabetes mellitus. Frequency is 3-7 d · wk. Intensity is 50-80% VO2R or HRR corresponding to a rating of perceived exertion (RPE) of 12 to 16 on a 6 to 20 scale. Time is 20-60 min · d continuous or accumulated in bouts of at least 10minutes to total 150 min · wk. Type is emphasize activities that use large muscle groups in a rhythmic and continuous fashion. Resistance training should be encouraged for people with diabetes mellitus in the absence of contraindications, retinopathy, and recent laser treatments. Frequency is 2-3 d · wk. Intensity is 2-3 sets of 8-12 repetitions at 60-80% 1RM. Time is 8-10 multijoint exercises of all major muscle groups. Type is emphasize proper technique, including minimizing sustained gripping, static work with isometric exercise, and the Valsalva maneuver to prevent an exacerbated BP response. Lifestyle interventions for weight loss that combine reductions in energy intake with increases in energy expenditure through exercise and physical activity. Exercise with a partner or under supervision to reduce the risk of problems associated with hypoglycemic events and cardiac events.

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➤**Educational background & professional experience**

1991-1995 Kosin University / B.S
2003-2007 Graduate School of Public Health Yonsei University / M.S

➤**Research interests**

Education & behavior

Travelling, sick day and other special situations

- Illness may cause high blood glucose levels or low blood glucose levels:
  Infections with fever often cause high BGLs
  Gastroenteritis (vomiting and diarrhea) illnesses often cause low blood glucose levels
- Travelling and holidays should not be restricted because your child has diabetes
- Planning ahead will help prevent any problems and ensure that travel and holidays are safe and enjoyable
- See your diabetes doctor and educator before the trip - especially for overseas trips
- Changes to timing and routines can be dealt with by planning ahead

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➤Educational background & professional experience

2002	Seoul National University, Food and Nutrition / M.D
2001-present	Samsung Medical Center, Dept. of Clinical Dietetics / Clinical Dietitian,
2014	Committee of Education, Korean Diabetes Association / Committee member
	Korean Association of Diabetes Dietetic Educators / General affairs

➤Research interests

Carbohydrate counting, Elderly diabetes mellitus

➤Brief list of publications

1. Cho JW, Kweon MR, Park YM, Woo MH, Yoo HS, Lim JH, Koo BK, Kim CH, Kim HJ, Park TS, Shin CH, Won KC, Lim S, Jang HC. A Survey of Diabetic Educators and Patients for the Revision of Korean Food Exchange Lists. Diabetes Metab J. 2011 Apr;35(2):173-181
2. Dal Lae Ju, Hak Chul Jang, Young Yun Cho, Jae Won Cho, Hye Sook Yoo, Kyung Suk Choi, Mi Hye Woo, Cheong Min Sohn, Yoo Kyoung Park, Ryo Won Choue. Special Report : Korean Food Exchange Lists for Diabetes: Revised 2010. 2011;12(4):228-245

Medical nutrition therapy for diabetes comorbidities

Medical nutrition therapy (MNT) is an integral component of diabetes management and diabetes self-management education and MNT for diabetes includes the process and the system by which nutrition care is provided for diabetic individuals and the specific lifestyle recommendations for that care.

Because individuals with CKD often have a compromised nutritional status and protein-energy malnutrition, maintaining and improving nutritional status while maintaining glycemic control are often the primary goals for medical nutrition therapy. A modified protein diet is recommended to reduce nitrogenous wastes in the body that may exacerbate further kidney damage. Energy intake and other nutrition recommendations (eg, potassium, phosphorus, and sodium) must also be considered for individuals with CKD.

Diabetes is an independent risk factor for cardiovascular disease in both men and women. CVD is the major cause of death in people with diabetes.

Individualized nutrition therapy is integral in the attainment of blood glucose, lipid, and blood pressure goals, and in the prevention and treatment of CVD in people with diabetes.

Interventions may include modest weight loss, glycemic control, reduction of sodium, saturated and trans fat, and dietary cholesterol intake, increased viscous fiber intake.

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➤Educational background & professional experience

1997	Yonsei University, College of Social Sciences, / B.A. in Social Welfare (Bachelor's of degree)
2005	Yonsei University Graduate School / M.A. in Social Welfare(Master's of degree)
2008-2009	Social Workers Study Group for Diabetes education, The Korean association of Medical Social Workers / president
2001-present	Yonsei University, Gangnam Severance Hospital, Department of Social Work / medical & psychiatric social worker

➤Research interests

Psychological adaptation of diabetic patients
Behavioral change for diabetic patients
Patient empowerment
Families of diabetic patients

➤Brief list of publications

1. Jee Hyun Lee, Hyun Jeong Jeon, Kyoung Ah Kim, Hong Woo Nam, Jeong Taek Woo, Kyu Jeung Ahn. Diabetes Education Recognition Program. The Journal of Korean Diabetes 13(4):219-224, 2012

Stress management of patients with diabetes

Acute or chronic stress may impair a patients' ability for self-care and diabetes control. So the identification and management of stress should be a part of a patient's overall treatment program. According to the studies of Miller, Schewchuk, Richards, main stresses of diabetes are the following: eating on time, learning about diabetes, controlling the desire for sweets, family and friends finding out about the disease, worries about weight and overall health condition, driving alone, difficulties in exercising, and fear of being a burden to the family. These can seem small and usual, but in real life these basic stresses can be the most challenging ones to overcome. Therefore diabetes educators should assess the stress level of the patients, and guide them to appropriate management methods. Negative methods of controlling the blood glucose level such as drinking, smoking and overeating should also be avoided.

A positive method is one that leads to changes in the physical, cognitive and relational aspects. The fundamentals are based on teaching the relationship between stress and diabetes so that the patient would be motivated to watch out for stress. Some methods for relaxation of the body and the mind are: deep breathing exercise, abdominal breathing, meditation, yoga, progressive muscle relaxation training, biofeedback, and other relaxation training. Stress is a very personal thing and usually stems from negative cognition of the situation, therefore eliminating stress by having a positive way of thinking and controlling anger coming from negative and self-destructive thoughts under stress are very important. In case of conflicts with other individuals, they learn to calm down first so that the situation would not get worse by bursting into rage, and they learn assertive training, which helps them explain which words or actions of the other individual affected them, and what kind of emotions they felt.

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➤Educational background & professional experience

2000	Seoul National University / MD
2001-2005	Seoul National University Children's Hospital, Department of Pediatrics / Resident
2008-2010	Seoul National University Children's Hospital, Department of Pediatrics / Fellow
2010-present	Inje University Ilsan Paik Hospital, Department of Pediatrics / Assistant Professor

➤Research interests

Diabetes mellitus, Obesity, Growth & puberty

➤Brief list of publications

1. Chung HR, Yang SW, Shin CH, Park KS, Lee YA, Kim JH, Lee SH, Kim JH. The association of variable number of tandem repeats of the insulin gene with susceptibility to type 1 diabetes among Korean subjects. Diabetes Metab Res Rev 2010;26:474-80.
2. Kang MJ, Kim JH, Lee SH, Lee YA, Shin CH, Yang SW. The prevalence of testicular adrenal rest tumors and associated factors in postpubertal patients with congenital adrenal hyperplasia caused by 21-hydroxylase deficiency. Endocr J 2011;58:501-8.
3. Choi JH, Park JY, Kim GH, Jin HY, Lee BH, Kim JH, Shin CH, Yang SW, Yoo HW. Functional effects of DAX-1 mutations identified in patients with X-linked adrenal hypoplasia congenita. Metabolism 2011;60:1545-50.
4. Lee SH, Kim JH, Kang MJ, Lee YA, Won Yang S, Shin CH. Implications of nocturnal hypertension in children and adolescents with type 1 Diabetes. Diabetes Care 2011;34:2180-5.

Current state of management and support system for diabetes camp in Seoul, Incheon and Gyeonggi-do

Diabetes Camp in Seoul, Incheon and Gyeonggi-do region has been held for 28 years. It is one of the most historic diabetes camp in Korea. The 29th Diabetes Camp will be held this year.

The camp was held for 4 days in the summer season. Participants are children and adolescents with type 1 diabetes aged 10-19 years. The parents or care givers of campers were not allowed to attend. Approximately 60 campers and 60 staffs were participated every year. The venue of the camp was changed almost every year.

Diabetes Camp was operated by Diabetes Camp Committee, which composed a chairperson, two assistant administrator, leaders of pediatricians, nurses, dietitians, social workers and volunteers. Operation expenses was supported by camper fees and sponsors.

The need for the diabetes camp increases with the increment of youth with type 1 diabetes. However there are difficulties to recruit campers and raise financial support. Therefore it is important to set up an appropriate system for the diabetes camp for children and adolescents.

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➤**Educational background & professional experience**

2002	Hanyang University College of Medicine / M.D
2012	Hanyang University College of Medicine / Ph.D.
2002-2007	Samsung Cheil Hospital, Department of Internal Medcine / Residency
2007-2009	Seoul National University / Fellowship
2009-2012	Hallym University College of Medicine / Instructor
2012-	Hallym University College of Medicine / Assistant professor

➤**Research interests**

Diabetes complications, Geriatric medicine, Endocrine oncology

➤**Brief list of publications**

1. Cheng Ji Jin, Sung Hoon Yu, Xiao-Mei Wang, Se Joon Woo, Hyo Jin Park, Hyun Chul Lee, Sung Hee Choi, Kyoung Min Kim, Jung Hee Kim, Kyong Soo Park, Hak Chul Jang, Soo Lim. The effect of lithospermic acid, an antioxidant, on development of diabetic retinopathy in spontaneously obese diabetic rats. PLoS One. 2014 Jun 6;9(6):e98232.
2. YC Hwang, HY Ahn, SH Yu, SW Park, CY Park. Atherogenic dyslipidaemic profiles associated with the development of Type 2 diabetes: a 3.1-year longitudinal study. Diabet. Med. 2014 Jan;31(1) :24-30.
3. Chang Won Won, Hyung Joon Yoo, Sung Hoon Yu, Chang Oh Kim, Lourdes Carolina I. Dumlao, Esthika Dewiasty, Jeffrey Rowland, Hao-Hsiang Chang, Jintang Wang, Masahiro Akishita, Tan Thai Lian, Christopher Lum, Om Prakahsh. Lists of geriatric syndromes in the Asian-Pacific geriatric societies. Eur Geriatr Med. 2013:4:335-338.
4. Sung Hoon Yu, Jun Goo Kang, Yoo-Cheol Hwang, Kyu Jeung Ahn, Hyung Joon Yoo, Hong Yup Ahn, Sung Woo Park, Cheol-Young Park. Increasing achievement of the target goals for glycemic, blood pressure and lipid control for adults with diagnosed diabetes in Korea. J Diabetes Invest, 2013:4:460-465.
5. Chan Soo Shin, Min Joo Kim, Sang Mi Shim, Jin Taek Kim, Sung Hoon Yu, Bo Kyung Koo, Hwa Young Cho, Hyung Jin Choi, Sun Wook Cho, Sang Wan Kim, Seong Yeon Kim, Seung-O Yang, Nam H. Cho. The prevalence and risk factors of vertebral fractures in Korea. J Bone Miner Metab. 2012;30:183–192.

Current status of operation and support in "KDA 2030 Camp"

Type 1 diabetes mellitus is a rare chronic condition in young Korean people. The prevalence of diabetes in adults 30 years and older reached 4 million in 2011 and the number of children and adolescents with diabetes is estimated to be at 57.5 per 100,000 as of 2011. But no precise data is available on the overall prevalence of type 1 diabetes in Korea. Some experts predict the prevalence to be below 1%. Therefore, most of the time, type 1 diabetes patients are treated as same as type 2 diabetes. Adolescents with type 1 diabetes accept much of the responsibility for their own care. Intensive management can delay the onset of microvascular complications as well as slow the progression. Therefore, improving self-management is a critical factor in making a difference in the course of type 1 diabetes. Diabetes self-management education is essential for all individuals with diabetes who want to achieve successful health-related outcomes. In most diabetes practices, intensive education is provided at diagnosis with follow-up education as needed. One could argue that everyone would benefit from periodic courses on details of diabetes care. Participants' lifestyles, knowledge, skills, attitudes, and disease characteristics change over time so that ongoing education is necessary and appropriate. So diabetes camp is an ideal place for continued education of adolescents with diabetes. Several studies have shown that diabetes camp has a beneficial effect on knowledge and self-management of the disease. In this topic, current status of operation and support in KDA 2030 Camp will be discussed.

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➤Educational background & professional experience

2001	Yonsei University College of Medicine / MD
2003-2007	Severance Children's Hospital / Residentship (Pediatrics)
2007-2010	Severance Children's Hospital / Clinical research fellow (Pediatric endocrinology)
2010-present	Gangnam Severance Hospital / Assistant professor

➤Research interests

Growth in childhood, Beta cell physiology in type 1 diabetes

➤Brief list of publications

1. Longitudinal standards for height and height velocity in Korean children and adolescents: the Kangwha study. Chae HW, Suh I, Kwon AR, Kim YJ, Kim YH, Kang DR, Kim HY, Oh SM, Kim HC, Kim DH, Kim HS. J Korean Med Sci. 2013 Oct;28(10):1512-7
2. The clinical measures associated with C-peptide decline in patients with type 1 diabetes over 15 years. Lee TH, Kwon AR, Kim YJ, Chae HW, Kim HS, Kim DH. J Korean Med Sci. 2013 Sep;28(9):1340-4.(corresponding author)
3. Final height and insulin-like growth factor-1 in children with medulloblastoma treated with growth hormone. Chae HW, Park YS, Kim DS, Kwon AR, Kim HS, Kim DH. Childs Nerv Syst. 2013 Oct;29(10):1859-63.
4. Hypodipsic hypernatremia leading to reversible renal failure following surgery for craniopharyngioma. Kwon AR, Ann JM, Shin JI, Chae HW, Kim HS. J Pediatr Endocrinol Metab. 2012;25(9-10):1027-30.
5. Spot urine albumin to creatinine ratio and serum cystatin C are effective for detection of diabetic nephropathy in childhood diabetic patients. Chae HW, Shin JI, Kwon AR, Kim HS, Kim DH. J Korean Med Sci. 2012 Jul;27(7):784-7.

Severance diabetes camp for children with diabetes: experience and limit

Severance diabetes camp for children with diabetes has been held every year since 1992, 4 days summer camp for patients only and 2 days winter camp for family members. About 100 people, 55 campers and 45 staffs (physicians, nurses, dietitians, social workers, recreation therapists, and old boys) join to summer camp usually. Patients between the ages of 10 and 18 with almost all type 1 diabetes have enjoyed this experience. Nowadays, college students can participate the camp as campers. Severance diabetes camp for young adults with diabetes was held just once at 2008. For winter camp, about 100 family members and 10 staffs participate.

Days are filled with sports activities, game, swimming, talent shows, campfires, dances, diabetes education by each section, and intensive education for new patients. Many campers join to the camp several times. Camp staffs try to teach self care and model appropriate diabetes to new campers and pay more attention to the poorly controlled patients during camp. The staffs use a variety of methods to offer age-appropriate diabetes knowledge and skills and help campers gain confidence and self-sufficiency.

Camps make a difference in the lives of children with diabetes, their parents and even the staff. However, the new educational methods are limited and interest of campers are decreasing. It is the important point to advance diabetes camp.

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➤Educational background & professional experience

1991-1997	Chungnam National University, College of Medicine, Daejeon, Korea / M.D. Degree
1999-2001	Chungnam National University,Graduate School, Daejeon, Korea / Master Degree
2001-2004	Chungnam National University,Graduate School, Daejeon, Korea / Ph.D. Degree
2004-2010	Department of Internal Medicine, Eulji University School of Medicine / Assistant professor
2010-present	Division of Endocrinology and Metabolism, Department of Internal Medicine, Chungnam University Hospital / Associate professor

➤Research interests

Insulin resistance, Adipose tissue inflammation, Beta cell

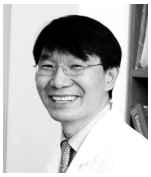
➤Brief list of publications

1. Ryu MJ, Kim SJ, Kim YK, Choi MJ, Tadi S, Lee MH, Lee SE, Chung HK, Jung SB, Kim HJ, Jo YS, Kim KS, Lee SH, Kim JM, Kweon GR, Park KC, Lee JU, Kong YY, Lee CH, Chung J, Shong M. Crif1 deficiency reduces adipose OXPHOS capacity and triggers inflammation and insulin resistance in mice. PLos Genet. 2013;9(3): e1003356. doi: 10.1371/journal.pgen.1003356. Epub 2013 Mar 14.
2. Lee IS, Lee JH, Kim HJ, Lee JM, Lee SK, Kim HS, Lee JM, Park KS, Ku BJ. Novel ERBB receptor feedback inhibitor 1 (ERRFI1) + 808 T/G polymorphism confers protective effect on diabetic nephropathy in a Korean population. Dis Markers. 2013;34(2):113-124
3. Hye-Mi Lee, Jwa-Jin Kim, Hyun Jin Kim, Minho Shong, Bon Jeong Ku and Eun-Kyeong Jo. Upregulated NLRP3 Inflammasome Activation in Patients With Type 2 Diabetes. Diabetes. 2013;62(1):194-204
4. Kim HJ, Park KS, Lee SK, Min KW, Han KA, Kim YK, Ku BJ. Effects of pinitol on glycemic control, insulin resistance and adipocytokine levels in patients with type 2 diabetes mellitus. Ann Nutr Metab. 2012;60(1):1-5
5. Kim TK, Kang YE, Kim JM, Hong WJ, Kim KS, Kim HJ, Kim YK, Ku BJ. Effects of Diabetic Camp in Type 2 Diabetic Patients. Korean J Med 2012;83(2):210-215.

Past, present and future of Chungcheong branch's diabetes camp

The Chungcheong branch of KDA has held a diabetes camp for adult patients with type 2 diabetes every August since 2005. The goal is to teach patients to manage their diabetes in their day-to-day lives, and to improve the quality of lives of type 2 diabetes patients and their families. Chungcheong diabetes camp program is composed with education about diabetes complication, self- management and diet, physical activity and recreation. About 70 campers from hospitals in the Chungcheong region participate in our diabetes camp. About 50 members(medical physicians, nurses and dietitians) attend the camp as staff and try to develop a better program based on our experience. However, there is a limitation in that patients who need education and these programs aren't able to attend such diabetes camps due to time and financial constraints. It is a hurdle that expenses are on the increase and financial support is less available. Therefore, it is time to think of a developing method and system for patients who actually require this program.

▌Panel Discussion ▐



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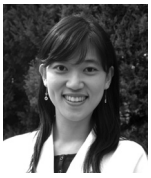

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➤Educational background & professional experience

1967	Harvard Medical School / MD
1970-1972	Mass General Hospital - Boston / Endocrinology Fellow
1984-present	Joslin Diabetes Center / Islet Section Chief
1990-present	Harvard Medical School / Professor of Medicine

➤Research interests

Islets of langerhans – dysfunction in diabetes and beta cell replacement therapy

➤Brief list of publications

1. O'Sullivan ES, Johnson AS, Omer A, Hollister-lock J, Bonner-Weir S, Colton CK, Weir GC. (2010). Islet cell aggregates are superior to islets for transplantation in microcapsules. Diabetologia, 53 (5): 937-45. PMC Journal – In Process.
2. Marselli L, Thorne J, Dahiya S, Sgroi DC, Sharma A, Bonner-Weir S, MarchettiP,Weir GC. (2010). Gene expression profiles of beta-cell enriched tissue obtained by laser capture microdissection from subjects with type 2 diabetes. Plos ONE, 5:e11499. PMCID:PMC2903480.
3. Annes J, Ryu J, Lam K, Carolan P, Utz K, Hollister-Lock J, Arvanites A, Rubin L, Weir GC, Melton D. (2012). Adenosine Kinase Inhibition Selectively Promotes Rodent and Porcine Islet β-Cell Replication. PNAS, 109 (10): 3915-3920. PMCID:PMC3309788.
4. Weir GC, Bonner-Weir S. Islet β cell mass in diabetes and how it relates to function, birth, and death. Ann N Y Acad Sci. 2013, Apr;1281:92-105. doi: 10.1111/nyas.12031. Epub 2013 Jan 30. Review. PMID: 23363033

Keynote lecture: The beta cell in diabetes

The human pancreas contains about one million islets and one billion beta cells. In type 1 diabetes, almost all of the beta cells are destroyed, while in type 2 diabetes, there is loss of about 40~70% of the cells. In both forms of diabetes beta cells are exposed to an abnormal environment of hyperglycemia, which leads to insulin secretory dysfunction, process called glucotoxicity. Thus, there are reductions in both actual beta-cell mass and in functional mass. The loss of beta cell efficiency may be reduced to as much as 70% of normal. This loss of functional mass is important because it is reversible, as has been best shown with bariatric surgery.

Beta cells subjected to glucose toxicity undergo marked changes in gene expression, which is considered by some to be dedifferentiation. The same issue with beta cell mass and function are faced by transplanted islets. There continues to be great interest in beta cell replacement therapy by either transplantation of regeneration. Great progress is being made with the conversion of embryonic stem cell to beta cells and in understanding the regenerative capacity of the adult human pancreas.

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➤Educational background & professional experience

1966	Rice University / BA
1971	Case Western Reserve University / PhD
1980-1981	University of Geneva, Switzerland / Visiting scientist
1986-present	Harvard Medical School / Professor
1994-present	Joslin Diabetes Center / Senior Investigator

➤Research interests

Islets, Regeneration, Growth of endocrine pancreas

➤Brief list of publications

1. Keenan HA, Sun J, Levine J , Doria A, Aiello LP, Eisenbarth GE, Bonner-Weir S, King GL. Residual Insulin Production and Pancreatic β Cell Turnover after 50 Years of Diabetes: Joslin Medalist Study. Diabetes 2010; 59:2846-53 PMCID: PMC2963543
2. Bonner-Weir S, Li W-C, Ouziel-Yahalom L, Guo L, Weir GC, Sharma A. β-cell growth and regeneration: replication is only part of the story. Diabetes 2010; 59:2340-2348.PMCID:PMC3740706
3. Jermendy A*, Toschi E. *, Aye T, Koh A, Aguayo-Mazzucato C, Sharma A, Weir GC, Sgroi D, Bonner-Weir S. Neonatal beta cells lack the specialized metabolic phenotype of mature beta cell. Diabetologia 2011, 54:594-604. PMCID: PMC3045081
4. Aguayo-Mazzucato C, Koh A, El Khattabi I, Li W-C, Toschi E, Juhl K, Mao K, Weir GC, Sharma A*, Bonner-Weir S*. MafA expression enhances functional maturity of neonatal beta-cells Diabetologia 2011,54:583-593. PMCID: PMC3047400
5. Aguayo-Mazzucato C, Zavacki AM, Marinelarena A, Hollister-Lock J, El Khattabi I, Marsili A, Weir GC, Sharma A, Larsen PR, Bonner-Weir S. Thyroid hormone promotes postnatal rat pancreatic beta cell development and glucose-responsive insulin secretion through MAFA. Diabetes 2013. 62:1569-80. PMCID: PMC3636623 .
6. Weir GC, Bonner-Weir S. Islet β cell mass in diabetes and how it relates to function, birth, and death. Ann N Y Acad Sci. 2013 Apr;1281:92-105. PMCID: PMC3618572
7. Bonner-Weir S, In't Veld P, Weir GC. Re-analysis of study of pancreatic effects of incretin therapy: Methodological deficiencies. Diabetes Obes Metab. 2014 2014 16:661-666. PMID: 24400596

Keynote lecture: Regeneration of the endocrine pancreas: can it lead to β cell replenishment in diabetes?

The regenerative process in the pancreas is of particular interest since diabetes, whether type 1 or type 2, results from an inadequate amount of insulin-producing β cells. While there has been progress in deriving insulin-producing cells from embryonic stem cells and from induced pluripotent stem (IPS) cells for β-cell replacement, there is increased interest in using endogenous sources for β-cell replenishment. Experimental rodent models provide evidence that replication of pre-existing β cells as well as differentiation of new β cells from progenitors (neogenesis) contribute to the normal, compensatory, and regenerative growth. Our data from the rodent regeneration model of partial pancreatectomy has led us to hypothesize that differentiated pancreatic ductal cells function as progenitors for new islets after birth, that with stimulus they replicate and regress to a less differentiated phenotype that is equivalent to that of embryonic pancreatic progenitors and these then redifferentiate to form new acini and islets. While we can only speculate about growth and regeneration mechanisms from autopsied human pancreas, recent studies have suggested that the lack of β-cell proliferation reported for human pancreas may be artifactual. Additionally the existence of scattered insulin positive cells in autopsied pancreas from persons with over 50 years of insulin dependent diabetes as well increases in small islets in those with type 2 diabetes support new β-cell formation in adult humans. Thus both pathways appear functional in all mammalian species studied but may make quantitatively different contributions in different species and under different conditions. The resultant important question is how can we induce further β-cell replenishment.

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➤**Educational background & professional experience**

1996-2000	Kyoto University Graduate School of Medicine / Student
2001-2006	Department of Diabetes and Clinical Nutrition, Kyoto University Graduate School of Medicine / Assistant Professor
2006-2010	Department of Diabetes and Clinical Nutrition, Kyoto University Graduate School of Medicine / Senior Lecturer
2010-2011	Department of Diabetes and Clinical Nutrition, Kyoto University Graduate School of Medicine / Associate Professor
2011-present	Department of Endocrinology, Metabolism and Nephrology, Kochi Medical School, Kochi University / Professor

➤**Research interests**

Islet biology

➤**Brief list of publications**

1. Sasaki M, Fujimoto S, Sato Y, Nishi Y, Mukai E, Yamano G, Sato H, Tahara Y, Ogura K, Nagashima K, Inagaki N: Reduction of reactive oxygen species ameliorates metabolism-secretion coupling in islets of diabetic GK rats by suppressing lactate overproduction. Diabetes 62: 1996-2003, 2013
2. Nishi Y, Fujimoto S, Sasaki M, Mukai E, Sato H, Sato Y, Tahara Y, Nakamura Y, Inagaki N: Role of mitochondrial phosphate carrier in metabolism-secretion coupling in rat insulinoma cell line INS-1. Biochem J 435: 421-430, 2011
3. Mukai E, Fujimoto S, Sato H, Oneyama C, Kominato R, Sato Y, Sasaki M, Nishi Y, Okada M, Inagaki N. Exendin-4 suppresses Src activation and reactive oxygen species production in diabetic GK rat islets in an Epac-dependent manner. Diabetes 60:218–226, 2011
4. Yoshihara E, Fujimoto S, Inagaki N, Okawa K, Masaki S, Yodoi J, Masutani H: Disruption of TBP-2/Txnip ameliorates insulin sensitivity and secretion without affecting obesity. Nature Commun 1:article no. 127, 2010
5. Kominato R, Fujimoto S, Mukai E, Nakamura Y, Nabe K, Shimodahira M, Nishi Y, Funakoshi S, Seino Y, Inagaki N: Src activation generates reactive oxygen species and impairs metabolism-secretion coupling in diabetic Goto-Kakizaki and ouabain-treated rat pancreatic islets. Diabetologia 51:1226-1235, 2008

Role of overproduction of ROS and lactate in impaired insulin secretion in diabetes

One of the characteristics of type 2 diabetes (T2DM) is that the insulin secretory response of β-cells is selectively impaired to glucose. In the GK rat, a genetic model of non-obese T2DM, glucose-induced insulin secretion (GIIS) is selectively impaired. The intracellular ATP elevation induced by high glucose is impaired in GK rats as well as in patients with T2DM. The impaired insulinotropic action of glucose in diabetic β-cells may be attributable to deficient ATP production derived from impaired glucose metabolism. Although there is evidence that islets in GK rat and human T2DM are oxidatively stressed, the association between oxidative stress and impaired intracellular ATP elevation in islets is yet unclear.

We propose that endogenous generation of reactive oxygen species (ROS) by activation of Src, a non-receptor protein-tyrosine kinase, plays an important role in GIIS in GK islets. Src was activated and Src inhibition restored the impairment of GIIS and ATP elevation in GK islets. In addition, GLP-1 signaling decreased Src activation and ROS production, and ameliorated impaired ATP elevation by high glucose dependently on Epac in GK islets.

12-h suppression of ROS by exposure to tempol, a superoxide dismutase mimic, plus ebselen, a glutathione peroxidase mimic (TE-treatment) improved GIIS and ATP elevation in GK islets. Lactate production was markedly increased in GK islets and TE-treatment reduced lactate production and protein expression of lactate dehydrogenase and hypoxia-inducible factor 1α (HIF1α). These results indicate that the Warburg-like effect, the characteristic aerobic metabolism in cancer cells by which lactate is overproduced with reduced linking to mitochondria metabolism, plays an important role in impaired metabolism-secretion coupling in diabetic β-cells and suggest that ROS reduction can improve mitochondrial metabolism by suppressing lactate overproduction through inhibition of HIF1α stabilization.

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➤Educational background & professional experience

2002-2004	University of Pennsylvania, PA, USA, Biomedical Graduate Sciences, Department of Genetics / MS Genomics
2004-2010	Columbia University Medical Center, NY, USA, Institute of Human Nutrition / PhD Metabolic Biology
2010-2012	New York Stem Cell Foudation / Post Doctoral Fellow
2012-2013	Chulalongkorn University, Bangkok, Thailand; Faculty of Dentistry and Biological Sciences / Instructor
2013-present	King Mongkut's University of Technology Thonburi, Bangkok, Thailand; Faculty of Science / Tenured-track Principle Investigator

➤Research interests

Mechanisms of human beta-cell failure
Biomarkers of human beta-cell dedifferentiation
Differentiation of human gut to insulin-producing cells

➤Brief list of publications

1. Talchai C, Xuan S, Lin HV, Sussel L, Accili D. Pancreatic beta-cell Dedifferentiation As Mechanisms Of Diabetic Beta-cell Failure. Cell 2012 Sep 14;150(6):1223-34. PubMed PMID: 22980982
2. Talchai C, Xuan S, Kitamura T, Depinho RA, Accili D. Generation of functional insulin-producing cells in the gut by Foxo1 ablation. Nat Genet. 2012 44: 406-412. PubMed PMID: 22406641
3. Talchai C, Lin HV, Kitamura T, Accili D. Genetic and biochemical pathways of Beta-cell failure in type 2 diabetes. Diabetes Obes Metab. 2009 Suppl 4: 38-45. PubMed PMID: 19817787
4. Talchai SC and Accili D. Adult beta cell growth and function is coupled by the role of Foxo1 during pancreatic endocrine progenitors development. Cell Metb. Submitted 2014
5. Talchai, C, and Accili D., Foxo1 ablation increases endocrine progenitor cells in the adult pancreas. Diabetes 2010

Adult pancreatic beta-cell mass and function is linked by Foxo1 regulation during endocrine progenitor differentiation

β-cell dysfunction in type 2 diabetes results from combined abnormalities of insulin production, secretion, and β -cell number. In addition, altered developmental programming of β-cell mass and function can cause β-cell dysfunction. Foxo1 plays a key role in maintaining adult β-cell function. But little is known about its embryonic role in pancreatic endocrine progenitor cell survival and β-cell replication as determinants of future β-cell function. We addressed this question by generating an allelic series of somatic Foxo1 knockouts at different stages of pancreatic development. Ablation of Foxo1 in pancreatic progenitors resulted in delayed activation of Neurogenin3 expression and its persistence into adulthood, which in turn resulted in a 7-fold increase of β-cell mass, accompanied by elevated levels of Sox9 and a twofold increase of pancreas size. Despite the increased mass, β-cells of mice lacking Foxo1 responded poorly to secretagogues, resulting in glucose intolerance and mild hyperglycemia. Foxo1 ablation in endocrine progenitor cells led to a similar increase in β-cell mass and impaired insulin secretion in adult animals, but neither to changes in pancreas size, nor to increased Sox9. In contrast, ablation of Foxo1 in terminally differentiation β-cells didn't increase β-cell mass. These findings suggest a narrow developmental window during which Foxo1 predetermines β-cell replication potential at the expense of β-cell function, and that inversely affects adult β-cell mass and function. Our results illustrate how developmental programming predisposes to development of type 2 diabetes in adults.

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➤Educational background & professional experience

1974-1979	University of Naples, Department of Genetics / PhD
1979-1985	Laboratoire de Génétique Moléculaire des Eucaryotes, CNRS / Fellow
1986-1989	The Salk Institute / Visiting research scientist
1990-2006	CNRS / Research Director
2006-present	University of California, Irvine / Professor

➤Research interests

Dr. Sassone-Corsi studies gene expression and signal transduction, with an emphasis on the links between cellular metabolism, epigenetics and the circadian clock.

➤Brief list of publications

1. Cardone L, Hirayama J, Giordano F, Tamaru T, Palvimo JJ, Sassone-Corsi P. (2005) Circadian clock control by SUMOylation of BMAL1. Science 309: 1390-1394.
2. Hirayama J, Sahar S, Grimaldi B, Tamaru T, Takamatsu K, Nakahata Y, Sassone-Corsi P. (2007) CLOCK-mediated acetylation of BMAL1 controls circadian function. Nature 450: 1086-90.
3. Nakahata Y, Sahar S, Astarita G, Kaluzova M, Sassone-Corsi P. (2009) Circadian control of the NAD+ salvage pathway by CLOCK-SIRT1. Science 324: 654-7.
4. Eckel-Mahan KL, Patel VR, de Mateo S, Orozco-Solis R, Ceglia NJ, Sahar S, Dilag-Penilla SA, Dyar KA, Baldi P, Sassone-Corsi P. Reprogramming of the circadian clock by nutritional challenge. (2013) Cell 155:1464-78.
5. Masri S, Rigor P, Cervantes M, Ceglia N, Sebastian C, Xiao C, Roqueta-Rivera M, Deng C, Osborne TF, Mostoslavsky R, Baldi P, Sassone-Corsi P. (2014) Genomic partitioning of circadian transcription by SIRT6 leads to segregated control of cellular metabolism. Cell (in press).

Epigenetics, metabolism and the circadian clock

Experimental and epidemiological evidence reveal the profound influence that industrialized modern society has imposed on human social habits and physiology during the past 50 years. This drastic change in lifestyle is thought to be one of the main causes of modern diseases including obesity, type 2 diabetes, mental illness such as depression, sleep disorders, and certain types of cancer. These disorders have been associated with disruption of the circadian clock, an intrinsic time-keeper molecular system present in virtually all cells and tissues. The circadian clock is a key element in homeostatic regulation by controlling a large array of genes implicated in cellular metabolism. Importantly, intimate links between epigenetic regulation and the circadian clock exist and are likely to prominently contribute to the plasticity of the response to the environment. I will present some experimental and epidemiological evidence showing how environmental factors such as stress, drugs of abuse and changes in circadian habits, interact through different brain areas to modulate the endogenous clock. Furthermore, I will point out the pivotal role of the deacetylases SIRT1 and SIRT6 as molecular effectors of the environment in shaping the circadian epigenetic landscape.

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➤Educational background & professional experience

2001-2004	Korea University / Assistant Professor
2004-2009	Korea University / Associate Professor
2005-2006	University of Texas / Research Fellow
2009-present	Korea University / Professor

➤Research interests

Adipokines & hepatokines, Sarcopenic obesity, Vascular inflammation

➤Brief list of publications

1. Hong HC, Hwang SY, Choi HY, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. The relationship between sarcopenia and non-alcoholic fatty liver disease (NAFLD): The Korean Sarcopenic Obesity Study (KSOS). Hepatology 2014 May;59(5):1772-8
2. Choi HY, Park JW, Lee N, Hwang SY, Cho GJ, Hong HC, Yoo HJ, Hwang TG, Kim SM, Baik SH, Park KS, Yoon B-S, Choi KM. Effects of a combined aerobic and resistance exercise program on C1q/TNF-related protein-3 (CTRP-3) and CTRP-5 levels. Diabetes Care 2013 Oct;36(10):3321-7
3. Choi KM, Hwang SY, Hong HC, Yang SJ, Choi HY, Yoo HJ, Lee KW, Nam MS, Park YS, Woo JT, Kim YS, Choi DS, Youn BS, Baik SH. C1q/TNF-related Protein-3 (CTRP-3) and Pigment Epithelium-Derived Factor (PEDF) Concentrations in Patients with Type 2 Diabetes and Metabolic Syndrome. Diabetes 2012 Nov;61(11):2932-6
4. Choi HY, Kim S, Yang SJ, Yoo HJ, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Association between adiponectin, resistin and vascular inflammation: Analysis with 18F-Fludorodeoxyglucose Positron Emission Tomography. Arterioscler Thromb Vasc Biol 2011 Apr;31(4):944-9
5. Kim TN, Park MS, Yang SJ, Yoo HJ, Kang HJ, Song W, Seo JA, Kim SG, Kim NH, Baik SH, Choi DS, Choi KM. Prevalence and determinant factors of sarcopenia in patients with type 2 diabetes: the Korean Sarcopenic Obesity Study (KSOS). Diabetes Care; 2010 Jul;33(7):1497-1499

Destination diabetes: exploring the pathways and junctions of the T2DM

Vildagliptin is a potent and selective dipeptidyl peptidase-4 (DPP-4) inhibitor, shown to increase the active glucagon-like peptide 1 (GLP-1) levels by approximately 2- to 3-fold, and significantly reduces both fasting and postprandial glucose levels in patients with type 2 diabetes mellitus (T2DM).

Vildagliptin is rapidly and well absorbed with good bioavailability (85%). The primary elimination route is hydrolysis by multiple organs. Vildagliptin has a low potential for drug interactions, as the involvement of cytochrome P450 enzymes is minimal (<1.6%) in the overall metabolism. Clinical pharmacokinetic (PK) studies have reported that vildagliptin does not affect the PK of metformin, pioglitazone, glyburide, amlodipine, valsartan, and simvastatin.

In the elderly patients, vildagliptin exposure increases by 30%, which is not considered to be clinically relevant. Vildagliptin has been established to be an effective and safe therapy in elderly patients with T2DM without dose adjustment. Although vildagliptin exposure increases by approximately 2-fold in patients with renal impairment, the increase in the exposure does not correlate with the severity of renal impairment, which may be attributable to the fact that the kidneys contribute to both the excretion and the metabolism of vildagliptin. Hepatic impairment as well as gender, body mass index (BMI), and ethnicity do not affect the PK of vildagliptin. These results suggest that vildagliptin can be safely used in a diverse patients group.

Vildagliptin has been shown to improve beta-cell function and enhance the sensitivity of alpha cell responsiveness to both suppressive effects of hyperglycemia and stimulatory effects of hypoglycemia in patients with T2DM.

Long-term randomized clinical trials have shown that vildagliptin 50 mg once or twice daily is effective, safe, and well tolerated as either monotherapy or combination with other anti-diabetic medications in patients with T2DM.

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➤Educational background & professional experience

1988	Chiba University / M.D.
1992-1996	Ludwig Institute for Cancer Research / Guest researcher
1996	Uppsala University / PhD
2009-present	Chiba University, Department of Medicine / Professor
2011-present	Chiba University Hospital / Deputy Director

➤Research interests

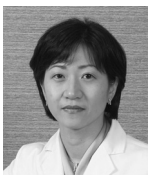
Metabolic disorders and atherosclerosis, Progeroid syndrome

➤Brief list of publications

1. Kobayashi K, Yokote K et al. Efficacy and safety of the dipeptidyl peptidase-4 inhibitor sitagliptin compared with α-glucosidase inhibitor in Japanese patients with type 2 diabetes inadequately controlled on sulfonylurea alone (SUCCESS-2): a multicenter, randomized, open-label, non-inferiority trial. Diabetes Obes Metab. 2014, Epub ahead of print.
2. Muto T, Yokote K et al. Concurrent loss of Ezh2 and Tet2 cooperates in the pathogenesis of myelodysplastic disorders. J Exp Med. 2013, 210(12): 2627.
3. Watanabe K, Yokote K et al. Sitagliptin improves postprandial hyperglycemia by inhibiting glucagon secretion in Werner syndrome with diabetes. Diabetes Care. 2013, 36(8): e119.
4. Teramoto T, Yokote K et al. Executive summary of the Japan Atherosclerosis Society (JAS) guidelines for the diagnosis and prevention of atherosclerotic cardiovascular diseases in Japan -2012 version. J Atheroscler Thromb. 2013; 20(6):517.
5. Takemoto M, Yokote K et al. Diagnostic criteria for Werner syndrome based on Japanese nationwide epidemiological survey. Geriatr Gerontol Int. 2013, 13(2): 475.

Lipid management in diabetes: potential role of pitavastatin in Asian patients

Diabetes is a major risk factor of atherosclerotic cardiovascular diseases (CVD). Patients with diabetes tend to show atherogenic lipid profiles related to insufficient insulin action including the appearance of small dense low-density lipoprotein (LDL), increase in the amount of remnant lipoproteins, and decrease in and functional disability of high-density lipoproteins (HDL). Cholesterol-lowering therapy by use of statin has been well established to prevent CVD in subjects with diabetes. As a result, the 2014 American College of Cardiology (ACC)/American Heart Association (AHA) guideline for cholesterol treatment defined diabetes as one of four "statin-benefit groups". In the guideline, patients with diabetes aged 40-75 and LDL-C $\geq$ 70 mg/dl are recommended to take either moderate- or high-intesity statin. However, suitability of ACC/AHA guideline in Asian patients remains to be proven. It is also still uncertain whether all patients with diabetes are similarly at very high risk equivalent to subjects with prior CVD. In addition, recent data suggest that statin usage is associated with increased risk of developing diabetes in non-diabetic population. Among various statins, pitavastatin is characterized for its potent LDL-C-lowering as well as TG-lowering and stable HDL-C-elevating effects. Moreover, clinical trials performed in Europe and Japan so far have not shown adverse effect of pitavastatin on glucose metabolism. In this presentation, the role of statin in management of diabetes with special emphasis on Asian population will be discussed.



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➤Educational background & professional experience

1994	Kynng-Hee University, College of Medicine, Seoul, Korea / M.D
1999	Depart. Of endocrinology & metabolism, Kynng-Hee University, College of Medicine, Seoul, Korea / PhD.
1999-2002	Samsung Medical Center, Seoul, Korea / Clinical Research Fellow
2002-2005	Hallym University College of Medicine, Seoul, Korea / Assistant Professor
2008-2009	Joslin Diabetes Center, Harvard Medical School / Visiting Researcher
2010-present	Kyung Hee University, College of Medicine, Seoul, Korea / Associate Professor

➤Research interests

Diabetic complication and vascular biology, hepatic insulin resistance, beta cell biology.

➤Brief list of publications

1. Chin SO(1), Hwang JK, Rhee SY, Chon S, Hwang YC, Oh S, Ahn KJ, Chung HY, Woo JT, Kim SW, Kim YS, Kang JH, Jeong IK. Risk factors for the progression of intima-media thickness of carotid arteries: a 2-year follow-up study in patients with newly diagnosed type 2 diabetes. Diabetes Metab J. 2013 Oct;37(5):365-74.
2. Chin SO, Rhee SY, Chon S, Hwang YC, Jeong IK, Oh S, Kim SW. Investigation of responsiveness to thyrotropin-releasing hormone in growth hormone-producing pituitary adenomas. Int J Endocrinol. 2013;2013:159858.
3. Hwang JK(1), Min KH, Choi KH, Hwang YC, Jeong IK, Ahn KJ, Chung HY, Chang JS.Bisphenol A reduces differentiation and stimulates apoptosis of osteoclasts and osteoblasts. Life Sci. 2013 Sep 17;93(9-11):367-72
4. Chin SO(1), Rhee SY, Chon S, Hwang YC, Jeong IK, Oh S, Ahn KJ, Chung HY, Woo JT, Kim SW, Kim JW, Kim YS, Ahn HY. Sarcopenia is independently associated with cardiovascular disease in older Korean adults: the Korea National Health and Nutrition Examination Survey (KNHANES) from 2009. . PLoS One. 2013;8(3):e60119.

Novel approach of dyslipidemia management in T2DM based on updated guideline & clinical trial

Cardiovascular disease is a significant cause of morbidity and mortality in patients with type 2 diabetes mellitus (T2DM). DM is now recognized as a risk equivalent for coronary heart disease.

Both primary and secondary prevention studies have showed strong evidence that aggressive statin therapy reduces cardiovascular end points in patients with DM.

In DM patients, current treatment guidelines recommend reduction of LDL-C to less than 100 mg/dL, regardless of baseline lipid levels or to 50% of baseline lipid levels. Lowering LDL-C to less than 70 mg/dL may provide even greater benefits, particularly in very high risk patients with DM and coronary heart disease.

This lecture will discuss the updated guidelines and clinical trials to treat dyslipidemia in patients with T2DM.

Oral presentations

Oral presentations

Oral presentation 1	Epidemiology
[OP1-1~OP1-5]	Friday 17 October, 13:00~14:00 / Room 6
Oral presentation 2	Microvascular complications
[OP2-1~OP2-5]	Friday 17 October, 13:00~14:00 / Room 7
Oral presentation 3	Islet biology & insulin secretion
[OP3-1~OP3-5]	Friday 17 October, 13:00~14:00 / Room 8
Oral presentation 4	Clinical diabetes
[OP4-1~OP4-5]	Friday 17 October, 14:00~15:00 / Room 6
Oral presentation 5	Metabolic syndrome & prediabetes
[OP5-1~OP5-5]	Friday 17 October, 14:00~15:00 / Room 7
Oral presentation 6	Insulin signaling / action
[OP6-1~OP6-5]	Friday 17 October, 14:00~15:00 / Room 8
Oral presentation 7	Therapeutics of diabetes
[OP7-1~OP7-5]	Saturday 18 October, 13:30~14:30 / Room 6
Oral presentation 8	Macrovascular complications
[OP8-1~OP8-5]	Saturday 18 October, 13:30~14:30 / Room 7
Oral presentation 9	Integrated physiology / obesity
[OP9-1~OP9-5]	Saturday 18 October, 13:30~14:30 / Room 8
Oral presentation 10	Behavior, nutrition, education & exercise
[OP10-1~OP10-5]	Saturday 18 October, 13:30~14:30 / Room 9

OP1-1 Epidemiology

Optimal cut off level of high-density lipoprote in cholesterol for prediction of cardiovascular disease: the comparison of the Korean and United States' national health and nutrition examination survey

Joon Ho Moon[1,2*], Min Kyong Moon[1,3], Bo Kyung Koo[1,3]

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Object: We compared high-density lipoprotein cholesterol (HDL-C) level in the Korean and U.S. population with stratified analysis according to age and sex and estimated the optimal cutoff value of HDL-C that best predicts the risk of cerebrovascular accident (CVA) and ischemic heart disease (IHD) in Koreans.

Methods: The Korean National Health and Nutrition Examination Survey (KNHANES) 2010~2012 and the National Health and Nutrition Examination Survey (NHANES) 2011~2012 were used for the Korean and U.S. population, respectively, and their HDL-C was compared using general linear model. To estimate the optimal HDL-C cutoff value that predicts CVA and IHD, sensitivity and specificity by different HDL-C levels were calculated. The optimal HDL-C cutoff was determined by r (r = √[(1-sensitivity)^2 + (1-specificity)^2]) on its minimal value.

Results: Mean HDL-C was significantly lower in KNHANES in both sex (P = 0.003 in men and P < 0.001 in women). Mean HDL-C in men was 46.1 (standard error [SE], 0.2) mg/dL in KNHANES and 47.7 (SE, 0.5) mg/dL in NHANES, respectively; in women, 51.2 (SE, 0.2) mg/dL in KNHANES and 58.3 (SE, 0.8) mg/dL in NHANES. The optimal HDL-C cutoff in prediction of CVA/IHD was 43 mg/dL and 48 mg/dL for Korean men and women, and 41 mg/dL and 56 mg/dL for U.S. men and women.

Conclusion: Our findings suggest that HDL-C was significantly lower in the Korean population compared to U.S. population in both sex. The optimal cutoff HDL-C value in predicting the risk of CVA/IHD is considered as 43 mg/dL for men and 48 mg/dL for women in the Korean population.

OP1-2 Epidemiology

The risk of future coronary heart disease according to the presence of type 2 diabetes mellitus and prior coronary heart disease in the Korean population: a population-based cohort study using national health Insurance claims data

Chang Hee Jung[1*], Gi Hyeon Seo[2], Sunghwan Suh[3], Ji Cheol Bae[4], Mee Kyoung Kim[5], You-cheol Hwang[6], Jae Hyeon Kim[4], Byung-Wan Lee[7]

Asan Medical Center, University of Ulsan College of Medicine, Department of Internal Medicine[1], Health Insurance Review and Assessment Service, Health Insurance Review and Assessment Service[2], Dong-A University Medical Center, Department of Internal Medicine[3], Samsung Medical Center, Sungkyunkwan University School of Medicine, Department of Internal Medicine[4], The Catholic University of Korea, Department of Internal Medicine[5], Kyung Hee University School of Medicine, Department of Internal Medicine[6], Severance Hospital, University of Yonsei University College of Medicine, Department of Internal Medicine[7]

Objective: Whether diabetic patients without a history of coronary heart disease (CHD) have the same risk of CHD events as non-diabetic patients with a history of CHD remains controversial. This study aimed to determine whether type 2 diabetes mellitus (T2DM) is a CHD equivalent in the development of future CHD in the Korean population.

