

Department of Pathophysiology and Therapy in Chronic Kidney Disease

Tatsuo Hosoya, *Professor*
Iwao Ohno, *Professor*
Yukio Maruyama, *Assistant Professor*

Satoru Kuriyama, *Professor*
Kimiyoichi Ichida, *Professor*

General Summary

Overview of education and research

This department aims to advance education and research to prevent the onset and development of chronic kidney disease (CKD) and to slow the increase in the number of patients with renal failure. The number of elderly patients undergoing hemodialysis (HD) for renal failure has increased markedly in Japan and has become a critical social and medical economic problem. One solution for this problem is to prevent the onset and progression of CKD and to reduce the number of patients requiring HD.

Another solution is to improve the quality of life for the rehabilitation of patients who have already undergone HD and to promote home HD (HHD) and continuous ambulatory peritoneal dialysis (CAPD) that can be performed at home. Both HHD and CAPD will greatly benefit patients undergoing HD, particularly patients who have difficulty visiting hospitals because of old age or disability. Furthermore, when the Great East Japan Earthquake occurred, it was shown that CAPD could be performed in disaster areas.

Research Activities

Prevention of CKD and its progression

Hyperuricemia has long been suggested to be a risk factor for the onset and progression of CKD, but definitive evidence was lacking, because an antihyperuricemic agent that could reduce uric acid levels effectively and safely in patients with renal dysfunction, such as CKD, was not available. Within the last 3 years, 2 novel antihyperuricemic agents that can be used effectively and safely in patients with renal dysfunction have been developed. The efficacy and safety of one agent, febuxostat, were investigated in patients with CKD IIIb and IV and reported at academic meetings and in a paper. Furthermore, a double-blind multicenter prospective clinical trial (FEATHER study: Febuxostat versus placebo randomized controlled trial regarding reduced renal function in patients with hyperuricemia complicated by chronic kidney disease stage 3) is in progress with more than 400 patients with CKD IIIa, b and the publication is on going.

The utility and safety of topiroxostat, another novel antihyperuricemic agent, was investigated in patients with CKD III and hyperuricemia, and its effects on renal function, blood pressure, and albuminuria were examined. The result that albuminuria decreased significantly in patients receiving topiroxostat was reported in a paper. The underlying mechanism of reduced albuminuria is being investigated in basic research, and the effect is being confirmed separately in a panel of primary diseases for renal failure. Furthermore, a

randomized clinical trial to examine the effect of urinary protein loss caused by diabetic nephropathy is in progress.

Efforts to promote CAPD

To promote CAPD, a method of HHD, our department has employed peritoneal dialysis coordinators and had them visit the homes of patients undergoing CAPD to solve the problems presented by the patients and their families. The patients were then asked to answer a questionnaire survey about CAPD; the results were analyzed and presented at academic meetings. Because we believe that HHD by CAPD cannot be promoted without the cooperation of nursing care facilities and health and welfare facilities, CAPD study meetings have been held periodically with colleagues in such facilities near Kashiwa Hospital.

Combination therapy with HD once a week has been tried in patients undergoing CAPD with disturbed peritoneal function or insufficient water removal. A retrospective study and a prospective study (EARTH Study: The study of evaluating adequateness replacement therapy) are ongoing as multicenter collaborative studies to elucidate the effectiveness of the combination therapy. The retrospective study has already been completed and is being prepared for publication, while the prospective study is fixed cases and the publication is ongoing.

Check-up and evaluation

Research regarding the onset and development of hyperuricemia and CKD is ongoing. The analysis of the FEATHER study will be completed in March 2016, and a manuscript is being prepared. That topiroxostat reduces albuminuria similarly in a variety of renal diseases has been verified and reported in a paper. Experiments are in progress to elucidate the underlying mechanism in basic studies.

While CAPD has been promoted in patients with renal failure at the Department of Nephrology and Hypertension of our medical school, we hope other institutions will participate in this project and help establish the clinical efficacy of PD and HD combined therapy. To this end, we would like to make proposals for fulfillment of the systems for patients undergoing CAPD, such as medical insurance and nursing care insurance.

Publications

Kuriyama S, Maruyama Y, Nishio S, Takahashi Y, Kidoguchi S, Kobayashi C, Takahashi D, Sugano N, Hosoya T, Yokoo T. Serum uric acid and the incidence of CKD and hypertension. *Clin Exp Nephrol.* 2015; **19**: 1127-34.

