

Department of Internal Medicine

Division of Diabetes, Metabolism and Endocrinology

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General Summary

We see over 15,000 patients a month in our department, and the numbers of patients are increasing every year. We mainly see patients with diabetes (including 10% of Type1 diabetes) as well as endocrinological disorders.

Clinically, we attempt to provide best healthcare to our patients with research evidence, clinical expertise, and patients' preferences. To accomplish this goal, we encourage the members of our division to perform basic and clinical research of high quality. With respect to education, we accept international students from other institutions. We conduct our trainees to improve their presentation skills. Finally, we strongly encourage our investigators to write manuscripts.

Research Activities

Diabetic complications

1. Molecular mechanisms governing intracellular signal transduction focusing on cell types relevant to diabetic complications
2. Roles of small GTP-binding protein Rho and Rho-kinase in renal, retinal, neuronal, and endothelial biology
3. Isoform-specific roles of Rho-kinase in pathogenesis of diabetic complications. Approaches to this study range from in vitro to in vivo using gene-targeting approaches in mice

Epidemiology

1. Clinical trials of the treatment with diabetic patients using continuous glucose monitoring (CGM) and Flash Glucose Monitoring (FGM)
2. A nationwide epidemiologic study of mortality in approximately 3,500 patients with type 1 diabetes was started in 1986 and has continued to provide much information about the prognosis of Japanese children with type 1 diabetes
3. A population-based study of childhood obesity and insulin resistance as well as diabetes in elderly and genetic factors has also continued in Niigata Prefecture
4. Epidemiological study using data consisted of more than 6,000 individuals with diabetes from 4 Jikei University hospitals

Molecular biology for pancreatic islets

Type 2 diabetes is known as a “bi-hormonal disorder” due to the dysregulated insulin and glucagon secretion. Reduced β cell mass is a major cause of dysregulated insulin secretion. Although a combination of high glucose and elevated FFAs (glucolipototoxicity) strongly induces β cell dysfunction and cell death, the underlying cause remains unclear. In addition, precise molecular mechanism of glucagon in α cells remains unclear. We found that serine/threonine kinase protein kinase c (Pkc) δ is involved in β cell death and glucagon secretion from α cells. Ongoing projects are as following.

1. Molecular mechanisms of Pkc δ -dependent β cell mass reduction under conditions glucolipototoxicity using β cell specific Pkc δ knockout mice and insulin-secreting mouse insulinoma (MIN6) cell line
2. Involvement of Pkc δ -pancreatic duodenal homeobox 1 (Pdx1) pathway is studied by chemically and genetically inhibition Pkc δ in MIN6 cell line
3. Molecular mechanisms of Pkc δ -dependent glucagon secretion under high glucose condition in glucagon-secreting α TC1 cell line
4. The association between Pkc δ and peptide tyrosine tyrosine signals in glucagon secretion using α TC1 cell line
5. Pkc δ function of insulin resistance in α cells is studied by chemically and genetically Pkc δ inhibition in α TC1 cell line and islets
6. To elucidate the molecular mechanism of Pkc δ *in vivo*, we are establishing α cell specific Pkc δ knockout mice
7. Physiological and histological characterization of *Prkcd* deficiency in α cell under the diabetic condition

Endocrinology

1. Basic research
 - 1) The role of 12-lipoxygenase on diabetic cardiomyopathy
 - 2) The role of BRS (baroreflex sensibility) on diabetic macroangiopathy especially effects of glycemic variability and blood pressure variability
 - 3) Effect of SGLT-2 inhibitors in diabetic model rats
 - 4) Effect of aldosterone in macula lutea degeneration
2. Clinical research
 - 1) Effect of SGLT-2 inhibitor in diabetic patients
 - 2) The role of BRS (baroreflex sensibility) on diabetic patients
 - 3) The durability of basal insulin affects day-to-day glycemic variability assessed by continuous glucose monitoring in type 2 diabetes patients
 - 4) Investigation of HbA1c, blood pressure and BW variability in type 2 diabetic patients.
 - 5) Achievement of HbA1c and Blood pressure and LDL-C goal of type diabetic patients (JDDM)

Publications

Bando H¹, Iguchi G¹, Okimura Y², Odake Y¹,
Yoshida K¹, Matsumoto R¹, Suda K¹,

Nishizawa H¹, Fukuoka H¹, Mokubo A³, Tojo K,
Maniwa Y¹, Ogawa W¹, Takahashi Y¹ (Kobe