Methods: We followed 2,168,698 subjects (mean ages 61.4 ± 9.9 years; men 52.8%) who had T2DM in 2008 and/or CHD in 2007~2008 (i.e., recent CHD). We used systematic datasets from the nationwide claims database of the Health Insurance Review and Assessment service of Korea, which is representative of the whole population of Korea, from January 2007 to December 2012. The primary study endpoint was the development of incident CHD after January 2009 among three groups based on their status of T2DM and recent CHD, i.e., T2DM only, recent CHD only, and both T2DM and recent CHD. Incident CHD was identified using selected codes for procedures related to coronary revascularizations.

Results: After adjustment for age and sex, patients with recent CHD only had 2.14-times the risk of incident CHD (95% CI, 2.20~2.27, P < 0.001) compared with patients with T2DM only. Patients with both T2DM and recent CHD demonstrated a 2- to 4-fold increased risk of incident CHD compared with subjects with recent CHD only and T2DM only, respectively. The risk of incident CHD also differed according to sex and age.

Conclusion: This analysis of data from the nationwide claims database revealed that T2DM is not a CHD risk equivalent in the Korean population. These results suggest that an appropriate strategy for CHD risk stratification in diabetic patients should be adopted rather than a 'blanket' approach to treatment in this population.

OP1-3 Epidemiology

Sarcopenia is associated with non-alcoholic fatty liver disease regardless of obesity and metabolic syndrome: nationwide surveys (KNHANES 2008~2011)

Yujung Yun[*], Yong-Ho Lee, Hye Jin Yoon, Jaehyun Bae, Byung-wan Lee, Eun Seok Kang, Hyun Chul Lee, Bong Soo Cha

Yonsei University College of Medicine, Department of Internal Medicine

Object: Although sarcopenia is associated with obesity-related comorbidities, their influence on non-alcoholic fatty liver disease (NAFLD) has not been fully determined. The aim of this study was to investigate the relationship between sarcopenia and NAFLD in the general population in Korea.

Methods: We conducted a cross-sectional study with nationally representative samples of 13,199 subjects from the Korea National Health and Nutrition Examination Surveys (KNHANES) between 2008 and 2011. Subjects with heavy alcoholics or positive results for serology tests of hepatitis B or C were excluded. NAFLD was defined by applying previously established models for NAFLD prediction such as Fatty Liver Index, or Hepatic Steatosis Index. Sarcopenic index (appendicular skeletal muscle mass as a percentage of body weight or ASM/Wt) measured by dual-energy X-ray absorptiometry was used to define sarcopenia.

Results: Sarcopenic index (ASM/Wt) was inversely correlated with all NAFLD predicting indices. After stratification with obesity (BMI ≥ 25 kg/m^2) or metabolic syndrome, sarcopenic subjects had significantly higher proportion of NAFLD regardless of the presence of obesity or metabolic syndrome. Multiple logistic regression analysis showed that sarcopenia, BMI, HOMA-IR, triglycerides, diabetes and smoking were significantly associated with the increased odds ratios (ORs) for the risk of NAFLD, whereas exercise and moderate drinking had decreased ORs for the risk of NAFLD. Furthermore, among subjects with NAFLD, sarcopenic subjects had higher proportion of severe liver fibrosis, assessed by using BARD score regardless of the presence of obesity or metabolic syndrome. In subgroup analysis, only obese subjects with preserved skeletal muscle mass who exercise regularly had a lower proportion of NAFLD compared to those who do not exercise.

Conclusion: This study can provide a strong evidence that sarcopenia is associated with liver fibrosis as well as NAFLD, regardless of obesity or metabolic syndrome.

OP1-4 Epidemiology

The relationship between sarcopenia and non-alcoholic fatty liver disease: the Korean sarcopenic obesity study

Ho Cheol Hong[*], Ja Young Ryu, Hye Jin Yoo, Ji a Seo, Nan Hee Kim, Sin Gon Kim, Sei Hyun Baik, Dong Seop Choi, Kyung Mook Choi

College of Medicine, Korea University, Division of Endocrinology and Metabolism, Department of Internal Medicine

Objective: Previous studies have shown that non-alcoholic fatty liver disease (NAFLD) and sarcopenia may share pathophysiological mechanisms, such as insulin resistance, inflammation, vitamin D deficiency, and decreased physical activity. However, their direct relationship has not been investigated.

Methods: The association between NAFLD and sarcopenia was examined in 452 apparently healthy adults enrolled in the Korean Sarcopenic Obesity Study (KSOS), an ongoing prospective observational cohort study. The liver attenuation index (LAI), which measured using abdominal computed tomography (CT), was used as a parameter for the diagnosis of NAFLD. Sarcopenia was defined using a skeletal muscle mass index (SMI) [SMI (%) = total skeletal muscle mass (kg) / weight (kg) × 100] that was measured by dual energy X-ray absorptiometry (DXA).

Results: After adjusting for age and sex, both SMI and LAI were negatively correlated with the homeostasis model assessment of insulin resistance (HOMA-IR) (P < 0.001) and high sensitivity C-reactive protein (hsCRP) (P < 0.001) as well as brachial-ankle pulse wave velocity (baPWV), an indicator of arterial stiffness. Furthermore, SMI and LAI had positive relationships with HDL-cholesterol, but both had a negative relationship with triglyceride, alanine aminotransferase (ALT), and total body fat. In a multiple logistic regression analysis, the odds ratio for NAFLD risk was 5.16 (95% CI = 1.63~16.33) in the lowest quartile of SMI compared to the highest after adjusting for potential confounding factors.

Conclusion: Individuals with lower muscle mass exhibited increased risk of NAFLD. This result may provide a novel insight into the mechanism linking between sarcopenia and NAFLD.

OP1-5 Epidemiology

Association between arsenic and diabetes mellitus in National Health and Nutrition Examination Survey 2007-8

Bernard Cheung[1*], Ching Lung Cheung[1], Tommy Tsang Cheung[1], Adrian Justin Cheung[1], Raymond Yau Hang Leung[1], Kwok Leung Ong[2]

University of Hong Kong, Department of Medicine[1], University of New South Wales, Australia, Centre for Vascular Research[2]

Objective: Whether exposure to arsenic in the environment is associated with diabetes is controversial. We therefore studied this association in the National Health and Nutrition Examination Survey (NHANES) 2007-8.

Methods: In NHANES 2007-8, urine arsenic was measured in around one-third of participants. After excluding children and those with missing fasting blood glucose or urine arsenic data, 591 participants were included in the analysis. There were 109 participants with diabetes, defined as glycosylated hemoglobin ≥ 6.5%, fasting serum glucose ≥ 126 mg/dL, self-reported previous physician diagnosis of diabetes, or self-reported use of anti-diabetic medication.

Results: Comparing the highest and lowest quintiles of total urine arsenic (〉 13.94 vs 3.38 μg/L), the odds ratio for diabetes is 1.71 (0.78~3.72) in the unadjusted model, but after adjustment for age, sex, ethnicity, education, body mass index, cotinine, blood mercury, urine creatinine and anti-hypertensive medication use, the odds ratio is 3.22 (1.21~8.56) (P = 0.022). The result remains significant after subtracting arsenobetaine concentration. However, if the highest and lowest tertiles are compared (〉 9.78 vs 〈 4.55 μg/L), the adjusted odds ratio is 2.38 (0.93~6.08) (P = 0.069).

Conclusion: High arsenic exposure (total urine arsenic 〉 13.94 μg/L) in one-fifth of Americans is associated with diabetes, but this association is attenuated at lower levels of exposure. Our results do not prove a causal link between arsenic and diabetes. However, as arsenic is present in drinking water and foods such as rice, it would be prudent to monitor the exposure of the general population to arsenic and keep it low.

OP2-2 Microvascular complications

Lipoprotein(a) predicts new onset of chronic kidney disease in patients with type 2 diabetes mellitus: a ten-year follow-up study

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Objective: We investigated factors that might influence the development of chronic kidney disease (CKD) in patients with type 2 diabetes.

Methods: From January 2000 to December 2002, a total of 1,367 patients with type 2 diabetes without CKD (estimated glomerular filtration rate [eGFR] ≥ 60 mL/min/1.73 m^2) were consecutively enrolled. Patients were devided into two groups according to their baseline serum Lp(a) levels (Lp(a) 〉 30 mg/dL vs Lp(a) ≤ 30 mg/dL). The estimated GFR was measured annually, and new onset CKD was defined as eGFR 〈 60 mL/min/ 1.73 m^2 using a Modification of the Diet in Renal Disease formula.

Results: Of the 1,367 patients who were enrolled in this study, 904 (66.1%) completed the follow-up evaluation. The median follow-up time was 9.8 years. The mean age was 56.0 ± 10.3 years, and the duration of diabetes was 8.5 ± 6.9 years. The baseline eGFR was 98.3 ± 25.6 mL/min/1.73m^2. During the follow-up period, 234 patients (25.9%) progressed to chronic kidney disease. The patients in the CKD group were older (P 〈 0.001), had hypertension (P 〈 0.001), a longer duration of diabetes (P 〈 0.001), higher baseline A1C levels (P 〈 0.001), higher rates of albuminuria (P 〈 0.001), and received more insulin and ACE inhibitor treatment (P 〈 0.001). A Cox hazard regression analysis revealed that the development of CKD was significantly associated with the high level of serum Lp(a) level (Lp(a) 〉 30 mg/dL vs Lp(a) ≤ 30 mg/dL: hazard ratio 3.4; 95% CI 2.50 − 4.54; P 〈 0.001) after adjusting for sex, age, diabetic duration, mean A1C, albuminuria, treatment of insulin, ACE inhibitor/ARB and lipid lowering agents.

Conclusion: In conclusion, the development of CKD from normal renal function was independently associated with serum Lp(a) level in patients with type 2 diabetes.

OP2-1 Microvascular complications

Changes in endothelial glycocalyx accessibility is associated with microvascular perfusion

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Objective: Changes in endothelial glycocalyx are one of the earliest changes in development of cardiovascular disease. The endothelial glycocalyx is both an important biological modifier of interactions between flowing blood and the vessel wall, and a determinant of organ perfusion. We hypothesize that deeper penetration of erythrocytes into the glycocalyx is associated with reduced microvascular perfusion.

Methods: The population-based prospective cohort study (the Netherlands Epidemiology of Obesity [NEO] study) includes 6,673 middle-aged individuals (oversampling of overweight and obese individuals). Within this cohort, we have imaged the sublingual microvasculature of 915 participants using sidestream darkfield (SDF) imaging together with a recently developed automated acquisition and analysis approach. Presence of RBC (as a marker of microvascular perfusion) and perfused boundary region (PBR), a marker for endothelial glycocalyx barrier properties for RBC accessibility, were assessed in vessels between 5 and 25 μm RBC column width.

Results: A wide range of variability in PBR measurements, with a mean PBR of 2.14 μm (range: 1.43~2.86 μm), was observed. Linear regression analysis showed a marked association between PBR and microvascular perfusion, reflected by RBC filling percentage (regression coefficient β: -0.034; 95% confidence interval: -0.037 to -0.031).

Conclusion: We conclude that microvascular beds with a thick ("healthy") glycocalyx (low PBR), reflects efficient perfusion of the microvascular bed. In contrast, a thin ("risk") glycocalyx (high PBR) is associated with a less efficient and defective microvascular perfusion.

OP2-3 Microvascular complications

Glycated albumin and the risk of nephropathy progression in patients with Korean type 1 diabetes

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Objective: We investigated the association between the ratio of serum glycated albumin (GA) levels to hyperglycemic levels (GA/A1c ratio) and the progression of diabetic nephropathy (DN) in Korean type 1 diabetes (T1D).

Methods: For this retrospective longitudinal study, we recruited patients who had undergone repeated both urine albumin excretion (UAE) and kidney functions using estimated glomerular filtration rate (eGFR) measurements as well as been tested consecutively for both A1c and GA levels every 3 or 6 months. Diabetic nephropathy (DN) was defined as increased UAE or decreased eGFR. The subjects were classified into two groups based on DN-progression (group I) and non-progression (group II). Mean values of A1c, GA and the GA/A1c ratio were compared between groups.

Results: Of the 154 subjects (69 men and 85 women) with 2.8 years mean follow up period of UAE, group I (n = 30) showed significantly longer diabetes duration (12y vs 8y, P = 0.004) and higher baseline albumin-creatinine ratio (ACR) (47.3 μg/mg vs 14.6 μg/mg, P = 0.004) than group II (n = 124). The mean GA (29.3% vs 24%, P = 0.004) and mean GA/HbA1C (3.2 vs 2.9, P = 0.037) were significantly higher in group I than group II. In multivariate logistic regression analysis, mean GA (OR = 1.98, P = 0.003) and mean GA/HbA1C (OR = 1.77, P = 0.007) were independently associated with the progression of DN after adjustment for other risk factors both models applied. In addition, ROC curve showed that mean GA (AUC = 0.69, 95% CI = 0.55~0.78, P = 0.004) alone had statistically significant AUCs compared with meanHbA1C (AUC = 0.6, 95% CI = 0.49~0.71, P = 0.088).

Conclusion: The present study showed that GA and GA/A1c ratio are more associated with DN progression than HbA1c as a glycemic index in Korean patients with T1D.

OP2-4 Microvascular complications

Effects of pentoxifylline on proteinuria and glucose control in type 2 diabetic patients: prospective randomized double blind multicenter study

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Objective: Pentoxifylline is a methylxanthine derivative with significant anti-inflammatory, anti-fibrotic properties, and anti-proliferative properties. Some studies have shown that pentoxifylline may have renoprotective effect in chronic kidney disease. However, previous studies had limitations due to a small sample size and heterogeneity of patient's characteristics. Therefore we investigated whether pentoxifylline has additive protective effect of reducing proteinuria in patients with diabetic nephropathy and residual proteinuria despite adequate therapy with angiotensin-converting enzyme inhibitor (ACEI) or angiotensin II receptor blocker (ARB). We also studied the effects of pentoxifylline on glycemic control and insulin resistance.

Methods: This was a prospective, randomized double blind, active control, multi-center study. The study protocol was approved by the ethics committee of the Korea Ministry of Food and Drug Safety. 174 patients with type 2 diabetes and albuminuria greater than 30mg/g of creatinine on treatment with ACEI or ARB were randomly assigned to receive pentoxifylline (1200 mg, daily (n = 87) or placebo (n = 87). The endpoint was the effect of pentoxifylline on proteinuria and glucose control, renal function, and inflammatory parameters.

Results: After 6 months, treatment with pentoxifylline did not change the amount of proteinuria. Although the estimated glomerular filtration rate (eGFR) decreased in the control group, there was no significant difference from the pentoxifylline group. Pentoxifylline led to a significant reduction in fasting plasma glucose, HbA1c, and homeostatic metabolic assessment (HOMA-IR).

Conclusion: Even though we did not find benefits in proteinuria reductions or preservation of renal functions by the addition of pentoxifylline to ACEIs or ARBs, pentoxifylline therapy improved glucose control and insulin resistance in patients with type 2 diabetic nephropathy.

OP2-5 Microvascular complications

Association between red blood cell deformability and diabetic retinopathy in patients with type 2 diabetes mellitus

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Objective: Red blood cell (RBC) deformability is an ability of RBC to change shape under stress. RBC deformability has been demonstrated to be impaired in diabetes mellitus. But, little is known about the association between impaired RBC deformability and type 2 diabetes mellitus (T2DM). The aim of this study was to determine the influence of RBC deformability on T2DM.

Methods: We conducted a cross-sectional study with 198 patients with T2DM who visited in Yeungnam university hospital from Mar. to Jul. 2014. Patients with end stage renal disease and who are taking a pentoxifylline and ginkgo biloba were excluded. RBC deformability was measured by using a Rheoscan-D (Rheo-Meditech, Seoul, Korea), and expressed as elongation index (EI). The EI was measured at 3 Pa. We divided the EI into quartile (Q1, Q2, Q3 and Q4 from lowest to highest EI).

Results: 193 patients (mean age 59.82 ± 12.29 years, M:F = 100:93) were finally included. EI had significantly negative correlation with the levels of glycated hemoglobin, and positive correlation with HOMA-B, respectively (β -23.52, P = 0.01 and β 520.03, P = 0.02, respectively). Patients with micro complications had lower EI compared with patietns without complications (EI 0.303623 vs. 0.310637, P = 0.01). Of them, patients with retinopathy had lower EI compared with patients without retinopathy (EI 0.300449 vs. 0.309653, P = 0.00), whereas patients with nephropathy or neuropathy and macro complications had no significant difference in EI. After adjustment for age, sex, hypertension, smoking, and lipids, lower EI remained significantly associated with the prevalence of diabetic retinopathy (Odd ratio for Q1 compared with Q4, 4.16; 95% confidence interval, 1.43~12.13).

Conclusion: In patients with T2DM, there are significant relationship between RBC deformability and glycemic control, beta cell function and diabetic retinopathy. These results suggest that decreased RBC deformabiliy is a useful surrogate marker for predicting diabetic retinopathy.

OP3-1 Islet biology/insulin secretion

Angiopoietin-1 contributes to the glucose homeostasis by regulating insulin secretion in diet induced obesity mice model

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Objective: The intensive vascular supply in pancreatic islets enables β-cell to regulate insulin secretion promptly in response to the change of blood glucose level. Angiopoietin-1 (Ang1) is one of the most potent factors which control angiogenesis during developmental and inflammatory condition. Recently a study reported that the overexpression of Ang1 in islets improved the engraftment rate of islet transplantation by enhancing revascularization. The aim of our study was to investigate the role of Ang1 on glucose homeostasis.

Methods: We used inducible systemic Ang1 knock out mice and pancreas β-cell specific Ang1 knock out mice. After 24 weeks of high fat diet, we tested insulin sensitivity and secretory function. Furthermore, we observed the islet morphology and β-cell proliferation.

Results: High fat diet for 24 weeks after systemic deletion of Ang1 at 10 weeks of age induced glucose intolerance in Ang1 null mice compared to wild type mice with no change in insulin sensitivity. The serum insulin concentration after 15 min of glucose challenge in vivo was lower in Ang1 null mice and glucose stimulated insulin secretion in the isolated islets from Ang1 null mice was also lower compared to wild type mice, suggesting that there might be a defect in insulin secretary function in Ang1 null mice. To further dissect this phenomenon, we investigated the state of glucose homeostasis in β-cell specific Ang1 null mice. β-cell specific Ang1 null mice still demonstrated glucose intolerance after 24 weeks of high fat diet compared to the wild type mice. In immunohistochemical staining, β-cell specific Ang1 null mice showed slight decrement in the β-cell area and Ki67-positive proliferating β-cell number.

Conclusion: Ang1 might be a key molecule to regulate insulin secretion in obesity mice model. Further investigation on the exact mechanism how Ang1 contributes to insulin secretion in the β-cell is warranted in the future.

OP3-2 Islet biology/insulin secretion

Glucose-induced lipophagy inhibition causes the lipid accumulation and dysfunction of pancreatic β-cells

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Objective: Neither glucose nor FFA alone cause clinically meaningful pancreatic β-cell toxicity, especially in subjects with normal or glucose intolerance. The down- and up-regulations of autophagy under the conditions of glucotoxicity and lipotocicity, respectively, are active in β-cells. We hypothesized that glucotoxicity-induced lipophagic insufficiency causes cytotoxic lipid accumulation resulting in glucolipotoxicty in β-cells.

Methods: Cell viability assessed by MTT as well as apoptosis by Anexin-V-FITC/PI, cleaved-caspase-3 and AO/PI staining were performed. For β -cell function, insulin contents and GSIS were done. Using real-time-PCR, mRNAs expressions on lipid synthesis, β-oxidation and lipolysis were investigated. SQSTM1/p62, LC3II, p-PERK, peIF2-α, ATF4, IRE1-α, GRP78 and CHOP were evaluated by western blot. Autophagy suppression and stimulation were conducted using siATG5 or ATG5 vector in along with autophagy inhibitors (wortmannin, 3-MA) and activator (trehalose).

Results: Neither 0.03 mM palmiate nor 20 mM glucose alone didn't change cell viability. However, treatment with palmitate + glucose were significantly toxic to INS-1 cells and primary islets (AO/PI). But apoptosis wasn't significant in INS-1 cells. Compared to other conditions, insulin contents and GSIS were significantly suppressed in islets. Palmitate-induced lipid was significantly higher in the presence of high glucose than low glucose. The mRNA expressions on lipid homeostasis in palmitate + glucose-treated cells were not significantly different than those in palmitate- or glucose-treated cells alone. Glucose suppressed the autophagy induction and flux in a time- and dose-dependent manner. Autophagy induction and flux were upregulated at 0.03 mM palmitate, but upregulated induction and inhibited flux were observed at 〉 0.5 mM palmitate. Teatment with 20 mM glucose + 0.03 mM palmitate reduced autophagy induction and flux. Also, UPR markers were reduced in accordance with decreased autophagy. Palmitate-induced triglyceride was significantly increased by siATG5, 3 MA or wortmannin. However, treatment with ATG5 vector or trehalose decreased palmitate-induced TG. Finally, trehalose restored insulin contents and GSIS in both palmitae and glucose treated islets.

Conclusion: These findings indicate that lipophagic insufficiency induced by glucotoxicity causes toxic lipid accumulation resulting in β-cell dysfunction.

OP3-3 Islet biology/insulin secretion

The effects of p38 MAPK inhibitor SB203580 on β cell function and apoptosis of db/db mice

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Objective: p38 mitogen-activated protein kinase (MAPK) pathway is involved in the islet endoplasmic reticulum stress and inflammation, which can promote β-cell dysfunction and apoptosis. The purpose was to investigate whether p38MAPK inhibitor SB203580 can improve β cell function and reduce its apoptosis of db/db mice by blocking p38MAPK pathway.

Methods: forty-two, 7-week-old, female db/db mice were randomly assigned into Dmo group and Dmi group. Twenty-four, 7-week-old female C57 mice assigned into Con group were wild-type control of db/db. The Dmi group was given a gavage of SB203580 15 mg/(kg*d) while the Dmo and Con group received distilled water. Evaluate the physiological index, islets β-cell mass and associated molecue expression of the mice.

Results: After SB203580 intervention, no significant difference was found in food intake or body mass between Dmi group and Dmo group. Four weeks after the intervention, blood glucose of fasting state and IPGTT of Dmi group was significantly lower than Dmo group for five weeks; HOMA β and HOMA IR of Dmi mice were significantly improved after 5 weeks of SB203580 intervention. Since 12 weeks old, the level of phosphorylation of p38MAPK in islets was higher in Dmo group than in Con group, and SB203580 could inhibit the phosphorylation effectively in Dmi group. mRNA expression levels of endoplasmic reticulum stress markers BIP and CHOP were statistically lower in the Dmi group than Dmo group after 7 and 9 weeks of SB203580 intervention; 7 weeks of SB203580 intervention significantly reduced the mRNA expression levels of apoptosis marker Bcl-2 and Bcl-2/Bax. no statistical difference was found between the islets β-cell mass of Dmi group and Dmo group.

Conclusion: p38MAPK inhibitor SB203580 could improve β-cell function and reduce its apoptosis by inhibiting the activity of p38MAPK of the db/db mice islets effectively. Thus it lowered the blood glucose of db/db mice.

OP3-4 Islet biology/insulin secretion

Ceramide effects on TXNIP expression in pancreatic β-cell

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Objective: Ceramide is a key player in the induction of pancreatic β-cell apoptosis, insulin resistance, and reduction of insulin gene expression. Thioredoxin-Interacting Protein (TXNIP) has also emerged as an important regulator in β-cell biology and diabetes development. Elevated TXNIP expression by high glucose and diabetes induced β-cell apoptosis whereas inhibition or knock-out of TXNIP protected β-cells dysfunction. However, the effects of ceramides on TXNIP expressions have remained largely unknown. To identify the mediator of ceramide in pancreatic β-cell dysfunction, we investigated the expression and pathophysiological role of TXNIP in response to ceramide to induce β-cell dysfunction and apoptosis in insulin producing cells.

Methods: INS-cells and primary rat islets were treated with ceramide and we measured TXNIP mRNA and protein expression. In addition, we also characterized the signaling pathways in response to ceramide.

Results: Ceramide treatment increased β-cell apoptosis and TXNIP expression as well as down regulated Insulin and PDX-1 expression. Moreover, ceramide treatment increased mitochondrial membrane potential loss resulting in cytochrome c release which leads to caspase-3 activation. Prolonged exposure to ceramide also activated several MAPKs, including p38 MAPK and JNK. Intriguingly, TXNIP knockdown attenuated INS-1 cell apoptosis, caspase-3 activation, reactive oxygen species production and morphological alterations due to ceramide.

Conclusion: Our data demonstrated that TXNIP might play an important role in the ceramide induced pathogenesis of β-cell damage and serving as a potential molecular target in the modulation of pancreatic beta cell dysfunction and failure.

OP3-5 Islet biology/insulin secretion

Exploration of pathways to diabetes with a mathematical model

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Objective: To understand progression of Type 2 Diabetes. Specifically, to investigate why fasting glcucose is not elevated much before onset of Type 2 Diabetes among IGT subjects.

Methods: We built a mathematical model which is governed by differential equations. By accounting for existing beta-cell mass and function data, we fitted the model to explain underlying mechanisms of pathogenesis of Type 2 Diabetes.

Results: We have developed a mathematical model for compensation and failure of beta-cell mass and function in response to insulin resistance and pre-existing genetic defects in insulin secretion (Ha and Sherman, Diabetes 63 (Suppl. 1A): 298 2014). This allows us to look at the mechanistic defects that underlie observed pathologies such as impaired fasting glucose (IFG), impaired glucose tolerance (IGT). The model supports associations based on experiments between IFG and excess hepatic glucose production and between IGT and peripheral insulin resistance. A core feature of the onset of Type 2 Diabetes identified by the model from these simulations is the crossing a threshold between healthy and diseased states. The existence of a threshold is supported by the results of partial pancreatectomy in rats and of bariatric surgery and weight loss in humans. Finally, the model has the potential to identify mechanistic defects by fitting longitudinal data from individual subjects, and use that information to make predictions of the future trajectory of the subject.

Conclusion: Both defects in insulin secretion and resistance contribute to progression of Type 2 Diabetes. The threshold showed the mechanism of progression to T2D through IGT pathways (fasting glucose is elevated much). The model makes predictions of the future trjectory of the the subject.

OP4-1 Clinical diabetes

Increased risk of fracture and post-fracture adverse events in patients with diabetes: two nationwide population-based retrospective cohort studies

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Objective: The relationship between diabetes and fracture is not completely understood. This study evaluated fracture risk and post-fracture mortality in patients with diabetes.

Methods: We identified 32,471 adults newly diagnosed with diabetes in 2000–2003 using Taiwan's National Health Insurance Research Database. A comparison cohort of 64,942 adults without diabetes was randomly selected from the same dataset, frequency matched by age and sex. Fracture events in 2000–2008 were ascertained from medical claims. Adjusted hazard ratios (HRs) and 95% CIs of fracture associated with diabetes were calculated. A nested cohort study of 17,002 patients with fracture receiving repair surgeries between 2004 and 2010 calculated adjusted odds ratios (ORs) and 95% CIs of adverse events after fracture in patients with and without diabetes.

Results: During 652,530 person-years of follow-up, there were 12,772 newly diagnosed fracture cases. The incidences of fracture for people with diabetes and without were 24.2 and 17.1 per 1,000 person-years, respectively (P < 0.0001). Compared with people without diabetes, the adjusted HR of fracture was 1.66 (95% CI 1.60~1.72) for people with diabetes. The ORs of postfracture deep wound infection, septicemia, and mortality associated with diabetes were 1.34 (95% CI 1.06~1.71), 1.42 (95% CI 1.23~1.64), and 1.27 (95% CI 1.02~1.60), respectively.

Conclusion: Diabetes was associated with fracture. Patients with diabetes had more adverse events and subsequent mortality after fracture. Prevention of fracture and post-fracture adverse events is needed in this susceptible population.

OP4-2 Clinical diabetes

Change in body mass index and progression to type 2 diabetes in women with a history of gestational diabetes

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Objective: Increased obesity in the development of type 2 diabetes (T2DM) has not been thoroughly evaluated in prospective manner in women with previous history of gestational diabetes (GDM). In this study, we investigated the effect of change in BMI on the development of T2DM in women with previous history of GDM.

Methods: Subjects with previous history of GDM were recruited and prospectively followed from four tertiary hospitals in Korea. The participants performed 75 g oral glucose tolerance test (OGTT) serially starting at 6 week and annually after the postpartum period. Change in BMI was calculated between the initial and the last visit of examination or at the onset of diabetes. For statistical analyses, subjects were stratified into the 3 groups based on the tertiles of BMI changes, and association with the onset of T2DM was examined.

Results: 418 subjects were included for analysis. Mean duration of follow up was 3.9 ± 1.8 years. The BMI change in each tertile was -1.8 ± 1.1, -0.2 ± 0.3, and 1.6 ± 1.2 kg/m^2, respectively. Incident diabetes was observed in 53 subjects (12.7%). Incident diabetes were found in 8.6%, 12.6%, and 16.9% in each tertile group (P = 0.039). Worsening of glucose tolerance status according to BMI change was observed in 21.6%, 25.2%, and 39.7% (P < 0.001). Changes in clinical (e.g. systolic and diastolic blood pressure) and biochemical parameters (e.g. fasting glucose, insulin, and lipid profiles) were significantly improved in the lowest tertile. When change in BMI was evaluated as a continuous variable, it was an independent predictor of incident diabetes even after adjusting for age and duration of follow up (P = 0.025).

Conclusion: This study demonstrates that postpartum BMI change during four years of follow up has a significant impact on the onset of diabetes. Our study implies that tight weight management after delivery in GDM population should be beneficial for the prevention of diabetes.

OP4-3 Clinical diabetes

Efficacy of mobile diabetes care based on a newly developed patient decision support system (PDSS)

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Objective: In this pilot study, the efficacy of a new mobile diabetes care system named 'Patient Decision Support System (PDSS)' was evaluated.

Methods: The PDSS consists of smartphone application, Bluetooth glucometer, activity tracker, and monitoring website for the medical team. Participants with type 2 diabetes were informed to measure blood glucose with supplied glucometer, to input daily diet, and to carry the activity tracker. Changes in HbA1c, fasting plasma glucose (FPG) and lipid profile after 12 weeks were analyzed. Summary of Diabetes Self-Care Activities (SDSCA) was checked before and after study.

Results: Total 29 subjects aged 53.7 ± 1.6 years completed the study. Initial HbA1c, FPG and BMI were 7.7 ± 0.1%, 140.9 ± 7.3 mg/dL, and 25.0 ± 2.8 kg/m^2. After 12 weeks, HbA1c (7.1 ± 0.1%, P = 0.0002) and FPG (120.1 ± 5.7 mg/dL, P = 0.0051) were significantly reduced, and initial HbA1c correlated with the change in HbA1c (r = -0.61, P = 0.0004). The subjects who checked glucose more showed the more reduced HbA1c (r = 0.53, P = 0.0029). We compared the group of glucose input ≥ 80% (good users, n = 20) with that of < 80% (no-good users, n = 9). In good users, HbA1c decreased from 7.8 ± 0.2% to 7.0 ± 0.1% (P = 0.0002) but in no-good users, HbA1c was not changed (7.4 ± 0.3% to 7.3 ± 0.3%, P = 0.57). As for SDSCA, scores of 'blood glucose testing' (P < 0.0001), 'general diet' (P = 0.0001), and 'exercise' (P = 0.0019) were dramatically improved, especially in good users.

Conclusion: Using PDSS for 12 weeks in patients with type 2 diabetes presented remarkable reduction in HbA1c, and the amount of reduction showed good correlation with number of glucose check. PDSS was recognized to be helpful for the patients to control their lifestyle. Based on this favorable result, multicenter, randomized-controlled study is under preparation.

OP4-4 Clinical diabetes

Atherosclerosis and insulin resistance were important predictors for long-term clinical remission in patients with newly diagnosed type 2 diabetes mellitus: results from a multicenter randomized trial

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Objective: We performed a multicenter randomized trial for long-term effects of early, short-term, intensive diabetes treatment modalities, and investigated the clinical predictors for long-term remission.

Methods: Newly diagnosed, drug-naïve type 2 diabetes mellitus (T2DM) patients (n = 97) were randomly assigned to receive either IIT (n = 50; multiple insulin treatment with glargine and glulisine) or combined oral anti-diabetic agent (COAD; n = 47; glimepiride and metformin) for early intensive treatment. Intensive treatment was performed in an outpatient setting and considered to be complete when HbA1c levels were < 7%, total insulin requirement was < 10 U/day, or after a period of 12 weeks. Patients were then followed-up for 104 weeks. After outcome verification, we compared the baseline and follow-up characteristics by clinical remission (A1c < 7% without medication) of the subjects.

Results: Following early intensive treatment, both groups achieved glycemic target within 12 weeks. However, mean treatment period was significantly shorter for the IIT group (P < 0.001). During the follow-up period, both groups maintained favorable levels of glycemic control, but mean HbA1c were lower (P = 0.064) and the clinical remission rate was significantly higher (P = 0.026) in the IIT group. When comparing the baseline characteristics by remission, prevalence of carotid plaque was significantly lower, and insulin sensitivity indices were significantly higher in the subjects who have maintained remission during the observation period (P < 0.05).

Conclusion: In conclusion, both interventions were effective for long-term glycemic control, but IIT patients exhibited a greater benefit in terms of clinical remission. In sub-analyses, atherosclerotic plaque and insulin resistance Indices at baseline were important predictors for remission.

OP4-5 Clinical diabetes

1,5-anhydro-D-glucitol can reflect hypoglycemia in patients with well controlled type 2 diabetes

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Objective: Although strict glycemic control is important in prevention of microvascular complications, recurrent hypoglycemia precludes it. Therefore, if there is a simple marker for a tendency of hypoglycemia, it would be helpful for strict glycemic control without hypoglycemia. 1,5-anhydro-D-glucitol (1,5-AG) has been suggested as a marker for short term mean glucose and postprandial hyperglycemia. The aim of this study was to evaluate the usefulness of 1,5-AG as a marker for hypoglycemia in well-controlled patients.

Methods: We enrolled 27 patients with type 2 DM taking sulfonylurea (n = 20) or insulin (n = 7), if they had experienced any hypoglycemic symptoms within 3 months and HbA1C was ≤ 7.5%. We developed a hypoglycemic scoring system by modifying the Clarke scoring system which is used for type 1 DM. Plasma 1,5-AG was measured in the subjects, and continuous glucose monitoring system (CGMS) was performed in the insulin users to analyze hypoglycemia and glycemic variability.

Results: The modified hypoglycemic score was significantly (P < 0.05) correlated with Clarke score (r =0.64), total bilirubin (r = 0.47), and body weight (r = -0.45). Log[1,5-AG] was also significantly correlated with the modified hypoglycemic score (r = -0.39) when it was adjusted by HbA1c. In the CGMS subgroups, area under the curve below 80mg/dL and the time percent when glucose levels below 80 mg/dL were correlated with insulin dose (r = 1.0, P < 0.001) and glucose variability indices, such as standard deviation of glucose, MODD, CONGA-2 and CV (all r = 1.0, P < 0.001), and with C-peptide (r = -1.0, P < 0.001). Modified hypoglycemia score was correlated with M100, J index and mean amplitude of glycemic excursions (MAGE) (all r = 0.9, P < 0.05), and log [1,5-AG] was negatively correlated with them (all r = -0.9, P < 0.05).

Conclusion: Modified hypoglycemia score was negatively correlated with 1,5-AG in well-controlled type 2 diabetes patients. In subgroup analysis with the insulin group, we could identified both the score and 1,5-AG levels were correlated with indices of mean glucose and glycemic variability.

OP5-1 Metabolic syndrome & prediabetes

Ceramide induced hepatic steatosis and autophagy in T2DM animal models : a critical role of ATF3

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Contents: Previously, we have demonstrated that chronic alcohol consumption promotes the development of metabolic syndrome via the impaired glucose and/or insulin homeostasis. However, the exact molecular mechanisms and its role involved in chronic ethanol consumption-induced the impairment of glucose homeostasis are not fully understood. Here, we know that serum levels of free fatty acid (FFA) and ceramide are significantly increased in chronic ethanol-fed mice model, correlated with the increase of hepatic steatosis, serum or hepatic triglyceride and TNF-a, which are remarkably attenuated in TNFR1-/-mice. In vitro HepG2 or primary hepatocytes, treated ethanol or palmitic acid highly induces lipid accumulation and the reduction of beta-oxidations, which were reversely attenuated by the pretreatment of myriocin, an inhibitor of ceramide production from FFA, suggesting the essential role of ceramide in ethanol or palmitic acid-mediated hepatic steatosis. Interestingly, we found that a stress inducible-transcription factor ATF3 may play as a novel target molecule involved in the regulation of hepatic steatosis by ethanol-FFA-ceramide axis. Ethanol- or palmitic acid-induced ATF3, which is also regulated by TNFR1-dependent pathway, is involved in the dysregulation of autophagy via excessive lipid accumulation. Ceramide-induced ATF3 inhibits the flux of autophagy, which is initiated by the formation of lipid vesicles together with oxidative stress and ER stress, and thus highly accumulates autophagosome in the cytoplasm resulting in hepatocytes apoptosis. Taken together, our studies suggest that hepatic steatosis induced in ethanol-fed mice is associated with the formation of ethanol-FFA-ceramide axis. And also, ATF3, considered as their target molecule, may play as a negative regulator in dynamic regulation of autophagy, thus it may trigger the lipotoxicity of hepatocytes via the autophagosome accumulation.

OP5-2 Metabolic syndrome & prediabetes

GDF15 is upregulated in adipose tissue with mitochondrial OxPhos dysfunction through the activation of mitochondrial stress pathway

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Objective: Growth differentiation factor (GDF15) is multifunctional member of the TGF-beta superfamily. GDF15, a secretory cytokine, can be induced in multiple cellular stimuli such as mitochondrial oxidative phosphorylation (OxPhos) dysfunction. To verify the role of GD15 in in vivo in the context of adipose mitochondrial OxPhos dysfunction, we have observed GDF15 expression in adipose tissue-specific Crif1, an essential factor of mitochondrial OxPhos biogenesis,-deficient mice.

Methods: To establish adipose tissue-specific mitochondrial OxPhos dysfunction, we generated adipose tissue-specific Crif1-dificient mice by crossing transgenic adiponectin-cre mice with floxed Crif1 mice (Crif1f/f, adipoq-cre).

Results: Adipose tissue-specific Crif1 deficient mice showed mitochondrial OxPhos dysfunction and mild insulin resistance. Mitochondrial OxPhos dysfunction induced by adipose tissue-specific Crif1 deficiency increased GDF15 expression in adipose tissue and increased plasma level. In vitro, we were induced to mitochondrial dysfunction by rotenone, oligomycin and CCCP, Mitochondrial inhibitors increased GDF15 expression through activating transcription factor 3 (ATF3)-dependent manner in 3T3-L1 pre/adipocyte cells.

Conclusion: Therefore, we suggest that GDF15 is induced in adipose-tissue specific mitochondrial OxPhos dysfunction and might be involved in insulin resistance in mice with adipose-specific mitochondrial OxPhos dysfunction.

OP5-3 Metabolic syndrome & prediabetes

Induction of angiopoietin-like protein 6 in adipose tissues in response to reduced oxPhos function

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Objective: Mitochondria play an important role of cellular respiration and its dysfunction is closely related with metabolic syndrome. Angptl family consists of 7 proteins, especially angptl3, 4, 6 were known to involved in the control of angiogenesis and metabolism. Specifically, whole body Angptl6-null mice mice showed severe obese phenotypes and lipid accumulation in skeletal muscle and brown adipose tissue with impaired energy expenditure. However, regulation of Angptl6 expression and its roles in the context of metabolic syndrome and diabetes are remained to be elucidated.

Methods: To characterize the regulatory factors in regulation of expression of Angptl proteins in adipose tissue, we treated rotenone, oligomycin and CCCP to 3T3-L1, IPB (immortalized primary brown adipocytes), C2C12, MIN6 and HepG2 cells. In addition, we observed expression of angptl factors in adipose tissue of adipose-specific Crif1-deficient mice which has specific mitochondrial OxPhos dysfunction.

Results: Induced mitochondrial dysfunction by OxPhos complex inhibitors increased expression of angptl6 in adipocyte cell lines (3T3-L1), but primary hepatocytes and Min6 did not produce angptl6 with treatment of mitochondrial inhibitors. The other family of Angptl proteins including Angptl3 and 4 were not induced by mitochondrial OxPhos complex inhibitor. These in vitro observation consistently verified in tissue specific Crif1-deficiency mice models in vivo. Increased Angptl6 expression was more strong in WAT of adipose tissue-specific Crif1-deficiency mice then expression level from the muscle of muscle specific Crif1-deficient mice.

Conclusion: These results demonstrated that mitochondrial OxPhos dysfunction increase Angptl6 expression in adipocytes in vitro and in vivo. Angptl6 may mediate the paracrine or endocrine actions for the regulation of microenvironments and lipid metabolism in adipose tissue stressed with mitochondrial dysfunction.

OP5-4 Metabolic syndrome & prediabetes

Gemigliptin inhibits tunicamycin-induced endoplasmic reticulum stress, apoptosis and inflammation in H9c2 cardiomyocytes

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Objective: The direct effects of dipeptidyl peptidase-IV (DPP-IV) inhibitors on endoplasmic reticulum (ER) stressinduced apoptosis and inflammation in cardiomyocytes have not been elucidated.

Methods: This study showed that treatment with gemigliptin attenuated ER stress-induced apoptosis in H9c2 cells.

Results: H9c2 cell viability,which was reduced by tunicamycin, was increased after DPP-IV inhibitor gemigliptin treatment. Gemigliptin significantly decreased the tunicamycin-mediated increase in glucose regulated protein 78 (GRP78) expression and ER stress-mediated signaling molecules such as protein kinase RNA-like endoplasmic reticulum kinase (PERK)/C-EBP homologous protein (CHOP) and inositol-requiring enzyme 1a (IRE1a)/c-Jun N-terminal kinase (JNK)-p38. Furthermore, gemigliptin effectively induced Akt phosphorylation in a dose-dependent manner. Using flow cytometry and Hoechst staining, we showed that treatment with Akt inhibitor significantly blocked the anti-apoptotic effects mediated by gemigliptin. The reduction in tunicamycin-induced GRP78 level and PERK/CHOP pathway activity by gemigliptin was reversed after treatment with Akt inhibitor.

Conclusion: In conclusion, gemigliptin effectively inhibited ER stress-induced apoptosis and inflammation in cardiomyocytes via Akt/PERK/CHOP and IRE1a/JNK-p38 pathways, suggesting its direct protective role in cardiovascular diseases.

OP5-5 Metabolic syndrome & prediabetes

Intima-medial thickness and the risk of developing diabetic nephropathy

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Objective: Intima-media thickness (IMT) has been used as a subclinical index of atherosclerosis. Some cross-sectional studies showed an association of increased IMT with diabetic nephropathy (DN), but few prospective study. We assessed the relationships between IMT and new development of DN in a prospective study.

Methods: We analyzed 2302 patients of T2D without DN (eGFR 〉 90 mL/min per 1.73 m^2 and ACR 〈 30 mg/g) at enrollment from a prospective cohort study (Korea National Diabetes Program database). New development of diabetic nephropathy was defined as eGFR decreased below 60 ml/min per 1.73 m^2 or ACR increased above 30 mg/g). Patients underwent B-mode ultrasonography to assess the IMT of the far walls of both common carotid arteries annually.

Results: Subjects were followed for a mean of 3.8 ± 1.8 years. Among 2302 patients, 468 patients developed new DN. The cumulative incidence of DN was 203/1000 persons and the incidence density was 160/1000 person-year. Those who developed DN (nDN) were older (57.3 ± 10.3 yr vs. 53.2 ± 8.9 yr, P 〈 0.001), higher systolic blood pressure (127 ± 15 mmHg vs. 124 ± 14 mmHg, P = 0.002), higher triglyceride (162 ± 103 mg/dL vs.151 ± 105 mg/dL, P = 0.05) and higher mean baseline IMT (0.84 ± 0.19 mm vs. 0.80 ± 0.18 mm, P = 0.001) than those who did not. nDN group showed higher IMT-progression than NDN but it did not reach statistical significance (0.021 ± 0.042 mm/yr vs. 0.016 ± 0.044 mm/yr, P = 0.161). With cox proportional hazard models adjusting for age, sex, systolic blood pressure, and triglyceride, the highest baseline IMT tertile increased the development of DN 1.48 times (95% CI = 1.048~2.820, P = 0.032) than the lowest baseline IMT tertile. However, IMT progression rate did not increase the development of DN.

Conclusion: These data suggest that baseline IMT could be a novel clinical indicator for developing DN in patients with T2D, whereas IMT progression was not. Further study controlling the influence of the glycemic control and the medication such as anti-platelet is needed.

OP6-1 Insulin signaling / action

Assessment of insulin resistance in lean women with polycystic ovary syndrome

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Objective: Polycystic ovary syndrome (PCOS) is associated with insulin resistance (IR) and subsequent impaired glucose tolerance and type 2 diabetes mellitus. IR in PCOS appears to be correlated with obesity. However, few studies have investigated IR in lean PCOS women. The objective of this study was to validate a simple measurement of IR in lean PCOS women using oral glucose tolerance test (OGTT).

Methods: We recruited 100 PCOS women (aged 16~~36 yr; 50 lean with mean BMI 20.4 ± 1.6 kg/m^2 and 50 overweight/obese with mean BMI 25.2 ± 2.3 kg/m^2) and age, BMI-matched 100 control women. A 75-g OGTT was performed, and we obtained samples for measurement of insulin and glucose at 0, 30, 60, 90, and 120 minutes. IR indices including the homeostasis-model assessment (HOMA)-IR, M30, M60, M90, M120 and Stumvoll index [0.226 - (0.0032 × BMI) - (0.0000645 × I120) - (0.00375 × G90)] were calculated from OGTT.

Results: Total and overweight/obese women with PCOS had higher values for 2-hour post-load glucose, fasting insulin, HOMA-IR, HOMA-M30, HOMA-M60, HOMA-M90, HOMA-M120 and lower values of Stumvoll index than the corresponding controls (all Ps 〈 0.05). Lean women with PCOS had higher values for 2-hour post-load insulin, HOMA-M120 and lower values for Stumvoll index than the corresponding controls (all Ps 〈 0.05). HOMA-M120 and Stumvoll index were significantly associated with free testosterone (β = 0.087 and -0.157, respectively) and HOMA-M120 was significantly associated with triglycerides (β = 0.111) after adjusted for age and BMI in lean PCOS women (all Ps 〈 0.05).

Conclusion: Lean PCOS women showed higher IR than age and BMI-matched controls. HOMA-M120 could be a simple and predictive tool to assess IR and is associated with hyperandrogenemia and hypertriglyceridemia in lean PCOS women.

OP6-2 Insulin signaling / action

Deletion of insulin and IGF-1 receptors in thyrocytes impaires thyroid development and eventually induce papillary carcinoma in mice

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Objective: Although TSH is the dominant hormonal regulator of thyroid gland growth and function, a variety of growth factors also influence thyroid hormone synthesis. These include insulin and insulin-like growth factor I (IGF-1). However, the role of insulin and IGF-1 signaling in thyroid function and development is incompletely understood.

Methods: We disrupted insulin and IGF-1 signaling by generating mice with combined thyrocyte-specific deletion of insulin receptor and IGF-1 receptor (DTIRKO).

Results: DTIRKO mice showed a retarded thyroid growth until P14 likely resulting from decreased expression of Foxe1, and Pax8. Surprisingly, thyroid glands of DTIRKO mice were markedly enlarged with goiter by 12 weeks of age. Furthermore, DTIRKO mice developed papillary carcinoma at 12 months potentially through the activation of TSH and EGF receptor.

Conclusion: Together, these data indicate that action of insulin and IGF-1 in early life regulate thyroid growth, but long-term deletion of both receptors in thyrocytes induce paradoxical tumorigenesis of thyroid glands.

OP6-3 Insulin signaling / action

Beneficial effects of TM25659, TAZ activator, on palmitate-induced insulin resistance through the induction of FGF21

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Objective: Transcriptional co-activator with PDZ binding motif (TAZ) plays a key role in the control of myogenic differentiation and muscle regeneration through its nuclear localization and subsequent interaction with master transcription factors. However, TAZ has not been reported to be related with insulin resistance in skeletal muscle. Therefore, we investigated the effects of TAZ on palmitate-induced insulin resistance.

Methods: In this study, to determine the effects of TAZ on palmitate-induced insulin resistance, we used TM-25659 as a modulator of TAZ, C2 myotubes, and C57BL6J mice. To investigate the mechanisms underlying the contribution of TM-25659 to palmitate-induced insulin resistance, we investigated relationships between expressions of FGF21 proteins and TM-25659 using immunoblotting and quantitative Real-Time PCR.