Mitarai T¹, Iwano M², Shiiki H³, Muso E⁴, Yumura W⁵, Kimura K⁶, Kawamura T, Hosoya T, Utsunomiya Y⁷, Yorioka N⁸, Furusu A⁹, Miyazaki M¹⁰, Tomino Y¹¹, Hiki Y¹², Matsumura O¹, Ando T¹³ (¹Saitama Med Univ, ²Univ Fukui, ³Uda City Hosp, ⁴Kitano Hosp, ⁵Int Univ Hlth Welfare Hosp, ⁶St. Marianna Univ Sch Med, ⁷Hoya Hosp, ⁸Hiroshima Kidney Org, ⁹Wajinkai Hosp, ¹⁰Miyazaki Med Clin, ¹¹Juntendo Univ Sch Med, ¹²Fujita Hlth Univ Sch Med, ¹³Jpn

Clin Res Support Unit). Prospective randomized trial of treatment for adult patients with intermediate-severity IgA nephropathy using multiple-drug combined therapy with or without Mizoribine (MZB). *Shinyaku to Rinsho.* 2015; **64**: 3-15.

Yamamoto T¹, Hidaka Y², Inaba M³, Ishimura E³, Ooyama H⁴, Kakuta H⁵, Moriwaki Y¹, Higami K⁶, Ohtawara A⁷, Hosoya T, Nishikawa H, Taniguchi A⁸, Ueda T⁹, Yamauchi T⁹, Fujimori S¹⁰, Mineo I¹¹, Yamanaka H⁸ (¹Hyogo Univ, ²Asakusa Cent Clin, ³Osaka City Univ, ⁴Ryogoku East Gate Clin, ⁵Kakuda Clin, ⁶Higami Hospl, ⁷Sanin Rosai Hosp, ⁸Tokyo Women's Med Univ, ⁹Univ Fukui Fac Med Sci, ¹⁰Teikyo Univ, ¹¹Toyonaka City Hosp). Effects of

febuxostat on serum urate level in Japanese hyperuricemia patients. *Mod Rheumatol*. 2015; **25**: 779-83.

Matsuo N, Yokoyama K, Tanno Y, Yamamoto I, Yokoo T. Combined therapy using peritoneal dialysis and hemodialysis may increase the indications for peritoneal dialysis in the United State. *Kidney Int*. 2015; **87**: 1259-60.

Fujimoto T, Nakada Y, Yamamoto I, Kobayashi A, Tanno Y, Yamada H, Miki J, Ohkido I, Tsuboi N, Yamamoto H, Yokoo T. A refractory case of subclinical antibody-mediated rejection due to anti-HLA-DQ antibody in a kidney transplant patient. *Nephrology (Carlton)*. 2015; **20** Suppl 2: 81-5.

Takamura T, Yamamoto I, Nakada Y, Katsumata H, Yamakawa T, Furuya M, Mafune A, Kobayashi A, Tanno Y, Miki J, Ohkido I, Tsuboi N, Yamamoto H, Yokoo T. Acute T cell-mediated rejection accompanied by C4d-negative acute antibody-mediated rejection and cell debris in tubulus: A case report. *Nephrology (Carlton)*. 2015; **20** Suppl 2: 70-4.

Yamakawa T, Kobayashi A, Yamamoto I, Nakada Y, Mafune A, Katsumata H, Furuya M, Koike K, Miki J, Yamada H, Tanno Y, Ohkido I, Tsuboi N, Yokoyama K, Yamamoto H, Yokoo T. Clinical and pathological features of donor/recipient body weight mismatch after kidney transplantation. *Nephrology (Carlton)*. 2015; **20** Suppl 2: 36-9.

Kobayashi A, Yamamoto I, Katsumata H, Yamakawa T, Mafune A, Nakada Y, Koike K, Mitome J, Miki J, Yamada H, Tanno Y, Ohkido I, Tsuboi N, Yokoyama K, Yamamoto H, Yokoo T. Change in glomerular volume and its clinicopathological impact after kidney transplantation. *Nephrology (Carlton)*. 2015; **20** Suppl 2: 31-5.

Yokoyama K, Nakashima A, Maruyama Y, Ohkido I, Yokoo T. Does bone structure accurately reflect serum FGF23 levels in patients with chronic kidney disease? *Kidney Int*. 2015; **88**: 640.

Nakashima A, Ohkido I, Yokoyama K, Mafune A, Urashima M, Yokoo T. Proton pump inhibitor use and magnesium concentrations in hemodialysis patients: a cross-sectional study. *PLoS One*. 2015; **10**: e0143656.