- Univ, ²Kobe Women's Univ, ³Mokubo Clinic). A novel thymoma-associated autoimmune disease: Anti-PIT-1 antibody syndrome. *Sci Rep*. 2017; **7**: 43060.
- Shimabukuro M^{1,2}, Tanaka A³, Sata M², Dai K⁴, Shibata Y⁶, Inoue Y^{3,5}, Ikenaga H¹, Kishimoto S⁴, Ogasawara K², Takashima A², Niki T², Arasaki O⁶, Oshiro K⁷, Mori Y, Ishihara M⁸, Node K²; Collaborators on the Effect of Miglitol on Glucose Metabolism in Acute Coronary Syndrome (MACS) Study (¹Fukushima Med Univ, ²Tokushima Univ, ³Saga Univ, ⁴Hiroshima City Hosp, ⁵Miyazaki Med Assoc Hosp, ⁶Tomishiro Central Hosp, ⁷Ohama Dai-ichi Hosp, ⁸Hyogo Coll Med). α -Glucosidase inhibitor miglitol attenuates glucose fluctuation, heart rate variability and sympathetic activity in patients with type 2 diabetes and acute coronary syndrome: a multicenter randomized controlled (MACS) study. *Cardiovasc Diabetol*. 2017; **16**: 86.**
- Tsutsui K, Nemoto M**. A case of beriberi with leg edema, pleural effusion, and anemia. *Annals of Clinical Case Reports*. 2016; **1**: 1067.
- Tsutsui K, Nemoto M**. A case report of fibromyalgia. *Annals of Clinical Case Reports*. 2016; **1**: 1176.
- Nishimura R¹, Sano H, Shirasawa T², Matsudaira T, Miyashita Y, Ochiai H², Kokaze A², Tajima N, Utsunomiya K (¹Univ Pittsburgh, ²Showa Univ). Changes in the Composition of Adiponectin Fractions over a 3-Year Period in Children: A Population-Based Cohort Study. *Child Obes*. 2016; **12**: 440-5.**
- Nishimura R¹, Sano H², Onda Y, Tsujino D, Ando K, Ebara F, Matsudaira T, Ishikawa S², Sakamoto T², Tajima N, Utsunomiya K (¹Univ Pittsburgh, ²Tsunan Town Hosp). Population-based cross-sectional study on insulin resistance and insulin-secretory capacity in Japanese school children. *J Diabetes Investig*. 2017; **8**: 672-6.**
- Shirasawa T¹, Ochiai H¹, Nanri H¹, Nishimura R, Ikeda K¹, Hoshino H¹, Kokaze A¹ (¹Showa Univ). Association between distorted body image and changes in weight status among normal weight preadolescents in Japan: a population-based cohort study. *Arch Public Health*. 2016; **74**: 39.**
- Yoon KH¹, Nishimura R, Lee J², Crowe S², Salsali A³, Hach T², Woerle HJ² (¹Seoul St. Mary's Hosp, ²Boehringer Ingelheim Pharma GmbH & Co. KG, ³Boehringer Ingelheim Pharmaceuticals, Inc). Efficacy and safety of empagliflozin in patients with type 2 diabetes from Asian countries: pooled data from four phase III trials. *Diabetes Obes Metab*. 2016; **18**: 1045-9.**
- Kawanami D, Matoba K, Sango K¹, Utsunomiya K (¹Tokyo Metropolitan Institute of Medical Science). Incretin-based Therapies for Diabetic Complications: Basic Mechanisms and Clinical Evidence. *Int J Mol Sci*. 2016; **17**. pii: E1223.**
- Kawanami D, Matoba K, Utsunomiya K**. Signaling pathways in diabetic nephropathy. *Histol Histopathol*. 2016; **31**: 1059-67.
- Tsujino D, Nishimura R, Onda Y, Seo C, Ando K, Morimoto A¹, Utsunomiya K (¹Morimoto Hosp). The relationship between HbA1c values and the occurrence of hypoglycemia as assessed by continuous glucose monitoring in patients with type 1 diabetes. *Diabetol Metab Syndr*. 2016; **8**: 53.**
- Hayashino Y^{1,2}, Izumi K^{1,3}, Okamura S^{1,2}, Nishimura R¹, Origasa H^{1,4}, Tajima N¹; JDCP study group (¹The Japan Diabetes Society, ²Tenri Hosp, ³The National Center for Global Health and Medicine, ⁴Univ Toyama). Duration of diabetes and types of diabetes therapy in Japanese patients with type 2 diabetes: The Japan Diabetes Complication and its Prevention prospective study 3 (JDCP study 3). *J Diabetes Investig*. 2017; **8**: 243-9.**
- Onda Y, Nishimura R¹, Ando K, Takahashi H, Tsujino D, Utsunomiya K (¹Univ Pittsburgh). Comparison of glycemic variability in Japanese patients with type 1 diabetes receiving insulin degludec versus insulin glargine using continuous glucose monitoring: A randomized, cross-over, pilot study. *Diabetes Res Clin Pract*. 2016; **120**: 149-55.**
- Onda Y, Sugihara S¹, Ogata T², Yokoya S³, Yokoyama T¹, Tajima N; Type 1 Diabetes (T1D) Study Group (¹Tokyo Women's Med Univ, ²Hamamatsu Univ, ³National Center for Child Health and Development, ⁴National Institute of Public Health). Incidence and prevalence of childhood-onset Type 1 diabetes in Japan: the T1D study. *Diabetic Medicine*. 2017; **34**: 909-15.**
- Takahashi H, Nishimura R¹, Onda Y, Ando K, Tsujino D, Utsunomiya K (¹Univ Pittsburgh). Comparison of glycemic variability in Japanese patients with type 1 diabetes receiving insulin degludec versus insulin detemir using continuous glucose monitoring: a randomized, cross-over, pilot study. *Expert Opin Pharmacother*. 2017; **18**: 335-42.**
- Takahashi H, Nishimura R, Onda Y, Ando K, Tsujino D, Utsunomiya K**. Prediction of nocturnal hypoglycemia unawareness by fasting glucose levels or post-breakfast glucose fluctuations in patients with type 1 diabetes receiving insulin degludec: A pilot study. *PLoS One*. 2017; **12**: e0177283.
- Suzuki R, Hayashi T, Asano H, Ohashi K, Sakamoto M, Tojo K, Utsunomiya K**. Prolonged QT Intervals in Isolated ACTH Deficiency: Case Report and Mini Review of Literature. *J Steroids Horm Sci*. 2016; **7**: 2.