Results: Treatment with TM-25659, TAZ stimulator, significantly blocked palmitate-inhibited glucose uptake and insulin signaling in C2 myotubes. To elucidate the preventing mechanism of TM-25659, we measured pro-inflammatory cytokines, TNF-alpha, IL-1-beta, IL-6, MCP-1, and FGF21 levels. TM-25659 inhibited production of pro-inflammatory cytokines and induced FGF21 mRNA and protein levels exposed to different doses of TM-25659. We also confirmed secretion of FGF21 from cells into cytosol by treatment of TM-25659. To determine whether TM-25659 show the same effects on C57BL6J mice, mice were injected with either vehicle or TM-25659 every other day for 1 week by IP. TM-25659 significantly increased FGF21 RNA and protein levels in mice skeletal muscles. Finally skeletal muscle cells were transfected by FGF21 siRNA and we tested FGF21 levels and beneficial effects of TM-25659 on palmitate-induced insulin resistance. TM-25659 could not rescue from palmitate-induced insulin resistance in FGF21 knockdown cells. From these results, TM25659, TAZ activator, protected palmitate-induced insulin resistance through the induction of FGF21.

Conclusion: In the present study, we suggest that TM-25659 may provide therapeutic potential as a treatment for insulin resistance and diabetes through the induction of FGF21.

OP6-4 Insulin signaling / action

Chronic oral exposure to bisphenol a induces glucose intolerance and insulin resistance

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Objective: Bisphenol A (BPA) is a widespread endocrine disruptor. Recent research suggests that BPA exposure is related to cardiovascular disease, type 2 diabetes and obesity. We investigated the in vivo effects of chronic oral BPA exposure on insulin resistance and glucose intolerance.

Methods: We administered 50 μg/kg body weight/day of BPA orally for 12 weeks to 4-6-week-old male mice on a high-fat diet (HFD). We evaluated the effects of BPA on glucose tolerance through intraperitoneal glucose tolerance test (IPGTT) and on insulin signaling through western blot analysis.

Results: Chronic oral exposure to BPA with HFD for 12 weeks in growing male mice induced glucose intolerance. IPGTT showed that the mice receiving HFD with BPA exhibited a significantly increased area under the curve compared with those receiving HFD only (119.9 ± 16.8 vs. 97.9 ± 18.2 mm · min, P = 0.027). The body weight, percent white adipose tissue and percent body fat in HFD mice were not different between the BPA treatments. However, BPA treatment did reduce Akt phosphorylation at position Thr 308 in skeletal muscle, although no significant changes were observed in hepatic or adipose tissue. BPA tended to decrease serum adiponectin and increase serum IL-6 and TNFα, though these were not statistically significant. The BPA treatment did not induce any detrimental changes in islet area or morphology or the insulin content of β cells.

Conclusion: Chronic oral BPA exposure in growing mice induced glucose intolerance and insulin resistance. Decreased Akt phosphorylation in skeletal muscle by way of altered serum adipocytokine levels might be one mechanism by which BPA induces glucose intolerance.

OP6-5 Insulin signaling / action

Saturated fatty acid-induced miR-29a impairs insulin signaling and glucose uptake through translational repression of IRS-1 in myocytes

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Objective: MicroRNAs have been shown to play an important role in insulin signaling, but its biological function in insulin resistance induced by saturated fatty acids (SFA) remains largely unknown. Recently, we have found that insulin resistance induced by mitochondrial dysfunction increased the expression of miR-29a in myocytes. Moreover, the expression of miR-29a was increased in skeletal muscle and liver of high fat diet-fed (HFD) mice. Although the miR-29 family is involved in a range of biological processes, it is unclear if and how miR-29a is linked to the regulation of insulin sensitivity in skeletal muscle.

Methods: We have analyzed the expression of miR-29a in skeletal muscle, liver, and blood of HFD mice and palmitate-treated myocytes. Next, we unveiled direct targets of miR-29a in insulin signaling intermediates. Finally, we investigated the insulin-stimulated phosphorylation of insulin signaling intermediates and glucose uptake in the presence or absence of the ectopic expression of miR-29a in myocytes.

Results: HFD mice and the treatment of SFA palmitate in myocytes exhibited impaired insulin signaling via a significant reduction of IRS-1. The expression of miR-29a was up-regulated by palmitate in a dose-dependent manner, and that miR-29a targeted IRS-1 3'UTR directly and repressed the expression of IRS-1 at the translational level. Furthermore, miR-29a was also up-regulated considerably in skeletal muscle and liver of HFD mice. The ectopic expression of miR-29a was found to cause a substantial decrease in IRS-1 expression, leading to impaired insulin signaling and insulin-stimulated glucose uptake in myocytes.

Conclusion: Here, we demonstrated that the expression of miR-29a is associated with high amount of SFA in vivo and in vitro, and that the up-regulation of miR-29a results in insulin resistance through translational repression of IRS-1 in skeletal muscle. These findings suggest a novel mechanism where miR-29a is causally related to the development of insulin resistance and diabetes.

OP7-1 Therapeutics of diabetes

Efficacy and safety of the DPP-4 inhibitor combined with insulin therapy in patients with type 2 diabetes: a systematic review and meta-analysis

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Objective: Glucose-lowering effect of the dipeptidyl peptidase-4 (DPP-4) inhibitor has been observed even in patients who were treated with insulin. In this study, we conducted a systematic review and meta-analysis on the efficacy and safety of the DPP-4 inhibitor combined with insulin therapy in patients with type 2 diabetes.

Methods: We conducted an electronic search of Medline, Embase, Lilacs, Cochrane Library and Clinicaltrials.gov databases up to June 2014. Randomized controlled trials were selected if they had at least 12 weeks of treatment duration, compared a DPP-4 inhibitor and insulin combination therapy (INS/DPP4i) with insulin alone (INS) in patients with type 2 diabetes mellitus, and described in English. The primary outcome was the change in hemoglobin A1c (HbA1c). The secondary outcomes included body weight change, fasting plasma glucose (FPG), hypoglycemia, and insulin doses.

Results: Of 2,578 potentially relevant studies, 9 studies met the inclusion criteria. INS/DPP4i therapy exhibited a greater HbA1c reduction than INS therapy (weighted mean difference [WMD], -0.55%; 95% CI -0.65, -0.44). A greater reduction in FPG was also observed in INS/DPP4i therapy (WMD, -10.13 mg/dl, 95% CI -14.14, -6.11). The incidence of hypoglycemia was similar between INS/DPP4i and INS therapy (relative risk [RR], 0.99; 95% CI 0.77, 1.28). Despite better glycemic control, INS/DPP4i did not elicit weight gain (WMD, -0.12kg; 95% CI -0.50, 0.26). In addition, INS/DPP4i therapy exhibited an insulin sparing effect compared to INS therapy (WMD, -4.10 units per day; 95% CI -7.40, -0.79).

Conclusion: Combined DPP-4 inhibitor and insulin therapy significantly improved glycemic control without increasing the risk of hypoglycemia and weight gain and exhibited an insulin sparing effect in patients with type 2 diabetes.

OP7-2 Therapeutics of diabetes

Predictive characteristics of patients achieving successful switching to oral hypoglycemic agents from insulin therapy

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Objective: To investigate clinical and laboratory parameters for predicting subjects with type 2 diabetes (T2D) who could maintain adequate glycemic control after switching to oral hypoglycemic agents (OHAs) from insulin therapy.

Methods: In this longitudinal-retrospective study, we recruited 275 patients with T2D who had been registered in 3 cohorts of newly initiated with insulin therapy, and followed up for 33 months. The subjects were divided into two groups according to either switching from insulin to OHAs (Group I) or not (Group II), and Group I was further classified into two sub-groups: either resumption with insulin (Group IB) or not (Group IA).

Results: Of 275 (61% men, mean age 58.5 years) patients treated with insulin initiation, 174 (63%) were switched to OHAs, resulting in 122 (44%) with Group IA, 52 (19%) with Group IB, and 101 (37%) with Group 2. Multiple logistic regression showed low BMI, high doses of insulin and lowest tertile of stimulated insulin secretory function assessed by PCGR (postprandial C-peptide-to-glucose ratio) (OR, 0.88, 1.05, and 2.17, respectively; 95% CI, 0.80~0.97, 1.03~1.07, and 1.08~4.37) were found to be independently associated with subjects who were ultimately unable to maintain OHA without using insulin (Group IB and Group II). In addition, the level of HbA1c at 6 month after switching to OHAs was a significant predictive parameter for successful switching to OHAs from insulin therapy, and also negatively associated with PCGR. In the ROC analysis, 1.49 of PCGR at baseline was the optimal cut-off value with sensitivity of 65% and specificity of 67%.

Conclusion: Both higher levels of PCGR at initiation of insulin therapy and HbA1c levels at 6 months after switching to OHAs might be important predictors for the successful maintenance of OHAs after switching from insulin therapy in Korean patients with T2D.

OP7-3 Therapeutics of diabetes

Application of pancreatic β-cell derived extracellcular microvesicles for the β-cell differentiation

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Objective: Islet cell transplantation has been considered as one of the potential approaches for treating Type I diabetes, which is characterized by the loss of pancreatic *β*-cell function and insulin content. However, its clinical application is hampered by the lack of donor islets, motivating many researchers to study efficient protocols, that use stem cells to differentiate into insulin producing cells (IPCs) as alternative sources of islets. Although many scientific reports raised the possibilities for the clinical application of differentiated IPCs, current IPCs producing protocols are both highly complicated and expensive due to differentiation inducing agents such as cytokines, growth factors, and chemicals etc. Furthermore, the roles of these agents in generating IPCs have not been fully elucidated yet. Such limitations led us to seek novel strategy to secure available IPCs.

Methods: *β*-cell derived microvesicles (*β*-MVs) themselves direct the differentiation of murine bone marrow derived cells (mBMDCs) into IPCs without any supplements of known differentiation inducing agents. These *β*-MVs mediated IPCs express murine *β*-cell specific transcripts and proteins within 7 days.

Results: we found mBMDCs can be differentiated into IPCs expressing mouse specific beta cell gene expression (Insulin, PDX-1, MafA, Neurogenin3 etc.) On the contrary, microvesicles from Endothelial cells (non-beta cells) did not affect the β-cell differentiation, suggesting unidentified key components in β-MVs that directly differentiate BMDCs into IPCs instead of simply transferring species specific transcripts or proteins. Moreover, transplantation of premature *β*-MVs directed IPCs attenuated hyperglycemia in diabetic mice induced by streptozotocin.

Conclusion: These results demonstrate that *β*-MVs contain much more information in IPCs differentiation, which could be applied in treating diabetic patients. This study was supported by a grant from the Innovative Research Institute for Cell Therapy (A062260) and a grant from the Korea Healthcare Technology R&D Project (A120273) by the Ministry of Health and Welfare, Republic of Korea.

OP7-4 Therapeutics of diabetes

Effect of rebamipide on gastrointestinal symptoms in patients with type 2 DM

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Objective: Atypical gastrointestinal symptoms are common in patients with type 2 diabetes mellitus (T2DM). The current study was designed to evaluate the symptom improvement after the administration of rebamipide, a mucoprotective drug that stimulates prostaglandin biosynthesis in patients with T2DM.

Methods: T2DM subjects whose age was 18 to 80 years with atypical gastrointestinal symptom were enrolled. Participants were obliged to answer DBSQ (Diabetes Bowel Symptom Questionnaire) before and after the 12 weeks administration of rebamipide and the change in gastrointestinal symptoms were assessed. DBSQ is comprised of 10 questions assessing the severity of gastrointestinal symptom by 1 to 6 scoring system. Follow-up assessments were done to identify drug related side effects at 6 weeks and 12 weeks.

Results: Total 107 patients were enrolled and 84 patients completed the study. Mean age was 65.0 ± 7.8, 24.8% of the subjects were male, and mean HbA1c level was 6.97 ± 0.82%. Rebamipide 100mg was administered three times daily for each participant. DBSQ total score was reduced from 24.9 ± 8.0 to 20.4 ± 7.3 before and after the administration of rebamipide demonstrating a significant change ($P < 0.001$). Each score of the variables assessing heartburn, reflux symptoms, postprandial dyspepsia, nausea or vomiting, abdominal bloating or distension, heartburn associated with gastric ulcer, abdominal pain, and constipation were improved after the administration of rebamipide ($P < 0.05$). However, there were no significant changes in irritable bowel symptoms and bowel incontinence. Severe adverse event was not reported throughout the study.

Conclusion: Treatment with rebamipide for 12 weeks could be an effective treatment option for atypical gastrointestinal symptoms in subjects with T2DM.

OP7-5 Therapeutics of diabetes

Comparisons of the effects of vildagliptin and glimepiride on glycemic variability and cardiovascular risk factors

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Objective: DPP-4 inhibitors induce insulin secretion in a glucose-dependent manner, therefore, they can improve glycemic variability by lowering mainly postprandial glucose levels. In this study, we designed a randomized, prospective, cross-over trial comparing glycemic variability between glimepiride and vildagliptin applying continuous glucose monitoring system (CGMS) in patients with type 2 DM. Moreover, we investigated several surrogate markers for cardiovascular diseases (CVD), too.

Methods: Twelve patients with type 2 diabetes mellitus whose HbA1c was over 7% on metformin monotherapy were randomized to vildagliptin 50 mg twice a day or glimepiride 1 mg twice a day for 3 months, and then switched to the other drug for 3 months. At the baseline, 3month and 6 month after enrollment, CGMS was applied to determine glycemic variability. In addition, we evaluated the following CVD-related markers: BP, pulse rate, BMI, waist circumferences, FBS, HbA1c, 1,5-AG, fasting insulin, c-peptide, lipid profile, high-sensitivity C-reactive protein, BNP, PAI-1, Lp(a), IMT and PWV.

Results: The subjects were 60 years old, having 5 years of DM duration and 26 kg/m^2 of BMI, under 1,250 mg/d of metformin in average. HbA1c before treatment was 7.7% for glimepiride and 7.1% for vildagliptin. After 3-month treatment, both vildagliptin and glimepiride did not change MAGE significantly, although there was an insignificant propensity to decrease MAGE in the vildagliptin group. Among other variables, glimepiride increased pulse rates as well as weight, BMI, waist circumference, and HOMA-B ($P < 0.05$). Vildagliptin marginally increased 1,5-AG ($P = 0.097$), which suggested improved postprandial hyperglycemia. However, unexpected increase in weight, BMI, and Lp(a) ($P < 0.1$) might aggravate CVD risk. At the baseline and after 3-month treatment, there were any statistical differences in the measured variables between the groups.

Conclusion: As a conclusion, glimepiride and vildagliptin had comparable effects on CVD surrogate markers during the short-term treatment in patients with type 2 diabetes.

OP8-1 Macrovascular complications

Dehydroepiandrosterone prevents free fatty acid-induced endothelial cell senescence by increasing autophagy

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Objective: Autophagy has emerged as a potentially important factor in the pathogenesis of atherosclerosis. Dehydroepiandrosterone (DHEA) is an adrenal steroid of great recent interest due to its anti-aging and anti-atherogenic effects; however, little is known about its role in autophagy and endothelial senescence. The aim of this study was to investigate whether DHEA prevents free fatty acid-induced endothelial senescence by enhancing autophagy.

Methods: Human aortic endothelial cells were treated with DHEA and linoleic acid (LA) was used as a representative free fatty acid. Senescence was determined by senescence-associated acidic b-galactosidase (SA-b-Gal) staining. The protein levels of LC3-I/LC3-II and p62 were measured by western blotting analysis. Co-localization of autophagy marker GFP-LC3 and RFP-LAMP were observed by confocal microscopy.

Results: Pre-treatment with DHEA inhibited LA-induced endothelial senescence. DHEA increased the conversion of LC3-I to LC3-II and decreased the level of p62, a protein degraded by autophagy, in a time- and dose-dependent manner. Similarly, the mRNA and protein level of autophagy related genes (i.e., Atg7 and Atg12) were increased after DHEA treatment. We next examined the effect of DHEA on LA-induced change of the autophagic machinery. Although both DHEA and LA treatment increased the conversion of LC3-I to LC3-II, treatment of LA increased p62 and decreased fusion of the autophagosome and the lysosome, which reflected decreased autophagic flux. However, pre-treatment with DHEA restored autophagic flux inhibited by LA. Furthermore, the inhibitory effect of DHEA on LA-induced endothelial senescence was abolished by transfection of LC3 siRNA. When we evaluated signaling pathways, inhibitors of ERK, p38, and JNK significantly decreased LC3 conversion induced by DHEA treatment. Chemical inhibition of JNK also decreased formation of the autolysosome stimulated by DHEA treatment and abolished the inhibitory effect of DHEA on LA-induced endothelial cell senescence.

Conclusion: In conclusion, DHEA prevents LA-induced endothelial senescence by restoring autophagy and autophagic flux through JNK activation.

OP8-2 Macrovascular complications

Association between hemoglobin A1c variability and subclinical coronary atherosclerosis in subjects with type 2 diabetes

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Objective: We examined the association between hemoglobin A1c (HbA1c) variability and subclinical coronary atherosclerosis in subjects with type 2 diabetes.

Methods: We used the multidetector coronary computed tomography (MDCT) data collected from the CORONOS-ADM Registry (registered with ClinicalTrials.gov), which enrolled subjects with type 2 diabetes who did not have a history of cardiovascular disease or angina symptoms. Intraindividual SD, CV and adjusted SD of serially measured HbA1c were calculated as indicators of HbA1c variability. Subclinical atherosclerosis was determined by coronary MDCT.

Results: A total of 612 subjects (357 men) were enrolled with mean age of 64.95 ± 8.91 years and baseline HbA1c of 7.66 ± 1.59%. They were categorized into two groups according to the median value of each HbA1c variability indicators: lower HbA1c variability (HbA1c-SD 〈 0.4952%, HbA1c-CV 〈 6.7816, adjusted HbA1c-SD 〈 0.4615%) and higher HbA1c variability (HbA1c-SD ≥ 0.4952 %, HbA1c-CV ≥ 6.7816, adjusted HbA1c-SD ≥ 0.4615 %). The proportion of subjects who had severe coronary calcification (coronary calcium score 〉 400) or soft plaque was higher in higher HbA1c variability group compared with lower HbA1c variability group, categorized by all three indicators of HbA1c variability. Also, subjects with significant coronary stenosis (≥ 50%) or soft plaque exhibited greater HbA1c variability. Multivariate logistic regression analysis showed that HbA1c variability was associated with severe coronary calcification and soft plaque, independent of mean HbA1c level and other confounding variables.

Conclusion: In subjects with type 2 diabetes, HbA1c variability is associated with subclinical coronary artery sclerosis, especially with severe calcification and soft plaque.

OP8-3 Macrovascular complications

Tetrahydrobiopterin restored cardiac function and structure in type 2 diabetic rats

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Objective: Diabetic cardiomyopathy is the major cause of mortality and morbidity in diabetes mellitus patients. Mitochondrial dysfunctions in type 2 diabetes play significant role in the development of diabetic cardiomyopathy. Tetrahydrobiopterin (BH4) is a multifunctional co-factor having potential to regulate mitochondrial function including its biogenesis and oxidative phosphorylation. The aim of this study is to test the mitochondria mediated therapeutic potential of BH4 in the treatment of diabetic cardiomyopathy.

Methods: Fifty weeks aged LETO and OLETF rats were used as control and type 2 diabetes animal models respectively. Onset of diabetes was confirmed by intravenous glucose tolerance test. Randomly selected OLETFs were administrated BH4 20 mg/kg/day bolus i.p. during 2 weeks (OLETF/BH4). BH4, total biopterin and BH4/total biopterin ratio was examined in heart and mitochondria. Cardiac functions were monitored by echocardiography. Mitochondria oxygen consumption, complex activities assay and ROS generation analysis were performed to figure out mitochondrial functional modulations.

Results: Administration of BH4 did not altered IGTT, body weight or blood component of OLETF. The mitochondrial BH4/ total biopterin ratio was significantly decreased in OLETF while, BH4 administration restored it. Echocardiography revealed contractile dysfunction in OLETF compared to LETO. BH4 treatment significantly increased left ventricular contractility in OLETF resulting in enhanced ejection fraction and fractional shortening. BH4 treatment also attenuated the left ventricular hypertrophy and fibrosis in OLETF. Proteomic analysis revealed intensive modulation of mitochondria respiratory chain complex and proteasome activity related proteins in OLETF and OLETF/BH4. Mitochondrial membrane potential, electron transport chain complex activity and ATP concentration were decreased in OLETF model and BH4 treatment successfully restored those. Interestingly, increased oxidative stress in OLETF heart tissues were significantly attenuated by BH4 treatment. Proteasome activity was significantly increased in OLETF while, BH4 treatment significantly attenuated it.

Conclusion: BH4 has therapeutic potential which corrected mitochondrial dysfunction resulting enhancement of LV contractility and structural remodeling in diabetic cardiomyopathy.

OP8-4 Macrovascular complications

Increased risk for coronary artery calcification in hypertriglyceridemic waist phenotype in apparently healthy Korean adults

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Objective: Hypertriglyceridemic waist (HTGW) phenotype is a simple and inexpensive screening parameter to identify people at increased risk for cardiovascular disease. We evaluated whether hypertriglyceridemic waist phenotype increases risk for coronary artery calcification in apparently healthy Korean adults

Methods: 32,186 participants (mean age, 80.2% men) in a medical health screening program, in whom coronary artery calcium score (CACS) was measured by multi-detector computed tomography, between 2010 and 2012, were analyzed. The subjects were divided into 4 groups according to the serum triglyceride (TG) and waist circumference (WC); normal WC-normal TG (NWNT), normal WC-high TG (NWHT), enlarged WC-normal TG (EWNT) and enlarged WC-high TG (EWHT). High serum TG was defined as TG ≥ 150 mg/dL and enlarged WC was defined as WC ≥ 90 cm for men and WC ≥ 85cm for women. The presence of coronary artery calcification (CAC) was defined by CACS 〉 0.

Results: 14.9% of study population had CAC. EWHT group showed the highest mean value for ln(CACS+1) among the four groups (0.63 ± 1.42, P 〈 0.05 in post-hoc analysis). When logistic regression analysis was performed with CAC as the dependent variable, EWHT group showed the highest odds ratio (OR) for CAC with NWHT group the second, and EWNT showed lower OR for CAC compared with EWNT group after adjustment for confounding variables (1.579, 1.302, 1.266 vs. NWNT as the reference group).

Conclusion: EWHT group showed the highest risk for CAC, and NWHT group showed higher risk for CAC than EWNT group, suggesting that hypertriglyceridemia could affect more to CAC than enlarged WC in apparently healthy Korean adults.

OP8-5 Macrovascular complications

The amount of C1q-adiponectin complex is higher in the serum and the complex localizes to perivascular fat tissues and the intimal-medial layer of blood vessels of coronary artery disease patients

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Objective: The complement component C1q triggers activation of the classical immune pathway. The amount of C1q–APN complex in serum correlates positively with atherosclerosis. We assessed the relationships between C1q related variables and the severity of coronary artery disease (CAD), and investigated the localization of the C1q–APN complex.

Methods: The sample included 153 subjects comprising healthy controls and patients with subclinical or overt CAD. We measured the serum concentrations of C1q, total APN, and high-molecular weight (HMW)-APN, and the amount of C1q–APN complex. We identified the sites of C1q–APN complex deposition in various adipose tissues and blood vessels.

Results: Serum concentrations of C1q and HMW-APN and the C1q/HMW-APN ratio were independently associated with the severity of coronary stenosis. The amount of C1q–APN complex was significantly higher in patients with CAD compared with controls. C1q and APN colocalized in perivascular areas of subcutaneous, visceral, and pericardial fat tissues, and the internal mammary artery of patients with severe CAD.

Conclusion: Serum C1q concentration and the C1q/HMW-APN ratio were independent markers of coronary artery stenosis. The amount of C1q–APN complex was significantly greater in serum from CAD patients, and the complex localized to perivascular areas in adipose tissue and blood vessels. The association between the increased amount of the C1q–APN complex and CAD should be investigated further. The C1q–APN complex may be a potential target for new treatments to protect against tissue damage in CAD. (This study was supported by the grant of the Korean Diabetes Association, Republic of Korea.)

OP9-1 Integrated physiology / obesity

Ileal transposition increases L-cell secretion and decreases plasma lipopolysaccharide levels in rats

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Objective: Ileal transposition (IT) is an experimental surgery to examine the effect of expedited delivery of unabsorbed nutrients to the distal small intestine. We examined the effect of IT on plasma lipopolysaccharide (LPS) levels, which is known to contribute to the pathogenesis of metabolic abnormalities associated with obesity.

Methods: Sprague-Dawley rats were underwent either IT (n = 9) or sham operation (n = 10). After 4 weeks, oral glucose tolerance tests (OGTT) were performed, and fasting plasma LPS and gut histology were analyzed.

Results: Food intake and body weight decreased in the IT group, but daily glucose levels were not different between groups. Fasting insulin levels and HOMA-IR were significantly lower in the IT group. During OGTT, incremental area under the curve (AUC) of insulin and total AUCs of glucagon, total GLP-1, and peptide YY (PYY) were significantly higher in the IT group. Gut histology showed that villi length and muscle thickness increased in the transposed ileum (IT) compared with the ileum in situ (sham). In the immunofluorescence assay, densities of GLP-1-positive or GIP-positive cells were not different between groups but the density of GLP-1- and GIP-co-expressing cells, which are known as K/L-cells, was significantly higher in the IT group (P = 0.021). Fasting plasma LPS levels were lower in IT group (P = 0.002), and they were significantly correlated with HOMA-IR (r = 0.755, P < 0.001). Interestingly, there was negative correlation between fasting plasma LPS and total AUC of PYY (r = -0.710, P = 0.001).

Conclusion: This study recapitulates that IT surgery improves insulin sensitivity and enhances the secretion of distal gut hormones such as GLP-1 and PYY. In addition, plasma LPS levels were reduced after IT surgery even in euglycemic rats which might be related with the improvement of insulin sensitivity and the increase of PYY secretion.

OP9-2 Integrated physiology / obesity

Regulation of energy balance by hypothalamic lipoprotein lipase regulator Angptl3

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Objective: Hypothalamic lipid sensing is important for the maintenance of energy balance and glucose homeostasis. Angiopoietin-like peptide 3 (Angptl3) is a critical regulator of circulating lipid clearance and metabolism. In the present study, we evaluated the potential role for Angptl3 in central metabolism and lipid sensing.

Methods: The expression of Angptl3 in hypothalamus was evaluated using immunofluorescent staining. After intracerebroventricular (ICV) injection of Angptl3, food intake, body weight and energy expenditure were monitored. To identify the signaling pathways of Angptl3, we monitored the activities AMPK, Stat3, Akt and LPL after ICV injection of Angptl3. Next, we evaluated the LPL inhibitor and activator could alter the effects of Angptl3 on metabolism. Finally, the molecular mechanisms mediating the metabolic effects of hypothalamic Angptl3 were studied.

Results: Angptl3 is highly expressed in the neurons of mediobasal hyothalamus (MBH), an important area in brain lipid sensing. Suppression of hypothalamic Angptl3 increased food intake but reduced energy expenditure and fat oxidation, thereby promoting weight gain. Consistently, ICV administration of Angptl3 caused the opposite metabolic changes, supporting an important role for hypothalamic Angptl3 in the control of energy balance. Notably, ICV Angptl3 significantly stimulated hypothalamic LPL activity. Moreover, co-administration of the LPL inhibitor apolipoprotein C3 antagonized the effects of Angptl3 on energy metabolism, indicating that LPL activation is critical for the central metabolic actions of Angptl3. Increased LPL activity is expected to promote lipid uptake by hypothalamic neurons, leading to enhanced brain lipid sensing. Indeed, ICV injection of Angptl3 increased long chain fatty acid (LCFA) and LCFA-CoA levels in the hypothalamus. Furthermore, inhibitors of hypothalamic lipid sensing pathways prevented Angptl3-induced anorexia and weight loss.

Conclusion: Our findings identify Angptl3 as a novel regulator of the hypothalamic lipid sensing pathway.

OP9-3 Integrated physiology / obesity

Exogenous treatment of soluble DLK1-Fc regulates fatty acid oxidation and gluconeogenesis via activation of AMPK

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Objective: Delta-like 1 homolog (DLK1) is an imprinted gene that inhibits adipogenesis and is associated with muscle hypertrophy in animal models. We aimed to investigate the metabolic effects of exogenous DLK1-Fc treatment in an animal model of diabetes.

Methods: Male db/db mice were randomly assigned to two groups: (1) vehicle-treated, and (2) DLK1-Fc-treated groups. DLK1-Fc (15 mg/kg) was intraperitoneally injected three times weekly for 4 weeks. Hepatic triglycerides were measured and oral glucose tolerance tests and insulin tolerance tests were performed. We also conducted glucose production assays in HepG2 cells and gene expression analysis (immunoblots and real-time PCR) to assess fatty acid oxidation and gluconeogenesis-related genes.

Results: Administration of DLK1-Fc significantly reduced fasting and random glucose levels in db/db mice. Hepatic triglycerides contents were significantly decreased and glucose tolerance and insulin tolerance were ameliorated in DLK1-Fc-treated mice. In the liver of db/db mice and HepG2 cells, DLK1-Fc treatment significantly increased phosphorylation of AMPK by 1.7 folds and ACC, indicating activation of fatty acid oxidation. Furthermore, DLK1-Fc treatment suppressed glucose production from HepG2 cells, which was blocked after administration of compound C. DLK1-Fc-treated HepG2 cells and liver tissues showed decreased expression of PEPCK and G6Pase, two essential enzymes for gluconeogenesis.

Conclusion: Our results show that exogenous treatment of DLK1-Fc regulates fatty acid oxidation and gluconeogenesis via activation of AMPK in db/db mice and HepG2 cells. This implicates that DLK1 may provide a novel therapeutic approach to treat non-alcoholic fatty liver disease and diabetes.

OP9-4 Integrated physiology / obesity

IL-34 is associated with obesity and insulin resistance

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Objective: IL-34 is a recently identified alternative ligand for colony-stimulating factor-1 receptor (CSF-1R). IL-34 and CSF-1 are regulators of differentiation, proliferation, and survival in mononuclear phagocytes. Here, we investigated the IL-34 serum concentration and expression in human adipose tissues and any associations with insulin resistance.

Methods: We recruited 19 nondiabetic obese women, 9 type 2 diabetic obese women, and 27 normal-weight women. Metabolic parameters, abdominal fat distribution, serum IL-34 concentration, and IL-34 mRNA expression were measured in abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT). In addition, the expression/secretion and putative effects of IL-34 were assessed in human differentiated adipocytes. Serum IL-34 concentration was measured before and 5-9 months after laparoscopic Roux-en-Y gastric bypass (RYGB) surgery was performed on the 20 obese patients.

Results: Regardless of diabetes status, obese patients demonstrated significantly higher serum IL-34 concentrations than controls. Serum IL-34 was significantly and positively correlated with insulin resistance-related metabolic parameters. IL-34 mRNA was significantly higher in VAT than SAT. IL 34 was expressed in adipocytes as well as nonadipocytes, and expression was significantly higher during adipogenesis. In differentiated adipocytes, the expression/secretion of IL-34 was enhanced by TNFα and IL-1β. In addition, IL-34 augmented fat accumulation and inhibited the stimulatory effects of glucose transport. Moreover, serum IL-34 significantly decreased following RYGB-induced weight loss.

Conclusion: The present study demonstrates, for the first time, that IL-34 is expressed in human adipose tissues and the circulating concentration is significantly elevated in obese patients. This suggests that IL-34 is associated with insulin resistance.

OP9-5 Integrated physiology / obesity

Implication of circulating irisin levels with brown adipose tissue and sarcopenia in humans

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Objective: Irisin is an exercise-induced novel myokine that drives brown-fat-like conversion of white adipose tissue and has been suggested to be a promising target for the treatment of obesity-related metabolic disorders. To assess the association of circulating irisin concentrations with brown adipose tissue (BAT) and/or sarcopenia in humans.

Methods: We examined irisin levels in 40 BAT-positive and 40 BAT-negative women detected by 18F-Fluorodeoxyglucose Positron Emission Tomography (18FDG-PET). In a separate study, we also examined 401 subjects with or without sarcopenia defined by skeletal muscle mass index (SMI) and appendicular skeletal muscle (ASM)/height2 using dual-energy X-ray absorptiometry (DXA).

Results: Among 6,877 consecutive 18FDG-PET scans in 4,736 subjects, 146 subjects (3.1%) had positive BAT scans. The BAT-detectable group and the matched BAT-undetectable group did not differ in circulating irisin levels measured using two different ELISA kits (P = 0.747 and P = 0.160, respectively). Serum irisin levels were not different between individuals with sarcopenia and those without sarcopenia using either kit (P = 0.305 and P = 0.569, respectively). Also, serum irisin levels were not different between groups defined by ASM/height2 using either kit (P = 0.352 and P = 0.134, respectively). Although visceral fat area and skeletal muscle mass showed significant difference according to tertiles of SMI levels, irisin concentrations did not differ.

Conclusion: Circulating irisin levels were not different in individuals with detectable BAT or those with sarcopenia compared to control subjects and were not correlated with skeletal muscle mass index.

OP10-1 Behavior, nutrition, education & exercise

Withdrawn

OP10-2 Behavior, nutrition, education & exercise

Seasonal changes of cardiovascular risk factors in Korean diabetic patients from the fifth Korean National Health and Nutrition Examination survey (KNHANES V)

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Objective: Cardiovascular (CV) disease is the leading cause of mortality in diabetes mellitus (DM) patients. Lifestyle, such as food intake and physical activity, in DM patients may be changed by temperature and weather. Therefore, cardiovascular risk factors will be affected by these lifestyle and weather changes. Investigating the seasonal changes in CV risk factors will help to manage DM patients. We investigated the seasonal changes of cardiovascular risk factors in Korean DM patients.

Methods: We analyzed the data of 1123 DM patients (aged 30 to 79 years) from the fifth Korea National Health and Nutrition Examination Survey (KNHANES V, from 2010 to 2012). They met the following criteria: 1) diagnosed diabetes by doctor , 2) checked HbA1c, and 3) recorded the exam date and diabetes duration. An analysis of covariance (ANCOVA) was performed to compare cardiovascular risk factors (hemoglobin A1c, blood pressure, lipid profile, and calorie intake) among periods divided by temperature above (May to July and August to October) or below (November to January and February to April) the yearly mean temperature, while statistically controlling for the covariates (age, sex, DM duration, DM treatment modality, residential area, year of examination, education, occupation, house income, smoking, alcohol, and obesity) which are related to CV risk factors.

Results: There were differences among groups in systolic blood pressure (P= 0.022), diastolic blood pressure (P = 0.034), LDL-cholesterol (P = 0.008), and carbohydrate intake (P = 0.047). There were no differences among groups in HbA1c (P = 0.147), Triglyceride (P = 0.469), HDL-cholesterol (P = 0.185), and calorie intake (P = 0.189). Total cholesterol were marginally significant difference among groups (P- 0.076).

Conclusion: We observed the differences of CV risk factors according to yearly mean temperature in Korean DM patients. These CV risk differences might be caused by the changes of physical activity related to temperature and weather. Seasonal changes of CV risk factors should be considered in the management of diabetic patients .

OP10-3 Behavior, nutrition, education & exercise

Health promotion intervention to improve the skills of controlling dietary pattern among school teachers, Colombo district, Sri Lanka

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Objective: To improve the nutritional practices among public school teachers in 1C schools, western province, Sri Lanka.

Methods: This intervention study was carried out based on school teachers (n = 72) who are employed in 1C schools in Colombo district. Intervention focused on improving the dietary pattern among school teachers. Anthropometric data including weight and height were measured using standard protocol, and BMI was calculated. Over weight and obesity was described according to the WHO guidelines. Life style intervention was delivered throughout 6 months, targeting basic promoting healthy eating and physical activities. Healthy nutritional practices were discussed through role play models. Continuously follow ups were carried out to ensure the quality of the intervention which focused on promoting healthy dietary practices among public school teachers.

Results: Mean age of the teacher was 40.3 years (SD 7.83). 15% were male. Before the intervention mean BMI in the group was 24.0 Kgm-2 . Following the intervention mean BMI in the group was 23.7 Kgm-2. Before the intervention mean weight was 60.74 kg (SD 8.5). Following the intervention mean weight among subjects was 60 kg (SD 7.97), the difference of the pre and post was significant (P = 0.00 CI = 95%). Qualitative analyses revealed that, teachers started consuming more vegetable and fruits. Also most of subjects in the target group have allocated time on leisure time physical activities. It was found that most of teachers has started to teach their students about healthy practices.

Conclusion: Lifestyle intervention through the health promotion approach can be used to improve nutritional practices among public school teachers who are attached to type 1C schools in Colombo district Sri Lanka. Also promoting healthy lifestyle among school teacher would useful to promote healthy practices among students.

OP10-4 Behavior, nutrition, education & exercise

The first-ever home health care service monitoring system for Cambodian diabetes mellitus patients

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International University, Phnom Penh, Cambodia, Medicine and Pediatrics[1], Preah Kossamak Hospital, Phnom Penh, Cambodia, Diabetology Department[2]

Objective: To delineate the usefulness of the state-of-the-art monitoring system, Home Health Care Service, being used with Cambodian Diabetes Mellitus (DM) patients in Preah Kossamak Hospital, Cambodia, in association with Soonchunhyang University and Bit Computer, South Korea.

Methods: 19 diabetic patients were exclusively selected. Among 19 patients, there are 13 males (68%) and 6 females (32%). Ranging from 25 to 72 years old, the median age is 53. Each patient was provided with a smartphone, a Blood Pressure Monitor, and a Blood Glucose Meter to measure their Systolic Blood Pressure (SBP), Diastolic Blood Pressure (DBP), Pulse, Fasting Plasma Glucose (FPG), and Post- Prandial Glucose (PPG) 4 times daily, and send them to server via the Internet. The five measurements above were compared from month to month, starting from 3rd week of March to the end of July 2014 (approximately 4.5 months).

Results: During the 4.5-month period, numbers of blood sugar measurement (FPG and PPG) were 3676, and blood pressure (SBP, DBP, and Pulse) being measured was 3749 times, which made the total measurements to 7425 times. By comparing 5 vital signs for each month, it shows that the total average of SBP (March~July) was 122.14 mmHg, which decreased from 128.60 (March) to 109.94 (July). Similarly, the total average of DBP, 77.35 mmHg, also dropped from 79.08 (March) to 76.42 (July). Likewise, Pulse lessened from 77.58 (March) to 71.88 (July), in which the total average was 75.38 BPM. Besides, the average of FPG lowered from 144.19 (April) to 138.73 mg/dL (July). Hence, the total average of FPG was 138.18 mg/dL. However, only PPG increased from 158.77 to 180.73 mg/dL (total average = 176.44 mg/dL).

Conclusion: The result indicates that by combining with medicine, regular exercise, and lifestyle change, this groundbreaking monitoring system would play an important role in treating diabetes in the future.

OP10-5 Behavior, nutrition, education & exercise

The effect of moderate intensity intermittent exercise on body composition of type 2 diabetic postmenopausal women

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Objective: Diabetes is a world-wide problem. Exercise and Diet are usually recommended for diabetes. Although dieting has been the major fat loss method, aerobic exercise programs have been shown to preserve fat-free mass.

Methods: Randomized controlled Trial (Septemver 2013~April 2014) Type 2 diabetic postmenopausal women aged (51~74 years) were recruited form Pusan, and surrounding communities. For all the patients, diet consultation was carried out. For the exercise group, 12-week moderate intensity intermittent exercise program was applied. To determine the effect of a 12-week intermittent exercise intervention, total body fat (%), total fat mass(g), toal lean mass(g), appendicular skeletal muscle mass (ASM, kg), weight adjusted ASM(%), height adjusted ASM (kg/m^2) were measured.

Results: A total 36 community dwelling diabetic females aged 61.3 ± 8.8 years in Korea were enrolled in this study. Mean duration of diabetes were 9.5 ± 7.9 years and BMI was 24.9 ± 2.8 kg/m^2. Baseline characteristics were not different. After 12 weeks, total fat (%) and total fat mass (g) were decreased in both diet only group and diet with exercise group (P = 0.017 vs P = 0.040 and P = 0.011 vs P = 0.017, respectively) from baseline. Weight adjusted ASM was significantly increased in diet with exercise group (P = 0.005), but not in diet only group (P = 0.820).

Conclusion: Moderate intensity intermittent exercise with diet resulted in significant increase in ASM index in type 2 diabetic postmenopausal women.

Poster exhibition

Poster exhibitions

▸ **Presentation Date: Friday 17 ~ Saturday 18 October, 2014**

▸ **Place: 6 Hall A, Exhibition Center II, KINTEX**

[PE1~PE16]	Behavior, nutrition, education & exercise
[PE17~PE55]	Clinical diabetes
[PE56~PE73]	Epidemiology
[PE74~PE75]	Insulin signaling / action
[PE76~PE90]	Integrated physiology / obesity
[PE91~PE98]	Islet biology / insulin secretion
[PE99~PE104]	Macrovascular complications
[PE105~PE114]	Microvascular complications
[PE115~PE130]	Metabolic syndrome & prediabetes
[PE131~PE145]	Therapeutics of diabetes

PE-1 Behavior, nutrition, education & exercise

Effect of exercise on cardiac autonomic function in type 2 diabetic patients

Rajesh Goit*

Nepalgunj Medical College, Department of Physiology

Objective: The aim of the study was to determine the effect of moderate aerobic exercise on cardiac autonomic function in type 2 diabetic patients.

Methods: Heart rate variability (HRV) of 20 patients with type 2 diabetes were assessed. Resting electrocardiogram (ECG) for the HRV analysis at spontaneous respiration was recorded for 5 min in supine position before and after six months of supervised aerobic training given thrice-a-week.

Results: In time domain measures, the square root of the mean of the sum of the squares of differences between adjacent RR intervals (RMSSD) [29.7 (26~34.5) vs. 46.4 (29.8~52.2) ms, $P = 0.023$] and percentage of consecutive RR intervals that differ by more than 50 ms (pNN50) [10.7 (5.5~12.7) vs. 26.1 (6.6~37.2) %, $P = 0.025$] were significantly increased after exercise. In frequency domain measures, low frequency (LF) [62.4 (59.1~79.2) vs. 37 (31.3~43.3) nu, $P = 0.003$) and LF/HF [1.67 (1.44~3.8) vs. 0.58 (0.46~0.59) % $P = 0.009$] were significantly decreased while high frequency (HF) [95 (67~149) vs. 229 (98~427) ms2, $P = 0.006$] and HF [37.6 (20.8~40.9) vs. 63 (56.7~68.7) nu, $P = 0.003$) were significantly increased after exercise. In Poincare plot, standard deviation perpendicular to line of Poincare plot (SD1) [21.3 (18.5~24.8) – 33.1 (21.5~37.2) ms, $P = 0.027$] was significantly increased after exercise.

Conclusion: These data suggest that thrice-a-week moderate intensity aerobic exercise for six months improves cardiac rhythm regulation as measured by HRV in type 2 diabetic patients.

PE-2 Behavior, nutrition, education & exercise

Evaluate of the risk criteria of diabetes mellitus type 2 among health care workers

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Second General Hospital , Diabetes Center

Objective: There is increasingly trend of diabetes mellitus type 2 in Mongolia due to unhealthy lifestyle behavior. The study was conducted the criteria from World Health Organization, Ministry of Health department, Millennium Challenge accountant Mongolia among health care workers including nurses, laboratory assistant and technicians.

Methods: The risk of criteria was evaluated by the questionnaire based on Diabetes Mellitus guideline and waist-line measurement was designed by anthropometry measurement.

Results: A total of 97% of the participants are female as of waist circumference, 63% (83) of female nurses and 50% (2) of male nurses were on the risk zone. 19% (24) of participants had arterial hypertension, 4% (5) had hyperglycemia, 29% (38) of the participants do exercise more than 10 minutes and 5 days a week. 29% (38) of them has sedentary job more than 6 hours a day. 14% (19) have a family history of DM. 65% (86) of them have minimum risk 30% (39) have under average risk, 4% (6) have over risk, 1% (1) have high risk of Diabetes mellitus type 2.

Conclusion: 1. According to the research 7% (5) of the total participants at risk to be diagnosed as Diabetes mellitus type 2 in next decades. 2. Between ages 25~44 female professions have 3 risk factors of total 7 risk factors of Diabetes mellitus type 2. 30% of them have under average risk 64% (84) of the participants had central obese (female ≥ 80 male ≥ 90), 71% of the participants don't do any exercise, 29% (38) of the total participants had sedentary over 6 hours per day there are the risk to be diagnosed as a Diabetes mellitus type 2. 3. There are many chances to prevent from Diabetes mellitus type 2 to change their unhealthy life behavior. We should create the seminar to change their unhealthy life behavior and to create healthy life style.

PE-3 Behavior, nutrition, education & exercise

The role of the diabetic nutritional education in diabetes management

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Objective: The diabetic nutritional education is a key component of diabetes medical nutrition therapy (MNT). In this study, we investigated the effect of the diabetes nutritional education on diabetes management, and whether the degree of understanding of the process of diabetes nutritional education is associated with improving diabetes control.

Methods: We recruited 354 adult patients with type 2 diabetes (men:176 women:178) who visited our hospital from June.2012 to May.2013. The patients were classified 3 group (group "A" patients, were not received the education; group "B", were received the nutritional education and fair degree of understanding of the process of diabetic nutritional education; and group "C", were, also, received the nutritional education and more degree of understanding than group "B"patients. We studied the difference levels of BMI, FBS, HbA1c, total cholesterol and LDL cholesterol among 3 groups, at the time of first education program and that of 12th months follow up.

Results: At 12 months later, the difference levels of BMI, FBS, HbA1c, total cholesterol and LDL cholesterol among 3 groups were analysed with ANOVA: FBS ($P < 0.09$) and HbA1c ($P < 0.03$) were decreased significantly, but BMI, total cholesterol, and LDL cholesterol were not different statistically.

Conclusion: In this study, we found that patient's degree of understanding of the process of diabetes nutritional education was associated with decreasing levels of HbA1c and FBS significantly. Hence, we have to carry out diabetic nutritional education more exactly and easily, so that patients could understand sufficiently. And It is necessary to develop educational tool that is more easily and readily comprehensible to patients with diabetes. According to this study, MNT provided dietition had a significant improvements in medical and clinical outcomes compared to that of non education. And it is necessary to increase participation in diabetic nutritional education.

PE-4 Behavior, nutrition, education & exercise

The number of participating times in DSME beneficial influenced on diabetes managements

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Objective: The Diabetes Self Management Education (DSME) is one of a essential element of diabetes management. Multiple studies have found that DSME was associated with improving diabetes knowledge, more clinical outcomes such as lower body weight, HbA1c, and lower cost of diabetes care. In this study, we evaluated the effects of the number of participating times in DSME on diabetes management in Type 2 diabetes.

Methods: We recruited 192 adult patients with type 2 diabetes who had been received the DSME at our hospital from Mar 2011 to Dec 2013. The patients were classified 3 group (group A patients, were not received the DSME; group B, were received the DSME on 1~2 times; group C, were received the DSME on more 3 times). We compared the difference of HbA1c, T-chol, LDL, BMI between initial and 12~15 month later of the DSME. One-way ANOVA were used for analysis.

Results: At the first time visit, baseline data of all patients is below that: mean age 63 ± 12.4 years, BMI 24.6 ± 3.7 kg/m^2, HbA1c 8.2 ± 2.4%, T- chol 180 ± 50.9 mg/dL, LDL 95 ± 35.3 mg/dL. The baseline in group "A", the mean age 61 ± 13.8 years, BMI 25.1 ± 3.6 kg/m^2, HbA1c 7.3 ± 1.6%, T- chol 176 ± 41.0 mg/dL, LDL 98 ± 31.5 mg/dL and in group "B", the mean age 62 ± 11.7 years, BMI 24.3 ± 4.0 kg/m^2, HbA1c 8.9 ± 2.6%, T- chol 186 ± 58.8 mg/dL, LDL 96 ± 39.0 mg/dL and in group "C", the mean age 62 ± 10.7 years, BMI 24.1 ± 3.1 kg/m^2, HbA1c 8.3 ± 2.6%, T-chol 174 ± 49.0 mg/dL, LDL 87 ± 34.1 mg/dL. At 12~15 months later, the levels of HbA1c decreased by 0.2 ± 1.1% in the A group, and decreased by 0.9 ± 1.9% in the B group, and decreased by 0.5 ± 2.0% in the C group. The mean difference of HbA1c value was statistically associated with the number of participation of DSME ($P < 0.024$).

Conclusion: In this study, we found that patient's the number of participating times in DSME was associated with decreasing levels of HbA1c. Therefore DSME can result in cost-savings and improving outcome. So we should recommend the patients participate in the DSME much more.

PE-5 Behavior, nutrition, education & exercise

Reducing children's television time and get their participation to improve the knowledge on NCDs in a middle income community in Sri Lanka

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Objective: To improve the knowledge on Non Communicable Diseases among adults with the participation of children and to reduce the television time.

