

Department of Internal Medicine

Division of Diabetes, Metabolism and Endocrinology

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General Summary

Physicians should practice patient-oriented medicine based on the concept of evidence-based medicine, which consists of research evidence, clinical expertise, and patients' preferences. To accomplish this goal, we encourage the members of our staff to do basic and clinical research. Areas of research include diabetes, metabolism, and endocrinology.

Research Activities

Epidemiology and evidence-based medicine

A nationwide epidemiologic study of mortality in approximately 1,500 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. A population-based interventional study of childhood obesity and glucose intolerance has also continued. Several clinical trials of the treatment of type 2 diabetes using continuous glucose monitoring are being performed.

Molecular diabetology and regenerative medicine

Increased cellular injury and reduced capacity in regeneration are novel therapeutic targets in diabetes. Our study group has succeeded in direct in vivo transfer of the CKD4 gene, a cell-cycle regulator. We have confirmed that regulated proliferation of mature beta cells results in restoration of glucose metabolism in diabetic mice. The result was presented in the 44th annual meeting of the European Association for the Study of Diabetes.

Our study group also has focused on the genetic epidemiology of the development of diabetes and its complications. This year a protocol was prepared for a new prospective study in a specific cohort with diabetes-susceptibility genes that have been identified with the genome-wide screening.

Insulin resistance and obesity

A series of basic research studies of insulin resistance were performed in Otsuka Long-Evans Tokushima Fatty rats. The effects of a new oral hypoglycemic agent (an inhibitor of dipeptidyl peptidase IV) on insulin resistance were investigated.

Dietary therapy

A highly monounsaturated enteral formula suppressed postprandial hyperglycemia without exaggerated insulin secretion better than did a high-carbohydrate enteral formula in patients with type 2 diabetes mellitus and in healthy subjects. Continuous glucose monitoring showed that a highly monounsaturated enteral formula significantly suppressed postprandial hyperglycemia and markedly reduced the 24-hour glycemic variations in patients with type 2 diabetes receiving tube feeding.

Diabetic vascular complications

Research has focused on the pathogenesis and treatment of diabetic vascular complications. Clinical studies have examined dietary therapy for type 2 diabetes. Experimental studies using vascular endothelial cells, mesangial cells, neural cells, and retinal pericytes have investigated the role of Krüppel-like factor 2, Rho/Rho-kinase, and the peroxisomal proliferator-activated receptor α -mediated signaling pathway in the pathogenesis of diabetic vascular complications and have provided evidence that these molecules are potential pharmacological targets in the treatment of diabetic vascular injury.

Endocrinology

The effect of azelnidipine, a unique dihydropyridine calcium-channel blocker, on aldosterone synthesis was evaluated in NCI-H295R, a human adrenocortical cell line. The involvement of corticotropin-releasing hormone receptor signaling against vascular inflammatory stress was evaluated using human aortic endothelial cells.

The potential role of cardiovascular stress in the regulation of the urocortin-corticotropin-releasing hormone receptor system was evaluated in HL-1 cardiomyocytes. Immunohistochemical analysis of resected tumor specimens obtained from patients with Cushing disease and subclinical Cushing disease was performed to evaluate the expression of 11β -hydroxysteroid dehydrogenase types 1 and 2 and glucocorticoid receptor. DNA molecular typing was performed in 2 cases of familial Graves disease associated with type 1 diabetes with strikingly homologous clinical features.

Publications

Barengo NC, Katoh S, Moltchanov V, Tajima N, Tuomilehto J. The diabetes-cardiovascular risk paradox: results from a Finnish population-based prospective study. *Eur Heart J* 2008; **29**: 1889-95.

Yokoyama J, Someya Y, Yoshihara R, Ishii H. Effects of high-monounsaturated fatty acid enteral formula versus high-carbohydrate enteral formula on plasma glucose concentration and insulin secretion in healthy individuals and diabetic patients. *J Int Med Res* 2008; **36**: 137-46.

Nemoto M, Sasaki T, Fujimoto K, Hiki Y, Nakai N, Ohashi T, Eto Y, Tajima N. Epistatic interaction of LPL and PPAR γ genes in adipocytes by exposure to dioxin. *Jikeikai Med J* 2008; **55**:

19-24.

Nishimura R, Tsujino D, Taki K, Morimoto A, Tajima N. Does HbA1c represent a valid index for tight control of glucose in type 1 diabetes? *Diabetes Res Clin Pract* 2008; **82**: e23-4.

Sakamoto N, Tojo K, Saito T, Fujimoto K, Isaka T, Tajima N, Ikeda K, Yamada H, Furuta N, Sasano H. Coexistence of aldosterone-producing adrenocortical adenoma and pheochromocytoma in an ipsilateral adrenal gland. *Endocr J* 2009; **56**: 213-9.

Ebisawa T, Tojo K, Tajima N, Kamio M, Oki Y, Ono K, Sasano H. Immunohistochemical analysis of 11β -hydroxysteroid dehydrogenase type 2 and glucocorticoid receptor in subclinical Cush-

ing's disease due to pituitary macroadenoma. *Endocr Pathol* 2008; **19**: 252-60.

Isaka T, Ikeda K, Takada Y, Inada Y, Tojo K, Tajima N. Azelnidipine inhibits aldosterone synthesis and secretion in human adrenocortical cell line NCI-H295R. *Eur J Pharmacol* 2009; **605**: 49-52.

Morimoto A, Nishimura R, Suzuki N, Matsudaira T, Taki K, Tsujino D, Miyashita Y, Ebara F, Ishikawa S, Tajima N. Low prevalence of metabolic syndrome and its components in rural

Japan. *Tohoku J Exp Med* 2008; **216**: 69-75.

Miyashita Y, Nishimura R, Nemoto M, Matsudaira T, Kurata H, Yokota T, Yokota K, Tojo K, Utsunomiya K, Tajima N. Prospective randomized study for optimal insulin therapy in type 2 diabetic patients with secondary failure. *Cardiovasc Diabetol* 2008; **29**: 7-16.

Matoba K, Tojo K, Nemoto M, Tajima N. A case of familial Graves' disease associated with type1 diabetes. *Intern Med* 2009; **48**: 701-4.