Department of Internal Medicine
Division of Nephrology and Hypertension

Takashi Yokoo, *Professor*
Makoto Ogura, *Associate Professor*
Nobuo Tsuboi, *Associate Professor*
Yukio Maruyama, *Assistant Professor*
Yoichi Miyazaki, *Professor*
Masato Ikeda, *Associate Professor*
Ichiro Ohkido, *Assistant Professor*
Nanae Matsuo, *Assistant Professor*

General Summary

Our department is one of the largest nephrology departments in Japan and includes all subspecialties of nephrology, i.e., from early chronic kidney disease (CKD) with proteinuria to dialysis and kidney transplantation. Therefore, our research groups are investigating diverse subjects and aim to eventually find new therapeutic strategies and mechanisms of disease progression, which may help decrease the number of patients with end-stage renal diseases.

Research Activities

Studies of immunoglobulin A nephropathy
A multicenter, prospective cohort study (The Japan IgA Nephropathy Cohort Study) is currently in progress. The study will validate the effectiveness of a series of therapeutic regimens, including tonsillectomy or corticosteroid therapy or both, which is widely accepted in Japan. The post-hoc analysis of this retrospective multicenter large-scale study is in progress to validate therapies for advanced cases of immunoglobulin A nephropathy at the time of biopsy diagnosis.

Studies on total nephron number counting
We have performed stereology-based total nephron number (TNN) counting for kidneys obtained at autopsy from Japanese subjects. The study revealed that the TNN in Japanese subjects is one of the lowest nephron counts yet reported. Through the combined use of images and biopsy specimens, a study to examine TNN in clinically available settings is currently in progress.

Studies of CKD-mineral and bone disorder
We previously reported that the DNA methylation patterns in calcium sensing receptor (*Casr genes*) and vitamin D receptor (*VDR*) genes were modified in the parathyroid glands of CKD-mineral and bone disorder (MBD). We then analyze the effect of histone modification and the cell cycle in the parathyroid glands of CKD-MBD. Furthermore, we are investigating how glial cells missing 2 (gcm2 genes) in the parathyroid gland, which is the essential transcription factor for parathyroid development in terrestrial vertebrates, affects parathyroid gland function. Magnesium was associated with the suppression of vascular calcification and the mortality in patients undergoing hemodialysis (HD). On the

basis of these findings, we have shown in a prospective cohort study that proton pump inhibitor use is associated with an increased risk of hypomagnesemia in patients undergoing HD (PLOS One 2015). Furthermore, we examined the association of mortality with levels of serum total magnesium and ionized magnesium. Because glycometabolism is now attracting attention in various fields, we investigated insulin resistance in patients with CKD of stages 2 to 4. Our study clarified the association of insulin resistance and fibroblast growth factor 23 in patients with CKD. To clarify the association of insulin resistance with all-cause mortality, cardiovascular events, and CKD-MBD in patients receiving HD, we are now performing a cohort study.

Studies of peritoneal dialysis

We have reported that the prevalence of peritoneal dialysis (PD)-associated peritonitis and outcome, including patient survival and technical survival, did not differ significantly in patients receiving PD between those who have or do not have diabetes. We have reported that the lipid profile was associated with the deterioration of residual renal function in patients starting PD. We are conducting clinical research on a bicarbonate/lactate-buffered neutral PD solution, the clinical efficiency of incremental PD, and peritoneal membrane pathology. Additionally, we have started using a newer ultrafine laparoscope to evaluate peritoneal injury.

Renal protective effects of azilsartan in a rat model of adenine-induced renal failure

Although daily urinary sodium excretion was decreased in rats to which adenine was not induced, azilsartan suppressed the decreasing sodium excretion, urinary protein excretion, and sympathetic nerve activity. We found that a molecular mechanism of renal protection by azilsartan is the effect for natrium transporter.

Relationship between clinical character of primary aldosteronism and hormone kinetics of the renin-angiotensin system

To simplify the diagnosis of primary aldosteronism, we are evaluating the relationship between clinical character of primary aldosteronism and the results of several challenge tests or adrenal venous sampling.

Basic study of kidney regeneration: Regenerative potential of induced pluripotent stem cells

We generated induced pluripotent stem cells (iPSCs) from patients undergoing HD due to diabetes nephropathy and glomerulonephritis (HD-iPSCs) as representatives of CKD-iPSCs or from healthy control subjects (HC-iPSCs). The HD-iPSCs differentiated into nephron progenitor cells (NPCs) with similar efficiency to HC-iPSCs. Additionally, HD-iPSC-derived NPCs expressed comparable levels of NPC markers and differentiated into vascularized glomeruli upon transplantation into mice, as HC-iPSC-derived NPCs. Our results indicate the potential of HD-iPSCs as a source of cells for kidney regeneration.