Methods: This community based intervention was carried in middle income community in Colombo district Sri Lanka. Intervention was delivered through children. Children were trained to measure height, weight and trained to calculate the BMI. Children made home visits (n = 32 houses) regularly and measured BMI and delivered the knowledge on NCDS. BP of households was measured by researcher. Each house was visited once a month by children. Pre and post level of knowledge were measured using specific format. In the meantime especial activities were carried out to improve the skills of children. Children were encouraged to invest their TV time for the community work. Pre and post time duration allocated for TV was assessed

Results: Before the intervention, adults (n = 18) 33.6% have not measured their height, adult (n = 36) 69.2% have not measured their weight. Adult (n = 22) 42.3% have not heard about the BMI while only 19.2% adult (n = 10) knew their BMI range. And also 44.2 % adults (n = 23) could name at least three NCDs. only 48% adult (n = 25) have measured BP in their life. 34.6 % adult could range the healthy BP range. Following six month evaluation, it was found that 61 % (n = 28) knew their BMI levels. 58.7% adult (n = 27) could remember their BMI levels while 82.6% (n = 38) could range the healthy BP range. Before the intervention average time spent on TV among children group were 4.5 hours. After six month of the intervention it was found that average time spent on TV were 2.5 hours.

Conclusion: Children's participation can significantly effect of improving knowledge on NCDs in a middle income community. Simultaneously this would useful to improve the various skills as well as positive qualities in life.

PE-6 Behavior, nutrition, education & exercise

Suicidal ideation and suicide attempts among diabetes mellitus: The Korea National Health and Nutrition Examination Survey (KNHANES IV, V) from 2007 to 2012

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Objective: The purpose of this study was to evaluate the mental health of subjects with diabetes mellitus (DM) and compare it with that of the general population of Korea.

Methods: This study was based on data from the Fourth Korean National Health and Nutrition Examination Survey (KNHANES IV, 2007~2009) and KNHANES V (2010~2012). Of the participants, we analyzed data on DM, depression, and suicidal ideation obtained from subjects aged ≥ 20 years (14,601 men and 19,464 women). We compared mental health outcomes of 3,846 patients with DM with those of 30,219 controls.

Results: Depressed mood for 2 or more continuous weeks was reported by 13.6% of normal glucose tolerance (NGT), 14.3% of impaired glucose intolerance (IFG), and 17.6% of DM patients. Suicidal thoughts were reported by 15.6% of IFG, 17.6% of DM, and 15.3% of NGT. Suicidal attempts were reported by 1.0% of IFG, 1.3% of DM, and 0.8% of controls. The crude odds ratio (OR) for depressive mood in those with DM was 1.376 (95% confidence interval [CI], 1.258~1.504), the OR for suicidal ideation in DM was 1.481 (95% CI, 1.361~1.611) and the OR for suicidal attempts in DM was 1.413 (95% CI, 1.021~1.956). Following multivariate analysis, the ORs for depression with DM were 1.178 (95% CI, 1.070~1.297), suicidal ideation with DM was 1.152 (95% CI, 1.050~1.263) and that for suicidal attempts were 1.413 (95% CI, 1.021~1.956).

Conclusion: In conclusion, these results add to the growing evidence that DM is associated with increased suicidal ideation and attempts among adults in the Korea.

PE-7 Behavior, nutrition, education & exercise

Effects of low-fat milk consumption on metabolic and atherogenic biomarkers in Korean adults with metabolic syndrome: a randomized controlled trial

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Objective: Previous studies of the health effects of low-fat milk or dairy consumption on metabolic syndrome have yielded inconsistent results. The aim of this study was to investigate the effects of low-fat milk consumption on metabolic syndrome-associated traits and inflammatory and atherogenic biomarkers in Korean adults with metabolic syndrome.

Methods: Overweight Koreans with metabolic syndrome (n = 58) were recruited and randomly assigned to either the low-fat milk or control group. The low-fat milk group was instructed to consume 2 packs of low-fat milk per day (200 mL twice daily) for 6 weeks, and the control group was instructed to maintain their habitual diet. Clinical investigations were conducted during the screening visit, on study day 0, and after 6 weeks.

Results: No significant differences in changes in body mass index, blood pressure, lipid profile, adiponectin, and levels of inflammatory, oxidative stress, and atherogenic markers were found between the low-fat milk and control groups. However, compared with the controls, significant favorable decreases in serum soluble vascular adhesion molecule-1 and endothelin-1 levels were found in the 12 subjects with high blood pressure and in the 18 subjects with hypertriglyceridemia in the low-fat milk group.

Conclusion: This study did not demonstrate an overall beneficial effect of low-fat milk consumption in the subjects with metabolic syndrome. However, low-fat milk consumption may have a favorable effect on atherogenic markers in the subjects with high blood pressure or hypertriglyceridemia.

PE-8 Behavior, nutrition, education & exercise

The relation between the family support and the adherence to dietary recommendations in T2DM patients

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Objective: It was shown that support of family was associated with self-management adherence among patients with diabetes in some studies. So we investigated the relation between the family support and the adherence of dietary recommendations with T2DM patients.

Methods: The survey was performed on 83 patients (male 55, female 28) with T2DM using the questionnaire. Questionnaire was consisted of 3 parts; individual characteristics (8 questions), usual eating habits and attitude (6 questions), the questions on family nutritional support and family-related barriers (14 questions, 3-point scale). And anthropometric and biochemical data (FBS, pp2hrs, HbA1c) were collected.

Results: The mean age of subjects was 57.4 ± 1.10 years and the mean duration of DM was 8.12 ± 0.86 years. The mean score of family support was higher than that of family-related barriers (respectively 2.29 ± 0.06, 1.92 ± 0.05, $P < 0.01$). The score of economic support was highest. The score of force to intake specific foods that not approved such as folk remedies was highest among those of family-related barriers. The score of overall family support was higher in male subjects compared to female subjects (2.53 ± 0.09, 2.07 ± 0.15, $P < 0.01$). The score of overall family support was correlated with balanced meal intake (r = 0.22, $P < 0.05$), regular meal time (r = 0.24, $P < 0.05$), and the subject's effort to adhere dietary recommendations (r = 0.34, $P = 0 < 0.01$). And the amount of meal was not correlated with the score of overall family support. However there was not shown significant correlation between glycemic control (FBS, pp2hrs, HbA1c) and the scores of family support.

Conclusion: Although we didn't find the significant correlation between glycemic control and family support, but we found that family support positively associated with adherence of some dietary recommendations. The improvement of family support may be influence the adherence of dietary recommendations among T2DM patients.

PE-9 Behavior, nutrition, education & exercise

Estimation of tomato consumption and the risk of metabolic syndrome in postmenopausal women -Utilization of Korean National Health and Nutrition Examination Survey-

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Objective: The objective of this study is to examine the relationship between tomato consumption and the risk of metabolic syndrome (MetS) in postmenopausal Korean women.

Methods: Data from the combined 2009~2011 Korean National Health and Nutrition Examination Survey (KNHANES) was analyzed. Tomato intake was assessed using the algorithms developed to analyze the demographic data of intakes of different tomato based food commodities such as "tomato, raw", "tomato, tomato juice", "tomato, tomato canned", "tomato sauce", and "tomato ketchup".

Results: Postmenopausal women (n = 5,258) were subgrouped according to the number of the MetS risk factor (RF 0, RF 1~2, RF 3). Anthropometric parameters, lipid profiles, fasting glucose, and tomato intake were analyzed. Corresponding to the number of the MetS RF, there was a decrease in tomato intake (20.40 ± 3.55, 15.97 ± 1.53 and 11.91 ± 1.62; P = 0.036). Tomato intake showed a negative correlation with waist (r = -0.028, $P < 0.05$). HDL cholesterol also showed a significant correlation with tomato intake (r = 0.029, $P < 0.05$).

Conclusion: In summary, the results show a relationship between tomato intake and MetS in postmenopausal Korean women.

PE-10 Behavior, nutrition, education & exercise

A study on dietary intake of T2DM patients according to weight status

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Objective: It has been well known that weight control is important for T2DM patients. Dietary management plays a critical role in weight control. The purpose of this study was to investigate whether dietary intake was different according weight status.

Methods: The subjects were 171 out-patients with T2DM. We divided the subjects into three groups according to BMI (normal (BMI < 22.9), 51 subjects; overweight group weight group (23.0 ≤ BMI < 24.9), 57 subjects; obese group (BMI ≥ 25.0), 63 subjects). Dietary intakes were examined by using 24hr recall method. Also we collected anthropometric and biochemical data.

Results: There were no significant differences in the gender distribution, age and glucose levels among three groups. There was tendency to increase total energy consumption according weight status (normal 1751.1 ± 424.4 kcal, overweight 1842.9 ± 369.1 kcal, obesity 1923.6 ± 542.4 kcal, $P = 0.135$), but it was not significant. There was no significant difference in macronutrient composition. The percentage of energy consumption to estimated requirement was significantly different among three groups (normal 98.5 ± 23.1%, overweight 104.2 ± 21.7%, obesity 111.0 ± 31.4%, $P < 0.05$). The amount of beverage consumption including alcohol was significant different (normal 140.8 ± 190.0 g, overweight 240.9 ± 242.5 g, obesity 269.4 ± 298.8 g, $P = 0.021$). HbA1c level was significantly correlated with total energy consumption (r = 0.390, $P = 0.007$) and the percentage of energy consumption to requirement (r = 0.325, $P = 0.026$) in normal weight group only. Intake amounts of beverages and alcohols drinks in food categories were significantly different (140.8 ± 190.0, 240.9 ± 242.5, 269.4 ± 298.8 g, $P < .05$). There was significant correlation between HbA1c and total energy intake (r = .390, $P = .007$) and energy intakes of requirement (r = .325, $P = .026$) in only normal weight group.

Conclusion: We found that obese subjects with T2DM consumed more energy compared to energy requirement. Obese T2DM patients are required to restrict calorie consumption for weight management and glycemic control. More concern on calorie intake will be needed during nutrition counseling or monitoring for obese T2DM patients.

PE-11 Behavior, nutrition, education & exercise

Mitochondrial DNA depletion disrupts mitochondrial physical status

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Objective: Mitochondrial dysfunction has been identified in various diseases including diabetes and heart diseases. Although mitochondria DNA (mtDNA) encodes 13 minimal proteins involved in oxidative phosphorylation, mutation or depletion of mtDNA could cause severe mitochondrial malfunction originated from mitochondria itself and crosstalk between nucleus and mitochondria. However, it is largely unknown what changes would be happened when mtDNA was depleted.

Methods: We established mtDNA depleted rat myoblast-like H9c2 cells by supplementing with ethidium bromide and uridine. After confirming depletion of mtDNA with quantitative PCR and gel electrophoresis, we investigated changes in mitochondrial physical parameters using flowcytometry and resistance to serum starvation and sodium nitroprusside insults.

Results: The mtDNA depeletion led to changes in cell morphology. The mtDNA depleted H9c2 cells showed lower in mitochondrial membrane potential, cardiolipin, calcium and free zinc contents than h9c2 naïve cells. Cytosolic and mitochondrial reactive oxygen species was significantly higher in mtDNA depleted H9c2 cells. Although oxygen consumption rate and cell proliferation were decreased, mtDNA depleted H9c2 cells were more resistant against serum deprivation and nitroprusside insults than h9c2 naïve cells. In addition, mtDNA depleted cells showed higher in nuclear encoded acetyl-CoA carboxylase and cyclophilin D protein level.

Conclusion: Taken together, mtDNA depletion caused drastic changes in tested mitochondrial physical parameters and these changes may be involved in disturbance in mitochondrial homeostasis and may lead to pathophysiological predisposition.

PE-12 Behavior, nutrition, education & exercise

Ursolic acid-induced elevation of serum irisin augments muscle strength during resistance training in men

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Objective: Ursolic acid (UA) is a type of pentacyclic triterpenoid carboxylic acid purified from natural plants. The anti-skeletal muscle atrophy of UA is well conducted but its effect upon skeletal muscle strength via irisin is still unknown in clinical trials. The purpose of this study was to examine the effect of resistance training with/without UA on muscle strength via irisin in men.

Methods: Sixteen male participants (age, 29.37 ± 5.14 years; body mass index= 27.13 ± 2.16 kg/m^2) were randomly assigned to resistance training (RT, n = 7) or RT with UA (RT + UA, n = 9). Both groups completed 8 weeks of intervention consisting of 5 sets of 26 exercise, with 10~15 repetitions at 60~80% at one-repetition maximum and a 60~90-s rest interval between sets, performed 6 times/week. UA or placebo was orally ingested as 1 capsule 3 times/day for 8 weeks. The following program was measured at pre and post intervention; body weight, insulin, insulin growth like factor-1 (IGF-1), irisin, and skeletal muscle strength.

Results: Body fat percentage was significantly decreased ($P < 0.001$) in RT + UA group, however, body weight, body mass index, lean body mass, glucose, and insulin levels were not changed. Plasma IGF-1 and irisin level were significantly increased compared with baseline levels in the RT + UA group ($P < 0.05$). Maximal right and left extension ($P < 0.01$), right flexion ($P < 0.05$) and left flexion ($P < 0.001$) were significantly increased compared with baseline levels in the RT + UA group.

Conclusion: These findings suggest that elevation of serum irisin associated with skeletal muscle function can be enhanced after RT with UA.

PE-13 Behavior, nutrition, education & exercise

Survey about knowledge of hypoglycemia of diabetic patient and status of hypoglycemic education in general hospital

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Objective: Hypoglycemia is the important event to affect compliance of diabetic medications and the mortality. So many studies have emphasized diabetes self-management education about hypoglycemia. Recently, many medical center, social health care center and broadcasts systems have various lectures and curriculums for diabetic patients, but we cannot be sure how effetively it goes on. We surveyed the actual insight about hypoglycemia of patients and evaluated the effects of educations.

Methods: We conducted survey for patients with diabetes who visited Keimyung University Dongsan Medical Center from June, 2014 to July, 2014. The questions sought information about personal history, symptom and definition of hypoglycemia, education experience and self-management about hypoglycemia,

Results: In 304 participants enrolled 85 (27.9%) patients have got one lecture at least (average 2.5 times). They were educated almost in medical center (72 patients, 84.7%). 212 patients (69.7%) keep self- monitoring blood glucose regularly. But few patients (51, 16.7%) knew exactly about the definition of hypoglycemia. Over the half patients (209 , 68.7%) have experienced hypoglycemia and 73 patients (24%) had hypoglycemia event once in a month at least recently. Among the 12 correct hypoglycemic symptom in questionnaire, they choose dizziness (162, 53.2%), tremor (157, 51.6%), sweating (103, 33.8%) mostly, but rare patients choose loss of consciousness (31, 10.1%), seizure (19, 6.25%). Moreover only 22 patients (7.2%) carries the card to present that they have diabetes. When they feel hypoglycemic symptom, most patients (144, 47.3%) ate candies first. Only 38 patients (12.5%) checked blood glucose before eating. To recover hypoglycemia they mostly answered to eat candy (167, 54.9%), fruit juice (79, 25.9%), chocolate (74, 24.3%) and few patients answered to take nuts (6, 1.9%), noodle (6, 1.9%), pizza (5, 1.6%).

Conclusion: In our study, we recognized most patients do not have chance about diabetic education and knowledge enough to manage hypoglycemia. Therefore more frequent and intensive diabetic education should be performed.

PE-14 Behavior, nutrition, education & exercise

Behavior and fear survey of hypoglycemia in general hospital

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Objective: Hypoglycemia is related with significant morbidity and mortality. In addition, fear of hypoglycemia is a big barrier for glucose control and results in poor adherence. However, we do not know exactly how much the patients worry about hypoglycemia. In this study, we investigated the behavior of diabetic patients to avoid hypoglycemia and the fear of hypoglycemia using questionnaire.

Methods: We conducted survey for patients with diabetes who visited Keimyung University Dongsan Medical center from June, 2014 to July, 2014. We surveyed about behaviors and anxiety using hypoglycemia fear survey II behavior and worry subscales. We divided 5 categories according to frequency and scored 1 to 5.

Results: 304 participants were enrolled. 209 (69.2%) participants had experienced hypoglycemia and 108 (51.6%) participants had at least one hypoglycemic event within a month. Participants who had experienced hypoglycemia had higher hemoglobin A1c, longer diabetic duration and more use of insulin. Mean score about behavior to avoid hypoglycemia is 21.69 ± 9.7 and worry for hypoglycemia is 26.35 ± 15.15. These score are higher than participants who had not experienced hypoglycemia (P 〈 0.000) About 5 % participants always act something to avoid hypoglycemia and worry about not recognizing hypoglycemia event and having hypoglycemia events alone.

Conclusion: A lot of patients had experienced hypoglycemia and worry about it. We pay more attention how anxious about hypoglycemia and educate what to do when they feel hypoglycemic symptoms, especially for patients who have higher chance to experience hypoglycemia.

PE-15 Behavior, nutrition, education & exercise

Stress and weight changes in type 2 diabetes

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Objective: Patients with diabetes are recommended to achieve and maintain a desirable body weight. The aim of the study was to assess the association between the body weight changes for 3 years and stress severity in Korean type 2 diabetic patients.

Methods: We examined 1,576 type 2 diabetic patients from the Korean National Diabetes Program cohort who completed dietary assessment and clinical evaluation at baseline and 3 years. Stress severities were assessed by BEPSI (Brief encounter psychosocial instrument). Dietary nutrient intake was assessed using FFQ, anthrometric and biochemical data were collected.

Results: Mean age was 52 ± 9.9 in men and 55 ± .8 9.6 in women. Body weight was increased by 1.5 ± 4.42 in men and 1.0 ± 4.4 in women. Body weight changes were associated with BMI, baseline body weight and peak body weight in their life. Higher BMI, baseline body weights and the age can predict lesser weight gain. Peak body weight in their life, fasting glucose and A1c predict the weight gain. Stress severity, calorie intake (% for recommend) and the sleeping time were not related to weight change.

Conclusion: Body weights increase in small amount during the follow up in type 2 diabetes. Its change were not related to stress or food intake. We should pay attention to weight gain in type 2 diabetic patient with high peak body weight and poor glucose profiles at baseline.

PE-16 Behavior, nutrition, education & exercise

Analysis of a improvement the knowledge of patients with diabetes education using the elementary evaluation questionnaire developed by Korean Diabetes Association

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Objective: Diet therapy has an important effect on glycemic control. Thus, nutrition education is an important part of DM education. For effective nutrition education, we examined the T2DM patients' nutrition knowledge.

Methods: We conducted a survey using the elementary evaluation questionnaire after the DM education. The questionnaire consists of 10 items and was developed by Korean Diabetes Association. Subjects were 53 T2DM patients (Male 33. Female 20) who participated in group diabetes education.

Results: Mean age of subjects was 54.6 ± 8.9 years and DM duration was 1.8 ± 2.7 years. Subjects of 92.5 % was had no experience DM education. The average number of correct answer was 8 knowledge evaluation items out of 10 items. The percent of correct answer was more than 83 % in all items except for two items. The two items that food to correct hypoglycemia and factor associated with appropriate calorie calculation were showed lower percentage of correct answers than other items to 30.2 % and 39.6 %, respectively.

Conclusion: In this study, it is expected that nutrition knowledge evaluation is helpful in effective education by reflecting knowledge evaluation results. Further studies on the knowledge evaluation for effective nutrition education in T2DM are needed.

PE-17 Clinical diabetes

Glycated albumin is a useful indicator for predicting beta cell dysfunction and impending diabetes in prediabetic condition

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Objective: Pre-diabetes is known as a pre-clinical stage of increased risk for overt diabetes mellitus (DM) and cardiovascular disease. Because glycated albumin (GA) has been suggested to have more potential for assessing insulin secretory dysfunction and glycemic fluctuation than HbA1c, we studied the clinical significance of GA in this stage.

Methods: We enrolled the 1379 anti-diabetic drug naïve subjects in retrospective, multi-center, cross-sectional manner. According to the 75-g OGTT, the subjects were classified as normal glucose tolerance (NGT), isolated IFG (i-IFG), isolated IGT (i-IGT), combined glucose intolerance (CGI) and DM subgroup. We analyzed clinical characteristics of these 5 groups including GA, insulin sensitivity (HOMA2%S), and insulin secretion (HOMA2%B) index.

Results: Mean GA was 11.6 ± 1.4, 12.3 ± 1.8, 12.3 ± 1.9, 13.0 ± 1.9, 18.8 ± 7.9 in NGT (n = 295, 21.4%), i-IFG (n = 257, 18.6%), i-IGT (n = 103, 7.4%), CGI (n = 257, 18.6%), and DM (n = 466, 34%) subgroup. After adjusting covariates, adjusted mean of GA was 12.2 ± 0.1, 12.2 ± 0.2, 13.1 ± 0.1 in i-IFG, i-IGT, and CGI subgroup (P 〈 0.001), and significantly higher in CGI group by post-hoc analysis. Adjusted mean of HbA1c was also significant, but not distinguished differences among these subgroups. Moreover, correlation coefficient between HOMA2%B and GA (r = -0.393, P 〈 0.001), and HOMA2%S and GA (r = 0.258, P 〈 0.001) was significantly higher than correlation with HbA1c. And these results were consistent after adjusting covariates.

Conclusion: We suggest that GA could be a better indicator for screening impending diabetes and assessing beta cell dysfunction in the subjects of pre-diabetic period.

PE-18 Clinical diabetes

Pharmacokinetics of once-weekly dulaglutide in special populations

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Objective: For use in a broad type 2 diabetes mellitus (T2DM) population, dulaglutide pharmacokinetics (PK) were characterized in subjects with renal or hepatic impairment.

Methods: Two separate open-label, single-dose studies assessed dulaglutide 1.5 mg PK in subjects with hepatic (n = 15) or renal (n = 32) impairment relative to healthy control subjects (n = 11 and 16, respectively). Both studies included mild, moderate, and severe impairment; the renal study also included end-stage renal disease.

Results: Dulaglutide exposure (area under concentration-time curve [AUC] and maximum concentration [Cmax]) was 〈 30% higher in renal impairment groups versus controls. There was no relationship between PK parameters and renal function based on estimated glomerular filtration rate. In addition, there was no statistically significant linear relationship at the 5% significance level between exposure and creatinine clearance. A statistically significant linear relationship was observed between creatinine clearance and dulaglutide apparent clearance; however, the relationship was weak based on its small slope (P = 0.0133) and goodness of fit (r2 = 0.1315). Across all hepatic groups, impaired subjects had lower exposure compared to controls. There was no trend in exposure relative to degree of hepatic impairment, with the largest difference observed in subjects with moderate impairment (Cmax and AUC values were approximately 70% and 67% of controls, respectively).

Conclusion: No notable differences in safety profiles were observed between subjects with hepatic or renal impairment and healthy subjects. There were no clinically relevant effects of renal or hepatic impairment on dulaglutide PK. Dulaglutide can be administered once weekly to patients with renal or hepatic impairment, without dose adjustment.

PE-19 Clinical diabetes

The 2-week fasting glucose as a predictor of response to once-weekly dulaglutide 1.5 mg

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Objective: To assess whether laboratory fasting blood glucose (FBG) in patients with type 2 diabetes mellitus (T2DM) measured early in treatment with the once-weekly glucagon-like peptide-1 receptor agonist dulaglutide (DU) 1.5 mg predicts treatment response.

Methods: Post-hoc analyses were conducted separately for two Phase 3 studies (AWARD-5, in combination with metformin, and AWARD-1, in combination with metformin and pioglitazone) in patients with T2DM receiving once-weekly DU 1.5 mg. In AWARD-5, FBG values were categorized at baseline and week 2 as: Low (L, 〈 142 mg/dL); Intermediate (I, ≥ 142 to 〈 185 mg/dL); or High (H, ≥ 185 mg/dL). Treatment response was assessed at week 12 (AWARD-5) or 13 (AWARD-1) and 26 (AWARD-5, AWARD-1) by composite efficacy endpoint (CEE): A1c 〈 7.0% or A1c reduction from baseline 〉 0.8% (if baseline A1c 〈 8.0%); 〉 1.1% (if baseline A1c ≥ 8.0% and 〈 9.0%); or 〉 1.6% (if baseline A1c ≥ 9.0%).

Results: In AWARD-5, mean baseline A1c for DU 1.5 mg (N = 304) was 8.1%. At baseline, mean FBG was 176 mg/dL, and 33% (n = 99), 32% (n = 97), and 36% (n = 108) of patients had FBG in L, I, and H categories, respectively. After week 2, mean FBG was 129 mg/dL, and 68% (n = 208), 21% (n = 64), and 11% (n = 32) of patients had FBG in L, I, and H categories, respectively. At week 26, mean A1c was 6.9%. There was a strong association between FBG at week 2 and achieving CEE at week 26 (P 〈 0.001). A higher percentage of patients in FBG category L (83% [172/208]) at week 2 met CEE at week 26 versus patients in FBG categories I (61% [39/64]; P 〈 0.001) and H (34% [11/32]; P 〈 0.001). Similar findings were seen using AWARD-1 data.

Conclusion: FBG values at week 2 may be an early and useful measurement for predicting response to once-weekly DU 1.5 mg in patients with T2DM.

PE-20 Clinical diabetes

Efficacy of long-acting once-weekly dulaglutide versus short-acting twice-daily exenatide in patients with type 2 diabetes mellitus: Post-hoc analysis to determine the influence of baseline HbA1c in the AWARD-1 trial

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Objective: To investigate the response to long- and short-acting glucagon-like peptide-1 receptor agonists based on baseline HbA1c levels. The AWARD-1 trial compared once-weekly dulaglutide 1.5 and 0.75 mg to placebo and exenatide 10 μg twice daily (BID) in patients with type 2 diabetes mellitus (T2DM) on metformin and pioglitazone.

Methods: The changes from baseline in HbA1c and percentages of patients reaching HbA1c targets (〈 7.0% and ≤ 6.5%) with dulaglutide 1.5 and 0.75 mg at 26 weeks were analyzed by baseline HbA1c (〈 8.5% and ≥ 8.5%) and compared with placebo and exenatide. Results are presented (least squares [LS] mean [standard error]) for the change from baseline in HbA1c and percentages achieving glycaemic targets, the 〈 8.5% group followed by the ≥ 8.5% group.

Results: The LS mean changes from baseline in HbA1c for dulaglutide 1.5 mg (−1.16% [0.07%]; −2.37% [0.10%]) were greater compared with placebo (0.17% [0.10%]; −0.76% [0.16%]) and exenatide (−0.64% [0.07%]; −1.86% [0.11%]; P 〈 0.001, all comparisons). For both baseline groups, significantly more patients taking dulaglutide 1.5 mg reached targets of 〈 7% HbA1c (92%; 47%) and ≤ 6.5% HbA1c (80%, 26%) compared with placebo (〈 7% HbA1c: 55%, 10%; ≤ 6.5% HbA1c: 32%, 3%) and exenatide (〈 7% HbA1c: 65%, 21%; ≤ 6.5% HbA1c: 50%, 9%) (P 〈 0.05, all comparisons). Dulaglutide 0.75 mg also demonstrated significant changes for both baseline groups versus placebo (P 〈 0.05, both outcomes, all comparisons). Statistical significance was not achieved when comparing dulaglutide 0.75 mg with exenatide in the baseline HbA1c ≥ 8.5% groups.

Conclusion: Regardless of baseline HbA1c, once-weekly dulaglutide 1.5 and 0.75 mg showed a robust reduction in HbA1c in this population of patients with T2DM.

PE-21 Clinical diabetes

Insulin lispro versus insulin aspart in type 2 diabetes subjects using continuous subcutaneous insulin infusion

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Objective: This phase 3b, randomized, double-blind, 32-week crossover trial compared insulin lispro (IL) with insulin aspart (IA) in subjects with type 2 diabetes mellitus (T2DM) on continuous subcutaneous insulin infusion (CSII). The primary objective was to demonstrate noninferiority of IL versus IA as measured by endpoint HbA1C (A1C) (noninferiority margin 0.4%). Secondary objectives included total daily insulin dose, weight change, and hypoglycemic events (rate and incidence) over each treatment period (TP).

Methods: After a 2-week lead-in period, 122 subjects were randomly assigned to IL (n = 60) or IA (n = 62) for 16 weeks (TP1) followed by a treatment crossover for an additional 16 weeks (TP2). At randomization, average A1C was 7.44%, and A1C was tested at the end of TP1 and TP2. Total daily insulin dose, weight, adverse events (AEs), and hypoglycemic events (overall, documented symptomatic, nocturnal, or severe) were recorded. Mixed-effects and generalized regression models that take into account repeated measurements were used for analyses.

Results: A total of 107 subjects completed the study, with 7 discontinuing in TP1 and 8 discontinuing in TP2. IL was noninferior to IA in endpoint A1C over TP1+TP2 (IL: 7.50% ± 0.12%; IA: 7.40% ± 0.12%). No statistically significant differences were found between treatments on total daily insulin dose (IL: 0.78 ± 0.04 U/kg; IA: 0.78 ± 0.04 U/kg), weight change (IL: 0.09 ± 3.03 kg; IA: 0.67 ± 3.26 kg), and incidence and rates of hypoglycemia (IL: 2.24 ± 0.28; IA: 2.38 ± 0.29). One case of severe hypoglycemia and one case of diabetic ketoacidosis were noted during the IA TP, but both IL and IA were well tolerated overall, with similar AEs reported.

Conclusion: The performance of IL and IA was similar over the 16-week TPs, with noninferior A1C and no significant difference in parameters measured, demonstrating that IL and IA can both be used safely and effectively in subjects with T2DM on CSII.

PE-22 Clinical diabetes

Fasting and postprandial hyperglycemiae: their relative contributions to the overall hyperglycemia and their determinants in Korean patients with type 2 diabetes

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Objective: Monnier et al. showed greater contributions of postprandial (PHG) and fasting (FHG) hyperglycemiae to overall hyperglycaemia at lower and higher HbA1c, respectively. However, it has never been studied in Korean diabetic patients. In addition, there have been few studies about determinant factors in postprandial and fasting glucose levels. Therefore, we assessed the relative contributions of PHG and FHG to the overall hyperglycemia and the influencing factors on PHG and FHG in Korean patients with type 2 diabetes.

Methods: We enrolled 195 Korean type 2 diabetic patients which did not take insulin or α-glucosidase inhibitor. They performed a seven-point self-monitoring of blood glucose (7-point SMBG) more than once during each month for 3 consecutive months. Glucose area under the curve (AUC) above 100 mg/dL was defined as AUC (total) to represent the overall hyperglycemia. The AUC above fasting glucose level was considered the postprandial hyperglycemia [AUC (PHG)]. The fasting hyperglycemia [AUC (FHG)] was calculated as [(AUC (total) - AUC (PHG)]. The relative contributions of PHG and FHG to overall hyperglycaemia were respectively defined as the proportions of AUC (PHG) and AUC (FHG) to AUC (TOTAL).

Results: The relative contribution of PHG showed a significant difference and gradual decrement according to increasing tertiles of HbA1c [55.3 ± 5.6, 42.0 ± 4.4, 33.5 ± 2.8%; P (ANOVA) = 0.002, P (TREND) 〈 0.001]. And the contribution of FHG was increased progressively with increasing tertiles of HbA1c [44.7 ± 5.6, 58.0 ± 4.4, 66.5 ± 2.8%; P (ANOVA) = 0.002, P (TREND) 〈 0.001]. Using multiple linear regression to adjust for age, sex and other covariates, only age (β = 0.181; P 〈0.05) and triglyceride (β = 0.150; P 〈 0.01) remained significant variables of the AUC (PHG) and AUC (FHG), respectively.

Conclusion: In Korean type 2 diabetic patients, postprandial hyperglycemia predominantly contribute to overall hyperglycemia at lower HbA1c level, whereas fasting hyperglycemia is a predominant contributor to it at higher HbA1c level. And age and plasma triglyceride are independent predictors of postprandial and fasting hyperglycemia, respectively.

PE-23 Clinical diabetes

Effect of maternal age at childbirth on insulin resistance: the 2010 Korean National Health and Nutrition Examination Survey

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Objective: Pregnancy and childbirth are stressful conditions for females. Insulin resistance increases during pregnancy as a result of various factors. This study aimed to assess insulin resistance according to maternal age at childbirth.

Methods: The data used in this study were obtained from the Korean National Health and Nutrition Examination Survey (KNHANES) conducted by the Korean Ministry of Health and Welfare in 2010. This study included a total of 2,233 non-diabetic females aged ≥ 30 years. Subjects were subdivided depending on their age at their first and last childbirth. Homeostasis model assessment of insulin resistance (HOMA-IR) was then performed in individuals from different age groups and obesity statuses.

Results: The age at first childbirth showed a negative relationship with HOMA-IR, both before and after adjustment for non-obese and non-abdominally obese females. After adjusting for age, lifestyle, and reproductive factors, the age at last childbirth had a positive relationship with HOMA-IR in non-obese and non-abdominally obese females. In multivariate logistic regression analysis, the age at first and last childbirth were significantly associated with highest quartile of HOMA-IR. The OR was 0.9 [95% CI 0.83~0.99] according to age at first childbirth, and 1.09 [95% CI 1.02~1.16] according to age at last childbirth in non-obese females.

Conclusion: In conclusion, our study suggests that insulin resistance is increased in females who experienced their first childbirth at a young age or last childbirth at a later age, particularly in non-obese individuals. Because these data suggest that childbearing age could be an independent risk factor for diabetes, a high-quality prospective study assessing childbearing age and insulin resistance should be performed.

PE-24 Clinical diabetes

The plasma levels of adiponectin in elderly prediabetic patients

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Objective: Adiponectin was shown to have substantial anti- inflammatory properties and it is a major modulator of insulin resistance and dyslipidemia. According to most studies for adiponectin and pre-diabetic patients, adiponectin levels are correlated with body components, lipid profiles, insulin resistance factors such as HOMA-IR. However, the significance of adiponectin in elderly pre-diabetics has not been recognized yet. Accordingly, this study was conducted to evaluate the relationship between adiponectin and clinical variables, body composition, insulin sensitivity and lipid profiles in elderly patients with pre-diabetes.

Methods: Out of 1993 subjects were recruited in the Korea Rural Genomic Cohort Study, 121 patients were chosen an age of over 65 years and pre-diabetes. All subjects underwent a 75g oral glucose tolerance test and blood chemistry after a 12-h overnight fast. The body composition was estimated by a bioelectric impedance analysis and the insulin sensitivity by fasting insulin, HOMA-IR and QUICKI method.

Results: The plasma level of adiponectin in the elderly pre-diabetic subjects was found to be lower than elderly normal glucose tolerant subjects (10234.5 ± 4397.7 pg/mL versus 12714.3 ± 4755.2 pg /mL, P 〈 0.01). The plasma concentrations of adiponectin in elderly pre-diabetic patients with MetS were lower than elderly pre-diabetic patients without MetS (11097.5 ± 4620.05 pg/mL versus 8612.2 ± 3477.6 pg/mL, P 〈 0.02). In a univariate analysis, adiponectin was inversely correlated with waist, waist to hip ratio, BMI, total muscle, visceral fat, visceral fat ratio. In a multivariate analysis, total body fat ratio only correlated with plasma adiponectin levels independently.

Conclusion: Elderly pre-diabetics and general pre-diabetics had no noticeable differences in clinical and biochemical characteristics of serum adiponectin. However, in elderly pre-diabetic patients, level of adiponectin was not correlated with glucose or insulin resistance. The major correlation factor of plasma adiponectin was total body fat ratio in elderly pre-diabetics.

PE-25 Clinical diabetes

Treatment of Gefitinib, an inhibitor of the epidermal growth factor receptor decrease serum cholesterol in patients with lung cancer

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Objective: Statin, the gold therapy of dyslipidemia, is effective in lowering serum cholesterol, but have several side effects and is not able to prevent cardiovascular events completely. After treatment with the epidermal growth factor receptor tyrosine kinase inhibitor, we discovered a decrease of serum cholesterol in mice with increased activity of EGFR by liver specific mig-6 knockout. However, EGFR TKI's contribution to human cholesterol metabolism is unclear. We studied to examine the cholesterol lowering effect of Gefitinib, an inhibitor of the EGFR tyrosine kinase, as target molecules for treating primary lung cancer.

Methods: We reviewed clinical and biochemical features in 299 patients with primary lung cancer who were treated with Gefitinib for at least 1 month. Serum cholesterol, serum triglyceride and body mass index (BMI) were measured before and after treatment of Gefitinib. For patients who underwent examination of EGFR mutation, we compared the result of serum cholesterol, serum triglyceride and BMI according to presence of mutation.

Results: Serum cholesterol level decreased significantly from 178.9 mg/dL to 164.4 mg/dL after Gefitinib treatment (P < .001, respectively). However there was no significant difference in serum triglyceride and BMI (P = .056 and P = .104, respectively). There were 54 patients who underwent examination of EGFR mutation among 299 patients. Cholesterol decreased 21.3 mg/dL in the group who had activating mutation, and it increased 3.1 mg/dL in the group without EGFR mutation (P = .003). There was no significant difference in triglyceride and BMI between the two groups divided by existence of EGFR mutation. (P = .151 and P = .539, respectively)

Conclusion: Cholesterol decreased significantly in lung cancer patients who underwent treatment with Gefitinib for 1 month and the effect was more significant in patients who had the EGFR activating mutation. From this study, we suggest EGFR TKI can be used for treatment not only as an anticancer drug but also as a drug for hypercholesterolemia.

PE-26 Clinical diabetes

Insulin poisoning with suicidal attempt

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Contents: An 60-year-old man was transferred to our Hospital because of self-injected insulin administration. He was suffered from his economic problem and he decided to suicidal attempt after alcohol ingestion. He was found unconscious by his family. He arrived to an emergency room where his plasma glucose was found to be 68 mg/dl after administration of glucose fluid by 119 paramedics. He regained full consciousness and his plasma glucose 118mg/dL after taking 50% glucose fluid. But he experienced repeated episodes of hypoglycaemia subsequently with infusion of 20% glucose fluid and with shooting of 50% glucose fluid. He attempted suicide by injecting himself subcutaneously with more than 2,000 units of 70% human insulin isophane suspension and 30% human insulin injection. Administration of dextrose intravenously was required for 4 days to maintain the capillary blood glucose without hypoglycemia. He recovered completely without any complication after monitoring blood glucose and titrating intravenous glucose carefully for nine days. We report the progress of hypoglycemia after suicidal insulin overdose in a type 2 diabetic patient to recover with doses of glucose fluid and the time course of insulin washout.

PE-27 Clinical diabetes

The effect of dietary fiber-enriched cereals on glycemic control and secretion of gut hormones

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Objective: It has been proposed that consumption of dietary fiber (DF) results in short-chain fatty acid (SCFA) production through microbial fermentation, and this may affects glucose and insulin concentrations by increasing GLP-1 secretion. However, the results are inconsistent in human studies. We aimed to assess the glucose lowering effect of DF-enriched cereal and changes in plasma GLP-1 and GIP in patients with T2DM.

Methods: Thirteen subjects with T2DM were provided with isocaloric study meals based on either DF-enriched cereal (DFC) or conventional cereal (CC) upon two separate admissions in a cross-over design. The study meals were given at 6 p.m., 10 p.m. on the admission day and 8 a.m. on the next day, followed by a hamburger as mixed meal at noon. Serial blood sampling was performed on the second day. Plasma glucose, GLP-1, GIP, insulin, glucagon, and non-esterified fatty acid (NEFA) were measured. Postprandial dynamic change of each parameter in DFC and CC were assessed.

Results: Compared to CC, DFC showed the lower plasma glucose levels at post-breakfast 2h (11.02 ± 0.71 mmol/L vs. 13.6 ± 0.85 mmol/L, P < 0.05) and the maximal elevation (5.65 ± 0.51 mmol/L vs. 7.79 ± 0.79 mmol/L, P = 0.0002). The iAUC of glucose during 0 to 4h was also reduced in DFC (P = 0.0002). However, there were no differences in plasma insulin, GLP-1 and GIP levels at each time point, neither in iAUCs between two groups. NEFA decreased after cereal ingestion to nadir at 2h and re-increased till mixed meal, with the higher peak in DFC (228.2 ± 16.0 mEq/L vs. 157.7 ± 18.3 mEq/L, P < 0.05).

Conclusion: DFC lowered the increment of postprandial plasma glucose, but did not change plasma insulin, GLP-1 and GIP levels. Without GLP-1- or GIP-induced insulin secretion, DF itself with low glycemic index improved hyperglycemia in patients with T2DM.

PE-28 Clinical diabetes

Comparison of intact incretin response between oral glucose and mixed meal tolerance tests in patients with type 2 diabetes

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Objective: Incretin responses to differing nutritional compositions in patients with type 2 diabetes (T2D) aren't well known. Therefore, we analyzed intact glucagon-like peptide 1 (GLP-1) and intact glucose-dependent insulinotropic polypeptide (GIP) responses after oral glucose and mixed meal loadings in T2D patients.

Methods: Glucose, insulin, C-peptide, and intact GLP-1 and GIP were measured at baseline (0') and at 30 minutes (30') during mixed meal tolerance test (MMTT) and 75 g oral glucose tolerance test (OGTT) in T2D patients. The diet for MMTT was composed of 95 g carbohydrates, 18 g protein, and 12 g fat. Patients taking GLP-1 agonist or DPP-4 inhibitor were excluded.

Results: A total 195 T2D patients (132 males and 63 females) were enrolled. Seventy-nine subjects had OGTT, and the remaining 116 patients underwent MMTT. After 30 min, glucose level was lower in MMTT group than in OGTT group (135.75 ± 3.56 vs. 148.13 ± 4.12 mg/dL; P = 0.012). There were no significant differences in 30' insulin (25.08 ± 1.58 vs. 20.18 ± 1.36 μIU/mL; P > 0.05), 30' C-peptide (3.73 ± 0.17 vs. 3.53 ± 0.17 ng/mL; P > 0.05), and 30' intact GLP-1 (11.59 ± 0.94 vs. 13.85 ± 2.02 pmol/L; P > 0.05) between MMTT and OGTT groups used by ANCOVA test. However, 30' intact GIP level was higher in MMTT group than in OGTT group (22.71 ± 0.38 vs. 20.92 ± 0.68 pmol/L, P = 0.003). We used multiple regression analysis to adjust for the baseline incretin levels, age, sex, HbA1c, and other covariates. Type of meal (β = 0.173; P = 0.023) and 0' intact GIP (β = 0.244; P = 0.002) remained independent correlates of 30' intact GIP level, and a change in C-peptide (β = 0.359; P < 0.001) and 0' intact GLP-1 maintained its independent association with 30' intact GLP-1 level.

Conclusion: In conclusion, mixed meal ingestion increase intact GIP level more than isolated glucose ingestion. However, postmeal intact GLP-1 level is related to β-cell function rather than type of meal. Thus, difference in nutritional composition influence intact GIP release more than intact GLP-1 release in patients with T2D.

PE-29 Clinical diabetes

Effect of black raspberry extract on metabolic parameters in patients with prediabetes; A randomized, double-blinded, placebo controlled trial

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Objective: Black raspberry (Rubus occidentalis) has been shown to have beneficial effects on glucose and lipid profiles in vitro. We investigated the effects of black raspberry extract on glycemic control and metabolic parameters in patients with prediabetes.

Methods: This study was a 12-week, randomized, double-blinded, placebo-controlled trial. A total of 44 patients (age 59.0 ± 8.2 years, female 70.5%, HbA1c 5.8 ± 0.4 %) were divided into 3 group; placebo (n = 13), low- (LRE, n = 14) or high-dose black raspberry extract (HRE, n = 17) groups. Nine-hundred or 1,800 mg of black raspberry extract was given orally daily in two divided doses for LRE and HRE group, respectively for 12 weeks.

Results: After 12 weeks, mean change of HbA1c and lipid profiles including cholesterol and triglyceride levels were not different between three groups. However, area under the curve for glucose obtained 2hr after 75g oral glucose tolerance test was significantly decreased in HRE group compared with placebo group (-24.6 ± 30.9 vs. +9.2 ± 32.7 mg/dL, $P < 0.05$) although LRE group did not show significant difference (+4.9 ± 38.7 mg/dL). Notably, the serum levels of monocyte chemoattractant protein (MCP)-1 and oxidized low-density lipoprotein (LDL) cholesterol levels were significantly decreased by treatment in a dose-dependent manner (MCP-1, -35.0 ± 75.1, +6.7 ± 57.1 and +34.4 ± 65.4; oxydized LDL cholesterol -19.7 ± 15.5, -13.1 ± 14.3 and -2.2 ± 11.0 in HRE, LRE and placebo group, respectively, all $P < 0.05$). The black raspberry extract was generally well-tolerated and did not produce severe adverse events.

Conclusion: Black raspberry extract showed favorable effects on glycemic control and vascular inflammatory markers after 12 weeks treatment in prediabetic patients. Further studies are needed to verify the long-term effects on the development of overt type 2 diabetes from prediabetes and also on prevention of the atherosclerotic vascular events.(NCT01964703)

PE-30 Clinical diabetes

Plasma levels of lysine, tyrosine, and valine during pregnancy are independent risk factors of insulin resistance and gestational diabetes in pregnant women

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Objective: This study compared the plasma concentrations of amino acids in pregnant women with and without gestational diabetes mellitus (GDM), and identified those associated with GDM, insulin resistance, and insulin secretion at 24~28 weeks of pregnancy.

Methods: Circulating amino acid levels were evaluated using high-performance liquid chromatography at 24~28 weeks of pregnancy in 25 non-GDM and 64 GDM women after adjusting for covariates such as maternal age, body mass index (BMI) before pregnancy, BMI and gestational age at screening GDM, and daily caloric intake. Backwards stepwise logistic regression analysis was used to identify the predictors of developing GDM, and homeostatic model assessments for insulin resistance (HOMA-IR) and β-cell function (HOMA-B).

Results: Circulating levels of amino acids except threonine and tyrosine were significantly higher in GDM women than non-GDM women. Along with the intakes of energy, protein, and fat from animal sources, the intakes of each amino acid were significantly higher in the GDM group without a direct correlation to plasma amino acid levels. The variation in GDM development was explained by maternal age, diastolic blood pressure, and serum lysine levels (R2 = 0.691). Height, BMI before pregnancy, systolic blood pressure, and serum tyrosine and valine levels accounted for the variation in HOMA-IR (R^2 = 0.589). The 53.3% variation of HOMA-B was explained by maternal age, BMI at GDM screening, serum insulin level at 1 h during the OGTT, and serum valine level.

Conclusion: The higher concentrations of circulating lysine, tyrosine, and valine during pregnancy were independently associated with GDM through modifying insulin resistance and secretion.

PE-31 Clinical diabetes

Insulin lispro low mixture twice daily versus basal insulin glargine and prandial insulin lispro once daily in East Asian and Caucasian type 2 diabetes mellitus patients

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Objective: This post-hoc analysis described efficacy and safety of insulin lispro low mixture (LM) twice daily versus bedtime insulin glargine plus prandial insulin lispro administered once daily before the largest meal (IGL) in East Asian (EA) and Caucasian type 2 diabetes mellitus patients who previously failed to reach glycemic targets on basal insulin glargine with metformin and/or pioglitazone.

Methods: This phase 4, randomized, open-label, multinational, multicenter trial included patients with glycosylated hemoglobin (HbA1c) between ≥ 7.5% and ≤ 10.5%, and fasting plasma glucose ≤ 6.7 mmol/L.

Results: Baseline mean (SD) HbA1c values were numerically similar between groups in EA (N = 79) and Caucasian (N = 278) patients (EA: LM = 8.78 [0.71] vs. IGL = 8.72 [0.90]; Caucasian: LM = 8.56 [0.78] vs. IGL = 8.51 [0.70]). Mean (SD) HbA1c significantly ($P < 0.001$) decreased from baseline to 24 weeks for both treatments in both subpopulations (EA: LM = -1.32% [0.96] and IGL = -0.89% [0.98]; Caucasian: LM = -1.24% [0.98] and IGL = -1.05% [0.97]). The proportion reaching HbA1c ≤ 7% at week 24 was LM = 33.3% and IGL = 22.9% for EA patients, and LM = 37.2% and IGL = 34.1% for Caucasian patients. Mean (SD) rate of hypoglycemia per 30 days was LM = 0.74 (1.16) and IGL = 1.22 (1.36) in EA patients, and LM = 1.38 (2.04) and IGL = 1.65 (2.43) in Caucasian patients. Mean (SD) change in weight gain was LM = 0.62 kg (2.78) and IGL = 0.51 kg (2.63) in EA patients, and LM = 1.77 kg (2.91) and IG = 0.67 kg (3.09) in Caucasian patients.

Conclusion: Improved glycemic control was observed in EA and Caucasian patients treated with either LM or IGL.

PE-32 Clinical diabetes

More elevated levels of glycated albumin over HbA1c as duration of diabetes increases: Limitation of glycated albumin as a glycemic monitoring index

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Objective: Previously, we reported that glycated albumin (GA) and GA/HbA1c ratios were significantly increased in subjects with longer duration T2D and with decreased insulin secretory function in cross-sectional study. We currently try to determine whether GA and GA/HbA1c ratios are affected by diabetes duration in subjects with T2D in longitudinal analysis.