Maruyama Y, Yokoyama K, Yokoo T, Shigematsu T, Iseki K, Tsubakihara Y (Jpn Soc Dialysis Ther). The different association between serum ferritin and mortality in hemodialysis and peritoneal dialysis patients using Japanese Nationwide Dialysis Registry. *PLoS One*. 2015; **10**: e0143430.

Mafune A, Iwamoto T, Tsutsumi Y (Jichi Med Univ), Nakashima A, Yamamoto I, Yokoyama K, Yokoo T, Urashima M. Associations among serum trimethylamine-N-oxide (TMAO) levels, kidney function and infarcted coronary artery number in patients undergoing cardiovascular surgery: a cross-sectional study. *Clin Exp Nephrol*. 2016; **20**: 731-9. Epub 2015 Dec 16.

Ikeda M, Nakao M, Hirano K, Yokoyama K,

Yokoo T, Joki N¹, Ando R², Shinoda T³, Inaguma D⁴, Yamaka T⁵, Komatsu Y⁶, Koike F⁷, Sakaguchi T⁸, Negi S⁹, Shigematsu T⁸ (Toho Univ, ²Musashino Red Cross Hosp, ³Kawakita General Hosp, ⁴Nagoya Daini Red Cross Hosp, ⁵Tokyo Yamate Med Ctr, ⁶Saint Luke's Int Hosp, ⁷Showa Univ Fujigaoka Hosp, ⁸Wakayama Med Univ). Possible prevention of dialysis-requiring congestive heart failure by angiotensin-II receptor blockers in non-dialysis Japanese patients with Stage 5 chronic kidney disease. *J Renin Angiotensin Aldosterone Syst*. 2015; **16**: 1175-84.

Utami SB^{1,2}, Mahati E¹, Li P¹, Maharani N¹, Ikeda N¹, Bahrudin U², Munemura C¹, Hosoyamada M³, Yamamoto Y¹, Yoshida A¹, Nakayama Y¹, Higaki K¹, Nanba E¹, Ninomiya H¹, Shirayoshi Y¹, Ichida K¹, Yamamoto K¹, Hosoya T, Hisatome I¹ (Tottori Univ, ²Diponegoro Univ, ³Teikyo Univ, ⁴Tokyo Univ Pharm Life Sci). Apoptosis induced by an uromodulin mutant C112Y and its suppression by topiroxostat. *Clin Exp Nephrol*. 2015; **19**: 576-84.

Kuriyama S, Nishio S, Kidoguchi S, Honda K, Takahashi Y, Sugano N, Maruyama Y, Hosoya T, Nakano T¹, Tanabe T¹, Stim E², Yokoo T (Hlth Manage Ctr Tokyo Regio Taxation Bureau Clin, ²Emergency Assistance). A greater association of hyperuricemia than of metabolic syndrome with the new incidence of chronic kidney disease. *Open J Nephrol*. 2016; **6**: 17-27. Epub 2016 Mar 30.

Nakao M, Yamamoto I, Maruyama Y, Nakashima A, Matsuo N, Tanno Y, Ohkido I, Ikeda M, Yamamoto H, Yokoyama K, Yokoo T. 33years of peritoneal dialysis-associated peritonitis: a single-center study in Japan. *Ther Apher Dial*. 2016; **20**: 60-5.

Yokoyama K, Kurita N¹, Fukuma S², Akizawa T³, Fukagawa M⁴, Onishi Y⁵, Kurokawa K⁶, Fukuhara S¹ (Fukushima Med Univ, ²Kyoto Univ Hosp, ³Showa Univ, ⁴Tokai Univ, ⁵Inst Hlth Outcomes Proc Evaluation Res, ⁶Natl Grad Inst). Frequent monitoring of mineral metabolism in hemodialysis patients with secondary hyperparathyroidism: associations with achievement of treatment goals and with adjustments in therapy. *Nephrol Dial Transplant*. Epub 2016 Mar 3. Epub ahead of print.

Reviews and Books

Nakashima A, Yokoyama K, Yokoo T, Urashima M. Role of vitamin D in diabetes mellitus and chronic kidney disease. *World J Diabetes*. 2016; **7**: 89-100.

Maruyama Y, Yokoyama K. Clinical efficacy of combined therapy with peritoneal dialysis and hemodialysis. *Renal Replacement Therapy*. 2016; **2**: 11.

Hosoya T. Asymptomatic Hyperuricemia. *Journal of General and Family Medicine*. 2016; **17**: 71-6.