Publications

Nakashima A, Yokoyama K, Kawanami D, Ohkido I, Urashima M, Utsunomiya K, Yokoo T. Association between resistin and fibroblast growth factor 23 in patients with type 2 diabetes mellitus. *Sci Rep.* 2018; **8:** 13999.

Tajiri S, Yamanaka S, Fujimoto T, Matsumoto K, Taguchi A, Nishinakamura R, Okano HJ, Yokoo T. Regenerative potential of induced pluripotent stem cells derived from patients undergoing haemodialysis in kidney regeneration. *Sci Rep.* 2018; **8:** 14919.

Amano H, Fukuda Y, Yokoo T, Yamaoka K. Interleukin-6 Level among Shift and Night Workers in Japan: Cross-Sectional Analysis of the J-HOPE Study. *J Atheroscler Thromb.* 2018; **25:** 1206-14.

Okabayashi Y, Tsuboi N, Amano H, Miyazaki Y, Kawamura T, Ogura M, Narita I, Ninomiya T, Yokoyama H, Yokoo T. Distribution of nephrologists and regional variation in the clinical severity of IgA nephropathy at biopsy diagnosis in Japan: a cross-sectional study. *BMJ Open.* 2018; **8:** e024317.

Katsuma A, Nakada Y, Yamamoto I, Horita S, Furusawa M, Unagami K, Katsumata H, Okumi M, Ishida H, Yokoo T, Tanabe K. Long-term survival in Japanese renal transplant recipients with Alport syndrome: a retrospective study. *BMC Nephrol.* 2018; **19:** 249.

Yamamoto I, Yamakawa T, Katsuma A, Kawabe M, Katsumata H, Hamada AM, Nakada Y, Kobayashi A, Yamamoto H, Yokoo T. Recurrence of native kidney disease after kidney transplantation. *Nephrology (Carlton).* 2018; **23:** 27-30.

Katsuma A, Nakada Y, Yamamoto I, Horita S, Katsumata H, Kobayashi A, Unagami K, Okumi M, Ishida H, Yokoo T, Yamaguchi Y, Tanabe K. Clinicopathological study of de novo membranous nephropathy of 'stage 0' after kidney transplantation. *Nephrology (Carlton)*. 2018; **23:** 63-9.

Hamada AM, Yamamoto I, Kawabe M, Katsumata H, Yamakawa T, Katsuma A, Nakada Y, Kobayashi A, Koike Y, Miki J, Yamada H, Kimura T, Tanno Y, Ohkido I, Tsuboi N, Yamamoto H, Yokoo T. Clinicopathological features and outcomes of kidney allografts in plasma cell-rich acute rejection: A case series. *Nephrology (Carlton).* 2018; **23:** 22-6.

Yamakawa T, Kobayashi A, Yamamoto I, Kawaguchi T, Imasawa T, Aoyama H, Akutsu N, Maruyama M, Saigo K, Yokoo T, Kitamura H. Impact of primary diabetic nephropathy on arteriolar hyalinosis lesions in patients following kidney transplantation. *Nephrology (Carlton).* 2018; **23:** 70-5.

Sagasaki M, Nakada Y, Yamamoto I, Kawabe M, Yamakawa T, Katsumata H, Mafune A, Katsuma A, Kobayashi A, Koike K, Koike Y, Miki J, Yamada H, Kimura T, Tanno Y, Ohkido I, Tsuboi N, Yamamoto H, Yokoo T. Antibody-mediated rejection due to anti-HLA-DQ antibody after pregnancy and delivery in a female kidney transplant recipient. *Nephrology (Carlton).* 2018; **23:** 81-4.

Ueda H, Miyazaki Y, Tsuboi N, Hirano K, Yokote S, Kobayashi E, Ogura M, Kawamura T, Ryuzaki M, Yokoo T. Clinical and Pathological Characteristics of Elderly Japanese Patients with IgA Vasculitis with Nephritis: A Case Series. *Intern Med.* 2018; **58:** 31-8.

Amano H, Kobayashi S, Terawaki H, Ogura M, Kawaguchi Y, Yokoo T. Measurement of daily sodium excretion in patients with chronic kidney disease; special reference to the difference between the amount measured from 24 h collected urine sample and the estimated amount from a spot urine. *Ren Fail.* 2018; **40:** 238-42.