Methods: We recruited 349 patients with T2D whose duration of diabetes was ≤ 1 year at Severance Diabetes Registry and who had been repeatedly measured for both serum GA and glycated hemoglobin (A1c) levels over four years. According to stimulated β-cell function assessed by PCGR (postprandial C-peptide-to-glucose ratio), the subjects were classified into two groups: lowest tertile group of PCGR (group I, n = 101) and middle or highest tertiles (group II, n = 248). Time-dependent variation of levels of A1c, GA and GA/A1c ratio were analyzed.

Results: During first 3 months, both A1c (7.7% to 6.9%) and GA (19.2% to 16.6%) levels were significantly decreased. Since then, the levels of A1c and GA were continuously maintained at lower levels up to about 3 years. From 3 years later, all glycemic indices were increased. Although A1c levels were not significantly increased, GA levels (from 39 to 51 months: 16.5% to 17.5%, P = 0.029) and GA/A1c ratio (from 27 to 51 months: 2.35 to 2.45, P = 0.033) were increased with significance. Compared to group II, group I showed significantly higher levels of GA, A1c and GA/A1c. ($P < 0.05$) In addition, increment of GA and GA/A1c was observed earlier time points in group I (at 15 months) than group II (at 39 months).

Conclusion: As type 2 diabetic duration goes, GA and GA/HbA1c ratios are more significantly increased than A1c. And it is more prominent in subjects with decreased β-cell function.

PE-33 Clinical diabetes

Metabolic and vascular characteristics of insulin resistance in Korean patients with type 2 diabetes

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Objective: To investigate the association of IR with metabolic and vascular disorders related to diabetes, we analyzed 7,109 Korean type 2 diabetic patients according to IR.

Methods: A total 7,109 patients with type 2 diabetes were recruited through Huh's Diabetes Center from January 2003 to June 2009. Insulin sensitivity was measured by a rate constant for plasma glucose disappearance (Kitt, %/min) using short insulin tolerance test. Subgroup analyses were performed according to the tertiles of Kitt.

Results: Mean age was 58.1 ± 10.1 years old, and 71.5% of diabetic patients had IR. Patients with the lowest tertile of Kitt (IR group) showed higher levels of metabolic parameters such as body mass index (BMI), visceral fat thickness, blood pressure, fasting blood glucose, HbA1c, total cholesterol, triglyceride and LDL cholesterol but lower HDL cholesterol compared to the patients with the highest tertile of Kitt (insulin-sensitive group). Mean and maximal IMT of carotid arteries was significantly higher in the patients with the lowest tertile of Kitt. As the value of Kitt was lower, the prevalence of metabolic and vascular disorders related to diabetes increased. In multiple regression analysis, IR was an independent risk factor for the metabolic and vascular disorders related to diabetes after adjusting for age, sex, duration of diabetes, BMI and HbA1c. Odds ratios for metabolic syndrome and carotid atherosclerosis in patients with the lowest tertile of Kitt were 3.108 (95% CI, 2.721~3.549) and 1.232 (95% CI, 1.069~1.418), respectively.

Conclusion: IR is not only prevalent but also an important predictor for metabolic and vascular disorders in Korean patients with type 2 diabetes. Beyond reducing the HbA1c, management focusing on IR such as life-style modification or using insulin-sensitizing agents should be evidently needed in patients with type 2 diabetes.

PE-34 Clinical diabetes

Efficacy and safety of teneligliptin, DPP-4 inhibitor, added to metformin in Korean patients with type 2 diabetes mellitus: a 16-week, randomized, double-blind, placebo-controlled trial (Phase III trial)

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Objective: To assess efficacy and safety of teneligliptin, DPP-4 inhibitor, in combination with metformin in Korean patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy.

Methods: Patients (hemoglobin A1c 7.0~10.0%, on stable metformin ≥ 1000 mg/day) were randomized 2:1 to teneligliptin 20 mg plus metformin (n = 137) or placebo plus metformin (n = 70). The primary end-point was the change in HbA1c from baseline to week 16.

Results: The differences between the teneligliptin and placebo groups for the change in HbA1c and fasting plasma glucose (FPG) levels were −0.78 ± 0.09% and −22.4 ± 3.3 mg/dL, respectively, at week 16. Moreover, a significant difference was observed between the teneligliptin group and the placebo group from week 4 to 16 in both parameters. Homeostasis model assessment of β-cell function (HOMA-β) were significantly increased in the teneligliptin group compared with those in the placebo group ($P < 0.001$). The incidence of adverse events and drug-related adverse events was similar among groups.

Conclusion: Addition of teneligliptin 20mg once daily to metformin was effective and generally well tolerated in Korean patients with type 2 diabetes mellitus inadequately controlled with metformin monotherapy. This trial was registered with ClinicalTrials.gov (no. NCT01805830).

PE-35 Clinical diabetes

Health-related quality of life in elderly with diabetes : The Korea National Health and Nutrition Examination Survey (KNHANES) 2007-2010

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Objective: Diabetes is one of the most common forms of chronic disease globally. It is important to detect and improvement of health-related quality of life (HRQoL) in elderly with diabetes because it is associated with glucose control and development of diabetic complication. We evaluated HRQoL in Korean diabetic elderly and identified independent factors associated HRQoL.

Methods: The research selected 4,872 diabetic elderly whose data of health condition and HRQoL exist and ages are older than 65, from the Korea National Health and Nutrition Examination Survey (KNHANES) 2007~2010. The variables included general characteristics, disease-related characteristics, anthropometric measurements and blood tests, and quality of life used the EQ-5D index.

Results: The percentages of elderly with diabetes were 16.7% (788/4,872). EQ-5D index score of elderly with diabetes was significantly lower to elderly without diabetes by 0.79 ± 0.011 and 0.84 ± 0.004, respectively ($P = 0.000$). Independent factors associated with quality of life in elderly with diabetes were age, monthly income, subjective health status, hours of sleep, suicidal thoughts, depression, drinking, walking exercise, and chronic diseases ($P < 0.05$).

Conclusion: In Korea, the quality of life of elderly diabetic patients was significantly lower compared to the elderly who do not have diabetes. Negative emotions, short hours of sleep, poor physical activity, having chronic disease, and low economic level was associated with degradation of the quality of life. In the management of elderly patients with diabetes, individualized approach is required that focus on improving the quality of life.

PE-36 Clinical diabetes

Withdrawn

PE-37 Clinical diabetes

Recurrent focal arm dystonia associated non-ketotic hyperglycemia

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Contents: Focal dystonia is a rare complication of non-ketotic hyperglycemia. Here, we report a case of type 2 diabetes with recurrent focal dystonia manifested as hyperglycemia-induced involuntary movement.

Case report: A 35-year-old woman with type 2 diabetes was admitted with intermittent muscle spasm affecting the left arm for 1 week. The onset was abrupt with episodes of painful tonic flexion of the left arm, and persisted variably from 30 seconds to 10 minutes. No focal neurological deficit was found on examination. Her plasma glucose was 410 mg/dL without ketoacidosis and HbA1c was 18.8%. Serum electrolytes were within normal limits. Brain MRI and EEG were normal. Finally the patient was diagnosed with focal dystonia associated with non-ketotic hyperglycemia. We treated her with intravenous insulin and fluids and dystonia completely disappeared within 2 days. She was discharged without antiepileptic drugs. And 3 years later, she had an exactly same episode of focal dystonia when glycemic control was lost. Uncontrolled hyperglycemia should be considered in the differential diagnosis of dystonia. It is important to keep blood glucose levels under control to prevent recurrent episodes.

PE-38 Clinical diabetes

Effects of valsartan and amlodipine on oxidative stress in type 2 diabetic patients with hypertension: a prospective, randomized, open label, multi-center study

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Objective: Antagonists of renin-angiotensin systems have been previously reported to reduce oxidative stress. The aim of this study was to compare the changes in oxidative stress markers after valsartan and amlodipine treatment, and we also compared the changes in metabolic parameters.

Methods: Type 2 diabetic subjects with hypertension aged from 30 to 80 who were not taking antihypertensive drugs were randomized into either valsartan (n = 33) or amlodipine (n = 35) groups and treated for 24 weeks. We measured serum nitrotyrosine and urine 8-hydroxydeoxyguanosine (8OHdG) as oxidative stress markers. Metabolic parameters including serum glucose, insulin, lipid profile and urine albumin and creatinine were also measured.

Results: After 24 weeks of valsartan or amlodipine treatment, systolic and diastolic blood pressure had decreased with no significant difference. Both groups showed a decrease of serum nitrotyrosine (7.74 ± 7.30 vs. 3.95 ± 4.07 nmol/L in valsartan group and 8.37 ± 8.75 vs. 2.68 ± 2.23 nmol/L in amlodipine group) with no significant difference between two groups. 8OHdG did not show any significant changes in both groups before and after their respective treatments. Other parameters including glucose, lipid profile, albumin-to-creatinine ratio and HOMA-IR showed no significant differences before and after treatment in both groups.

Conclusion: In conclusion, Valsartan and Amlodipine reduced the oxidative stress marker in type 2 diabetic patients with hypertension.

PE-39 Clinical diabetes

The role of soluble cluster determinant 36 (CD 36) as predicting type 2 diabetes in Korean

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Objective: Soluble CD36, member of class B scavenger receptor family, has been known to be progressively related to the severity of insulin resistance and atherosclerosis in the human population. However, its role still remains unclear in type 2 diabetes. The aim of this study is to investigate the relationship between sCD36 and type 2 diabetes (T2DM) in Korean.

Methods: This was a cross-section study and 159 Korean subjects were recruited at Yeungnam University Hospital. T2DM was defined as fasting plasma glucose (FPG) ≥ 126 mg/dL, HbA1c ≥ 6.5%, or self-reported hypoglycemic medication use. We measured anthropometric parameters, sCD36, HbA1c and HOMA indexes.

Results: After excluding Type 1 DM (n = 3), finally 156 subjects were included. T2DM group included 76 patients and age, sex-matched control groups were 80 individuals. T2DM group showed higher HbA1c, FPG and total cholesterol (T-Cho) and triglyceride (TG) than control group. sCD36 level were significantly increased in T2DM (DM: control = 208.73 ± 85.06 pg/mL: 57.08 ± 30.09 pg/mL, $P < 0.05$). In all subjects, sCD36 was positively correlated with HbA1c, FPG, HOMA-IR ($P < 0.05$; r = 0.726, 0.585, 0.248, respectively), and negatively with HOMA-B% (r = -0.264). But sCD36 was only correlated with HbA1c in each DM and control group. sCD36 was significantly associated with HbA1c regardless of diabetes in linear regression analysis adjusted for body mass index, blood pressure, T-Cho, TG, HDL-chol and insulin. In multivariate regression analysis, sCD36 significantly predict the development of diabetes (OR = 1.04; C.I 1.03~1.05, $P = 0.000$).

Conclusion: Regardless of diabetes, sCD36 was associated with HbA1c and insulin resistance, and inversely related with insulin secretary function. sCD36 showed significant correlation with HbA1c in each non-DM and DM group, and the risk of prevalence for diabetes was elevated as sCD36 increased. These results suggested that sCD36 is useful surrogate marker to predict diabetes in Korean.

PE-40 Clinical diabetes

Metabolomic profiles associated with DPP4i in type 2 diabetes

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Objective: Analysis of human metabolites has provided valuable insights into human diseases. Dipeptidyl peptidase-4 inhibitors (DPP4i) are oral glucose-lowering drugs with metformin for type 2 diabetes (T2D). In this study, metabolites associated with DPP4i in T2D patients were analyzed by targeted metabolomic approaches.

Methods: Serum of diabetes patients was divided by metformin-alone group and metformin + DPP4i combination group to investigate metabolites profiles associated with diabetes drugs. AbsoluteIDQ p180 kit was used to quantify 186 metabolites from patients. T-test and partial least-squares discriminant analysis (PLS-DA), were performed to identify significant metabolites statistically.

Results: Statistical analyses showed significant differences in metabolite profiles between metformin alone group and metformin + DPP4i combination group. From the t-test and PLS-DA analysis, sixteen metabolites were identified showing significantly different levels between groups ($P < 0.05$, VIP > 1.5). The combination group of metformin + DPP4i showed increased levels of asymmetric dimethylarginine (ADMA) and total dimethylarginine (DMA) metabolite and decreased levels of phosphatidylcholines and amino acids such as phosphatidylcholine acyl alkyl C40: 4, phosphatidylcholine acyl alkyl C40: 5, glutamine, lysine and tyrosine.

Conclusion: These comprehensive metabolic profiles could provide novel effects of DPP4i on blood metabolites of T2D patients as well as novel clinical implications of DPP4i.

PE-41 Clinical diabetes

Clinical and biochemical characteristics in type 2 diabetes mellitus with visceral obesity and nonalcoholic fatty liver disease

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Objective: Nonalcoholic fatty liver disease (NAFLD) has recently been defined as the hepatic expression of metabolic syndrome. Both visceral obesity (VO) and NAFLD play important roles in developing insulin resistance (IR). The aim of this study was to investigate differences in clinical and metabolic characteristics according to VO and/or NAFLD in Korean subjects with type 2 diabetes mellitus (DM).

Methods: A total of 2,598 (male 1,196 and female 1,402) DM subjects who visited our clinic from 2003 to 2012 were enrolled. We divided each gender into three groups as follows: control, only VO, and VO with NAFLD groups. Insulin sensitivity was assessed by the rate constant of plasma glucose disappearance (Kitt %/min) using a short insulin tolerance test; IR was defined as Kitt of less than 2.5. And visceral fat thickness (VFT) and fatty changes of liver were examined by ultrasonography.

Results: The prevalence of diabetic subjects who had VO and NAFLD (30.8% in male and 46.6% in female, respectively) was higher than that of those who had only VO. In addition, waist circumference and VFT were increased in the following order: control, only VO, and VO with NAFLD groups. IR was significantly higher in subjects who had VO than the control group, and most prominently in the VO with NAFLD group. In female subjects, most of the lipid profiles and HbA1c levels in the NAFLD combined group were definitely higher compared to the other two groups, but part of these differences diminished in male. Moreover, there was significant difference in the odds ratio (OR) for IR between control and only VO or VO with NAFLD groups (1.139 vs. 2.930 in male, and 1.826 vs. 3.509 in female, respectively).

Conclusion: These findings indicate that DM subjects who show VO and NAFLD can have more adverse effects on their metabolic parameters than those who show only VO.

PE-42 Clinical diabetes

Frequent hypoglycemia attack in known diabetic patients for 1 month

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Objective: We report a case of frequent hypoglycemia suddenly developed in a patient with uncontrolled diabetes.

Methods: A 40-year-old woman was referred to our clinic with hypoglycemia of 1 month's duration. She had a 12-year history of diabetes and the HbA1c measured 4 months ago was 11.8%.

Results: At presentation, she had anti-glutamic acid decarboxylase (GAD) antibody and wasn't taking any medication over 2 weeks. Serum C-peptide and insulin levels at 72h-fasting test revealed that the hypoglycemia resulted from endogenous hyperinsulinemia. A Positron Emission Tomography-Computed Tomography (PET-CT) image disclosed a 1.5x1.0 cm sized hypermetabolic mass in the pancreatic head with diffuse multiple hypermetabolic lesions in the liver. The biopsy of the hepatic lesion was performed and the histologic finding was compatible with liver metastasis of pancreatic neuroendocrine tumor. Immunohistochemical staining for insulin was negative.

Conclusion: Features of interest in this case included: (1) Whereas she had massive liver metastasis of pancreatic neuroendocrine tumor, she had uncontrolled diabetes until quite recently and had short duration of hypoglycemia with 1 month. (2) Although the hypoglycemia resulted from endogenous hyperinsulinemia, an immunohistochemical staining of the metastatic liver mass for insulin was negative. Considering above features, this patient seemed to have malignant insulinoma presenting a non-functioning metastatic liver tumor.

PE-43 Clinical diabetes

Drug utilization pattern and clinical risk factors in type 2 diabetic patients with hypoglycemia

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Objective: Hypoglycemia is increasing complication of diabetes as strict control of HbA1c levels was emphasized to diabetic patients. Longer duration of diabetes, older age, irregular intake of diet and intensive medical treatment for lowering HbA1c levels are the risk factors of hypoglycemia. Recently, new anti diabetic agents which rarely cause severe hypoglycemia were developed and have been used increasingly. We designed the retrospective study to identify the changes of anti diabetic medication trend and to reveal association with hypoglycemic event.

Methods: We conducted retrospective analysis of medical records of 698 patients who visited as hypoglycemia to emergency center of Inha university hospital from august 1, 2009 to september 30, 2013. Individual characteristics, risk factors, blood chemistry including HbA1c levels, types of medication and length of hospital stay were obtained and then analyzed by annually.

Results: 377 of patients were selected according to the inclusion criteria. A mean age was 69.5 ± 13.0 years and a mean disease duration was 14.1 ± 9.2 years. A mean HbA1c level was 6.93 ± 1.50 %. A mean blood glucose level as checked in the EMC was relatively high with 73.5 ± 84.5 mg/dL, because 18% of patients were given the glucose supplement before admission. Renal function of patients was relatively decreased with a mean serum creatinine level of 2.60 ± 2.74 mg/dL and with a mean eGFR of 50.1 ± 33.6 mL/min. 37.1% of patients took insulin and 55.4% of patients took sulfonylurea. DPP4 inhibitor was taken by 8% of total patients and proportion of DPP 4 inhibitor usage had increased annually from 2009 to 2013 ($P < 0.001$).

Conclusion: Severe hypoglycemia is frequent in older diabetic patients, subjects with low HbA1c levels, or nephropathy. Therefore, personalized attention is warranted, especially in long-term diabetics with multiple comorbidities. Outcome was not different among patients with the different anti-diabetic drug.

PE-44 Clinical diabetes

Association of PAX4 R192H genetic variation with risk of gestational diabetes mellitus

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Objective: PAX4 (paired box gene 4) encodes a transcription factor that plays an essential role in the differentiation of insulin-producing beta cells. It has been reported that genetic variation in PAX4 results in maturity onset diabetes of the young and is also associated with development of type 2 diabetes. The objective of this study is to evaluate the association between genetic variation of PAX4 and risk of gestational diabetes mellitus (GDM).

Methods: Single nucleotide variation rs2233580G 〉 A, which results in nonsynonymous mutation (R192H) of PAX4 was selected for genotyping. The variant was genotyped with TaqMan method in 869 Korean GDM women and carefully selected 632 nondiabetic control subjects.

Results: There was a significant difference in risk allele (A) frequency between GDM group (10.5%) and control group (6.4%) (P 0.00013). When the genotype frequency was compared, the rs2233580 variant was significantly associated with risk of GDM (odd ratio 1.62, 95% confidence interval 1.25~2.12, P 0.00033) in additive model. However, there was no significant difference in various metabolic parameters including blood pressure, body mass index, and fasting glucose in non-diabetic control subjects.

Conclusion: We found that PAX4 R192H rs2233580 G 〉 A variant was significantly associated with the risk of GDM. Further studies are required to elucidate the role of this variant in the pathogenesis of GDM.

PE-45 Clinical diabetes

PWV but not ABI is correlated linearly with FRS, UKPDS CHD and UKPDS stroke risk score in Korean adult T2DM

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Objective: Pulse wave velocity (PWV) and Ankle-brachial index (ABI) are well known non-invasive parameters that measure arterial stiffness and arteriosclerosis. Increased arterial stiffness measured by PWV and decreased ABI are related with increased cardiovascular event. Framingham Risk Score (FRS) in general population and United Kingdom Prospective diabetes Study (UKPDS) risk score in type 2 diabetes were well known clinical cardiovascular disease (CVD) Risk measurement tool. To elucidate the correlation between PWV with known CVD risk scores such as FRS and UKPDS CHD and stroke risk score and ABI simultaneously.

Methods: From April 2010 to April 2012, total 210 (110 = men and 104 = women) numbers of Type 2 diabetes subjects who were admitted in the Kosin University Gospel Hospital were included. Brachial-ankle Pulse Wave Velocity (BaPWV, m/sec), mean ankle brachial index (ABI), age (years), diabetes duration (months), systolic blood pressure (sBP, mmHg), total cholesterol (mg/dL), HDL (mg/dL), triglyceride (mg/dL), Framingham Risk Score (FRS), United Kingdom Prospective Diabetes Study (UKPDS) CHD score, United Kingdom Prospective Diabetes Study (UKPDS) Stroke score were measured. Data was analyzed by using SPSS 18.

Results: The BaPWV were correlated with FRS (γ = 0.306 P < 0.01), UKPDS CHD (γ= 0.378 P<0.01) and UKPDS stroke Risk (γ= 0.380 P < 0.01). The BaPWV were correlated with FRS (γ = 0.414 P < 0.01), UKPDS CHD (γ = 0.358 P < 0.01) and UKPDS stroke Risk (γ = 0.360 P < 0.01). The BaPWV were correlated with FRS (γ = 0.442 P < 0.01), UKPDS CHD (γ = 0.505 P < 0.01) and UKPDS stroke Risk (γ = 0.404 P < 0.01). BaPWV was not correlated with ABI (γ = 0.074 P < 0.286).

Conclusion: BaPWV is well correlated with FRS, UKPDS CHD and UKPDS Stroke Risk scores but not with ABI. That suggest BaPWV can be a good marker for predict cardiovascular disease in known t2DM patient but mean ABI cannot be.

PE-46 Clinical diabetes

Hypoglycemic status of elderly patients with type 2 diabetes mellitus in current clinical practice

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Objective: This study aimed to clarify the hypoglycemic status of elderly patients with type 2 diabetes mellitus (DM) who presented to the emergency department of the Presbyterian Medical Center.

Methods: One hundred and fifty four patients who experienced a hypoglycemic event (glucose < 70 mg/dL with hypoglycemic symptoms) presented to the emergency department between July 1, 2013 and June 30, 2014. Among them, 91 patients had type 2 DM and were receiving treatment with oral antidiabetic medications and/or insulin.

Results: Among the 91 type 2 DM patients, 18 were < 70 years of age (group 1) and 73 were ≥ 70 years of age (group 2). There were 39 (42.8%) male patients and 52 (57.2%) female patients. The incidence of hypoglycemia-related admission was higher in group 2 than in group 1 patients (45% vs. 33.3%). Among 36 patients who were admitted, 17 (43%) had a history of DM-related admission in the past 2 years. The mean glucose and glycated hemoglobin levels at the time of the hypoglycemic event were lower in group 2 than in group 1 (40.19 vs. 42.4 mg/dL and 6.31% vs. 7.47%, respectively). Regarding the type of medication, the rate of oral hypoglycemic agent (OHA) with sulfonylurea (SU) use was 71.4% - it was higher in group 2 than in group 1 (80.8% vs. 38.8%) - and the insulin use was 24.1%. On average, group 1 was prescribed 6.22 medications, but no antidiabetic medications, and group 2 was prescribed 6.86 medications.

Conclusion: Advanced age, SU use, recent hospitalization, and polypharmacy (> 5 medications) are reported strong predictors of hypoglycemia in the elderly. Our study shows that the incidence of hypoglycemia and related admission increased with age. In addition, the use of SU and polypharmacy were an important part of elderly hypoglycemia in current clinical practice.

PE-47 Clinical diabetes

Cardiometabolic risk is more correlated with visceral fat thickness measured by ultrasonography than waist circumference in Korean type 2 diabetic patients

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Objective: Many studies demonstrated positive relationships between the amount of visceral abdominal fat and several cardiometabolic risk factors than that of total body fat in type 2 diabetic patients. Ultrasound (US) measurements have been recently shown to correlate better with cardiometabolic risk factors than anthropometric measurements. The aim of our study was to evaluate and compare relationships of body mass index (BMI), WC, and visceral fat thickness (VFT) on cardiometabolic risk factors in type 2 diabetic subjects.

Methods: 265 type 2 diabetic patients participated in the study: 141 men (mean age 58.8 ± 12.4 years) and 124 women (mean age 60.0 ± 13.0 years). US procedures were performed by the same examiner using a 3.5-MHz probe. Two US measurements of visceral (VFT) and subcutaneous fat (SFT) were taken. US-determined VFT was defined as the distance between the internal face of the rectus abdominis muscle and the anterior wall of the aorta. The metabolic syndrome was defined by NCEP-ATP III guideline.

Results: Strong positive correlations existed between VFT and BMI, VFT and WC, and BMI and WC (r = 0.68, r = 0.79, r = 0.81, respectively, P < 0.01). BMI and VFT were positively correlated with diastolic BP, although correlation coefficients were lower for BMI than for VFT. BMI, WC, and VFT were also significantly correlated with plasma triglycerides and Framingham risk score, but VFT only were correlated with HDL-cholesterol and LDL-cholesterol. Age- and sex-adjusted associations of adiposity measures with presence of the metabolic syndrome and high CHD risk were significant in VFT. The odds ratios of having the metabolic syndrome and high CHD risk were greater for VFT than for BMI and WC.

Conclusion: VFT shows the better association with cardiometabolic risk than WC. This study suggests that VFT measured by ultrasonography may be used as a complementary measure to identify CHD risk in Korean type 2 diabetic patients.

PE-48 Clinical diabetes

Clinical determinant correlated with BaPWV in advanced Korean adult type 2 diabetes subjects

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Objective: Brachial ankle Pulse wave velocity (BaPWV) is a well known non invasive parameter that measure arterial stiffness. Increased arterial stiffness is related with increased cardiovascular event and mortality in type 2 diabetes mellitus (T2DM). T2DM subject is high risk group of developing cardiovascular disease. Clinical parameters that determinate BaPWV in T2DM were inconsistent and inconclusive in many studies. To elucidate the correlation between BaPWV with known clinical parameters associated with increased cardiovascular disease and to demonstrate the clinical determinants of increased BaPWV in Korean adult type 2 diabetes patients are our objectives.

Methods: From April 2010 to April 2012, Type 2 diabetes subjects who were admitted in the Kosin University Gospel Hospital were included. Brachial-ankle Pulse Wave Velocity (BaPWV, m/sec), Mean ankle brachial index (ABI), Age (years), DM duration (months), Systolic Blood pressure (BP, mmHg), Body mass index (BMI, m/Kg^2), Albumin Creatinine Ratio (ACR), Fasting Blood Sugar (FBS, mg/dL), HbA1C (%), 25-(OH) Vitamin D (IU), Total cholesterol (mg/dL), HDL (mg/dL), Triglyceride (mg/dL), Homeostatic model assessment of insulin restance (HOMA)-IR, Homeostatic model assessment (HOMA)-β were measured. Data was analyzed by using SPSS 18.

Results: Total 210 (110 = men and 104 = women) numbers of Type 2 diabetes were included. There were no differences of BaPWV between groups regardless of smokings. BaPWV is positively correlated with age and current systolic blood pressure (sBP) without regard to antihypertensive medication. Diabetes duration and HOMA-IR is positively correlated with increased BaPWV only in men after adjustment of age and sBP. Blood glucose status including FBS, post prandial 2 hour glucose and HbA1C did not correlated with BaPWV. Lipid parameters including total cholesterol, LDL-cholesterol and HDL-cholesterol were not correlated with BaPWV. Degree of microalbuminuria, obesity nor 25(OH)D3 was associated with increased BaPWV after adjustment of age and systolic blood pressure.

Conclusion: BaPWV is strongly determined by age and current systolic blood pressure irrespective of antihypertensive medication in both gender in Korean T2DM subjects. Diabetes duration and insulin resistance only affect BaPWV in male not in female T2DM subjects.

PE-49 Clinical diabetes

Long-term remission in patients with type 2 diabetes mellitus treated with insulin pump therapy

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Objective: Intensive insulin therapy (IIT) can improve β-cell function and result in glycemic remission in early type 2 diabetes mellitus (T2DM). However, it is not known whether IIT could induce long-term remission and remission in patients with long duration of T2DM.

Methods: Retrospective chart review was performed for insulin pump treated T2DM remission cases who visited to outpatient clinic of Konkuk University Chungju hospital from March to June in 2014. Remission was defined as normal fasting and postprandial glucose level for 6 month after discontinuation of all anti-diabetic medication. Vales were presented as median (minimum-maximum) or mean ± standard deviation.

Results: Eighteen patients (8 males, 10 females) were enrolled during 4 months. Age at diagnosis was 51 (32~57) years and duration of T2DM was 0.9 (0.0~23.0) years. Two (11.1%) patients were newly diagnosed and 16 patients (88.9%) were on oral anti-diabetic medications. Initial HbA1c level was 7.4 ± 2.1 %. After conversion to insulin pump therapy, total daily insulin dose was 55 (22~344) IU. Time to remission was 23 (5~108) months and duration of remission was 25 (7~108) months. During the follow-up of 4.5 (1.7~10.0) years, 4 subjects had relapse of T2DM and restarted insulin pump. In 14 patients with sustained remission, the latest HbA1c levels were significantly lower than initial levels (7.7 ± 2.1 → 6.1 ± 0.4 %, P = 0.009). The latest body mass index was also significantly decreased (25.2 ± 3.4 → 24.4 ± 3.7, P = 0.033). Disposition index was significantly increased from 0.14 ± 0.09 (initial) to 0.35 ± 0.15 (maximum) (P = 0.002). In 4 relapsed subjects, duration of remission was 16 (7~36) months. The latest HbA1c levels after relapse were 6.2 ± 0.5%.

Conclusion: Insulin pump therapy improved β-cell function and induced long-term glycemic remission regardless of T2DM duration.

PE-50 Clinical diabetes

Effects of metformin on TSH and thyroid hormone levels in type 2 diabetic patient with differentiated thyroid cancer

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Objective: Suppressive therapy with levothyroxine is the main step in treatment of differentiated thyroid cancer. Recent studies have suggested that metformin may have a suppressive effect on TSH level.

Methods: We performed a cross-sectional analysis among 30 subjects with type 2 diabetes underwent total thyroidectomy due to differentiated thyroid cancer during five years and were receiving levothyroxine suppression therapy. Patients were divided into two groups depending on metformin use: the non-metformin group included 10 patients; the Metforim group 20 patient. TSH and thyroid hormone values were measured after 3months after treatment.

Results: The mean age, weight, BMI and TSH level were not significantly different between the metformin and the non-metformin. However, Levothyroxine dosage was significantly differences between the metformin and the non-metformin groups: 172.2 μg in the non-metformin group versus 162.5 μg in the MF group (P = 0.5).

Conclusion: Patients receiving metformin treatment need a lower thyroxine dose than patients who do not receive the drug of the patients with diabetes mellitus type 2.

PE-51 Clinical diabetes

Comparison of HbA1c and OGTT to diagnose diabetes in Korean children

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Objective: Recently, the American Diabetes Association introduced HbA1c test for diagnosing diabetes with a cut point of ≥ 6.5% in addition to criteria based on either fasting plasma glucose (FPG) or 2 hour plasma glucose tolerance test (OGTT). The aim of this study was to evaluate the corelation between plasma glucose (FPG and 2-h OGTT) and HbA1c for diagnosing diabetes in Korean children.

Methods: A total of 143 children without known diabetes completed an OGTT and HbA1c sampling between 2010 to 2013. Diabetes was defined as a 2-h OGTT ≥ 200 mg/dL, FPG ≥ 126 mg/dL or HbA1c ≥ 6.5%.

Results: Of 49 children with diabetes, 44 (89.8%) were diagnosis by only HbA1c, 42 (85.7%) by 2-h OGTT, and 31 (63.3%) by FPG. Diagnostic sensitivity and specificity of diabetic criteria was 90.0% and 100.0% for HbA1c: 85.7% and 100.0% for 2-h OGTT and 63.3% and 100.0% for FPG. Substantial agreement existed for HbA1c and FPG criteria (κ coefficient = 0.695, P < 0.001), HbA1c and 2-h OGTT criteria (κ coefficient = 0.880, P < 0.001) and HbA1c and FPG and/or 2-h OGTT criteria (κ coefficient = 0.818, P < 0.001) for diagnosing diabetes. HbA1c had the highest estimated area under the curve (AUC) among 3 diagnostic criteria. The AUC of HbA1c for identifying diabetic subjects according to FPG or 2-h OGTT criteria was 0.970 and 0.943. And, we found that an HbA1c level of 6.35% had higher sensitivity than 6.5%, and improved positive predictive value and negative predictive value.

Conclusion: As a screening test for diagnosing diabetes, HbA1c is useful better than FPG and 2-h OGTT in children and adolescents. But, because of low sensitivity of HbA1c ≥6.5%, we recommend that children with HbA1c of 6.35% to 6.5% should be tested OGTT to confirm diagnosis of diabetes.

PE-52 Clinical diabetes

The effect of hemodialysis on HbA1c level in diabetic patients

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Objective: Hemoglobin A1c (HbA1c) is widely used for diabetes diagnosis and monitoring as it highly correlates with blood glucose levels and outcomes. But the correlation between HbA1c and blood glucose levels in dialysis patients is considered different from that of normal patients because of special conditions in dialysis patients, including the uremic milieu. Hemoglobin A1c may be reduced because reduced urea after hemodialysis. Therefore, we sought to find the difference between predialysis and postdialysis HbA1c for hemodialysis patients.

Methods: We included 8 diabetic patients and 3 non-diabetic patients with hemodialysis. We measured the Hemoglobin A1c by just before hemodialysis and after 4 hours of hemodialysis. Additionally, we checked the basic characteristics of patients including hemodialysis duration, Kt/v, URR and Labile HbA1c. The HbA1c was analyzed by Bio-Rad variant II Hba1c analyzer.

Results: After hemodialysis, the HbA1c level was decreased 0.075 ± 0.04 (P = 0.02)% in diabetes group whereas in non-diabetes group there was no change of HbA1c level. The hemoglobin level and erythropoietin doses which could affect the HbA1c level had no significant differences between two groups. The basic characteristics of patients' age, hemodialysis duration, height, weight, BMI, blood pressure was similar. The Kt/v (1.26 ± 0.20 vs 1.59 ± 0.15, diabetes vs non diabetes, P = 0.03) and URR (64.91 ± 6.9 vs 75.43 ± 2.03, diabetes vs non diabetes, P = 0.004) were higher in non diabetes groups. However, pre-dialysis HbA1c (6.43 ± 1.20% vs 5.30 ± 0.45%, diabetes vs non diabetes, P = 0.05) and Labile HbA1c (2.51 ± 0.33% vs 2.2 ± 0.17%, diabetes vs non diabetes, P = 0.08) were higher and the difference of Labile HbA1c after hemodialysis was significantly observed (-0.16 ± 0.24% vs 0.13 ± 0.15%, diabetes vs non diabetes, P = 0.05) in diabetes group.

Conclusion: HbA1c level of diabetes patients was decreased after hemodialysis. It might be associated with the reduction of labile HbA1c level.

PE-53 Clinical diabetes

Pregabalin-induced cortical negative myoclonus in type 2 diabetic patients on peritoneal dialysis

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Contents: Pregabalin is an anticonvulsant drug which can be used to treat partial epilepsy and neuropathic pain. It is usually considered a first line agent for the treatment of pain associated with diabetic neuropathy, post-herpetic neuralgia, and central neuropathic pain. Most common adverse effect is dizziness and drowsiness, and myoclonus is infrequent adverse effect of pregabalin. Cortical negative myoclonus is rarely reported. Here we report a case of a patient who underwent cortical negative myoclonus caused by pregabalin. A 62-year-old man was admitted to the emergency department with intention tremor of both upper and lower extremities. He had end-stage renal disease due to diabetic nephropathy and had been treated with peritoneal dialysis for 5 years. Recently, he had been admitted to our hospital for a tip amputation of right first toe due to diabetic foot disease. During hospitalization, 6 days before the symptom occurred, he started taking pregabalin 150mg a day for neuropathic pain. Physical examination, neurologic examination, magnetic resonance imaging of the brain and electroencephalography was performed. There was no evidence of structural disease or epilepsy. He was diagnosed pregabalin-induced cortical negative myoclonus. After discontinuation of the drug, he gradually improved. We concluded that pregabalin rarely can cause cortical negative myoclonus in patient with chronic kidney disease.

PE-54 Clinical diabetes

Free fatty acid as a surrogating marker of β-cell improvement

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Bucheon St

Objective: Free fatty acids (FFAs) have two aspects. The one is a physiologically important energy substrates and the other is insulin resistance in all major insulin target organs. The aim of this study is to evaluate the relationship between dynamic measurement of FFAs during oral glucose loading test and beta cell recovery, and whether FFAs has a predicting role in evaluating beta cell recovery after early intensive insulin therapy in patients with newly diagnosed type 2 diabetes.

Methods: 40 newly diagnosed type 2 diabetes patients who met the American Diabetic Association diagnostic criteria were recruited from the diabetic center of Bucheon St. Mary's Hospital, the Catholic University of Korea between March 2009 and March 2010. Forty subjects were admitted to the hospital and received a 12-week course of intensive insulin therapy and completed the 75 g oral glucose tolerance test (OGTT) both before and after intensive insulin therapy.

Results: After 3 month of intensive insulin therapy, 13 patients became prediabetes pattern (Impaired fasting glucose or Impaired glucose tolerance) on follow up OGTT. We categorized subjects who show improved glycemic control as pre-DM group and others who still remain DM as DM group. After treatment, there were significant differences in HOMA2-b (P = 0.003), insulinogenic index (P = 0.025), disposition index (P = 0.009) and non-significant differences in HOMA2-IR, fasting FFA concentration between pre-DM group and DM group on follow up OGTT. After trestment, the suppression of FFAs after the glucose load improved in pre-DM group.

Conclusion: Three-months insulin therapy improved the suppression of FFAs after oral glucose in newly diagnosed type 2 DM patients, possibly due to improved β-cell function. Improved regulation of postprandial plasma FFAs concentration could be a surrogate marker of improved β-cell function.

PE-55 Clinical diabetes

Clinical characteristics of Korean double diabetes

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Objective: Double (unstable) diabetes is generally defined as type 1 diabetes mellitus (TIDM) with insulin resistance (IR). This combination can lead to inadequate glycemic control even with higher insulin doses, thereby probably increasing risk of cardiovascular (CV) complications. The phenotype of double diabetes may be related to the genetic and lifestyle factors, and weight gain caused by intensive insulin therapy. The aim of this study was to investigate the clinical and metabolic parameters according to the degree of IR in Korean TIDM.

Methods: We evaluated 203 patients with TIDM (men 100, women 103) whose fasting C-peptides were ≤ 0.6 ng/mL and who were treated with insulin. Insulin sensitivity was assessed by the rate constant of plasma glucose disappearance (kitt%/min) using short insulin tolerance test in all patients,: the low tertile of kitt was considered relatively insulin-resistant group. And visceral fat thickness (VFT) and carotid intima-media thickness (CIMT) were measured by ultrasonography.

Results: In both genders, fasting glucose and HbA1c levels were significantly higher in the low tertile group than in the high tertile one. It should be clinically emphasized that the fluctuation in blood glucose (hyperglycemia and hypoglycemia) might be severe in spite of high insulin dose to maintain euglycemic state. Interestingly enough, there were no differences in VFT and CIMT, as well as DM duration, body mass index, waist circumference, and lipid profiles between the two groups.

Conclusion: Except for difficulties related to glycemic control, the influence of IR on most of metabolic parameters in Korean double diabetes was not clear. However, this result suggests that lifestlye modification and the use of insulin sensitizers should be used to control unstable hyperglycemia in double diabetes.

PE-56 Epidemiology

Comparison of medication adherence and patient characteristics in patients with diabetes between rural and urban cohorts in South Korea

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Objective: Diabetes mellitus (DM) is a major cause of death and disability, and regular administration of medications is important in its management. A better understanding of the factors associated with medication non-adherence or underuse should help to improve adherence, and thereby provide for a more favorable treatment outcome. The objectives of this study was to assess prevalence of and identify factors associated with non-adherence to medication in rural versus urban population in Korea.

Methods: In this large, community-based cross-sectional study, data on DM patients from rural and urban area obtained during biennial health examinations in 2011~2012 were analyzed. Demographic information, and anthropometric and laboratory test results were collected. The study population of rural and urban cohorts was further categorized into two groups according to medication adherence: those who were currently on anti-diabetic medication, and those who did not take the medication despite knowing that they were diabetic.

Results: A total of 1,675 residents diagnosed as diabetic were included in this study, and comprised 803 patients from the rural area and 872 patients from the urban area. Over half of the study population (55.76%, 934 patients) belonged to the non-adherent group. The incidence of taking anti-diabetic medications was higher in the rural (52.4%) than in the urban (36.7%) cohort. There was a significant association between medication non-adherence and age, male gender, drinking, high BP, high total cholesterol, and lack of family history of diabetes, but not with incomes, smoking status, exercise, marital status, and occupation.

Conclusion: Despite the proven beneficial effects of anti-diabetic medications in the management of DM, we observed low rates of medication use, particularly in the urban area. Therefore, there is a need for effective strategies that will lead to improved medication adherence.

PE-57 Epidemiology

The incidence and prevalence of diabetes mellitus and related atherosclerotic complications in Korea: a national health insurance database study

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Objective: The incidence and the prevalence of type 2 diabetes mellitus (T2DM) and macrovascular complications in Korea were estimated using the Health Insurance Review and Assessment (HIRA) database from 2007~2011, which covers the claim data of 97.0% of the population in Korea.

Methods: T2DM, coronary artery disease (CAD), cerebrovascular disease (CVD), and peripheral artery disease (PAD) were defined according to ICD-10 codes. We used the Healthcare Common Procedure Coding System codes provided by HIRA to identify associated procedures or surgeries. For calculating incidence, we excluded cases with preexisting T2DM within 2 years before the index year. Poisson distribution was assumed for calculating 95% confidence intervals for prevalence and incidence rates.

Results: The prevalence of T2DM in Korean adults aged 20 – 89 years was 6.1~6.9% and the annual incidence rates of T2DM ranged from 9.5~9.8/1,000 person-year (PY) during the study period. The incidence rates of T2DM in men and women aged 20 – 49 years showed decreasing patterns from 2009 to 2011 ($P < 0.001$); by contrast, the incidence in subjects aged 70~79 years showed increased patterns from 2009 to 2011 ($P < 0.001$). The incidence rates of CAD and CVD in patients newly diagnosed with T2DM were 18.84/1,000 PY and 11.32/1,000 PY, respectively, in the year of diagnosis. Among newly diagnosed individuals with T2DM who were undergoing treatment for PAD, 14.6% underwent angioplasty for CAD during the same period.

Conclusion: Our study measured the national incidences of T2DM, CAD, CVD, and PAD, which are of great concern for public health. We also confirmed the relatively higher risk of CAD and CVD newly detected T2DM patients compared to the general population in Korea.

PE-58 Epidemiology

Increased risk of diabetes and post-diabetes adverse events in patients with stroke: Two nationwide retrospective cohort studies

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Objective: The relationship between stroke and diabetes is not completely understood. This study evaluated diabetes risk and post-diabetes adverse events in patients with stroke.

Methods: We identified 7681 adults newly diagnosed with stroke in 2000-2003 using Taiwan's National Health Insurance Research Database. A comparison cohort of 30,724 adults without stroke was randomly selected from the same dataset, frequency matched by age and sex. Diabetes events in 2000~2008 were ascertained from medical claims. Adjusted hazard ratios (HRs) and 95% CIs of diabetes associated with stroke were calculated. A nested cohort study of 21,147 patients with inpatient care for diabetes between 2004 and 2010 were calculated adjusted odds ratios (ORs) and 95% CIs of adverse events after diabetes in patients with and without stroke.

Results: During 222,477 person-years of follow-up, there were 8183 newly diagnosed diabetes cases. The incidences of diabetes for people with stroke and without were 69.5 and 30.0 per 1,000 person-years, respectively ($P < 0.0001$). Compared with people without stroke, the adjusted HR of diabetes was 3.45 (95% CI 3.26~3.66) for people with stroke. The ORs of post-diabetes pneumonia, urinary tract infection, and mortality associated with stroke were 1.28 (95% CI 1.07~1.53), 1.49 (95% CI 1.30~1.71), and 1.55 (95% CI 1.07~2.24), respectively.

Conclusion: Stroke was associated with diabetes risk. Patients with stroke had more adverse events and subsequent mortality after diabetes. Prevention of diabetes and post-diabetes adverse events is needed in this susceptible population.

PE-59 Epidemiology

The study of epistasis effects for type 2 diabetes in Korean population-based cohort

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Objective: Type 2 diabetes (T2d) is a kind of common disease, its prevalence is rapidly increasing. Although many casual variants related T2d have been reported from genome-wide association studies (GWASs), the variants explain a small proportion of the heritability. Recently, GWAS using multiple phenotypes have been conducted to overcome low power problem of simple GWAS, so we conducted multi-association for detecting new casual variants and study of epistasis effects of casual variants.

Methods: We conducted multi-association (both multi traits-unit SNP and multi traits-multi SNPs) using the Korea Association Resource (KARE) cohort. In our study, 8443 individuals are analyzed for association with T2d while adjusting age and sex. For study of epistasis effect of casual variants, we consider gene and region-based multi SNPs.

Results: We replicated the well-established common variants related T2d and identified some new casual variants. For detection of loci which have epistasis effects, we analyzed loci that contain casual variants and found some interesting loci.

Conclusion: In our study, we identified some casual variants and found some loci which may have epistasis effect. Our results will be helpful in future studies such as predictions of T2d.

PE-60 Epidemiology

Association of genetic variants related lipid traits in the Korean population

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Objective: Diabetes mellitus is the most frequent endogenous cause of lipid metabolism-disorder. Many of the lipid metabolism steps are regulated by insulin related to the diabetes mellitus. To evaluate whether exonic variants are associated with triglyceride (TG), high density lipoprotein (HDL) and low density lipoprotein (LDL) levels involved in the lipid metabolism, we conducted an association using large-scale exome chip with the KARE data (N = 8,842).

Methods: A total of 240K SNPs were genotyped using Illumina HumanExome Chip (ver. 1.1). SNP quality control was carried out to exclude SNPs with a high missing call rate (> 5%), monomorphic or low Hardy-Weinberg equilibrium P value ($P < 1 \times 10^{-6}$). For the analysis of dyslipidemia-related traits (LDLc, HDLc and TG) and TG, subjects receiving lipid-lowering therapy and TG > 400 mg/dL were excluded from analysis. Measurements of TG, HDLc were transformed with the natural log to achieve a normal distribution. Association analyses were performed using SAS, PLINK and EPACTS after adjusting for age, sex and recruitment area.

Results: We identified previously reported 45 SNPs and newly associated 6 SNPs. The most significant association was for the SNP in the gene on 11q23 that plays an important role in regulating in the plasma TG level and a major risk factor for coronary artery disease.

Conclusion: Further replication studies and functional characterization are warranted to validate these results.

PE-61 Epidemiology

Higher association of non-alcoholic fatty liver disease with coronary artery calcification than abdominal obesity

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Objective: Non-alcoholic fatty liver disease (NAFLD) and abdominal obesity often coexist and act synergistically to increase the risk of developing subclinical atherosclerosis. However, which of NAFLD or abdominal obesity is more related to atherosclerosis than each other. The aim of this study was to determine which is more related with subclinical atherosclerosis assessed by coronary artery calcification (CAC) between NAFLD or abdominal obesity.

Methods: In 21,335 male participants in a health screening program (mean age 41 years), ultrasound measurements of fatty liver and a multi-detector computed tomography for CAC score (CACS) were performed. The presence of CAC was defined by CACS 〉 0. Subjects were divided into four groups according to the presence of NAFLD and abdominal obesity assessed by waist-hip ratio (WHR) 〉 0.9: group without either abnormalities, group with only abdominal obesity, group with only NAFLD and group with both abnormalities.

Results: There were 2,385 subjects (11.2%) with CAC. The proportion of subjects with CAC was the highest in abdominal obesity only group (23.2%). After adjustment for age, diabetes history, hypertension, dyslipidemia, cigarette smoking and physical inactivity, the odds ratio (OR) for CAC was the highest in group with both abnormalities. NAFLD only group showed significantly increased OR for CAC compared with abdominal obesity only group [1.492 (95% confidence interval (CI) 1.348~1.652) vs. 1.284 (95% CI 1.150~1.434)].

Conclusion: NAFLD is more closely associated with CAC compared with abdominal obesity assessed by WHR. NAFLD could be assumed to be the independent determinant for subclinical atherosclerosis assessed by CAC.

PE-62 Epidemiology

Maternal age at first delivery is associated with the risk of metabolic syndrome in postmenopausal women: from 2008~2011 Korean National Health and Nutrition Examination Survey

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Objective: Recent cross-sectional study demonstrated that maternal earlier age at first childbirth (≤ 19 years) is correlated with a higher risk of diabetes in postmenopausal women. In this study, we aimed to evaluate whether age at first delivery are associated with the risk of metabolic syndrome (MetS) in postmenopausal women.

Methods: A total of 4,261 postmenopausal women were analyzed using data generated from Korea National Health and Nutrition Examination Surveys (2008 −2010). Total subjects were divided into three groups according to maternal age at first delivery as follows: 1. ≤ 20 years (n = 878), 2. 21~25 years (n = 2314), and 3. ≥ 26 years (n = 1069).

Results: Approximately 40% of subjects had MetS. The prevalence of MetS showed a gradual increase with decreasing maternal age at first delivery (≥ 26 years = 30.9% vs. 21~25 years = 39.9% vs. ≤ 20 years = 50.8%, respectively, P 〈 0.001). In Pearson correlation analysis, maternal age at first delivery was negatively correlated with BMI, waist circumference, glycated hemoglobin, triglyceride, and HOMA-IR. After adjustments for age, current smoking, alcohol drinking, physical activity, total energy intake, number of pregnancies, age at menarche, and hormone replacement therapy, the odd ratios (ORs) for predicting the presence of MetS increased gradually with decreasing maternal age at first delivery (≥ 26 years vs. 21~25 years vs. ≤ 20 years: OR [95% CI] = 1 vs 1.32 [1.12-1.57] vs. 1.64 [1.32~2.04], respectively). Earlier maternal age at first delivery (≤ 20 years) was significantly associated with central obesity (OR [95% CI] = 1.735 [1.41~2.13]), elevated blood pressure (1.261 [1.02~1.57]), high triglyceride (1.33 [1.07~1.66]), and low HDL-cholesterol (1.34 [1.08~1.64]).

Conclusion: Our findings suggest that earlier maternal age at first delivery is independently associated with a higher risk of MetS in postmenopausal women.

PE-63 Epidemiology

Metabolically healthy sarcopenic subjects is associated with diabetes mellitus: Korea National Health and Nutrition Examination Surveys (2008-2010)

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Objective: Recently, sarcopenia has been suggested to be associated with dysglycemic conditions. However, the risk of diabetes mellitus in sarcopenia appears to be influenced by the coexistence of other metabolic abnormalities. Therefore, we examined the risk of diabetes in metabolically healthy sarcopenic subjects.

Methods: A total of 8,812 participants (3,812 men and 5,010 women) aged 45 years and over were analyzed using data from Korea National Health and Nutrition Examination Surveys (2008~2010). We defined the subjects with two or more components of metabolic syndrome as metabolically unhealthy and sarcopenia as height-adjusted appendicular skeletal muscle that was 1 standard deviation below the sex-specific mean for the young reference group. Therefore, subjects were subdivided as follows: metabolically healthy non-sarcopenia (MHNS), metabolically unhealthy non-sarcopenia (MUHNS), metabolically healthy sarcopenia (MHS) and metabolically unhealthy sarcopenia (MUHS).

Results: The prevalence of diabetes was 1.3% in MHNS, 21.3% in MUHNS, 3.8% in MHS and 24.7% in MUHS, respectively (P 〈 0.001). After adjusting for confounding factors, including age, body mass index (BMI), lifestyle behaviors (current smoking, alcohol drinking, physical activity and total energy intake) and hormone replacement therapy (in women), metabolically healthy sarcopenic subjects were significantly associated with diabetes (odds ratio: 2.645, 95% CI = 1.114~6.282 in men; odds ratio: 2.352, 95% CI = 1.115~4.961 in women) compared with metabolically healthy non-sarcopenic subjects. However, the odds ratio of MHS was relatively lower than those of MUHNS (odds ratio: 14.036, 95% CI = 6.112~32.231 in men; odds ratio: 18.104, 95% CI = 9.814-33.395 in women) and MUHS (odds ratio: 17.551, 95% CI = 7.706-33.974 in men; odds ratio: 18.736, 95% CI = 10.011-35-065 in women).

Conclusion: The risk for diabetes mellitus was significantly higher in metabolically healthy sarcopenic subjects compared with metabolically healthy non-sarcopenic subjects. However, metabolic health is a more important determinant for diabetes than muscle mass status.

PE-64 Epidemiology

Association analysis for fasting plasma glucose levels using exome array

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Objective: Hyperglycemia, the chronic elevation of blood glucose level, is the primary indicator of type 2 diabetes (T2D). Genome-wide association studies have increased our understanding of the genetic basis of diabetes and related traits such as fasting plasma glucose (FPG). In this study, we aimed to identify exonic variants associated with FPG levels in Korean non-diabetic subjects.

Methods: A total of 240K single nucleotide polymorphisms (SNPs) were genotyped using Illumina HumanExome Chip (ver, 1.1). SNP quality control was conducted to exclude SNPs with a high missing call rate (〉 0.05), monomorphic or low Hardy-Weinberg equilibrium P value (P 〈 1.0×10^{-6}). For the analysis of FPG, diabetic subjects were excluded according to the following criteria: (1) clinical history of diabetes or diabetic therapy, (2) fasting plasma glucose ≥ 126 mg/dL or plasma glucose 2-h after ingestion of 75 mg oral glucose load ≥ 199.8 mg/dL, (3) age of disease onset ≥ 40 years. Measurements of FPG were transformed with the natural log to achieve a normal distribution. Association analyses were performed using PLINK and EPACTS after adjusting for age, sex, and body mass index (BMI).

Results: We identified a total of eight SNPs significantly associated with FPG levels in non-diabetic subjects (P 〈 1.0×10^{-6}). Of the eight SNPs, we found a newly associated variant in exon.

Conclusion: Our findings provide genetic evidence for the associations with FPG levels in Korean population. Further replication studies and functional evaluations are needed to validate these results.

PE-65 Epidemiology

The risk of incident type 2 diabetes in metabolically healthy obesity in Korean population: The role of systemic inflammation

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Objective: We investigated whether the metabolically healthy obese (MHO) phenotype was associated with an increased risk of incident type 2 diabetes in a Korean population.

Methods: Studied participants were 36,135 Koreans (21,075 men and 15,060 women) without type 2 diabetes. They were classified into four groups according to the baseline metabolic health and obesity: metabolically healthy, non-obese (MHNO), metabolically unhealthy, non-obese (MUNO), MHO and metabolically unhealthy obese (MUO). Metabolic health status was assessed by common clinical markers: blood pressure, triglycerides, HDL-cholesterol, and fasting plasma glucose. Cut-off value for obesity was a body mass index of 25.0 kg/m^2.

Results: At baseline, 16.7% of subjects were categorized as MHO. Among the obese subjects, 55.2% (6,039 out of 10,948) were categorized as metabolically healthy. During a median follow-up of 36.5 months (ranged from 4.8 to 81.7 months), 635 individuals among 36,135 (1.8%) developed type 2 diabetes. Crude incidence rate of type 2 diabetes was 0.6% (133/20,491) in MHNO, 3.1% (145/4,696) in MUNO, 1.5% (88/6,039) in MHO and 5.5% (269/4,909) in MUO, respectively. Compared to MHNO group, the MHO group had a significantly increased risk of incident type 2 diabetes compared to the MHNO group [multivariate-adjusted HR, 1.57 (95% CI 1.16~2.11)]. However, the risk of MHO group was attenuated when we further stratified subjects into low systemic inflammation (i.e., hsCRP 〈 0.05 mg/dL) and high systemic inflammation (i.e., hsCRP ≥ 0.05 mg/dL) groups [multivariate-adjusted HRs, 1.61 (95% CI 0.77~3.34) in MHO/low systemic inflammation and 3.73 (95% CI 2.36-5.88) in MHO/high systemic inflammation].

Conclusion: MHO subjects showed a substantially increased risk of incident type 2 diabetes compared with MHNO subjects. The level of systemic inflammation partially explained this increased risk of incident type 2 diabetes among obese phenotypes.

PE-66 Epidemiology

Association of abdominal visceral fat measurement using dual-energy X-ray with cardiometabolic disease: the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) Study

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Objective: Abdominal VAT, the largest visceral fat depot in the human body with more than 10 times the volume of pericardial fat, is significantly correlated with cardiovascular disease risk factors, the metabolic syndrome, and systemic markers of inflammation. To examine the association between cardiometabolic disease and visceral adipose tissue (VAT) measurements using a dual-energy X-ray absorptiometry (DXA) based approach.

Methods: We included 800 healthy subjects (302 men, 498 women), aged 30~64 years from the Cardiovascular and Metabolic Diseases Etiology Research Center. Total body DXA scans were acquired using the Lunar iDXA (GE Healthcare, Madison, WI) instrument. A venous blood sample was drawn from study participants after fasting for 〉 8 h or overnight. Hypertension was defined as taking medication to treat hypertension or having a blood pressure of ≥ 140/90 mmHg. Diabetes mellitus was defined as taking oral hypoglycemic intake or insulin administration or having a fasting plasma glucose concentrations ≥ 126 mg/dL or 2-h plasma glucose concentrations of ≥ 200 mg/dL or HbA1c ≥ 6.5%. The definition of the metabolic syndrome (MetS) used NCEP/ATP III criteria.

Results: Gender-specific, age-adjusted multiple logistic regression analysis showed that for both men and women, DXA VAT was significantly associated hypertension, diabetes and metabolic syndrome. After additional adjustment for BMI and waist circumference, the odds ratio (log-transformed VAT) for hypertension was 3.32 (95% CI 1.38~7.98) for men and 3.07 (95% CI 1.48~6.36) for women. The odds ratio for diabetes for men was 2.62 (95% CI 0.67~10.31) and for women was 6.39 (95% CI 1.90~21.47), MetS for men was 8.13 (95% CI 2.25~29.37) and for women was 14.18 (95% CI 4.14~48.56).

Conclusion: After adjustment for age, BMI, and waist circumference, VAT measured using DXA showed a significant association with cardiometabolic disease. Our study suggests VAT is a valuable indicator of cardiometabolic risk.

PE-67 Epidemiology

Bone and mineral metabolism and incident diabetes: A prospective study

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Objective: Bone and mineral metabolism plays an important role in glucose metabolism, whether markers of bone and mineral metabolism can predict diabetes remains largely unknown. We aimed to evaluate the association of markers of bone and mineral metabolism with incident diabetes.

Methods: A total of 1702 male and 4394 female Southern Chinese aged 20 or above, who were free of diabetes at baseline, participated in this prospective cohort study with a median follow-up of 10.2 years. Markers of bone and mineral metabolism (bone mineral density [BMD], serum alkaline phosphatase [ALP], parathyroid hormone, albumin-adjusted calcium, total calcium, and phosphate) were measured at baseline. Dietary calcium intake was estimated from a validated food frequency questionnaire. Incident diabetes data were retrieved from the electronic medical record.

Results: In 59130.9 person-years of follow-up, 631 participants developed diabetes. Serum ALP (highest quartile, hazard ratio [HR] 1.41; 95% confidence interval [CI] 1.06~1.88; as compared to the lowest quartile) and total calcium (third quartile, HR 1.42; 95% CI 1.12~1.8; highest quartile, HR 1.42; 95% CI 1.11~1.79; as compared to the lowest quartile) were significantly association with incident diabetes. No significant association was observed for other bone and mineral metabolism markers. Addition of serum ALP and total calcium to age, sex and BMI significantly improved integrated discrimination and category-less net reclassification index. Significant interactions with BMI and age were observed. Greater total calcium intake was significantly associated with lower incident diabetes (comparing extreme quartile, hazard ratio 0.78; 95% confidence interval 0.61~0.98).

Conclusion: In this prospective study, elevated serum ALP, total calcium, and probably lower total calcium intake were associated with incident diabetes. Adding serum ALP and total calcium to basic clinical risk factors significantly improved risk prediction. Bone and mineral metabolism may play a role in diabetes development and risk prediction.

PE-68 Epidemiology

Association of serum 25-hydroxyvitamin D with insulin resistance and β-cell dysfunction: the Cardiovascular and Metabolic Diseases Etiology Research Center (CMERC) Study

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Objective: Vitamin D is characterized as a regulator of homeostasis of bone and mineral metabolism by promote calcium and phosphate absorption in the intestines. It is also play an important role in modifying the risk of cardiometabolic outcomes. The aim of this study was to investigate a cross-sectional associations of serum 25-hydroxyvitamin D [25(OH)D] levels with insulin resistance and β-cell dysfunction in Korean.

Methods: We included 800 healthy subjects (302 men, 498 women), aged 30~64 years from the Cardiovascular and Metabolic Diseases Etiology Research Center. Serum 25(OH)D, HOMA-IR and HOMA β were measured. Serum 25(OH)D was determined using a chemiluminescence immunoassay. Insulin resistance were calculated using homeostasis model assessment (HOMA) of insulin resistance and the Matsuda insulin sensitivity index for oral glucose tolerance tests [10000/ sqrt (glucose 0 × insulin 0 × glucose 120 × insulin 120)]. And β-cell function was determined using both the HOMA β and disposition index [(insulin 30~insulin 0)/ (glucose 30~glucose 0) × 1/ insulin 0). Insulin resistance were defined as the HOMA-IR of higher than 75%tile, the Matsuda index of lower than 25% tile, and β cell dysfunction was defined as the index of higher than 75% tile.

Results: The participants in the lowest tertile of serum 25(OH)D had the highest prevalence of insulin resistance (HOMA-IR, OR = 1.73, 95% CI = 1.17~2.56; Matsuda index, OR = 1.34, 95%CI = 0.83~2.16). After adjusting for age, gender, waist, alcohol intake, smoking status, physical exercise, compared with the highest tertile group, the lowest tertile group of serum 25(OH)D was increased the prevalence of insulin resistance (HOMA-IR, OR = 1.62, 95%CI = 1.03~2.56). But, there was no significant associations of serum 25(OH)D with β -cell function (HOMA β, OR = 0.77, 95%CI = 0.50~1.18; disposition index, OR = 0.78, 95% CI = 0.51~1.19).

Conclusion: This study shows that serum 25(OH)D concentration was independently associated with insulin resistance, but there was no significant association with β-cell function. Further studies are required to explore the underlying mechanisms.

PE-69 Epidemiology

Utilization of medications to lower blood pressure, glucose and lipids among people with type 2 diabetes in the National Health and Nutrition Examination Survey 1999-2010

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Objective: Changes in drug treatment of diabetes in the United States were studied using data from the National Health and Nutrition Examination Survey 1999~2010.

Methods: Data on 3094 participants aged ≥ 20 with diagnosed type 2 diabetes were analyzed. The use of medications for lowering blood glucose, blood pressure (BP), and lipids in the past month was assessed by questionnaire. Data from two survey cycles were combined together to produce estimates for each 4-year period.

Results: Utilization of all 3 types of medications increased significantly from 1999~2002 to 2007~2010 (P < 0.01). Usage of metformin increased from 34.8% to 53.8% during this period (P < 0.001), which was the most common medication for diabetes in 2003~2010, and half of subjects taking metformin could achieve glycated hemoglobin less than 7.0% in 2007~2010. Dipeptidyl peptidase-4 (DPP-4) inhibitors, approved in 2007, were used by 7.4% of the participants in 2007-2010. Usage of angiotensin receptor blockers (ARB) and beta-blockers increased from 7.4% to 21.4%, and from 15.3% to 31.8%, respectively, across the 12-year period (both P < 0.001). Usage of statins doubled in 1999-2010 and 52.2% of subjects took statins by 2007~2010 (P < .001).

Conclusion: There were significant increases in the use of glucose, BP and lipid lowering medications during 1999-2010, especially in the use of metformin, ARB and beta-blockers. The increased BP drug prescription could lead to improved BP control. Metformin is the recommended first line drug for diabetes, while DPP-4 inhibitors began to be used after their introduction. Although statins were widely used about half of the participants did not take them.

PE-70 Epidemiology

Methylomic analysis of type 2 diabetes discordant monozygotic twins

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Objective: Type 2 Diabetes is known as genetic disease in which several markers from GWA studies were revealed. But heritability explained by GWAS was found to be only marginal. To understand missing heritability of T2D GWAS, we turn our focus to epigenomic difference which might explain external environmental effect such as food, behavior etc.

Methods: Among analysis strategies of epigenomics, study on disease discordant monozygotic twin in which only one member of twin sibling acquired disease provides strong evidence for epigenetic effect on the disease. Several Monozygotic twin (MZ) studies told us high percentage of MZ twin develop discordant disease occurrence especially in Rheumatoid Arthritis and Diabetes. From 743 blood DNA samples of MZ twins deposited in Korea National Biobank, we found 12 T2D discordant MZ twins. We analyzed DNA methylation profile on 12 T2D discordant MZ twins using Infinium450K Beadarray Chip to identify causative epigenomic change of T2D in the condition that influence of genetic factor was minimized.

Results: From analyzed methylation profile, pathway analysis revealed T2D associated pathways, such as Glycosaminoglycan degradation and Fatty acid elongation as significantly enriched in single MZ pair. Insulin related genes, such as IRE-BP1, KATNAL2, COPS2, IRX4, ZNF710 and FOXP1 were identified as significantly differential methylated gene with 10 % methylation difference cutoff in 3 more twins.

Conclusion: Methylomic profiling on MZ T2D disease discordant twin can identify more relevant and novel marker for diabetes associated epigenetic change.

PE-71 Epidemiology

People with peripheral arterial disease and diabetes are associated with clinically significant weakness

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Objective: Low lean mass is associated with weakness, limited mobility, and increased risk of mortality. In the recent effort of Foundation for the National Institutes of Health (FNIH) Sarcopenia Project, an appendicular lean mass (ALM) cutpoints for clinically significant weakness were derived. Peripheral arterial diseases (PAD) and diabetes have been shown to be associated with reduced lean mass. However, whether these diseases are associated with clinically significant weakness remain unknown. In the current study, we aimed to investigate whether PAD and diabetes are associated with clinically significant weakness as defined by the FNIH Sarcopenia Project.

Methods: Data on 4841 participants aged ≥ 40 years of the National Health and Nutrition Examination Survey 1999~2004 were examined. ALM was measured using Dual Energy X-ray Absorptiometry. Logistic regression was used to assess the association of diabetes and PAD with low lean mass. Low lean mass was defined as ALM < 19.75 kg in men and ALM < 15.02 kg in women.

Results: In the simple model adjusted for age, sex, BMI, and race/ethnicity, participants with PAD alone and both PAD and diabetes were associated with low lean mass with an odds ratio (OR) of 1.65 (95% confidence interval [CI]: 1.07~2.56) and 2.07 (95% CI: 1.10~3.89), respectively. No association was observed between diabetes and low lean mass. After further adjustment for smoking, drinking, exercise, hypertension, estimated glomerular filtration rate, microalbuminuria, serum biomarkers of liver function, and cardiometabolic biomarkers, participants with both PAD and diabetes remained significantly associated with low lean mass (OR: 2.08; 95% CI: 1.03~4.19). No association was observed for diabetes only and PAD only with low lean mass.

Conclusion: People with both diabetes and PAD had a higher likelihood of low lean mass and hence clinically significant weakness. Intervention to improve muscle mass and strength may be useful to improve mobility and reduce risk of mortality in these people.

PE-72 Epidemiology

Impaired glucose intolerance in Korean and Filipino women living in Korea

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Objective: Diabetes risk changed as immigrant populations adopt new lifestyles. Therefore we started the Filipino Women's Dietary and Health Study. We first compared the prevalence of fasting hyperglycemia among Filipino women and Korean women.

Methods: Participants included volunteer, community-dwelling women, aged ≥ 20 years, and were recruited at churches, and multicultural family support center. Participants were fasting more than 12 hour. And we taken the blood sampling and participants undergo interviews. We also selected age matched Korean women from 2009 KNHANES dataset.

Results: Filipino women were more obese than Korean women [body mass index (23.5 ± 4.2 vs. 22.7 ± 3.7, P = 0.034), waist circumference (80.3 ± 12.3 vs. 76.3 ± 9.8, P < 0.001)]. However, Filipino women showed lower fasting blood glucose level (85.7 ± 11.1 vs. 91.1 ± 15.4, P < 0.001). And there were no different in insulin resistance (Homa-IR; 2.30 ± 2.77 vs. 2.17 ± 1.30, P = 0.444). The prevalence of impaired glucose tolerance (FBS > 100 mg/dL) was more higher in Korean women (11.8% vs. 6.1%, P = 0.033).

Conclusion: Korean women is more slender but prone to IGT than Filipino women.

PE-73 Epidemiology

The Filipino women's diet and health study: design and methods

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Objective: Immigration from the Asian neighboring countries has been rising dramatically in South Korea because of marriage primarily between Korean men with foreign women. The Filipino women rank third among other Asian wives. Our main objective was to determine whether there are similarities and differences in risk factors and morbidities between Filipino women who are married to Korean men living in Korea, and Filipino married women living in Philippines.

Methods: Filipino women whose age is 19 or over were recruited in Philippines (n = 139) and Korea (n = 165) between July 2013 and July 2014. Demographic, anthropometric and blood pressure measurements, medical history, health-related behavior, and quality of life factors were assessed from both groups. At present, blood samples and toenail clippings, and questions related to children's health were only obtained from the participants in Korea. Participants either had the in-person interview or self-administration of questionnaires, except for the 24-hour recall that was directly interviewed. Anthropometric, blood pressure measurements, and blood collection were administered by trained professionals. The research protocol was approved by Sookmyung Women's University and informed written consent was obtained from the participants.

Results: No results presented since this is only a design and methods of The Filipino Women's Diet and Health Study

Conclusion: The results of this study are expected to help our understanding in the etiology and development of diseases among Filipino women. Knowing the risk factors and health backgrounds is essential for a healthy multi-culturally filled society. Furthermore, the results of this study can help healthcare policy makers target specific health problems and could inform prevention initiatives that improve maternal and child health.

PE-74 Insulin signaling / action

Association between thyroid nodule and insulin resistance

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Objective: Chronic sustained hyperinsulinemia appears to play a role in the nodulogenesis. Recently, studies on association between insulin resistance and thyroid nodule have been reported. Therefore, this study was undertaken to evaluate the association between metabolic components defining insulin resistance and thyroid nodule.

Methods: The study included 677 women who received screening in the Haundae Paik Hospital between March 2011 and August 2013. All the subjects were screened for the thyroid nodule and evaluated by serum insulin levels and biochemical prameters. Insulin resistance was evaluated using homeostasis model assessment (HOMA-IR). All subjects were euthyroid, euglycemic state.

Results: The age of the patients ranged from 21 to 80 years with a mean of 50.26 years. Body mass index (BMI) ranged from 16.10 to 47.30 kg/m^2 with a mean of 22.96 kg/m^2 In total subjects, the frequency of thyroid nodule was 66.5%. The subjects with thyroid nodule had higher weight, waist, BMI, SBP, and DBP. But metabolic components including glucose, insulin, and lipid profiles were similar between the groups. And, HOMA-IR was not a significant correlation with thyroid nodule.

Conclusion: There was not a significant correlation between insulin resistance and thyroid nodule in our study.

PE-75 Insulin signaling / action

Angiotensin II increases insulin binding in L6 cells

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Objective: Angiotensin II (ATII) can increase insulin resistance by interfering insulin signaling pathway at the various steps in insulin target tissues in individuals with hypertension, obesity, or type 2 DM. Interfering insulin signaling pathway at the various steps in insulin target tissues is thought to be the underlying mechanism of insulin resistance by ATII. Insulin should bind to insulin receptor to have biological actions. We have already observed ATII inhibited insulin binding to insulin receptor in bovine aortic endothelial cells. However, the effect of ATII on insulin binding in muscle is still unclear. In this study, we investigated the effect of ATII on the binding capacity between insulin and insulin receptors in L6 cells.

Methods: To observe whether insulin binding was affected by ATII, we treated 10-7 M ATII for 10 minutes to L6 cells, with or without ATII receptor blocker (eprosartan, 0.02, 0.2, 2, 20 and 200 μM) for 30 minutes. We also investigated Akt phosphorylation (ser473) after ATII treatment.

Results: ATII increased insulin binding capacity up to 15% in L6 cells. Pretreating with eprosartan dose dependently recovered decreased insulin binding capacity by ATII. AT II decreased Akt phosphorylation.

Conclusion: The increase of insulin binding capacity by ATII might be due to compensate mechanism for inhibited insulin signaling by ATII. ATII increased insulin binding capacity but decreased Akt phosphorylation in L6 cells. Decreased insulin binding capacity by ATII was recovered after ATII receptor blocker treatment. ATII might effect insulin resistance by diversiform mechanisms depending on tissue types.

PE-76 Integrated physiology / obesity

Expression of Non-LTR retrotransposons specific transcripts in diabetic rats

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Objective: Basic objectives were to analyze the transcriptional regulation of L1Rn elements in response to diabetes induced stress.

Methods: Real time PCR analysis using RNA isolated from various organs from old and young male alloxan induced diabetic wistar rats was carried out to determine the change in L1 transcripts.

Results: There was no significant change in the expression of L1Rn in various organs after diabetes.

Conclusion: The results of this investigation indicate that there is no transcriptional actvtion of LINE1 retroelements in alloxan induced diabetes. It remains to be studied if there is change in rates transposition in diabetes.

PE-77 Integrated physiology / obesity

Prolonged very low caloric restriction improves the endothelial glycocalyx in obese type 2 diabetic subjects

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Objective: Prolonged caloric restriction of obese type 2 diabetes mellitus (T2DM) patients has been shown to improve the systemic inflammatory state. We tested whether obese T2DM patients on a very-low caloric diet (VLCD) with or without exercise for 16 weeks also show improved endothelial glycocalyx health.

Methods: Plasma levels of syndecan-1 and thrombomodulin, as a marker of glycocalyx health, was measured in plasma sample of obese T2DM patients (n = 27) along with lean and obese controls (n = 56, 52, respectively) at baseline, directly after VLCD (4 months), and during follow-up period (6 month and 18 month post baseline).

Results: At baseline, shed syndecan-1 and thrombomodulin levels were not different between the obese diabetic subjects and non-diabetic lean- or obese controls. However, repeated measurements of the syndecan-1 levels in time showed a significant decrease after intervention, which sustained up to 14 months after VLCD and returning to a eu-caloric diet (mean difference: -21.98 ± 4.91 ng/mL [$P < 0.001$], -13.24 ± 3.91 ng/mL [$P = 0.014$], and -10.68 ± 3.74 ng/mL [$P = 0.051$] respectively for 4-, 6-, and 18 months post baseline). Although thrombomodulin decreased non-significantly after intervention (-0.86 ± 0.31 ng/mL, $P = 0.064$), it steadily returned to baseline during follow-up. Even though syndecan-1 is localized in both the vascular endothelium and liver sinusoids, no interaction between shed syndecan-1 levels and liver enzyme markers (AST, ALT) was observed, suggesting a vascular origin.

Conclusion: In conclusion, prolonged very low caloric restriction diet in obese T2DM patients improves glycocalyx health which in turn results in a sustained protective effect, even after returning to a eu-caloric diet.

PE-78 Integrated physiology / obesity

Cabenoxolone prevents ER stress induced apoptosis in hypothalamic neuron

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Objective: Hypothalamus has been appreciated to be the headmaster to regulate energy balance by coordinating peripheral homeostatic activities including nutrient sensing, appetite control, energy expenditure, and carbohydrate and lipid metabolism. Hypothalamic endoplasmic reticulum (ER) stress is known to be increased in obesity. Induction of ER stress on hypothalamic neurons has been reported to cause hypothalamic neuronal apoptosis and malfunction of energy balance eventually resulting in obesity. Cabenoxolone is a nonselective gap junction decoupler and 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) inhibitor. 11β-HSD1 converts inactive glucocorticoid to an active form. Cabenoxolone has shown an anti-apoptotic effect in several studies. In this study, the effect of cabenoxolone on ER stress in hypothalamic neurons was investigated.

Methods: Primary rat embronal hypothalamic neurons were cultured for in vitro study. Injection of tunicamycin and cabenoxolone into third ventricle of mice was performed using the stereotaxic apparatus. Western blotting, immunocytochemistry, and immumohistochemistry were used for measurement of protein expression such as ATF6, CHOP, cleaved capase3, and cleaved PARP etc. Cell viability and ROS was measured with MTT assay and DCF-DA (2',7'-dichlorofluorescein diacetate) assay , respectively.

Results: Tunicamycin induced ER stress increased apoptosis and reactive oxygen species on mice hypothalamic neuron. Cabenoxolone was shown to decrease tunicamycin induced ATF6 and CHOP expression, reactive oxygen species, and apoptosis of hypothalamic neuron. Injection of cabenoxolone into the third ventricle in C57/BL6 mice before tunicamycin treatment decreased tunicamycin induced ATF6 and CHOP expression in hypothalamus.

Conclusion: Therefore, the result of this study suggests that cabenoxolone has a preventive effect against ER stress induced apoptosis on hypothalamic neuron. Further study is warranted to clarify the effect of cabenoxolone on hypothalamic regulatory functioning of energy balance in obesity.

PE-79 Integrated physiology / obesity

Effects of pyruvate dehydrogenase kinase (PDK) on adipocyte differentiation

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Objective: Adipose tissue is considered as an endocrine organ contributing to the maintenance of energy homeostasis. Excessive accumulation of adipose tissue in the body may cause the development of obesity and obesity-related diseases. The mitochondrial pyruvate dehydrogenase complex (PDC) regulates the balance between oxidation of glucose and lipids, depending on nutritional status, and thus plays the role of metabolic switch for fuel selection. PDC activity is inhibited by pyruvate dehydrogenase kinases (PDKs). Four PDK isoenzymes (1~4) are known to be expressed in a tissue-specific manner in mammals. In this study, we examine the effect of PDKs on adipocyte differentiation.

Methods: We used retroviral system for the stable overexpression of PDK1 or PDK2 in 3T3-L1 cells. Also PDK1 and PDK2 specific shRNA were stably transfected into 3T3-L1 cells to establish PDK1/2 knockdown cells. Adipogenic differentiation of 3T3-L1 cells were evaluated by Oil red O staining. The expression of adipocyte specific gene was determined by western blot and real-time PCR.

Results: Of PDKs isoforms, expression level of PDK1 and PDK2 was dramatically increased during adipocyte differentiation of 3T3-L1 cells. In addition, overexpression of either of PDK1 or PDK2 augmented adipocyte differentiation, accompanied with increased expression level of key adipogenic markers such as C/EBPalpha, PPARgamma, ADD1 and FAS. Futhermore, silencing of both PDK1 and PDK2 showed decrease in adipocyte differentiation.

Conclusion: We found that PDK1 and PDK2 regulate adipocyte differentiation. These results suggest that PDK1 and PDK2 are potential therapeutic targets for the treatment of patient with obesity and obesity related diseases.

PE-80 Integrated physiology / obesity

DPP4 has a pro-inflammatory action on LPS-primed macrophages that is ameliorated by DPP4 inhibitor

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Objective: Some studies showed anti-inflammatory effects of selective DPP4 inhibitor in patients with type 2 diabetes. And, soluble DPP4 has been considered as an adipokine of which actions need to be further characterized. In the present study, we investigated the pro-inflammatory actions of soluble DPP4 and anti-inflammatory effects of DPP4 inhibitor in RAW264.7 macrophages.

Methods: The effects of DPP4 and its inhibitor, vildagliptin, on inflammatory pathway in macrophages were evaluated after stimulation with LPS. And, the inhibition of DPP4 signaling was also evaluated by treating the cells with mannose 6-phosphate (M6P), which inhibits the binding of soluble DPP4 to its IGF-II/M6P receptor.

Results: Vildagliptin decreased JNK phosphorylation and NF-κB activation in a concentration-dependent manner in LPS-stimulated macrophages. Soluble DPP4 treatment in LPS-primed macrophage caused more iNOS expression and higher production of NO and cytokines (TNF-α, IL-6 and IL-1β) than in LPS-treated cells, while JNK phosphorylation was not different. Vildagliptin suppressed iNOS expression and NO and cytokine production in both LPS- and LPS+DPP4-stimulated macrophages. In addition, combined treatment with vildagliptin and M6P has more anti-inflammatory effects compared to vildagliptin treatment alone in LPS+DPP4-stimulated cells.

Conclusion: Our findings suggest that soluble DPP4 has a pro-inflammatory action in macrophages while DPP4 inhibitor has strong anti-inflammatory effects. Further studies are required to clarify DPP4-mediated inflammation pathway in macrophages.

PE-81 Integrated physiology / obesity

Adipokines and insulin resistance in gestational diabetes mellitus according to age to pregnancy

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Objective: Pregnancy in women aged 35 years or older is becoming increasingly prevalent. The aim of this study was to evaluate adipokines concentration and insulin resistance in gestation diabetes mellitus (GDM) according to age to pregnancy.

Methods: We enrolled total 60 pregnant women with GDM. All subjects underwent a 100g oral glucose tolerance test (OGTT) during the 24th-28th weeks of gestation. The subjects were classified into two groups: (1) pregnancy before the age of 35 (n = 31), (2) pregnancy after the age of 35 (n = 23).

Results: GDM with pregnancy in women aged 35 years or older was decreased adiponectin levels, elevated resistin levels, decreased leptin levels compared with GDM with pregnancy before the age of 35. However, there was not statistically significant difference (P = 0.349, P = 0.747 and P = 0.311). In GDM with advanced maternal age, leptin was not correlated HOMA-IR and pre-pregnancy BMI. However, in GDM with before the age of 35, leptin was significantly correlated with HOMA-IR and pre-pregnancy BMI (P = 0.043 and P = 0.14). In GDM with pregnancy before the age of 35, HOMA-IR was significantly higher in pre-pregnancy BMI $<$ 25 kg/m^2 group compared with pre-pregnancy BMI $\geq$ 25 kg/m^2 group (P = 0.032).

Conclusion: This study showed that in GDM with advanced maternal age adipokines were not a significant correlation with insulin resistance. Adipokines may not be associated with insulin resistance in GDM with advanced maternal age.

PE-82 Integrated physiology / obesity

SIRT3-SDH-GPR91 signaling in hepatic stellate cell activation

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Objective: Nonalcoholic fatty liver disease (NAFLD), the most common liver disorder in Western countries can progress to liver fibrosis. SIRT3 is NAD+ depedent deacteylase that act as energy sensors and modulate metabolic processes which are localized to mitochondria. Recently it is known that NAFLD is associated with reduced SIRT3 activity and SIRT3 regulates the succinate dehydrogenase (SDH), which converts succinate into fumarate. Succinate, a Kreb's cycle intermediate and a lignad for GPR91 has been recently characterized as a hormone-like signaling molecule in metabolic diseases. This study was designed to test the possibility that SIRT3 is involved in the genesis of liver fibrosis via SDH and GPR91 pathway in hepatic stellate cells (HSC).

Methods: LX-2 cells, human immortalized hepatic stellate cell, was used. The effect of SIRT3 siRNA or sirtinol, a SIRT inactivator, on α-SMA expression of HSC was measured by Western blotting. SDH activity in LX-2 cell lysate were measured using the Enzyme Activity Assay Kit.

Results: SIRT3 siRNA transfection decreased SDH activity and increased GPR 91(Succinate receptor) expression and increased increased α-SMA expression in HSC. On the other hand, treatment of resveratrol, a SIRT3 activator, increased SDH activity and decreased GPR91 expresssion and decreased α-SMA expression in HSC.Treatment of succinate significantly increased GPR91 expression and α-SMA production in HSC. Palmitic acid treatment decreased SIRT3 production and increased GPR91 and α-SMA production in HSC. GPR91 si RNA trasfection showed decreased α-SMA production in HSC.

Conclusion: Our study suggested that SIRT3 is involved in hepatic stellate cell activation via SIRT3- SDH-GPR91 pathway.

PE-83 Integrated physiology / obesity

Increased expression of ATP-binding cassette transporter A1 (ABCA1) by cilostazol may be a possible mechanism for its protective effect against hepatic steatosis

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Objective: Cilostazol, a selective inhibitor of phosphodiesterase 3, which has been widely used in patients with atherosclerotic diseases, is known to have additional beneficial effects on dyslipidemia. ATP-binding cassette transporter A1 (ABCA1) plays a critical role in the regulation of intracellular cholesterol levels in hepatocytes. We aimed to investigate the effect of Cilostazol on hepatic steatosis and its underlying mechanism related to ABCA1.

Methods: Male C57BL/6 mice were randomly divided into three groups: (1) fed normal chow diet with vehicle, (2) fed high-fat diet (HFD) with vehicle, (3) fed HFD with Cilostazol. Cilostazol (30 mg/kg) was orally administered once daily for 10 weeks. Oral glucose tolerance test was done and liver tissues were examined. HepG2 cells were also used as an in vitro model by incubating with saturated fatty acid (palmitate) in the presence or absence of Cilostazol.

Results: In HFD-fed mice, Cilostazol treatment significantly decreased hepatic fat and liver weight. Cilostazol-treated mice also showed improved glucose tolerance and decreased levels of serum LDL, VLDL and total cholesterol. The expressn of ABCA1 was significantly increased in the liver of Cilostazol-treated mice by 2.4 folds (P $<$ 0.05) compared to HFD-fed control mice. In palmitate-treated HepG2 cells, lipid accumulation was significantly decreased after treatment with Cilostazol. Palmitate reduced the expression of ABCA1, which was restored with Cilostazol treatment by 1.3 folds (P $<$ 0.05). The HDL-cholesterol levels in the cell cultured media were also increased, while intracellular LDL and VLDL-cholesterol levels were decreased in HepG2 cells treated with palmitate and Cilostazol compared to those with palmitate only.

Conclusion: Our results showed that Cilostazol ameliorated hepatic steatosis and increased ABCA1 expression in the hepatocytes. This implicates that Cilostazol may have a beneficial role in the treatment of non-alcoholic fatty liver disease.

PE-84 Integrated physiology / obesity

Psychological stress induce insulin resistance, as well as endothelial dysfunction, via inflammation and ER stress activated by corticotropin releasing hormone

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Objective: Psychological stress may contribute to atherogenesis, although the underlying mechanism is poorly understood yet. We studied on the pathogenesis of stress-induced endothelial dysfunction and insulin resistance with specific focus on inflammation and ER stress pathways.

Methods: Immobilization stress (IS) was applied (2 hr/d) for 14 d to male 8-wk OLETF rats, whereas control groups comprised of rats without IS (n $\geq$ 7 for each). NO release by acetylcholine 10-5 nM were directly measured aorta's inner surface, using electrochemical NO microsensor. Plasma was used for insulin and several metabolic indices. Western blot analysis and RT-qPCR were performed at rat tissues, HUVEC endothelial cell line, and U937 cells.

Results: 14d-IS decreased acetylcholine (Ach)-induced NO production, measured by direct NO electrochemical microsensor, from the aorta along with decreased expression of eNOS mRNA compared with control group. 14d-IS did not significantly change plasma glucose, but increased plasma insulin (342.5 ± 6.3 vs. 496.0 ± 51.6 pg/ml, P $<$ 0.05) and HOMA-IR (3.1 ± 0.2 vs.4.7 ± 0.5 mmol/LxμIU/mL, P $<$ 0.05) compared with control group. IS increased phosphorylation of both IRS1 serine and ERK, and increased expression of ER stress marker BiP. IS also increased translocation of NF-kB subunit p65 into nuclear fraction, and increased mRNA expression of both TNF-α and MCP-1 in the liver. Real-time RT-qPCR study showed that 1d-IS increased expression of CRH mRNA and urocortin 2 mRNA in the hypothalamus by 2.5 folds and expression of CRH receptor type 2 mRNA in the aorta by 7.8 folds compared with control group. In cultured monocyte U937 cells, CRH induced translocation of NF-kB subunit p65 into nuclear fraction, and increased expression of BiP, and MCP-1 mRNA. In cultured HUVECs, CRH pretreatment inhibited insulin-stimulated eNOS phosphorylation at Ser1177.

Conclusion: Psychological stress impairs both endothelial function and insulin sensitivity probably via activation of NF-kB-mediated inflammation and ER stress pathways by CRH.

PE-85 Integrated physiology / obesity

Expression of biglycan in human adipose tissues and its role in the pathogenesis of obesity-induced inflammation

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Objective: Biglycan, a non-fibrillar component of extracellular matrix (ECM), is released from the matrix by the action of proteolytic enzymes upon tissue stress or injury. The soluble form of biglycan can bind to toll-like receptor (TLR) 2/4 on macrophages, resulting in secretion of proinflammatory cytokines and chemokines. We hypothesized that overexpression of biglycan might participate in inflammatory reactions in adipose tissues of obese humans and thereby, contribute to the pathogenesis of obesity-related disorders such as insulin resistance.

Methods: We recruited 21 non-diabetic obese women, 11 type 2 diabetic obese women, and 59 normal-weight women. Metabolic parameters, abdominal fat distribution, and biglycan mRNA expression in abdominal subcutaneous adipose tissue (SAT) and visceral adipose tissue (VAT) were measured. In addition, the induction of biglycan was tested by co-culturing human preadipocytes or differentiated adipocytes with THP-1 macrophages.

Results: Regardless of diabetes status, obese patients demonstrated significantly higher levels of biglycan mRNA in both VAT and SAT. Biglycan mRNA was expressed in adipocytes as well as non-adipocytes, but predominantly in the latter. Biglycan mRNA in fat depots was significantly and positively correlated with insulin resistance-related metabolic parameters. In both fat depots, biglycan mRNA was independently related with CD68 mRNA. In addition, co-culture with macrophage significantly elevated biglycan mRNA in human preadipocytes and differentiated adipocytes.

Conclusion: Our data provide clear evidence that biglycan plays a key role in initiating and amplifying inflammatory responses in expanding adipose tissues during the development of obesity in humans and suggest that enhanced biglycan expression in adipose tissues may contribute to the pathogenesis of obesity-related disorders such as insulin resistance.

PE-86 Integrated physiology / obesity

Mitochondrial oxidative phosphorylation (OXPHOS) dysfunction leads to insulin resistance and increase myokines secretion in C2C12 cells

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Objective: Skeletal muscle has been recognized as an endocrine organ recently. Myokines are cytokines or other peptides that produced and secreted by muscle and act as paracrine, autocrine or endocrine. Mitochondrial oxidative phosphorylation (OXPHOS) dysfunction is suggested as an etiologic mechanism of insulin resistance. We investigated the alteration of myokine secretion in OXPHOS dysfunction induced insulin resistance state.

Methods: C2C12 cells were treated with OXPHOS inhibitors (oligomycin, rotenone, antimycin-A) for 12 or 48 hours. We measured the changes of proteins involved in OXPHOS and insulin signaling pathway by western blotting. We measured ATP contents levels after OXPHOS inhibitors treatment by luminescence assay. Cell viability was measured by Cell Count Kit-8 (CCK-8). We extracted total RNAs from C2C12 cells and compared the expression of myokines expression by real time polymerase chain reaction (RT-PCR). FGF21 levels in cell supernatant were measured by radioimmunoassay kit. To discover novel myokines associated with OXPHOS dysfunction in muscle, we performed microarray analysis using Agilent mouse chip.

Results: Mitochondrial complex 3 and complex 4 were decreased by OXPHOS inhibitors (antimycin-A, rotenone) after 48 hours treatment. Phosphorylation of Akt and IRS-1 was decreased by OXPHOS inhibitors. Intracellular ATP contents were reduced approximately 13% and 30% by rotenone and oligomycin, respectively (both, $P < 0.05$). mRNA expression of FGF21, IL-6 and Adipoq, were increased significantly ($P < 0.01$, $P < 0.01$, $P < 0.001$, respectively) with OXPHOS inhibitor treatment, while Fndc5 and IL-15 were decreased (both, $P < 0.001$). FGF21 levels were increased to 3.3-fold in supernatant of cells treated with oligomycine compared to the control ($P < 0.01$). In microarray analysis, we confirmed increase of FGF21 and IL-6 and found altered expression of several candidate myokines with oligomycin treatment.

Conclusion: Skeletal muscle secretes various myokines, like FGF21 and IL-6, in OXPHOS dysfunction mediated insulin resistance state which might have a role in glucose and lipid metabolism.

PE-87 Integrated physiology / obesity

Identification of serum metabolites associated with BMI risk allele of FTO gene in a population-based study

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Objective: It has been reported previously that the fat mass- and obesity-associated gene (FTO) rs9930506 minor allele (A) has the strongest association with body mass index (BMI) and shows correlateswith increased risk of obesity and Type 2 diabetes (T2D) in various studies. Here, we aimed to investigate the association of FTO gene variant rs9939609 and serum metabolic alteration in 2,577 individuals from the Korea Association Resource (KARE) cohort.

Methods: The FTO rs9939609 genotyping was performed in 2,577 individuals using SNP database of Korea Association Resource Project (KAREBrowser). To perform a serum metabolic profile with the same subjects for genotyping, liquid chromatography with tandem mass spectrometry (LC-MS/MS) and flow injection analysis tandem mass spectrometry (FIA-MS/MS) were used to quantify 186 metabolites, including acylcarnitines, amino acids, biogenic amines, glycerophospholipids, sphingolipids, and hexose in baseline serum samples. Statistical methods including wilcoxon rank sum test, multivariate logisticand linear regression analyseswere used for selection ofserum metabolites associated with FTO genotype.

Results: Among the 2,577 individuals, 610 subjects carried the FTO minor allele (A) and 1,967 subjects carried wild type allele. 134 metabolites $P < 0.05$) to be significantly altered in FTO risk allele carriers. The identified metabolites are not only relevant to choline-containing phospholipid metabolic pathway, but also include previously reportedmetabolic marker of obesity and T2D according to BMI.

Conclusion: Using targeted metabolomics with genome wide association approach, we identified alterations of phospholipid metabolism in subjects with FTO rs9939609 genotype. This may reflect a genotype-mediated metabolic abnormality prior to the development of increasing BMI.

PE-88 Integrated physiology / obesity

Expression patterns of genes required for mitochondrial biogenesis in rodent model of obesity

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Objective: Mitochondria are the site of oxidative energy production in eukaryotic cells and it has been hypothesized that impaired mitochondrial function leads to accumulation of lipid metabolites and altered insulin signaling. However, specific regulatory mechanism of mitochondrial biogenesis in metabolic organs of obesity remains unclear. Therefore we investigate the expression of genes that involved in mitochondrial transcription, translation, and apoptosis in white adipose tissue, muscle, and liver by metabolic stimulus.

Methods: The serum glucose level of ob/ob mice and lean mice at 10 weeks of age were evaluated. The expression of multiple genes involved mitochondrial biogenesis (NRF1, PGC-1a, POLRMT, Tfam, TFB1M, TFB2M, MTERFd2, POLr2A, POLr2B, Tid1, mortalin, Crif1, C7Orf30, Mtrf1) of adipose tissue, liver, and muscle from in lean mice and ob/ob mice were evaluated by real-time quantitative PCR.

Results: Obese mice weighed 2.0 fold more than lean mice. Fasting glucose levels and glucose levels after glucose administration were higher in ob/ob mice than in lean mice. In obese mice, genes involved in mitochondrial transcription such as Tfam, TFB1M, and TFB2M of adipose tissue expressed higher than those of lean mice, but their expression in liver and muscle are not significantly different from control. Genes involved in mitochondrial translation such as Crif1, C7Orf30, Mtrf1 of adipose tissue expressed higher than those of lean mice, but their expression in liver and muscle are not significantly different from lean mice. Mortalin, that related with mitochondrial apoptosis, of adipose tissue expressed higher than that of lean mice.

Conclusion: Interestingly, the expression of genes involved in mitochondrial transcription, translation and apoptosis expressed higher than lean mice, in only adipose tissue. We conclude that obesity is related to upregulated genes required for mitochondrial biogenesis in adipose tissue, and these changes may result from compensation of mitochondrial dysfunction in the insulin resistance state.

PE-89 Integrated physiology / obesity

Glucagon like peptide-1 receptor agonist directly attenuated hepatic steatosis by regulation of LXR-alpha

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Objective: Recently, many extra-pancreatic effects of Glucagon like peptide-1 (GLP-1) have been demonstrated. But, the direct effect of GLP-1 receptor agonist, exendin-4 (Ex-4) on the liver is not clear. Therefore we investigated the direct effect of Ex-4 on the lipid metabolism in high fat (HF) fed C57BL/6J (C6J) mice and Hep3B cell line. In addition, we investigated the role of Ex-4 in the transcriptional regulation of liver X receptor alpha (LXRa).

Methods: Human hepatoma cell line (Hep3B cell) was treated with 0.5 mM palmitate with or without 100 nM exenitide treatment. 20 μg/kg Ex-4 was injected i.p to the HF fed C57BL/6J mice for 9 weeks. Saline treatment mice and pair-feeding mice were control groups. The LXRa mRNA expression and its lipogenic target genes (i.e., SREBP1c, FAS, SCD-1 and DGAT-1) were assessed by reverse transcriptase-mediated polymerase chain reaction (RT-PCR). The protein expression of associated with lipid metabolism was examined by Western blot. These effects of Ex-4 were abolished by Ex 9~39. It suggested that GLP-1R is involved in this metabolic progress.

Results: EX-4 reduced fat accumulation and steatosis under Oil red staining in HEP3B cells and liver of HF fed mice. It reduced lipogenic gene such as LXR alpha, SREBP-1, FAS, SCD-1, DGAT-1 and increased the gene expression of fatty acid beta oxidation such as CPT-1, PPAR-alpha in Hep3B cell treated with 0.5mM palmitate and hepatocyte of HF fed C57BL/6J mice.