Okabe M, Takamura T, Tajiri A, Tsuboi N, Ishikawa M, Ogura M, Ohashi R, Oda T, Yokoo T. A case of infection-related glomerulonephritis with massive eosinophilic infiltration. *Clin Nephrol.* 2018; **90:** 142-7.

Honda K, Kobayashi A, Niikura T, Hasegawa T, Saito Z, Ito S, Sasaki T, Komine K, Ishizuka S, Motoi Y, Kubota T, Yamamoto H, Yokoo T. Neutropenia related to an azathioprine metabolic disorder induced by an inosine triphosphate pyrophosphohydrolase (ITPA) gene mutation in a patient with PR3-ANCA-positive microscopic polyangiitis. *Clin Nephrol.* 2018; **90:** 363-9.

Okabayashi Y, Tsuboi N, Nakaosa N, Haruhara K, Kanzaki G, Koike K, Shimizu A, Fukui A, Okonogi H, Miyazaki Y, Kawamura T, Ogura M, Shimizu A, Yokoo T. A Case of Hepatic Glomerulosclerosis with Monoclonal IgA1-κ Deposits. *Case Rep Nephrol.* 2018; **2018**: 4748357.

Sasaki T, Okabe M, Tosaki T, Honda Y, Ishikawa M, Tsuboi N, Yokoo T. Proteinuric glomerulopathy in an adolescent with a distal partial trisomy chromosome 1. *CEN Case Rep.* 2018; **7:** 253-8.

Sasaki T, Tsuboi N, Haruhara K, Okabayashi Y, Kanzaki G, Koike K, Kobayashi A, Yamamoto I, Ogura M, Yokoo T. Bowman Capsule Volume and Related Factors in Adults With Normal Renal Function. *Kidney Int Rep.* 2018; **3:** 314-20.

Okabe M, Motojima M, Miyazaki Y, Pastan I, Yokoo T, Matsusaka T. Global polysome analysis of normal and injured podocytes. *Am J Physiol Renal Physiol.* 2019; **316:** F241-52.

Haruhara K, Tsuboi N, Sasaki T, Amano H, Tanaka M, Koike K, Kanzaki G, Okabayashi Y, Miyazaki Y, Ogura M, Yokoo T. Volume Ratio of Glomerular Tufts to Bowman Capsules and Renal Outcomes in Nephrosclerosis. *Am J Hypertens.* 2019; **32:** 45-53.

Yamada T, Tatsumi N, Anraku A, Suzuki H, Kamejima S, Uchiyama T, Ohkido I, Yokoo T, Okabe M. Gcm2 regulates the maintenance of parathyroid cells in adult mice. *PLoS One.* 2019; **24:** e0210662.

Katsumata H, Ikemiyagi M, Hirai T, Kanzawa T, Ishii R, Miyairi S, Fukuda H, Saiga K, Okumi

M, Ishii Y, Yokoo T, Tanabe K. Impact of activated invariant natural killer T cells on the expansion of regulatory T cell precursors in murine thymocytes in vitro. *Immunol Lett.* 2019; **206:** 41–8.

Okonogi H, Kawamura T, Joh K, Koike K, Miyazaki Y, Ogura M, Tsuboi N, Hirano K, Matsushima M, Yokoo T, Horikoshi S, Suzuki Y, Yasuda T, Shirai S, Shibata T, Hattori M, Akioka Y, Katafuchi R, Hashiguchi A, Hisano S, Shimizu A, Kimura K, Maruyama S, Matsuo S, Tomino Y. A grading system that predicts the risk of dialysis induction in IgA nephropathy patients based on the combination of the clinical and histological severity. *Clin Exp Nephrol.* 2019; **23:** 16–25.

Ogawa K, Hirano K. Warning from constricted and wrinkled internal jugular vein. *Clin Exp Nephrol.* **23**: 285–6.

Kishida K, Maruyama Y, Asari K, Nakao M, Matsuo N, Tanno Y, Ohkido I, Ikeda M, Yokoyama K, Yokoo T. Clinical outcome of incident peritoneal dialysis patients with diabetic kidney disease. *Clin Exp Nephrol.* 2019; **23:** 409–14.

Reviews and Books

Maruyama Y. Does Combined Therapy with Peritoneal Dialysis and Hemodialysis Improve Prognosis? *Contrib Nephrol.* 2018; **196:** 64–70.

Kanzaki G, Okabayashi Y, Nagahama K, Ohashi R Tsuboi N, Yokoo T, Shimizu A. Monoclonal Immunoglobulin Deposition Disease and Related Diseases. *J Nippon Med Sch.* 2019; **96:** 2–9.