Conclusion: In conclusion, GLP-1 receptor agonist, Ex-4 significantly decreased hepatic steatosis and increased insulin sensitivity. Also, Ex-4 directly reduced hepatic fat accumulation through down regulation of lipogenic gene expression and up-regulation of lipid oxidation gene.

PE-90 Integrated physiology / obesity

Effects of laparoscopic adjustable gastric banding in morbid obese with diabetes patients

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Objective: Laparoscopic adjustable gastric bandastric banding(LAGB) has been associated with improvement homoglobin A1c in the morbidly obese patients.

Methods: We performed a retrospective study of morbidly obese patients who had LAGB (N = 108). We was performed with respect to age, sex, body mass index, and hemoglobin A1C (HbA1C). We compare with morbidly obese patients (MO) and morbidly obese with diabetes patients (MOD). Outcomes assessed were changes in body mass index, HbA1C, and obesity degree at 6 month.

Results: The mean age of MO and MOD patients at baseline was 31 and 36 years, respectively. The mean baseline glycated hemoglobin level was 5.5% in MO and 7.1% in MOD, and the mean baseline body-mass index was 33.6 in MO and 38.3. Obeisty degree was 159.1% in MO and 180.7% in MOD. At 6 months after LAGB, the mean baseline glycated hemoglobin level was 5.4% in MO and 5.7% in MOD, and the mean baseline body-mass index was 31.8 in MO and 29.7 in MOD. Obeisty degree was 128.0% in MO and 139.9% in MOD.

Conclusion: Among morbid obese patients with type 2 diabetes, LAGB resulted in HgA1c and BMI significantly decreased.

PE-91 Islet biology / insulin secretion

Orexin a potentiates glucose-stimulated insulin secretion through a cAMP/Epac2 signaling pathway in pancreatic beta cells

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Objective: Orexin A (OXA) is a hypothalamic neuropeptide implicated in the regulation of food intake, energy homeostasis and arousal. Orexin receptors are found in the endocrine pancreas; however, little is known about its function. In this study, a physiologic role of OXA in glucose homeostasis was investigated in vivo. In addition, the effect of OXA on insulin secretion and their intracellular target molecules were identified in pancreatic beta cells.

Methods: After acute administration of OXA, intraperitoneal glucose tolerance tests were performed in normal mice. The expression of orexin receptor 1 (OXR1) was detected by immunofluorescence. Insulin secretion from perifused mouse pancreatic islets was measured by ELISA. The intracellular calcium ([Ca2+]i) levels were detected using confocal microscopy.

Results: In glucose tolerance test, exogenous OXA significantly caused the transient increase in plasma insulin levels. Subsequently, OXA also caused the long-lasting increase in plasma leptin levels after the insulin level increase. In primary pancreatic beta cells, OXR1 was well expressed and OXA augmented the first phase of glucose-stimulated insulin secretion. The OXA increased [Ca2+]i levels through the mobilization of intracellular Ca2+ stores via the cAMP/Epac-dependent pathway. This insulinotropic effect of OXA was decreased in Epac2 knockout mouse beta cells.

Conclusion: These results suggest that OXA may be a significant regulator of both insulin and leptin secretion and play an important role in blood glucose homeostasis. As a physiological regulator of blood glucose level, OXA may have a therapeutic potential for improving blood glucose control in type 2 diabetes.

PE-92 Islet biology / insulin secretion

Protective effect of GLP-1 on pancreatic beta-cells via KATP channel-mediated pathway

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Objective: To elucidate whether GLP-1 also facilitate closure of KATP channels in specific conditions, like beta cell exhaustion.

Methods: Resting membrane potential was measured at using a perforated whole cell patch clamp technique.

Results: In normal condition, GLP-1 facilitated closure of KATP channels, resulting in enhancement of glucose-induced insulin secretion in rat pancreatic beta cells. For inducing beta cell exhaustion, cells were treated with high glucose (17 mM glucose) for 2h. After 2 h, 20 nM GLP-1 was treated with high glucose for 30 min. In contrast to previous finding, GLP-1 induced membrane hyperpolarization via KATP channel activation (opening). This GLP-1-induced KATP channel activation was dependent on intracellular PI3K activity.

Conclusion: These results suggest that GLP-1 might induce beta cell "rest" by activating KATP channel in the state of beta cell exhaustion. And it can protect pancreatic beta cell against overwork-induced cell apoptosis and prevent the development of diabetes. As a physiological modulator, GLP-1 can control beta cell excitability by controlling KATP channel activity.

PE-93 Islet biology / insulin secretion

Effect of rHMGB-1A on hypoxia/cytokine-induced islet cell damage

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Objective: High-mobility group box 1 (HMGB1), a damage –associated molecular pattern protein, is a pro-inflammatory cytokine. In a mouse model, islet damage by hypoxia induces HMGB1 synthesis and release. HMGB1 released from islets soon after their transplantation has been shown to trigger innate immune rejection with activation of DC, NKT cells and neutrophils, leading to the early loss of transplanted islets. During this process, direct effect of hypoxia-induced HMGB1 release on islet viability is not clear, even though murine islets express potential receptors of HMGB1, such as TLR2, TLR4 and RAGE. The box A domain of HMGB1 (rHMGB-1A) exerts an anti-inflammatory effect by inhibiting HMGB1. The aim of this study is to determine whether the blocking of HMGB1with rHMGB-1A can attenuate mouse islet cell damage under hypoxia or cytokine treatment.

Methods: rHMGB-1A was expressed and purified by consecutive chromatographies. Isolated mouse islets were exposed to hypoxia or to inflammatory cytokines with or without rHMGB-1A. Cell viability was determined by propium iodide (PI) staining or Annexin-V(AV)-PI flowcytometry.

Results: Purified rHMGB-1A demonstrated an anti-inflammatory effect, reducing TNF-α release in HMGB1- or LPS- activated macrophages. Exposure to hypoxia (1% or 5% O2 for 24 h) or cytokine treatment (5 ng/mL IL-1β, 100 ng/mL IFNγ, and 100 ng/mL TNFα for 24 h) reduced islet cell viability, as shown by the presence of red PI-positive (dead) cells. The number of red cells was not reduced in islets that had been pretreated with rHMGB-1A (0.5 - 10 ug/mL). Apoptotic cell death was also not decreased in hypoxia or cytokine-treated islets with rHMGB-1A pretreatment in AV-PI flowcytometry.

Conclusion: Our data show that HMGB1 blockade may not provide direct islet protection during early posttransplant period, although it may reduce islet damage indirectly by decreasing innate immune response.

PE-94 Islet biology / insulin secretion

The Akt/FoxO1/p27 pathway mediates the proliferative action of procyanidol oligomers in pancreatic β cells

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Objective: Procyanidol oligomers are bioactive flavonoid compounds from fruits and vegetables that possess insulinomimetic properties, decreasing hyperglycaemia in streptozotocin-diabetic rats and stimulating glucose uptake in insulin-sensitive cell lines. In this study, we analysed the effect of Procyanidol oligomers as grape-seed extract on modulating proliferation in beta-cells.

Methods: INS-1 rat insulinoma cells were exposed to different concentrations of Procyanidol oligomers. MTT assay was performed to evaluate pancreatic β -cell proliferation. The expression of Akt/FoxO1/p27 was detected by quantitative real-time PCR and Western blotting.

Results: The results revealed that in comparison to the non-treatment group, stimulating INS-1 cells with 10 ug/mL procyanidol oligomers caused *β*-cell proliferation to be significantly enhanced. The mRNA levels of p27 in INS-1 cells declined upon treatment with procyanidol oligomers compared to the non-treatment group. Western blot analysis revealed that the phosphorylation of Akt and FoxO1 was markedly elevated following exposure to procyanidol oligomers. Moreover, LY294002, a phosphatidylinositol 3-kinase (PI-3K) inhibitor, significantly abrogated procyanidol oligomers induced effects.

Conclusion: we conclude that procyanidol oligomers increased the *β*-cell mass by upregulating *β*-cell proliferation and that the proliferative action of procyanidol oligomers in *β* cells was mediated by activation of PI-3K/Akt, which resulted in inactivation of FoxO1 and decreased p27.

PE-95 Islet biology / insulin secretion

ERK activation pathway plays a pivotal role in glucolipotoxicity-induced HIT-T15 beta cell damage

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Objective: Glucolipotoxicity (GLT) of pancreatic beta cells caused by elevated circulating free fatty acids and high glucose has been recognized to be a crucial factor contributing to beta cell dysfunction and beta cell loss in type 2 diabetes. Many factors and their related signal pathways (oxidative stress, ER stress, disruption in Ca2+ homeostasis etc.) have been reported to be involved in GLT-induced beta cell damage and recent research has shown that mitogen-activated protein kinase (MAPK) signaling pathways are activated in response to GLT-induced cellular stress, however, the overall underlying mechanisms remained poorly understood.

Methods: We treated insulin-secreting HIT-T15 pancreatic beta cells with 25 mM glucose and palmitic acid (PA) or oleic acid (OA) mixed with 10% BSA to induce GLT and observed its effect on cell apoptosis by using following methods: Assessment of cell viability: MTT assay. Measurement of apoptosis by DAPI staining and DNA fragmentation by agarose gel electrophoresis. Protein expression was evaluated by Western blot. For additional treatment study, cells were pretreated with either U0126 or AICAR for 1 h and then co-treated with 0.1 mM PA or OA for 16 h. All results are expressed as a mean ± S.D. Statistical analysis was performed using one-way analysis of variance (ANOVA) with a subsequent Tukey's multiple comparison test. A P value 〈 0.05 was used as a threshold for statistical significant.

Results: PA, but not OA, induced apoptosis in beta cells by activation MAPK family members: ERK, p38, JNK, and the AMPK activator (AICAR) and ERK inhibitor (U0126) reduced GLT-induced apoptosis by inhibiting MAPKs. Also we revealed that ERK is located upstream of p38 and JNK.

Conclusion: MAPKs, especially ERK, play a pivotal role in GLT-induced beta cell damage and AMPK activation and ERK inhibition can restrain the activity of this pro-apoptotic pathway.

PE-96 Islet biology / insulin secretion

The expression mechanism of lipocalin-2 by inflammatory cytokines in islet β-cells

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Objective: Lipocalin-2 is highly expressed in insulin target tissues such as liver and adipose tissue and it is known to be involved in glucose metabolism, insulin sensitivity and obesity. however, little is known about the expression of LCN-2 in pancreatic *β*-cells. Therefore, we examined the mechanisms by interleukin-1β (IL-1β) and interferon-γ (IFN-γ) induce LCN-2 expression in RINm5F β-cells.

Methods: RINm5F cells were treated with IL-1β or IL-1β plus INF-γ. LCN-2 protein and mRNA expressions were examined. LCN-2 promoter activity was evaluated. EMSA was performed to examine the binding of transcription factors to LCN-2 promoter. Actinomycin D chase study was performed to examine LCN-2 mRNA stability.

Results: IL-1*β* significantly induced LCN-2 expression while IFN-γ alone did not induce it. IFN-γ significantly potentiated IL-1*β*-induced LCN-2 protein and mRNA expression. However, IFN-γ failed to potentiate IL-1β-induced LCN-2 promoter activity and binding activity of transcription factors on LCN-2 promoter. LCN-2 mRNA stability and transcription factors NF-κB and STAT-1 were not involved in the stimulatory effect of IFN-γ on IL-1β-induced LCN-2 expression. Meanwhile, Western Blot and promoter analyses showed that NF-κ B was a key factor in IL-1β-induced LCN-2 expression.

Conclusion: IL-1*β* induces LCN-2 expression via NF-kB activation in RINm5F β -cells. IFN-γ significantly potentiated IL-1*β*-induced LCN-2 expression at mRNA and protein level but not at promoter level and the stimulatory effect of IFN-γ is independent of NF-κB and STAT-1 activation. These data suggest that LCN-2 may play a role in *β*-cell function under an inflammatory condition.

PE-97 Islet biology / insulin secretion

Protective effect of physiological short-term GLP-1 treatment against glucotoxicity in pancreatic β-cells

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Objective: GLP-1 exerts anti-apoptotic properties in pancreatic *β*-cell in type 2 diabetes mellitus. A main cause of the apoptosis is glucotoxiciy. However, the anti-apoptotic mechanism of GLP-1 and the duration for which GLP-1 should stimulate *β*-cells have not been fully determined. This study was to elucidate whether a short-term, physiological treatment with GLP-1 can be effective against *β*-cell apoptosis in response to high glucose, and its molecular mechanisms.

Methods: INS-1 cells were cultured in RPMI-1640 and the common bile duct was cannulated and perfused through the pancreatic duct with HBSS containing collagenase (1 mg/mL, Collagenase Type V) to obtain the isolated islets. The anti-apoptosis effect of GLP-1 in INS-1 cells was investigated using a live cell movie analyser and cell viability was measured using the MTT assay. After the INS-1 cells were transfected with scrambled siRNA (scRNA), siRaptor or siRictor for 48 h, they were treated with GLP-1 for 30 min. After that the insulin secreted into the medium was collected and measured using an insulin enzyme immunoassay kit. Finally, the insulin level was standardized to the total protein content measured using the bicinchoninic acid assay

Results: The protective effects of GLP-1 were related with PI3K/AKT S473 phosphorylation. Indeed, the increase in AKT S473 phosphorylation led to suppression of FoxO-1. Moreover, GLP-1-induced AKT S473 activation and FoxO-1 suppression were abolished by the selective inactivation of mTORC2 using siRNA directed towards the rapamycin-insensitive companion of the target of rapamycin. The protection effect of GLP-1 in *β*-cell apoptosis via glucotoxicity was also abolished by the selective inactivation of mTORC2. This report provides evidence that physiological short-term treatment with GLP-1 is sufficient to protect against glucotoxicity-induced *β*-cell apoptosis.

Conclusion: The effect of GLP-1 may be mediated by FoxO-1 suppression through the PI3K/mTORC2/AKT S473 phosphorylation signalling pathways.

PE-98 Islet biology / insulin secretion

Pancreatic stellate cells within the pancreatic islet might play a pathogenic role in islet fibrosis in type 2 diabetes

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Objective: The activation of pancreatic stellate cells (PSCs) is thought to be a potential mechanism underlying islet fibrosis, which may contribute to progressive β-cell failure in type 2 diabetes. Quiescent PSCs express the intermediate filament proteins including desmin and glial fibrillary acidic protein (GFAP). During activation, PSCs also express α-smooth muscle actin (a-SMA). In the normal pancreas, PSCs are located in the periacinar space. However, the presence of PSCs within the islet and the role of these cells in islet fibrogenesis in type 2 diabetes are not known.

Methods: We studied 14 week-old Sprague Dawley rats and Otsuka Long-Evans Tokushima Fatty (OLETF) rats, an animal model of type 2 diabetes. OLETF rats were divided into early diabetes group (aged 〉 20 weeks; O-Early group, n = 4) and late diabetes groups (aged 〉 20 weeks; O-Late group, n = 4). Long-Evans Tokushima Otsuka (LETO; L-Early group, n = 4; L-Late group, n = 4) rats were used as non-diabetic controls.

Results: Desmin-positive cells were 1.38 ± 0.29% of all islet cells in the pancreas of Sprague Dawley rats (n = 3). GFAP-positive cells were also found within the islet. The AUCglucose in the O-Late group was significantly higher as compared with the O-Early group or the L-Late group. Islet fibrosis was marked in OLETF rats, up to 20~25% while it was little in LETO rats. The percentage of a-SMA-positive cells within the islet in the O-Late group was significantly higher as compared with the O-Early group (1.90 ± 0.06% vs. 0.88 ± 0.08%, $P = 0.032$) or the L-Late group (1.90 ± 0.06% vs. 1.01 ± 0.04%, $P = 0.016$). Finally, the AUCglucose was significantly correlated with the percentage of a-SMA-positive cells within the islet in all animals ($r = 0.80$, $P < 0.001$).

Conclusion: In conclusion, our data suggest that PSCs are present within the pancreatic islet and activation of these cells might play a role in the development of islet fibrosis in type 2 diabetes.

PE-99 Macrovascular complications

Serum bone morphogenic protein 4 (BMP-4) levels in coronary artery disease (CAD) according to the presence of diabetes and/or hypertension

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Objective: Previously we reported that serum BMP-4 levels are inversely associated with surrogate markers of arterial stiffness and carotid atherosclerosis in patients with type 2 diabetes mellitus (T2DM). The aim of this study was to evaluate the association between serum BMP-4 levels and CAD with/without T2DM or hypertension (HTN).

Methods: Total 877 subjects who undergone coronary angiography (CAG) to evaluate the presence of CAD were consecutively enrolled. According to the findings from CAG, study populations were subdivided into CAD (+) and (-) group. Furthermore, subgroup analysis according to the presence of T2DM and/or HTN was done. Serum BMP-4 levels were measured using a human BMP-4 ELISA kit in all study subjects. Various anthropometric, metabolic and social parameters were also evaluated.

Results: Serum BMP-4 levels were negatively correlated with total cholesterol, LDL cholesterol and low transformed triglycerides ($P < 0.05$) in T2DM (+) group regardless of the presence of HTN. And this relationship between serum BMP-4 levels and lipid parameters was still valid in the CAD (+) T2DM (+) group, whereas it disappeared in the CAD (-) group. However, serum BMP-4 levels were not significantly different between CAD (+) and (-) group regardless of the presence of T2DM or HTN.

Conclusion: Serum BMP-4 levels were not different in our study subjects when compared according to the presence of CAD. However, serum BMP-4 levels were inversely associated with lipid parameters in T2DM with CAD which is a similar finding as our previous study. So further analysis will be needed to elucidate the relationship between serum BMP-4 levels and CAD in the presence of T2DM.

PE-100 Macrovascular complications

Increased risk of stroke and post-stroke outcomes in patients with diabetes: two nationwide studies

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Objective: The relationship between diabetes and stroke is not completely understood. This study evaluated stroke risk and post-stroke mortality in patients with diabetes.

Methods: We identified 24,027 adults newly diagnosed with diabetes in 2000~2003 using Taiwan's National Health Insurance Research Database. A comparison cohort of 96,108 adults without diabetes was randomly selected from the same dataset, with frequency matched by age and sex. Stroke events in 2000~2008 were ascertained from medical claims. Adjusted hazard ratios (HRs) and 95% CIs of stroke associated with diabetes were calculated. A nested cohort study of 22,348 hospitalized stroke patients between 2000 and 2009 calculated adjusted odds ratios (ORs) and 95% CIs of adverse events after stroke in patients with and without diabetes.

Results: During 821,563 person-years of follow-up, there were 4,629 newly diagnosed stroke cases. The incidences of stroke for people with diabetes and without were 10.1 and 4.5 per 1,000 person-years, respectively ($P < 0.0001$). Compared with people without diabetes, the adjusted HR of stroke was 1.75 (95% CI 1.64~1.86) for people with diabetes. The ORs of post-stroke pneumonia, urinary tract infection, and mortality associated with diabetes were 1.28 (95% CI 1.10~1.37), 1.57 (95% CI 1.44~1.71), and 1.59 (95% CI 1.36~1.87), respectively.

Conclusion: Diabetes was associated with stroke. Patients with diabetes had more adverse events and subsequent mortality after stroke. Prevention of stroke and post-stroke adverse events is needed in this susceptible population.

PE-101 Macrovascular complications

Association of serum C1q/TNF-related protein-9 concentration with arterial stiffness in subjects with type 2 diabetes

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Objective: Although recent animal studies have suggested that C1q/tumor necrosis factor-related protein-9 (CTRP9) is more likely to be involved in the regulation of vascular function, more specifically atherosclerosis, in rodents, little is known about whether serum CTRP9 level is associated with atherosclerosis in humans. The aim of this study was to investigate whether serum CTRP9 concentration is associated with atherosclerosis by measuring brachial ankle pulse wave velocity (baPWV) in subjects with type 2 diabetes. In addition, we examined the clinical and biochemical variables associated with serum CTRP9 concentration.

Methods: We measured circulating CTRP9 and total adiponectin levels in 278 subjects (169 men and 109 women; mean age of 58.3 years) with type 2 diabetes. Measurements of baPWV were performed in all subjects.

Results: Serum CTRP9 concentration was positively correlated with baPWV. This correlation was significant even after adjusting for total adiponectin levels. In multiple linear regression, serum CTRP9 concentration was independently associated with increased baPWV. Female gender, higher BMI, and HOMA-IR were significantly associated with elevated serum CTRP9 concentration in subjects with type 2 diabetes.

Conclusion: Serum CTRP9 concentration was significantly and positively associated with arterial stiffness in patients with type 2 diabetes, suggesting that CTRP9 might be important in the regulation of arterial stiffness in humans.

PE-102 Macrovascular complications

Association of metabolically abnormal but normal weight (MANW) and metabolically healthy but obese (MHO) individuals with arterial stiffness and carotid atherosclerosis

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Objective Despite recent interest in differential impact of body size phenotypes on cardiovascular outcomes and mortality, studies evaluating the association between body size phenotypes and indicators of atherosclerosis are limited. This study investigated the relationship of metabolically abnormal but normal weight (MANW) and metabolically healthy but obese (MHO) individuals with arterial stiffness and carotid atherosclerosis in Korean adults without cardiovascular disease.

Methods A total of 1012 participants (575 men and 437 women, mean age 50.8 years), who underwent a health examination between April 2012 and May 2013 were prospectively enrolled based on inclusion and exclusion criteria. Study subjects were classified according to body mass index (BMI) and the presence/absence of metabolic syndrome.

Results The prevalence of metabolically healthy normal weight (MHNW), MANW, MHO, and metabolically abnormal obese (MAO) were 54.84%, 6.42%, 22.83%, and 15.91%, respectively. Individuals with MANW had significantly higher brachial-ankle pulse wave velocity and maximal carotid intima-media thickness values than those with MHO, after adjusting for age and gender (P = 0.026 and P = 0.018, respectively). The odds ratio (OR) of arterial stiffness and carotid atherosclerosis in the MANW group were significantly higher than in the MHNW group in unadjusted models. Furthermore, multivariable models showed that increased OR of carotid atherosclerosis in the MANW group persisted even after adjusting for confounding factors (OR = 2.98, 95% CI = [1.54, 5.73], P = 0.011).

Conclusion Compared to MHNW or MHO subjects, Korean men and women with the MANW phenotype exhibited increased arterial stiffness and carotid atherosclerosis.

PE-103 Macrovascular complications

Structural and functional alterations of thoracic aorta in type II diabetic rats

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Objective: Vascular dysfunction plays a key role in the pathogenesis of diabetic vascular disease. The aim of this study was to compare the histological structure and vascular function in the thoracic aorta of control and diabetic rats. We investigated the change of vascular structure and function in diabetic rats and the effect of tetrahydrobiopterin (BH4) on such alterations.

Methods: We used LETO (control) and Otsuka Long- Evans Tokushima Fatty (OLETF, diabetic model) rats. OLETF rats injected with Tetrahydrobiopterin (BH4). Aortic isometric tension and effect of Phe and Ach were measured in the thoracic aorta of three rats. Histological analysis was performed using Hematoxylin-Eosin and Masson's Trichrome stains for elastin and collagen, respectively. Furthermore, we performed western blot to determine the differences in contractile protein expression in the thoracic aortic regions between control and diabetic rats.

Results: The thoracic aorta from OLETF showed lower tension than LETO- rat's thoracic aorta, and OLETF+BH4 recovered contraction to a similar level of LETO. The Ach induced relaxation in OLETF and OLETF + BH4 is significantly lower than in LETO rat (P < 0.001). BH4 levels were significantly lower in diabetic rats compared with control (P < 0.001). In the histological study, we observed that OLETF rat's tunica media area was significantly thicker in LETO and OLETF + BH4 (P < 0.001).

Conclusion: These data suggest that OLETF rats aortic regions has lower capacity for relaxation with thicker tunica media, which is related to the occurrence of diabetic vascular disease. Therefore, BH4 supplementation is a potential therapeutic option of diabetic vascular disease.

PE-104 Macrovascular complications

The application of computational vascular modeling to study pathophysiology of diabetes mellitus

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Objective: Hyperglycemia and the lack of insulin are major pathophysiological features of diabetes mellitus. Computational model of diabetic vessel has not developed to study the regulation of blood properties. Therefore, we generated a regulated dynamic viscosity model and compared it to the normal condition model. An understanding of the biomechanical properties of the artery can provide important insight into the vessel biology under pathophysiological conditions.

Methods: In this study, the effects of regulated dynamic viscosity on blood flow and wall shear stress were simulated numerically in which the physiological flow through the vessel was computed for using commercial software, COMSOL Multiphysics 4.4. Applying the incompressible Navier-Stokes equation, the blood was assumed to follow a fully developed Newtonian laminar flow, and pressure boundary condition was regulated in the inlet and outlet portions of the blood vessel. Vascular wall was assumed to be a rigid solid that is non-permeable and non-slip.

Results: The results showed that at same pressure values, the flow velocity was lower in the diabetes mellitus blood vessel model than in the normal blood vessel. Diabetes mellitus model exhibited higher the pressure values in the vascular wall and in the blood. Using the simplified blood vessel model, the degree of distortion of the blood vessel due to blood flow was assessed. Upon blood entry into the blood vessel, the distortion of the vessel wall was observed, with the highest wall shear stress occurring in the vicinity of inner part.

Conclusion: Our study demonstrates that the computational model of the blood vessel could evaluate related factor of diabetic vascular dysfunction and that model parameters can be extracted for further interpretation of biomechanical properties.

PE-105 Microvascular complications

The relationship between anemia and the initiation of dialysis in patients with type 2 diabetic nephropathy

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Objective: Anemia is associated with various poor clinical outcomes in chronic kidney disease patients. The aim of present study was to investigate the anemia which affected the degree of dialysis initiation and the initiation time of dialysis in type 2 diabetic nephropathy patients.

Methods: This observational, retrospective study included 130 type 2 diabetic nephropathy patients, in Korea. The existence of anemia, the degree of dialysis initiation and the initiation time were reviewed. The clinical characteristics and variables were also compared.

Results: The levels of hemoglobin and serum creatinine were significantly correlated with the dialysis initiation (P value 〈 0.05). During the 10-year follow-up period, the patients with anemia showed rapid decline of renal function and caused more dialysis initiation (54.1 vs. 5.4%, P value 〈 0.05) compare to the patients without anemia. There was a significant difference in average time to initiate dialysis (45.1 months [8.0~115.8] in patients with anemia vs. 68.3 months [23.3~108.8] in patients without anemia, P value 〈 0.01). The risk to the dialysis initiation was significantly increased in patients with anemia compared to the patients without anemia (adjusted hazard ratio: 8.1, [95% confidence interval: 2.4~27.0], P value 〈 0.05).

Conclusion: Anemia is associated with rapid decline of renal dysfunction and the faster initiation of dialysis in diabetic nephropathy patients. Therefore, clinicians should have an earlier special attention to anemia during the management of diabetes.

PE-106 Microvascular complications

Assessing two different cardiovascular risk assessment scoring systems and their relations with albuminuria in patients with newly diagnosis with type 2 diabetes

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Objective: We aimed to compare the ASCVD cardiovascular risk assessment scores released from 2013 ACC/AHA guideline and traditional Framingham 10-year cardiovascular risk score in patients with newly diagnosis with type 2 diabetes. And we also examined their associations with albuminuria.

Methods: We investrigated 290 patients from 40 years to 79 years who newly diagnosed with type 2 diabetes at the Pusan National University Yangsan Hospital. The ASCVD cardiovascular risk scores were calculated and the patients were divided as high risk groups (ASCVD risk score ≥ 7.5%) and low risk groups (ASCVD risk score 〈 7.5%). Framingham risk scores were also calculated and the scores were classified as high risk (≥ 10%) and low risk (〈 10%).

Results: In a total of 290 patients, 95 (32.8%) patients had a low ASCVD risk score and 195 (67.2%) had a high ASCVD risk score. The risk of developing CVD was more in males than females. The prevalence of albuminuria was more in the high risk group. In low risk group, 46 (48.4%) patients were reclassified as higher risk group according to Framingham risk score. But in high risk group, only 4 (2%) patients were reclassified as lower risk group according to Framingham risk score. The risk factors for albuminuria were different between the low CVD risk groups and high-CVD risk group in adjusted multivariate regression model. In low risk group, lower total bilirubin (OR 0.104) and higher Framingham 10-year risk score (OR 1.160) were significantly related albuminuria. In high risk group, higher SBP (OR 1.025) and higher ASCVD score (OR 1.022) showed significantly positive relation with albuminuria.

Conclusion: Two different cardiovascular risk assessment scores did not completely predict occurrence of albuminuria in patients with newly diagnosis with type 2 diabetes. Framingham risk score in low risk group and ASCVD risk score in high risk group showed positive relation with albuminuria.

PE-107 Microvascular complications

Estimating glomerular filtration rate from cystatin C and creatinine, vascular disease, in persons with diabetes in the Korea

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Objective: Cystatin C is an alternative filtration marker for estimating GFR, since it is less influenced by age and muscle mass compared with creatinine. So we estimated glomerular filtration rate from both cystatin C and creatinine, in persons with diabetes and compared the association of eGFRcr and eGFRcys with complications of diabetes.

Methods: We collected the retrospective data for 250 patients with diabetes with or without diabetic complications and 150 patients with non-diabetes from 2009 to 2013 in Pusan National University Yangsan Hospital. We estimated the kidney function among persons with diabetes using the 2012 CKD-EPI cystatin C and 2009 CKD-EPI creatinine equations.

Results: In the population with diabetes, when estimated kidney function by eGFRcys, 10% of patients has reduced kidney function and 2% of patients without diabetes. By eGFRcr, 10.8% of patients has reduced kidney function and 2.7% of patients without diabetes. The risk of albuminuria, retinoatphy, peripheral artery disease, and coronary artery disease were increased with lower eGFRcys rather than lower eGFRcr. When analyzed by spearman correlation analysis, risk of albuminuria was higher with low eGFRcys(R = -0.336, P 〈 0.001) compared with eGFRcr (R = -0.313, P 〈 0.001).

Conclusion: Lower eGFRcys was more strongly associated with diabetes complications than eGFRcr, especially at the risk of albuminuria.

PE-108 Microvascular complications

Charcot neuropathic arthropathy in diabetes: learning lessons from case review

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Contents: Charcot neuropathic arthropathy (CN) is one of the most devastating complications characterized by acute fractures, dislocations and joint destruction in a diabetic patient with neuropathy. However, acute phase of CN is often misdiagnosed as infection, deep vein thrombosis, acute gout or inflammatory arthritis. There is currently no universally accepted criterion for the diagnosis of acute CN. Furthermore, patients with diabetes have a greater frequency of infection such as respiratory, genitourinary and soft tissues. Therefore, the diagnosis of acute CN is likely to be delayed unless the physician has a high index of suspicion. Herein, we report a case of acute CN of foot that is initially misdiagnosed as osteomyelitis. 52-year-old male patient visited our emergency department complaining of red-swollen foot. Spiking fever and chilling, elevated levels of serum hs-CRP and ESR, abnormal signal intensity in the metatarsal and tarsal bones and fluid collections in joint spaces on the foot MRI suggested osteomyelitis with septic arthritis. However, fever and chilling was persisted despite of systemic antibiotics treatment and cultures of blood showed no bacteremia. Therefore, clinical reassessment was done. The patient had been diagnosed with diabetes for 15 years and had multiple chronic complications including neuropathy. There was no skin ulceration in the involved foot. He had a mild cough and a myalgia. Chest radiograph showed no infiltrative lesion, however serologic test for influenza was positive. After treatment with antiviral drug, fever was subsided and inflammatory markers were improved. Off loading with total contact cast lead to improvement of swelling of the foot. However, 2 month later, there was swelling of contralateral ankle which was similar to the right foot. Bilateral CN is reported in as many as 30% of cases. Therefore, prophylactic support is needed for the contralateral foot to minimize the risk of bilateral acute CN.

PE-109 Microvascular complications

Dehydrozingerone ameliorates diabetic nephropathy

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Objective: Curcumin has anti-oxidant and anti-inflammatory activities on diabetic nephropathy. Dehydrozingerone (DHZ) is a curcumin analogue and has anti-tumor and anti-oxidant effects. But, its effects on diabetic nephropathy are poorly understood. We investigated the effects of DHZ on diabetic nephropathy.

Methods: We divided experimental animals into three groups such as 1) normal (n = 10), 2) 60% fat diet (HFD, n = 10) and 3) HFD with DHZ (100 mg/kg per day, n = 10) for 12 weeks. And we collected 24 hours urine, serum and kidney tissues. Serum glucose, insulin, total cholesterol and leptin including urine albumin levels were analyzed by enzyme-linked immunosorbent assay (ELISA). And renal morphological changes were confirmed by immunohistochemistry (IHC) and electron microscopy (EM). Molecular changes were analyzed by immunoblotting. We treated DHZ (20 μM) for 24 hours in high glucose (30 mM, HG) stimulated podocytes.

Results: DHZ significantly reduced body weight, fasting blood glucose and insulin resistance. And it also decreased albuminuria through the recovery of thickened glomerular basement membrane, podocyte effacement and decreased slit pore numbers. In renal cortex, reduced phospho-AMPK and nephrin expressions as well as increased arginase 2 and CD68 expressions were recovered after DHZ treatment. In vitro study, increased ROS stimulated by HG in podocytes was reduced in DHZ treated group.

Conclusion: These results indicate that DHZ ameliorates diabetic nephropathy through anti-inflammatory and antioxidant effects.

PE-110 Microvascular complications

Amubulatory 24-hr heart rate and heart rate variability monitoring with simultaneous physical activity in real life for healthy and type 2 diabetes subjects : nocturnal tachycardia and characteristics in HRV abnormalities in diabetes patients

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Objective: We aimed at measuring diurnal change in heart rate and heart rate variability and analyzing their abnormalities and association with physical activity through recording them for 24-hours in real life.

Methods: To monitor HR, HRV and physical activity simultaenously and continuously we applied a new medical device (T-REX, Taewoong Medical, Gyeonggi do, Korea) to 73 healthy (control group) and 71 type 2 diabetes (diabetes group) subjects for 24 hours from 5:00 P.M. to 5:00 P.M. following day in real life. To assess autonomic function, high frequency and LF/HF ratio was used. We observed 24 hr fluctuation of HR and HRV including resting stage and their change according to physical activity. All variables were also analyzed according to subgroups with duration of diabetes.

Results: Although physical activity was similar in both groups, heart rate was more increase in diabetes group all day long and the difference was more predominant in nighttime. High frequency was markedly decreased and LF/HF ratio was more increased in diabetes group. Such the change of HR and HF was more significant for monitoring during resting time. Abnormalities of HR and HF was shown even in early stage of diabetes and more aggravated with duration of diabetes. Difference of HR was marked in nighttime among three subgroups. LF/HF ratio was much more increased in early stage of diabetes and decreased with duration of diabetes. HF was markedly depressed in all grades of physical activity in diabetes group. Although there was no difference in HR among three subgroups, change of HF and HF/HF was different in patients with long duration of diabetes.

Conclusion: We demonstrated predominant nocturnal tachycardia and abnormalities in HRV in diabetes group including patients with early stage of diabetes. Such the long-term monitoring could be helpful for more sensitive diagnosis of autonomic dysfunction and prediction of severity of diabetes.

PE-111 Microvascular complications

The prevalence and the associated factors of diabetic microvascular complications in patients with newly diagnosed type 2 diabetes

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Objective: The aim of this study was to assess the prevalence of diabetic microvascular complications and to identify the clinical and biochemical characteristics related to these complications in patients with newly diagnosed type 2 diabetes.

Methods: Four hundred and seventy-two subjects with newly diagnosed type 2 diabetes were recruited. The fasting biochemistries were measured. Microvascular complications of diabetes were evaluated in all patients.

Results: The mean age of subjects was 53.1 ± 13.6 years. The mean HbA1c, and body mass index (BMI) was 8.8 ± 2.5%, and 24.7 ± 3.6 kg/m^2, respectively. The prevalence of any form of microvascular complication was 25.8%. The prevalence of diabetic retinopathy, nephropathy, and neuropathy was 12.7%, 9.3%, and 7.8%, respectively. The risk factors for diabetic retinopathy were increasing age (odds ratio [OR] = 1.032, 95% CI = 1.006~1.058, P = 0.014), increasing triglyceride (OR = 1.004, 95% CI = 1.001~1.006, P = 0.008), increasing systolic blood pressure (OR = 1.019, 95% CI = 1.002~1.037, P =0.030). The risk factors for diabetic nephropathy were increasing age (OR = 1.046, 95% CI = 1.021~1.072, P 〈 0.001) and increasing HbA1c (OR = 1.143, 95% CI = 1.015~1.287, P = 0.028). The risk factors for diabetic neuropathy were increasing age (OR = 1.200, 95% CI = 1.040~1.385, P = 0.012), increasing triglyceride (OR = 1.015, 95% CI = 1.001~1.030, P = 0.038), and increasing HbA1c (OR = 1.867, 95% CI = 1.029~3.388, P = 0.040).

Conclusion: About a fourth of the newly diagnosed type 2 diabetic patients had some form of microvascular complication; diabetic retinopathy was the most common complication.

PE-112 Microvascular complications

Predicted 4-year risk of major CVD of diabetic patients

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Objective: Objective of this study was to evaluate Predicted 4-year risk of major CVD of DM patients.

Methods: Cross-sectional study included 80 (40 male and 40 female) DM patients with mean age 66.32 ± 7.94 years old. Predicted 4-year risk of major CVD was calculated by using ADVANCE Risk Engine of the George Institute for Global Health, Australia. Ten parameters (age at diagnosed diabetes, duration of diabetes, sex, atrial fibrillation, retinopathy, HbA1C, pulse pressure, hypertension, albuminuria and Non HDL-cholesterol) were used for risk calculation.

Results: Our study relieved that average age of diabetes diagnosis was 54.98 ± 9.37 years old and mean diabetes duration was 11.35 ± 7.46 years. DM patient with atrial fibrillation, retinopathy and hypertension were 0 (0%), 20 (16%) and 77.5 (62%). Mean level of HbA1C was 7.74 ± 1.5%. Mean level of microalbuminuria was 49.99 ± 94.02 mg/L. Non HDL cholesterol was 3.61 ± 1.08 mmol/L. Mean Predicted 4-year risk of major CVD was 6.69 ± 6.22% (Range 0.6~23.0%). DM patients with 〈 10%, 11~20% and 〉 20% Predicted 4-year risk of major CVD were 64 (80%), 12 (15%) and 4 (5.0%).

Conclusion: In the present study 80% of DM patients have less than 10%, 15% have 11~20% and 5.0% have more than 20% Predicted 4-year risk of major CVD. Microalbuminuria (P 〈 0.001), total cholesterol (P 〈 0.027) and population age (P 〈 0.042) are respectively correlated.

PE-113 Microvascular complications

Association between 45T/G Polymorphism of adiponectin gene and diabetic microvasculoar complications in Korean type 2 diabetes

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Contents: Adiponectin is an adipose tissue-specific protein which expressed by adipocytes and is an important regulator of lipid and glucose metabolism. Several adiponectin gene polymorphisms have been associated with risk for insulin resistance, cardiovascular disease. In this study, we investigated to examine the association between adiponectin 45T/G polymorphism and diabetic microvascular complications in Korean type 2 diabetes. A total of 761 subjects with type 2 diabetes were enrolled in this study. Diabetic microvascular complications were evaluated by the available medical records and laboratory findings. All subjects were genotyped for the adioponectin 45T/G polymorphism using the polymerase chain reaction-restriction fragment length polymorphism technique. The prevalence of end stage renal disease was higher in the patients with GG genotype compared to those with TG+TT genotype (7.5% vs. 1.5%). The prevalence of non-proliferative diabetic retinopathy was higher in the subjects with TG genotype compared to those with GG and TT (54.4% vs 40.5% vs 5.1%). This study showed that adioponectin 45T/G polymorphism may be associated with diabetic microvascular complications in type 2 diabetes. Adiponectin genotype could be used as a susceptibility marker to predict the risk of diabetic microvascular complications.

PE-114 Microvascular complications

Inverse association between serum total bilirubin levels and diabetic peripheral neuropathy and other microvascular complications in patients with type 2 diabetes

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Objective: Considerable evidence suggests that higher bilirubin concentration is associated with reduced prevalence of peripheral arterial disease and lower-limb through its antioxidant and anti-inflammatory activities. We investigated the relationship between serum total bilirubin (TB) levels and diabetic peripheral neuropathy and other microvascular complications in Korean patients with type 2 diabetes.

Methods: This cross-sectional study involved 1,343 patients with type 2 diabetes (635 men and 708 women; mean age, 56.7 ± 10.6 years).The subjects were stratified based on gender-specific tertiles of TB values and analyzed with respect to diabetic microvascular complications.

Results: According to the tertiles of TB, there was a linear increase in prevalence of retinopathy,, nephropathy, and peripheral neuropathy (all *P* for trend 〈 0.001). The age- and sex-adjusted odds ratios (ORs) for retinopathy, nephropathy, and neuropathy in the highest versus lowest the TB tertile were 0.35 (95% confidence interval 0.25~0.48), 0.55 (0.41~0.74), and 0.46 (0.31~0.68), respectively. The association between TB levels with retinopathy and diabetic peripheral neuropathy was remained significant further adjusting for other potential confounding factors including other microvascular complications.

Conclusion: TB was strongly associated with of retinopathy and peripheral neuropathy in Korean patients with type 2 diabetes. Further investigation is needed to validate the predictive value of serum TB on chronic diabetes complications.

PE-115 Metabolic syndrome & prediabetes

Relationship between high normal TSH levels and metabolic syndrome components in type 2 diabetic subjects with euthyroidism

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Objective: Obesity and insulin resistance are key features of the metabolic syndrome (MetS). Thyroid hormones as modulators of adaptive thermogenesis can potentially contribute to development of obesity. The purpose of our study is to observe a relationship between TSH and components of MetS in type 2 diabetic subjects with euthyroidism.

Methods: A total of 120 subjects with type 2 diabetes were recruited for this study from November 2012 to June 2014. Subjects were included in the study with TSH values between 0.3 and 4.5 mU/L, who did not take any thyroid medication and had a similar iodine diet. The study subjects were weighed and their anthropometric indices were taken. Lipid parameters, fasting plasma glucose, HbA1c, eGFR, blood pressure (BP) were documented, and TSH were measured by an electrochemiluminescence immunoassay. Statistical analysis was performed by using SPSS 18 (*P* value 〈0.05 was considered significant).

Results: The mean age of the participants was 60.6 ± 11.6 years with a BMI of 25.3 ± 3.1 kg/m^2. Serum TSH levels were significantly and positively associated with BMI, systolic and diastolic BP, serum triglyceride and HbA1c levels, whereas negatively with eGFR. Subjects with a TSH in a higher normal range (2.5~4.5 mU/I, n = 58) had a significantly higher BMI (26.7 ± 3 vs. 24.1 ± 2.7) and this relation remained significant adjusted for age and sex (*P* 〈 0.001). The research shows, that when TSH is in low normal range, the number of patients with non- compensated diabetes (HbA1c 〉 7%) decreases from 27.5% to 12.5% (*P* = 0.02, adjusted for age and sex). In addition, there was no significant correlation between FT4 and total T3 levels with MetS components.

Conclusion: In type 2 diabetic subjects with euthyroidism we found significant association between high normal TSH levels and components of metabolic syndrome. High normal TSH levels were associated with more non-compensated diabetic subjects.

PE-116 Metabolic syndrome & prediabetes

Loss of pyruvate dehydrogenase kinase 4 attenuates high fat diet induced ER stress in skeletal muscle

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Contents: Diabetes is associated with reduced insulin sensitivity in skeletal muscle caused by increased circulating blood glucose and fatty acid level. Increased fatty acid metabolism is linked with augmentation of unfolded proteins in Endoplasmic-reticulum (ER) which subsequently activates unfolded protein response (UPR). However, the detailed mechanism by which fatty acid metabolism causes ER stress remain elucidated. PDK4 has known to regulate usage of energy source between glucose and fatty acid by regulating the activities of pyruvate dehydrogenase (PDH) which is a key enzyme for the conversion of pyruvate to Acetyl-CoA. To identify the role of PDK4 in high fat induced ER stress, we took advantage of PDK4 knockout mice. We found out that high fat diet dramatically increased PDK4 expression level and stimulated ER stress, evidenced by increased activities of ATF6, Chop, Ire1, PERK, Eif2a. Interestingly, the activities of ER stress markers were diminished in PDK4 knockout mice, suggesting PDK4 has a critical role in high fat diet induced ER stress. Our study indicated that PDK4 is a major regulator of ER stress in skeletal muscle dysfunction induced by high fat diet.

PE-117 Metabolic syndrome & prediabetes

Association between lipoprotein (a) and nonalcoholic fatty liver disease in nondiabetic subjects

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Objective: NAFLD (Nonalcoholic fatty liver disease) has been considered as a manifestation of metabolic syndrome. Lipoprotein(a) [Lp(a)] is well known for an independent risk factor for cardiovascular disease, and attract attention as a promising biomarker for metabolic diseases. However, whether Lp (a) is related to NAFLD is unknown. Thus, the aim of our study was to investigate the association between serum Lp (a) and NAFLD among nondiabetic Korean adults.

Methods: Data were analyzed from 2242 nondiabetic Korean adults who underwent health screening examination. Anthropometric profiles were measured according to a standardized protocol. Fasting plasma glucose (FPG), insulin, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), lipids (triglycerides [TG], high-density lipoprotein cholesterol [HDL-C], and total cholesterol [TC]) and lipoproteins (Apolipoprotien B [Apo B], Apolipoprotien AI [Apo AI], Lp(a)) were measured. Insulin resistance was estimated based on the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR). Diagnosis of fatty liver disease was based on an abdominal ultrasonography and NAFLD was classified into three groups according to severity.

Results: BMI, SBP, DBP, FPG, TC, TG, LDL-C, Apo B, Apo AI, AST, ALT, insulin and HOMA-IR increased according to the severity of NAFLD, whereas HDL-C and Lp(a) levels decreased. And we found that the prevalence of NAFLD significantly decreased across Lp(a) tertiles. Also BMI, FPG, TG, insulin and HOMA-IR decreased with Lp(a) levels. In age and sex adjusted multivariable logistic regression analysis, Lp(a) level had decreased odds ratio (ORs) for the presence of NAFLD. The inverse relationship remained significant, even after adjusting for metabolic risk factors (ORs: II = 0.84, III = 0.63; 95% CI: II = 0.62~1.13, III = 0.26~0.86, respectively, $P < 0.01$), but this association was attenuated after adjustment for insulin resistance. (ORs: II = 1.00, III = 0.78; 95% CI: II = 0.68~1.42, III = 0.54~1.13, respectively, $P = 0.33$)

Conclusion: Our results indicated that Lp(a) concentration was associated inversely with factors of metabolic syndrome and NAFLD in nondiabetic Korean adults.

PE-118 Metabolic syndrome & prediabetes

The effect of metabolic syndrome on metabolic profiles in Korean boys' plasma and urine

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Objective: The prevalence of childhood obesity is rapidly increasing worldwide with obesity-related diseases, and Korea is no exception. Metabolic syndrome, a major pathology led by obesity, is known to develop complications such as type 2 diabetes and arteriosclerosis. Thus, we investigated specific biomarkers of metabolic syndrome in early stage of life, which could be useful for targeting and controlling future obesity-complications.

Methods: In all, 186 plasma metabolites were analyzed in 246 Korean boys from the Korean Child Obesity Cohort Study using the AbsoluteIDQ™ p180 Kit. For comparison of metabolic profile, subjects were classified into normal-weight (NW, n = 90; BMI percentile < 85th), obese without metabolic syndrome (MS-, n = 109), and obese with metabolic syndrome (MS+, n = 47) groups.

Results: We observed that 7 amino acids and 4 biogenic amines in plasma significantly increased with obesity and/or metabolic syndrome. Specifically, Glutamate, Asymmetric dimethyl-arginine (ADMA), and Kynurenine were significantly higher in MS+ group than other two groups. On the other hand, 6 amino acids (Glycine, Threonine, Asparagine, Glutamine, Citrulline, and Ornithine) and 2 biogenic amines (Creatinine and Taurine) in the MS+ group were significantly lower than normal-weight and the MS- group. As for urinary metabolite profile, the MS+ group showed significantly the lowest excretion of glutamine and alpha amino adipic acid (alpha AAA). The Alanine, Aspartate, and Glutamate metabolism turned out to be a significantly altered metabolic pathway in both plasma and urine.

Conclusion: These metabolic changes with childhood obesity and metabolic syndrome might serve as early indicators of further obesity-complications. This study was supported by research grants from the Korea National Institute of Health (4845-302-210-13, 2012-NG64001-00).

PE-119 Metabolic syndrome & prediabetes

Applied repeated measurement data analysis: genome-wide association study of metabolic syndrome and related traits in the Korean Association REsource Study

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Objective: We conduct a genome-wide association study to find common genetic variation occurring risk of the metabolic syndrome (MetS) and related traits (Central obesity, Dyslipidemia, Blood pressure, and Fasting plasma glucose) in Korean.

Methods: The Korean Association Resource (KARE) project data, one of the ongoing prospective epidemiological studies, has been utilized. In total, 8842 individuals and 350364 SNPs were analyzed after quality control procedures. For several years, various definitions for the MetS have been developed but definition of MetS is still debated. Here, we chose NCEP definition from among these. As the efficient strategies for genetic association analysis, we established GWA study of MetS and six traits (include waist circumference, HDL-cholesterol, triglyceride TG, systolic blood pressure SBP, diastolic blood pressure DBP, and fasting plasma glucose) with four repeated measurements for each individual. The linear mixed model was used to adjust the intra-subject correlation of response measurements.

Results: We performed 7 GWA analyses and identified several new susceptibility loci. Results from GWAS of MetS related phenotypes showed that their common genetic variations are at least partly overlapping with significant variants of MetS.

Conclusion: Our findings suggest that several genes from MetS are the core genetic background of other MetS components traits. It is a little evidence for pleiotropy linking central obesity, dyslipidemia, Blood pressure, and Fasting plasma glucose to the MetS and may give useful guideline to help understand etiology of MetS for further study.

PE-120 Metabolic syndrome & prediabetes

Alcohol drinking before pregnancy causes the abnormal fetus development by maternal metabolic disorders

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Contents: Alcohol drinking before or during pregnancy poses serious health risks to the unborn child such as prematurity, low or high birth weight, fetal death and fetal alcohol syndrome. We found that exposure of ethanol resulted in a decrease in the pregnancy rate as compared with pair-fed mice, but no different in survival rate. Also, birth weight in postnatal 0 day (P0) of ethanol-fed mice was higher than those of pair-fed mice, but thereafter, in P14 and P21, growth retardation appeared in the child of ethanol-fed mice. The macrosomia phenomenon in ethanol-fed mice is strongly associated with the dysregulation of glucose metabolism and triglyceride accumulation in maternal liver during the pregnancy. Hepatic inflammatory chemokines and cytokines are also markedly increased in ethanol-fed mice. These events may be caused by oxidative stress via ethanol-metabolism pathway since the detrimental fetal development and impaired glucose metabolism are strongly attenuated by the injection of 4-methylprazol, an inhibitor of CYP2E1. Taken together, our results suggest that ethanol consumption before pregnancy is a major causing factor for the detrimental fetus development via maternal metabolic disorders, especially on the dysregulation of glucose or insulin metabolism in maternal liver.

PE-121 Metabolic syndrome & prediabetes

Resolvin D1 reduces ER stress-induced apoptosis and triglyceride accumulation through JNK pathway in HepG2 cells

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Objective: Research has indicated that stress on the endoplasmic reticulum (ER) of a cell affects the pathogenesis of metabolic disorders such as obesity, type 2 diabetes mellitus, and non-alcoholic fatty liver disease (NAFLD). Resolvins, a novel family derived from x-3 polyunsaturated fatty acids, have anti-inflammatory and insulin sensitizing properties, and it has been suggested that they play a role in the amelioration of obesity-related metabolic dysfunctions.

Methods: This study showed that pretreatment with resolvin D1 (RvD1) attenuated ER stress-induced apoptosis and also decreased caspase 3 activity in HepG2 cells.

Results: RvD1 significantly decreased tunicamycin-induced triglycerides accumulation as well as SREBP- 1 expression. However, tunicamycin-induced ER stress markers were not significantly affected by RvD1 treatment. Moreover, RvD1 treatment did not affect the tunicamycin-induced expression of chaperones that assist protein folding in the ER. These results suggest that RvD1-conferred cellular protection may occur downstream of the ER stress. This was supported by the finding that RvD1 significantly inhibited tunicamycin-induced c-Jun N-terminal kinase (JNK) expression, although P38 and ERK1/2 phosphorylation were not affected. In addition, anisomycin, a JNK activator, increased caspase 3 activity and apoptosis as well as triglycerides accumulation and SREBP1 expression, and RvD1 treatment reversed these changes.

Conclusion: In conclusion, RvD1 attenuated ER stress-induced hepatic steatosis and apoptosis via the JNK-mediated pathway. This study may provide insight into a novel underlying mechanism and a strategy for treating NAFLD.

PE-122 Metabolic syndrome & prediabetes

Dihomo γ-linolenic acid induces endoplasmic reticulum stress through arachidonic acid in human liver SK-HEP I cells

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Objective: Dihomo γ-linolenic acid (DGLA), one of polyunsaturated fatty acids, is converted to arachidonic acid (AA) by Δ5 desaturase. Fatty acid composition affects the pathogenesis of metabolic disorders, such as obesity and type 2 diabetes mellitus. DGLA is associated with obesity and insulin resistance; however, the functional mechanism of DGLA is not yet clear. To examine the relationships between DGLA and ER stress responses or lipid accumulation, we investigated the changes of ER stress responses to the DGLA treatment in SK-Hep I human liver cells.

Methods: Human liver cells (SK-HEP I) were treated with BSA-conjugated DGLA. The protein expressions of GRP78, peIF2a, CHOP, SREBP1, FAS and SCD1 were determined by western blot. The amount of triglyceride was quantitated by spectro-colorimetric method and enzymatic assay kit.

Results: DGLA treatment increased ER stress response markers (GRP78, peIF2a, CHOP) compared to BSA treatment (control). CP24879 (Δ6/Δ5 desaturase inhibitor) treatment did not affect GRP78 expression. Also, DGLA increased TG accumulation alongside with increased protein expression involved in lipid metabolism, such as SREBP1, FAS and SCD1.

Conclusion: DGLA treatment increased ER stress responses in human hepatocytes. The induced ER stress seems to regulate lipid metabolism via SREBP1, accompanying with triglyceride (TG) accumulation in SK-HEP I cells. However, inhibition of AA production from DGLA blocked ER stress responses. DGLA may contribute to lipid accumulation via AA production –mediated ER stress responses.

PE-123 Metabolic syndrome & prediabetes

Effects of nut consumption on metabolic syndrome in Korean adults- A randomized controlled dietary intervention trial

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Objective: Nut consumption has been studied for its cardio-protective effects. However, clinical intervention studies have shown inconsistent findings, and no intervention study has been conducted in the Korean population. Therefore, this study aimed to investigate the effects of nut consumption on metabolic parameters and biomarkers related to inflammation, oxidative stress, and endothelial function in Korean adults with metabolic syndrome.

Methods: A randomized, controlled, parallel, dietary intervention study was designed. Subjects with metabolic syndrome and body mass index ≥ 23 kg/m^2 were randomized to the Nut group, which were supplemented with 30 g/day of mixed nuts including walnuts, peanuts, and pine nuts for 6 weeks; or allocated to the Control group. A total of sixty subjects were included in the final analysis. Metabolic markers were evaluated at baseline and at the end of the study.

Results: Total cholesterol and non-high-density lipoprotein cholesterol levels were significantly improved in the Nut group compared with the Control group (P = .022 and P = .043, respectively). Biomarkers related to inflammation, oxidative stress, and endothelial function did not significantly change from baseline in either group.

Conclusion: A usual diet supplemented with mixed nuts for 6-weeks led to favorable effects on some lipid parameters in Korean adults with metabolic syndrome. The findings might explain a possible mechanism of the cardioprotective effects of nut consumption.

PE-124 Metabolic syndrome & prediabetes

Asymmetric dimethylarginine (ADMA) induces insulin resistance and glucose uptake dysfunction in C2C12 myotubes

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Objective: Asymmetric dimethylarginine (ADMA), an endogenous inhibitor of nitric oxide synthase (NOS), is metabolized by dimethylarginine -dimethylaminohydrolase (DDAH). Abnormalities in DDAH could be associated with an accumulation of ADMA and insulin resistance in skeletal muscle. Thus, we investigated the effect of muscle-derived DDAH/ADMA on insulin sensitivity using cell models.

Methods: C2C12 myotubes were treated with ADMA or palmitate for 18 h. The mRNA expressions of DDAHs, IRS-1, GLUT4, eNOS, and PTP1B were determined by real-time PCR. The protein expressions of PTP1B, IRβ, pTyr1150/1151IRβ, Akt, pSer473Akt, and GLUT4 were observed using western blotting. DDAH enzyme activity was assayed by determining L-citrulline formation, and glucose uptake assay was performed using 2-(N-(7-nitrobenz-2 -oxa-1,3 -diazol-4-yl)amino)-2-deoxyglucose (2-NBDG).

Results: We observed significant accumulation of ADMA in insulin-resistance cell model. ADMA treatment inhibited DDAH activity and its mRNA expression. Moreover, the treatment markedly reduced tyrosine phosphorylation of insulin receptor. And also, the ADMA treatment led to decrease of mRNA expression levels of IRS-1, GLUT4, and eNOS, but led to increase of PTP1B. Consistently, the ADMA treatment significantly inhibited glucose uptake in C2C12 myotubes.

Conclusion: The accumulated ADMA seems to be involved in insulin resistance through regulation of DDAH activity and its expression, as well as modulation of insulin signaling. Taken together,we suggest that ADMA could be a new therapeutic target of preventing insulin resistance.

PE-125 Metabolic syndrome & prediabetes

Anti-diabetic effects of soy leaf extracts and pinitol in high-fat diet-fed C57BL/6J mice

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Objective: Soy (Glycine max) leaves contain the different and various phenolic compouds compared to soybeans. The extract of 95% ethanol from soy leaves (95ESL) is a rich source of pterocarpans having the anti-diabetic effects. Pinitol (PT) is a well-known anti-diabetic component, and a water-soluble soy carbohydrate. This study investigated the anti-diabetic effects of the 95ESL and PT in an high-fat diet (HFD)-induced diabetic mice.

Methods: Six-week-old male C57BL/6J were randomly divided into normal diet (ND), HFD (60 kcal% fat diet), 95ESL (HFD with 1% 95ESL wt/wt), and PT (HFD with 0.15% PT wt/wt). Body weight was monitored every week and the metabolic parameters of collected blood samples were analyzed. Also, histological analyses of pancreas, abdominal white adipose tissue (WAT), and liver were conducted. To investigate the anti-diabetic mechanism of 95ESL and PT, the mRNA levels of diabetes-related genes in tissues were examined by real time qRT-PCR.

Results: After a 12-week feeding period, treatment of 95ESL and PT reduced the body and WAT weight, and decreased the plasma levels of HbA1c and insulin. The plasma TC and TG levels of PT group were significantly decreased: on the other hand, those of 95ESL group did not differ significantly. The areas of pancreatic β-cells in 95ESL and PT groups were significantly increased in comparison to that in HFD group. PT treatment strongly improved the expressions of major markers for development of pancreatic β-cells, Ngn3, Pax4, and MafA in pancreas. Besides, 95ESL and PT regulated the gluconeogenesis factors in liver, and improved insulin sensitivity through the regulation of IRS1, IRS2, and GLUT4 in WAT.

Conclusion: Supplementation of 95ESL and PT exert anti-obesity and anti-diabetic effects in a diabetic animal model, and enhanced the insulin sensitivity in pancreas and WAT and the glucose metabolism in liver.

PE-126 Metabolic syndrome & prediabetes

Oleic acid reduces palmitic acid-induced lipotoxicity by AKT activation in HepG2 cells

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Objective: Fatty acids are crucial for cell survival, however, their over-accumulation triggers lipotoxicity that leads to cell death. It has been known oleic acid (OA) to be less toxic than palmitic acid (PA) and to attenuate PA-induced lipotoxicity. The mechanisms are not fully understood. We investigated the protective role of OA on PA-induced lipotoxicity in HepG2 cells.

Methods: HepG2 cells were treated with different concentration of PA and/or OA conjugated with 10% BSA. After 24 h, cell viability and triglycerides accumulation were determined by MTT assay and Oil Red O staining, respectively. Protein expressions were detected by Western Blotting. In order to investigate the role of JNK or AKT in lipotoxicity, cells were pre-treated with JNK inhibitor (SP600125), AKT inhibitor (Wortmannin), AKT activator (GW9508) for 1h and co-treated with PA and/or OA for 24h. Data were represented by mean ± SD. Differences between the means were calculated using one-way analysis of variance (ANOVA) with a Tukey's Multiple Comparison Test ($P < 0.05$).

Results: Intra-cellular triglycerides accumulation of two fatty acids did not differ although PA was more toxic to HepG2 cells than OA. PA, but not OA, induced lipotoxicity in JNK-dependent manner. Apoptotic proteins: P53 was increased, Bcl-2 was decreased in cells treated with PA. But OA did not activate them. OA treatment or SP600125 reduced PA-induced JNK activation and cell death. OA or GW9508 increased AKT phosphorylation and decreased PA-induced JNK activation. However, OA with Wortmannin did not affect PA-induced JNK activation.

Conclusion: Despite equal cellular steatosis, PA causes JNK activation leading to lipotoxicity and OA reduces it by AKT activation in HepG2 cells.

PE-127 Metabolic syndrome & prediabetes

The association of serum increased fatty-acid binding protein 4 level with reduced lung function in apparently healthy Korean adults

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Objective: The aim of this study was to access the association of lung function with serum fatty -acid binding protein (FABP) in apparerntly healthy Korean adults.

Methods: In 388 participants in a health screening program, Force Exploratory Volume (FEV) 1 and Forced Vital Capacity (FVC) were assessed with standard spirometry. Subjects with obstructive (n = 7) and restrictive (n = 15) lung disease were excluded from the analysis. Serum FABP4 level was measured by enzyme-linked immunosorbent assay. 364 subjects (66.4% men, mean age 41 years) were included in the final analysis.

Results: Serum FABP4 level showed significant negative correlation with FVC (% predicted) even after adjustment for confounding variables (r = -0.043, P = 0.027), while serum FABP4 showed insignificant negative correlation with FEV1 (% predicted). When logistic regression analysis was performed with being in the lowest quartile of FVC or FEV1 with dependent variable, ln (FABP4) showed significantly increased odds ratio of 2.34 and 2.11 for reduced lung function after adjustment for confounding variables (95% confidence interval (CI) 1.17~5.04, P = 0.023, 95% CI 1.07~4.36, P = 0.036) respectively.

Conclusion: These results indicate that increased FABP4 level showed increased risk for reduced lung function in apparently healthy Korean adults.

PE-128 Metabolic syndrome & prediabetes

Prediabetes with high 30-minute postprandial plasma glucose levels had β-cell dysfunction and insulin resistance similar to diabetes

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Objective: The current diagnostic criteria for diabetes were established based on the fasting glucose, 2-hour postprandial glucose and HbA1C. However, 30-minute postprandial glucose (PP30), which reflects an early phase insulin secretion, had not been used for clinical implications. The aim of this study was to access the difference in index of β-cell function, metabolic factors and progression to type 2 diabetes (T2DM) according to PP30 level.

Methods: A total 1,888 subjects, who had suspected abnormal glucose tolerance or family history, were performed 75-g oral glucose tolerance tests (OGTT) at time 0, 30 and 120 min. All subjects were classified as having normal glucose tolerance (NGT, n = 141), prediabetes (IGT or IFG, n = 688), or T2DM (n = 1059) according to the OGTT results. We calculated insulinogenic index and HOMA-IR. We identified the characteristics of prediabetes with PP30 over 200 mg/dl compared to those with PP30 below 200 mg/dL.

Results: Newly diagnosed T2DM and prediabetetic subjects had significantly lower insulinogenic index (0.19 ± 0.2 vs 0.49 ± 0.8 vs 0.87 ± 0.6, $P < 0.001$) and higher HOMA-IR (4.0 ± 4.4 vs 3.0 ± 1.8 vs 1.9 ± 1.5, $P < 0.001$) and aggravated metabolic factors (BMI, lipid profile) compared to subjects with NGT. In addition, prediabetes with PP30 over 200 mg/dL had lower insulinogenic index (0.32 ± 0.6 vs 0.58 ± 0.66, $P < 0.001$) and higher HOMA-IR (3.3 ± 2.5 vs 2.9 ± 1.5, P = 0.023) compared to those with lower PP30. However, there were no significant differences in metabolic factors according to PP30 level. 16% of prediabetic subjects progressed to T2DM and mean intervals to progression were 30.9 months and mean follow-up duration were 62.1 months. While 14.3% of prediabetes with PP30 below 200mg/dl progressed to T2DM, 21.4% of prediabetes with PP30 over 200 mg/dL progressed to T2DM.

Conclusion: Prediabetes with PP30 over 200mg/dl showed β-cell dysfunction and insulin resistance similar to T2DM. This study suggests that prediabetic subjects with high PP30 should be monitored closely.

PE-129 Metabolic syndrome & prediabetes

Anti-inflammatory and anti-adipogenic effects of water dropwort (Minary) in diabetic KK-Ay mice

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Objective: Water dropwort (Minary, Oenanthe javanica D.C.) is a one of the multi frequency vegetable in Korea. In previous study, we investigated the effects of ethanol extracts from Minary on glucose and lipid metabolism in cell culture experiments. Thus, the present study was to examine the effect of Minary on the change of pro-inflammatory cytokines, obesity, glucose and lipid-related metabolic dysfunction in obese diabetic KK-Ay mice.

Methods: 4-week-old male KK-Ay mice were used in this study and randomly assigned to the control group (60% fat calory diets), 5% or 10% Minary group. Freeze-dried Minary powder was mixed with 60% high fat diet and pair-fed for 4 weeks. Pioglitazone (PIO) and Bezafibrate (BEZA) were used as positive control group. After 12 hour fasting, serum and each tissue were used for analysis.

Results: Total intestinal fat and renal fat mass of the 5% Minary group were significantly decreased compared with the control group. Renal fat mass of the 5% Minary group was reduced similar to the BEZA group. MCP-1 (Monocyte chemotactic protein 1) of 10% Minary group were significantly decreased compared with the control group. Serum GOT (Glutamic-oxaloacetic transaminase) and GPT (Glutamic-pyruvic transaminase) were significantly decreased compared with the control group. Liver macrophage infiltration of 10% Minary group was significantly decreased by level of PIO group compared with the control group.

Conclusion: It is concluded that Minary showed suppressive effect related metabolic syndrome parameters in high fat diet induced obese diabetic KK-Ay mice. These results indicate that Minary-rich diet helps to prevent metabolic syndrome.

PE-130 Metabolic syndrome & prediabetes

Effects of hepatic Sirt1 knockdown on inflammation

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Objective: Sirtuin1 (Sirt1), the mammalian homolog of Sir2, is an NAD-dependent protein deacetylase. Recent studies have suggested that Sirt1 plays an important role in modulating metabolic and physiological processes including inflammation. The purpose of this study is to investigate whether hepatic Sirt1 knockdown induces inflammation in vitro and in vivo and to elucidate underlying molecular mechanisms.

Methods: RNA interference (RNAi)-mediated gene silencing was performed for Sirt1 knockdown. AML12 mouse hepatocytes were transfected with small interfering RNA (siRNA) for 48 hours. Male ICR mice, aged 10 weeks, were divided into two groups: 1) control (CON) and 2) Sirt1 knockdown group (Sirt1 KD). siRNA was delivered into mouse liver using tail vein injection. After 72 hours, serum and liver tissues were collected. Sirt pathway components, NOD-like receptor family, pryin domain containing 3 (NLPR3) inflammasome, and inflammatory markers were evaluated by real-time PCR.

Results: Knockdown of Sirt1 did not affect body weight. Sirt1 knockdown led to the down-regulation of Sirt6 gene expression. Also, peroxisome proliferator-activated receptor gamma coactivator 1-alpha (PGC1-α) and forkhead box protein O1 (Foxo1) gene expressions were significantly decreased by inhibition of Sirt1. Hepatic adiponectin mRNA was significantly reduced by Sirt1 knockdown ($P < 0.05$). Knockdown of Sirt1 resulted in increased aquaporin 9 ($P < 0.01$). The expression of interlukin-6 (IL-6) in Sirt1 KD was two times higher than CON.

Conclusion: These data demonstrated that Sirt1 knockdown up-regulated pro-inflammatory marker IL-6 by suppressing Sirt6, PGC1-α, Foxo1, and adiponectin. Further studies will be needed to investigate the effect of hepatic Sirt1 knockdown in long-term on inflammation.

PE-131 Therapeutics of diabetes

The effectiveness of blood β-ketone testing in patients with diabetic ketosis: A systematic review & meta-analysis

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Objective: The safety and effectiveness of Blood β-ketone testing by using self-monitoring β-ketone strip on diabetic patients.

Methods: Clinical effectiveness of blood β-ketone testing was assessed through correlation with reference test that measured blood β-ketone value through gas chromatography or enzyme method, diagnostic accuracy, time taken for the test and time taken for confirmative diagnosis of diabetic ketosis by selecting literatures on researches that conducted this test on ketosis(suspected) patients or diabetic ketosis(suspected) patients. Each of the stages from literature search to application of selection standards and extraction of data were carried out independently by the Subcommittee along with 2 assessors.

Results: Blood β-ketone testing displayed high level of correlation in the range of r = 0.92~0.99 with blood β-ketone test that uses enzyme method as the reference standard. Regarding the diagnostic accuracy, sensitivity of 0.816, specificity of 0.743. The time taken for the test was 30 seconds for the intervention test, which is shorter than that of the blood β-ketone test that uses enzyme method.

Conclusion: Blood β-ketone testing was assessed to be a safe and effective test to monitor ketosis and assess the level of risk of ketosis by measuring the blood β-ketone on ketosis (suspected).

PE-132 Therapeutics of diabetes

The influence of total or sub-total gastrectomy on the glucose control in diabetic and non-diabetic patients

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Objective: Although bariatric surgery including diverse type gastrectomy has recently emerged as a potentially useful treatment for type 2 diabetes, it is not clear until now whether gastrectomy can give beneficial effect on glucose metabolism or not. Therefore, in this study,we investigated changes of glucose levels according to the subtotal or total gastrectomy in type 2 diabetic and non-diabetic patients.

Methods: From Jan 2010 to May 2014,77 diabetic and 89 non-diabetic patients who underwent gastrectomy at Chon-buk national university hospital, South Korea were included and we compared the fasting plasma glucose levels, HbA1c, and anti-diabetic management between before and after gastrectomy.

Results: After gastrectomy, 99 patients (60.7%) showed reduced FPG levels at the point of 1 year, and 89 patients (50.9%) showed reduced FPG at the point of 3 years, irrespective of diabetes. Among 77 diabetic patients, the decrease of FPG was observed in 55 patients (71.4%) and 31 patients (40.3%) at 1 year and 3 years after gastrectomy, respectively. Among 89 non-diabetic patients, at the point 1 year and 3 years after gastrectomy, 44 patients (51.2%) and 58 patients(67.4%) showed reduced FPG levels. In the patients of reduced FPG after gastrectomy, average values of decreased FPG of diabetic patients and non-diabetic patients are as follows : -30.3 ± 31.4 vs -41.8 ± 38.7 after 1 year, -43.5 ± 45.0 vs -35.5 ± 28.1 after 3 years. There were no statistically significant differences according to the diabetes and time passage ($P > 0.05$). On the contrary, after gastrectomy, FPG levels of 28.6% and 59.7% diabetic patients and 48.8% and 32.6% non-diabetic patients were increased after 1 year and 3 years, respectively.

Conclusion: Gastrectomy did not show consistent results in the glucose reduction in diabetic or non-diabetic patients, and over around half of patients, FPG levels were rather increased after gastrectomy. Moreover, glucose level can be increased in diabetic and non-diabetic patients although gastrectomy in this study were performed due to gastric malignancy treatment. Therefore, bariatric surgery including gastrectomy needs to be performed with care, and OGTT may be necessary to assess or predict glucose state after gastrectomy.

PE-133 Therapeutics of diabetes

Ezetimibe stimulates glucagon-like peptide 1 secretion by extracellular signal-regulated kinase 1/2

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Objective: Ezetimibe is known as a Niemann-Pick C1-Like 1 (NPC1L1) inhibitor and has been used an agent for hypercholesterolemia. In our previous study, ezetimibe administration improved glycemic control and increased glucagon like peptide-1 (GLP1), an incretin hormone with anti-diabetic properties. However, the mechanism(s) by which ezetimibe stimulates GLP1 secretion are not fully understood. Thus, the specific aim of this study was to investigate the mechanism(s) by which ezetimibe stimulates GLP1 secretion.

Methods: To investigate the role of ezetimibe in glycemic control and GLP1 secretion, male KK/H1J mice were fed either AIN-93G (NC) or a 45% high fat diet (HF) supplemented with ezetimibe (10 mg/kg/day) for 6 weeks. The effect of ezetimibe on dipeptidyl peptidase-4 (DPP4) activity was determined in vivo and in vitro using ezetimibe-administrated rats and human recombinant DPP4 with various concentrations of ezetimibe. The direct effects of ezetimibe on GLP1 secretion and L cell secretory mechanisms were examined in human NCI-H716 intestinal cells.

Results: Ezetimibe supplementation significantly ameliorated HF-increased glucose and insulin resistance in the type 2 diabetic KK/H1J mouse model. Serum and intestinal active GLP1 levels were significantly increased by ezetimibe in HF-fed animals. However, mRNA expression of genes involved in intestinal GLP1 synthesis was not altered. Furthermore, ezetimibe did not inhibit the activity of either in vivo or in vitro DPP4. In human NCI-H716 intestinal cells, ezetimibe significantly stimulated active GLP1 secretion, which was accompanied by the activation of extracellular signal-regulated kinase 1/2 (ERK1/2). Incubation of ERK inhibitor (PD98059) in NCI-716 cells prevented ezetimibe-increased GLP1 secretion.

Conclusion: These findings suggest a possible novel biological role of ezetimibe in glycemic control to stimulate intestinal GLP1 secretion by ERK activation.

PE-134 Therapeutics of diabetes

Linagliptin, a dipeptidyl peptidase-4 inhibitor, in patients with type 2 diabetes and chronic liver disease

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Objective: Linagliptin is mainly excreted via entero-hepatic system. In pharmacokinetic studies it is reported that no dose adjustment is required for patients with hepatic impairment. Nonetheless, there are few studies that focus on patients with type 2 diabetes and chronic liver disease. Therefore, we reviewed the changes of hepatic and glycemic parameters in patients with type 2 diabetes and chronic liver disease treated with linagliptin.

Methods: We collected data of all patients with type 2 diabetes and chronic liver disease who had taken linagliptin for more than three months at our center. Baseline and follow-up HbA1c, fasting plasma glucose, aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, bilirubin, prothrombin time (PT) were analyzed. We divided patients into three categories; chronic hepatitis with medication (such as antiviral agents for viral hepatitis or immunosuppressant agents for autoimmune hepatitis, n = 25), chronic hepatitis without medication (n = 13) and liver cirrhosis (n = 32). In addition,cirrhotic patients were grouped by Child-Pugh classification (A, B and C, n = 25,3,4 respectively). Primary endpoint was the change in HbA1c from baseline to the last follow-up. Secondary endpoint was the change in hepatic parameters.

Results: Seventy patients(male 60%; mean age 58 ± 9 years; diabetes duration 8 ± 7 years; treatment duration 9 ± 4 months; baseline HbA1c 7.5 ± 1.7%) were included in this retrospective analysis. Mean change in HbA1c from baseline was -0.6% (P = 0.01) in all patients with chronic liver disease, whereas the levels in AST, ALT, albumin, bilirubin and PT were not significantly changed. In the group with higher HbA1c at baseline (8.0 ± 2.0%; chronic hepatitis under treatment), HbA1c was significantly decreased by 1.0% (P = 0.02) and hepatic deterioration was not observed. In cirrhotic patients, the level of HbA1c(baseline vs. follow up; 6.9 ± 1.2 vs. 6.8 ± 1.3%, P = 0.57) as well as hepatic parameters were not changed during treatment.

Conclusion: Our analysis showed linagliptin is an efficacious and well-tolerated treatment option in patients with chronic liver disease; moreover, linagliptin could be considered in patients with liver cirrhosis and chronic hepatitis under treatment.

PE-135 Therapeutics of diabetes

Glucose lowering effect of FGF21 analogue, LY2405319, on streptozotocin-induced diabetic mice

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Objective: Fibroblast growth factor 21 (FGF21) has known to improve insulin sensitivity and glucose metabolism in obesity and type 2 diabetes. However, beneficial effect of FGF21 in insulin deficient state has not yet been investigated. Here, we investigated the effects of FGF21 analogue, LY2405319 on glucose homeostasis in streptozotocin-induced insulin-deficient mice (STZ mice).

Methods: OGTT, PET-CT, real-time PCR, IHC, transmission electron microscopy, etc.

Results: Hepatic FGF21 expressions and plasma FGF21 levels were reduced on STZ mice compared to control mice and LY2405319 lowered blood glucose levels compared with placebo STZ mice. Intriguingly, STZ mice showed an absence of glucose uptake in brown adipose tissue (BAT), which was evident by PET scan. Insulin deficiency impaired glucose utilization for the maintenance of BAT triacylglycerol reserves and resulted in mitochondria with absent or swollen cristae and had decreased lipid vacuoles. LY2405319 recovered the expression of metabolic genes which are related triacylglycerol synthesis and lipolysis for non-esterified fatty acid supply to the mitochondria and restored BAT function. The ability of LY lowering blood glucose level was compromised after removing inter-scapular BAT in STZ-mice compared with the sham operated STZ-mice.

Conclusion: In conclusion, our study demonstrated that improvement of BAT glucose metabolism by LY could be alternative approach for the treatment of insulin deficient diabetes.

PE-136 Therapeutics of diabetes

Higher prevalence of metformin-induced vitamin B12 deficiency in sulfonylurea combination compared with insulin combination in patients with type 2 diabetes: A cross-sectional study

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Objective: Long-term and high-dose treatment with metformin is known to be associated with vitamin B12 deficiency in patients with type 2 diabetes. We investigated whether the prevalence of B12 deficiency was different in patients treated with different combination of hypoglycemic agents with metformin during the same time period.

Methods: A total of 394 patients with type 2 diabetes treated with metformin and sulfonylurea (S + M group, n = 299) or metformin and insulin (I + M group, n = 95) were consecutively recruited. The vitamin B12 and folate levels were quantified using the chemiluminescent enzyme immunoassay. Vitamin B12 deficiency was defined as vitamin B12 ≤ 300 pg/mL without folate deficiency (folate 〉 4 ng/mL).

Results: The mean age of and duration of diabetes in the subjects were 59.4 ± 10.5 years and 12.2 ± 6.7 years, respectively. The mean vitamin B12 level of the total population was 638.0 ± 279.6 pg/mL. The mean serum B12 levels were significantly lower in the S+M group compared with the I+M group (600.0 ± 266.5 vs. 757.7 ± 287.6 pg/mL, P 〈 0.001). The prevalence of vitamin B12 deficiency in the metformin-treated patients was significantly higher in the S+M group compared with the I+M group (17.4% vs. 4.2%, P = 0.001). After adjustment for various factors, such as age, sex, diabetic duration, duration or daily dose of metformin, diabetic complications, and presence of anemia, sulfonylurea use was a significant independent risk factor for B12 deficiency (OR = 4.74, 95% CI 1.41~15.99, P = 0.012).

Conclusion: In conclusion, our study demonstrated that patients with type 2 diabetes who were treated with metformin combined with sulfonylurea require clinical attention for vitamin B12 deficiency and regular monitoring of their vitamin B12 levels.

PE-137 Therapeutics of diabetes

Efficacy and safety of dulaglutide versus sitagliptin in Korean patients with type 2 diabetes mellitus

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Objective: To compare the efficacy and safety of dulaglutide, a once-weekly, long-acting glucagon-like peptide-1 receptor agonist, with sitagliptin and placebo in metformin-treated Korean patients with type 2 diabetes mellitus (T2DM).

Methods: This subgroup analysis of a Phase 3, adaptive, double-blind, parallel arm, multinational, 104-week study1 assessed Korean patients (N = 98; mean age: 54.2 years, HbA1c: 8.2%; weight: 73.0 kg; T2DM duration: 8.3 years) randomized to dulaglutide 1.5 mg (n = 27), dulaglutide 0.75 mg (n = 25), sitagliptin 100 mg (n = 31), or placebo (replaced with sitagliptin after 26 weeks; n = 15).

Results: In Korean patients, decreases (least square mean ± standard error) in HbA1c at 52 weeks (analysis of covariance with the last observation carried forward) were greater for dulaglutide (1.5 mg: -1.46 ± 0.19%; 0.75 mg: -1.19 ± 0.20%) than sitagliptin (-0.73 ± 0.18%). Decreases in body weight at 52 weeks (mixed-effects, repeated measures) were -3.01 ± 0.60 kg, -1.37 ± 0.61 kg (dulaglutide 1.5 mg, 0.75 mg), 0.94 ± 0.54 kg (sitagliptin). Treatment-emergent adverse events (TEAEs) at 104 weeks were similar in all groups; the incidence of gastrointestinal TEAEs was 51.9%, 52.0% (dulaglutide 1.5 mg, 0.75 mg), 25.8% (sitagliptin). The incidence of serious AEs at 104 weeks was 14.8%, 4.0%, (dulaglutide 1.5 mg, 0.75 mg), 12.9% (sitagliptin). Although fewer Korean patients had body mass indexes (BMI) ≥ 30 kg/m^2 (22.4%) and ≥ 27 kg/m^2 (57.1%) than global patients (55.6% and 80.0%, respectively), decreases in HbA1c and body weight at 52 weeks were observed for Korean patients (taking dulaglutide 1.5 mg, 0.75 mg, and sitagliptin 100 mg) regardless of BMI subgroup.

Conclusion: This subgroup analysis supports dulaglutide for metformin-treated Korean patients with T2DM. Efficacy and safety findings for Korean patients were consistent with those reported for the global population [1]. The small number of patients in this subgroup analysis limits definitive conclusions about comparisons within and between treatment groups 1. Nauck M. et al. Diabetes Care. 2014. DOI: 10.2337/dc13-2761.

PE-138 Therapeutics of diabetes

Aerobic and resistance exercise improves mitochondrial function by downregulation of uncoupling proteins in type 2 diabetic heart

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Objective: Uncoupling proteins (UCPs) are mitochondrial transporters which mediate mitochondrial proton leak and decreasing ATP production. Overexpression of UCPs in diabetic hearts reduced cardiac energy efficiency resulting chronic heart failure. Here, we assessed the effect of aerobic or resistance exercise on the protein expression level alteration of UCPs in type2 diabetic heart.

Methods: Twenty five-week-old Otsuka Long Evans Tokushima Fatty (OLETF) rats were divided into 3 groups; sedentary (SED), aerobic exercise (EXA), and resistance exercise (EXR). EXA and EXR rats were exercise trained for 12 weeks and the effect of aerobic or resistance exercise on OLETF diabetic rats were investigated by glucose tolerance tests, lipid profiles, echocardiography, and mitochondrial functional studies.

Results: Both exercise successfully improved hyperglycemia and hyperlipidemia in OLETF rats. In their cardiac function, SED rats showed lower stroke volume (SV), decreased left ventricular chamber size and higher relative wall thickness ratio (RWT), indicating pathological cardiac remodeling, while EXA and EXR rats improved SV by increased LV chamber or cardiac contractility, respectively. SED rats also showed disrupted mitochondrial morphology and impaired mitochondrial function, whereas both of exercise training improved of those abnormalities. Importantly, both exercise commonly increased cardiac glucose transporter 4 (GLUT 4), glucose utilization protein level, whereas decreased fatty acid metabolism regulated proteins, including carnitine palmitoyltrasferase 1 (CPT 1) and UCPs (UCP 2 and UCP 3) compared to SED group.

Conclusion: These data demonstrate that aerobic or resistance exercise training restored mitochondrial and cardiac dysfunction in type 2 diabetic hearts via shifting energy utilization and enhancing cardiac energy efficiency.

PE-139 Therapeutics of diabetes

Efficacy of pioglitazone when substituted for glimepiride in Korean type 2 diabetics with inadequate triple combination therapy of glimepiride, sitagliptin and metformin

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Objective: To evaluate the clinical efficacy of pioglitazone for reducing plasma glucose levels in Korean subjects with type 2 diabetes mellitus during a 24-week treatment period.

Methods: Our study design involved the substitution of 15 mg pioglitazone for tapering dose of glimepiride with inadequate triple combination therapy regimens of glimepiride, sitagliptin and metformin. We enrolled 59 subjects (men 28, women 31, mean age 57 ± 11 yr) with type 2 diabetes, who visited Huh's Diabetes Center from 2013 to 2014. Insulin sensitivity was directly assessed by short insulin tolerance test as a rate constant for plasma glucose disappearance (kitt, %/min) after intravenous injection of regular insulin (0.1 U/kg of b.w.).

Results: After 24 weeks treatment, the change from glimepiride (0.5-2 mg) to piogitazone (15 mg) produced a statistically significant reduction in mean HbA1c level (-1.00 ± 0.9%, P < 0.01). The proportion of treatment goal (HbA1c < 7%) was increased from 0% to 30%. The lipid profiles showed that TG level was decreased (-42.3 ± 46.6 mg/dL, P < 0.01) and HDL-cholesterol level increased (+4.4 ± 10.1 mg/dL, P < 0.01) compared with baseline. The insulin sensitivity was significantly improved (+1.119 ± 0.932 %/min, P = 0.015).

Conclusion: The change from glimepiride to pioglitazone in patients with inadequate triple combination therapy of glmepiride, sitagliptin and meformin for 24 weeks significantly improved glycemic control and showed favorable lipid profiles and insulin sensitivity in Korean subjects with type 2 diabetes mellitus.

PE-140 Therapeutics of diabetes

Effects of DPP4 inhibitor (Vildagliptin) on protection of osteoporosis in diabetic rat

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Objective: Recently incretin hormone-based therapies including glucagon-like peptide-1 (GLP-1) agonist and dipeptidylpeptidase-4 (DPP-4) inhibitors have been used as new treatment options to control glucose levels in patients with type 2 diabetes mellitus. Incretin hormone-based therapies have many beneficial effects including physiologic stimulation of insulin from beta cell and preservation of islet mass and several extra-pancreatic effects on the heart and endothelium. But the effect on bone is not exactly evaluated. The aim of the present study was to evaluate whether DPP-4 inhibitor (Vildagliptin) has the protective effect on bone in Type 2 diabetic animal model.

Methods: Male Zucker Diabetic Fatty (fa/fa) rats aged 12-week-old were randomized to 5 weeks treatment with the vildagliptin (10 mg/kg, n = 3), pioglitazone (30 mg/kg, n = 3), vildagliptin and pioglitazone (vildagliptin 10 mg/kg and pioglitazone 30 mg/kg, n = 3) or food only (control, n = 3). During the experiment, fasting blood glucose and body weight were measured twice a week. An intraperitoneal glucose tolerance test (IPGTT) (2 g/kg), intraperitoneal insulin tolerance test (IPITT) (2 U/kg), and blood sampling were carried before treatment and after 5 weeks treatment. After 5 weeks treatment, we sacrified rats and got bone under lumbar vertebrae. Bone mineral density (BMD) and bone mineral content (BMC) were analyzed by dual-energy X-ray absorptiometry (DEXA). And micro-CT was done.

Results: Vildagliptin group made no significant difference in body weight and blood glucose level compared to control group. But other two groups showed significantly increased body weight, decreased blood sugar level and improved insulin resistance. Vildagliptin group showed increased BMD, but pioglitazone group showed decreased result compared to control group. Vildagliptin and Pioglitazone group showed significant increase in BMD compared to pioglitazone group. Micro-CT analyses showed that taking of vildagliptin increased trabecular bone volume and thickness and reduced trabecular spacing.

Conclusion: Treatment with vildagliptin for 5 weeks was associated with increase of BMD in Diabetic rat. Vildagliptin may have the protection of Osteoporosis in Diabetic rat.

PE-141 Therapeutics of diabetes

GLP-1 receptor agonist, exendin-4 mediated Nrf2 nuclear translocation reduces lipotoxicity-induced fat accumulation and hepatocyte apoptosis by reducing ER stress

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Objective: Recent studies reported that exendin-4 reduces high fat diet (HFD)-induced hepatic steatosis and enhances cell survival. In addition, exendin-4 inhibits the glucolipotoxicity-induced ER stress and β-cell apoptosis. The aim of this study was to determine whether exendin-4 on reduces fatty liver and cell death through modulating ER stress.

Methods: HepG2 cells were treated with 0.5 mM palmitate with or without 10 nM exendin-4 and cell survival was measured by MTT assay. Western blots and PCR was performed. Nrf2 translocation was determined by immunofluorescene stain and Western blot with nuclear and cytoplasmic extraction. High fat diet (HFD) was fed to C57B/6J mice for 8 weeks and 20 nM/g exedin-4 was administered. Oil red O staining was used to measure liver fat loads in HepG2 cells and mouse liver. For Nrf2-siRNA transfection, the cell were transfected with Nrf2-siRNA or Nrf2-scramble siRNA for 48 h upon plating the cell in a 12-well. The transfected cells were treated with 0.5 mM palmitate with or without exendin-4 for 24 h and confirmed protein level and RNA level.

Results: Saturated fatty acid (palmitate) treatment reduced cell survival and increased CHOP and caspase-12 levels in HepG2 cells. In addition, palmitate treatment induced the activation ER stress pathway including Bip, p-PERK, p-eIF2α, IRE1α, spliced form of XBP-1, and nuclear fraction of Nrf2. Exendin-4 treatment reduced palmitate induced apoptosis and lipid load in HepG2 cells. Also, ER stress markers and nuclear form of Nrf2 were reduced by exendin-4 treatment. Compared with control mouse, HFD fed mouse liver showed increased levels of ER stress markers, including Bip, CHOP, p-PERK, p-eIF2α, IRE1α, spliced form of XBP-1, AND nuclear form of Nrf2, and liver triglyceride accumulation and exendin-4 treatment partially reversed ER stress and hepatic steatosis.

Conclusion: GLP-1 receptor agonist, Exendin-4 mediated Nrf2 nuclear translocation reduces lipotoxicity-induced fat accumulation and hepatocyte apoptosis by reducing ER stress.

PE-142 Therapeutics of diabetes

Anti-diabetic effect of a novel PPARγ agonist DMDC (2',4'-Dihydroxy-6'-methoxy-3',5'-dimethylchalcone) isolated from Cleistocalyx operculatus

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Objective: It is well known that thiazolidinediones (TZDs) improve insulin resistance and increase glucose utilization in peripheral tissues. Recent studies, however revealed that TZDs increase myocardial infarction and weight gain, therefore treatment of TZDs for diabetes has been limited. Here, we investigate a novel PPARγ agonist DMDC isolated from Cleistocalyx operculatus. In this study, we examined the effects of DMDC on fatty acid oxidation, glucose transport and adipocyte differentiation.

Methods: To determine whether DMDC is an agonist of PPARγ, we examined the effect of DMDC on PPRE-tk promoter acitivity. Fatty acid oxidation assay and glucose transport assay were performed in C2C12 myotube using radio isotope C14-palmitic acid and H3-Glucose. 3T3-L1 adipocyte differentiation was determined by Oli-red-O staining after dose-dependent treatments of DMDC.

Results: Similar to rosiglitazone (one of TZDs), DMDC increased PPRE-tk promoter activity. Fatty acid oxidation was significantly increased by treatment of DMDC in myotube. Unexpectedly, DMDC totally blocked 3T3-L1 adipocyte differentiation, while rosiglitazone promoted adipogenesis.

Conclusion: DMDC has a PPARγ stimulating activity as TZDs have, however, DMDC does not induce the differentiation of fat cells. Therefore, DMDC may be useful for treatment of diabetes.

PE-143 Therapeutics of diabetes

Comparative efficacy of vildagliptin and sitagliptin with type 2 diabetes mellitus in real life clinical practice

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Objective: Previous metaanalysis study and a matching-adjusted indirect comparison of randomized trials have shown that vildagliptin 50 mg administered twice daily was associated with greater reduction of HbA1c level and fasting plasma glucose than with sitagliptin 50 mg administered once daily. These evidence on the efficacy of vildagliptin versus sitagliptin has been obtained from clinical studies, which were usually conducted in a restricted and highly regulated environment and may, thus, not necessarily reflect real life clinical practice of diabetes management. The aim of this study was to compare glycaemic control with vildagliptin 50 mg twice daily versus sitagliptin 100mg once daily with type 2 diabetes in real life clinical practice.

Methods: In this retrospective study, we retrieved data for subjects who were on twice-daily 50 mg vildagliptin or once-daily 100 mg sitagliptin on stable metformin doses for at least 6 months. The primary efficacy analysis was a comparison of the change from baseline HbA1c.

Results: A total of 104 patients were analysed. 60 patients were treated with sitagliptin and 44 were treated with vildagliptin. The mean age was 57 years (range, 34~77 years). The baseline HbA1c were 7.88 ± 1.14 (vildaglipin) and 7.72 ± 0.99% (sitagliptin). Mean changes in HbA1c following the addition of vildagliptin or sitagliptin to stable metformin therapy after 6 months were -1.27% and -1.21%, respectively. There was no statistically significant difference ($P = 0.42$).

Conclusion: Both sitagliptin and vildagliptin significantly lowered HbA1c level from baseline. But vildagliptin was not significant different on HbA1c lowering compared with sitagliptin. The study included a small number. This may have an effect on the statistical significance of the results. Also, studies have reported that compared with once-daily dosing, a significantly lower proportion of patients with twice-daily dosing reported optimal concordance. This also another reason that our results were differ from previous metaanalysis study and a matching-adjusted indirect comparison of randomized trials.

PE-144 Therapeutics of diabetes

Lobeglitazone improves the cellular dysfunction induced by glucotoxicity in target cells

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Objective: Peroxisome proliferator-activated receptor- γ (PPARγ) is the main target of the drug class of thiazolidinediones (TZDs), used in diabetes and other diseases that feature insulin resistance. The aim of this study was to assess the effect of lobeglitazone, a novel PPARγ agonist on the highly reducing sugar, 2-deoxy-D-ribose (dRib)-induced glucotoxicity in several target cells in vitro.

Methods: Adipocytes (3T3-L1), pancreatic beta cells (RIN), vascular endothelial cells (CPA), hepatocytes (HepG2), and osteoblastic cells (MC3T3-E1) were cultured with or without a PPARγ agonist, lobeglitazone in the presence of dRib. Cell viability was monitored using a cell counting kit, while the induction of apoptosis was analyzed using a cell death ELISA kit. Intracellular oxidative stress was measured by fluorometric analysis of DCFH oxidation using DCFH-DA as the probe. In addition, cell specific genes and antioxidant enzyme genes were analyzed by real-time PCR.

Results: In all five cell lines, dRib reduced cell survival dose dependently, while it markedly increased intracellular levels of reactive oxygen species (ROS), apoptosis. However, pretreatment of cells with lobeglitazone did not attenuate all the dRib-induced effects. In adipocytes, lobeglitazone stimulated cell differentiation and gene expression (adiponectin, PPARγ and antioxidant enzyme). In pancreatic beta cells, lobeglitazone stimulated insulin secretion and expression of insulin gene and PDX-1 gene. In vascular endothelial cells, lobeglitazone improved the gene expression of cell adhesion molecules (ICAM, E-selectin) and MCP-1. In hepatocytes, lobeglitazone improved the gene expression of antioxidant enzymes and hepatocyte specific genes, such as SREBP-1c and FAS. In osteoblastic cells, lobeglitazone improved the gene expression of cell differentiation (collagen, osteocalcin) and antioxidant enzymes (SOD1and GPX1).

Conclusion: Lobeglitazone showed the improvement of cellular dysfunction induced by glucotoxiciy in target cells. The results support a potential role of lobeglitazone in treating type 2 diabetes.

PE-145 Therapeutics of diabetes

Anti-diabetic effect of evogliptin, a novel DPP4 inhibitor, in overt hyperglycemic, hypertriglycemic, and insulin-resistant mice

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Objective: Evogliptin is a novel and potent dipeptidyl peptidase4 (DPP4) inhibitor under the late stage development for the treatment of type 2 diabetes. Several DPP4 inhibitors were studied on the long-term antidiabetic efficacy using high-fat diet (HFD) and streptozotocin (STZ)-induced diabetic mice, which appear overt hyperglycemia and hypertriglycemia. In this study, we aimed to investigate long-term efficacy and the pancreatic role in HFD/STZ mice.

Methods: In this study, we aimed to investigate long-term efficacy and the pancreatic role in HFD/STZ mice. For this study, hyperglycemic, hypertriglycemic and insulin-resistant HFD/STZ mice were selected at three weeks after STZ injection. Evogliptin was given to mice as a drug-diet admixture as 0.1% and 0.3% for 100 mg/kg and 300 mg/kg, respectively.

Results: After 10-week-treatment, 0.3% evogliptin significantly lowered non-fasting blood glucose levels, and improved impaired glucose tolerance and insulin resistance as well. Alteration of plasma biochemical parameters and pancreatic structure after evogliptin treatment also supported this result. Then the contribution of pancreatic role in early glucose control of evogliptin was further studied in 2-week-treated HFD/STZ mice. Blood glucose was significantly lower than that of HFD/STZ control with significant alteration in plasma GLP-1 and lipid parameters. Although increased PDX-1 expression was observed in pancreas, relative beta cell area was not significantly altered by treatment yet.

Conclusion: These results suggested that the preservation of pancreatic beta cells mainly contribute to the long-term efficacy of evogliptin.

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