Department of Pathophysiology and Therapy in Chronic Kidney Disease

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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 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 be 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 IIIab and hyperuricemia.

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.

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 (The study of evaluating adequateness replacement therapy: EARTH Study) are ongoing as multicenter collaborative studies to elucidate effectiveness of the combination therapy.

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 2 years, and a manuscript is being prepared. It is necessary to verify whether topiroxostat reduces albuminuria similarly in a variety of renal diseases and 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 status of PD coordinators. 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, Sugano N, Takane K, Kobayashi A, Otsuka Y, Hosoya T. Intensive antihypertensive treatment with angiotensin receptor blocker combined with hydrocholorthiazide reduces urinary angiotensinogen in patients with type 2 diabetes mellitus. *Open J Nephrol.* 2013; **3:** 89-96.

Matsuo H[1], Ichida K[2], Takada T[3], Nakayama A[1], Nakashima H[1] , Nakamura T[1], Kawamura Y[1], Takada Y[1], Yamamoto K[4], Inoue H[1], Oikawa Y[5], Naito M[6], Hishida A[6], Wakai K[6], Okada C[1], Shimizu S[1], Sakiyama M[1], Chiba T[1], Ogata H[1], Niwa K[5], Hosoyamada M[7], Mori A[8], Hamajima N[6], Suzuki H[3], Kanai Y[9], Sakurai Y[1], Hosoya T, Shimizu T[10], Shinomiya N[1] ([1]Nat Defense Med Coll, [2]Tokyo Univ Pharm Life Sci, [3]Univ Tokyo, [4]Kyushu Univ, [5]Toho Univ, [6]Nagoya Univ, [7]Teikyo Univ, [8]Seirei Prevent Health Care Ctr, [9]Osaka Univ, [10]Midorigaoka Hosp). Common dysfunctional variants in ABCG2 are a major cause of early-onset gout. *Sci Rep.* 2013; **3:** 2014.

Yokoyama K, Taniguchi M[1], Fukagawa M[2] ([1]Kyushu Univ, [2]Tokai Univ). A Japanese approach for CKD-MBD. *Kidney Int Suppl (2011).* 2013; **3:** 451-6.

Maruyama Y, Taniguchi M[1], Kazama JJ[1], Yokoyama K, Hosoya T, Yokoo T, Shigematsu T[2], Iseki K[1], Tsubakihara Y[1] ([1]Jpn Soc Dialysis Ther, [2]Wakayama Med Univ). A higher serum alkaline phosphatase is associated with the incidence of hip fracture and mortality among patients receiving hemodialysis in Japan. *Nephrol Dial Transplant.* 2014; **29:** 1532-8. Epub 2014 Mar 18.

Watanabe K, Yokoyama K, Yoshida H, Tanno Y, Ohkido I, Yokoo T. Chest X-ray may serve as a screening examination for coronary artery calcification in dialysis patients. *Kidney Int.* 2014; **85:** 710.

Sugano N, Yokoyama K, Kato N[1], Hara Y, Endo S, Mitome J, Kin T[2], Tokudome G[3], Kuriyama S, Hosoya T, Yokoo T ([1]Shinagawa Jin Clin, [2]Kawagoe Ekimae Clin, [3]Tokyu Hosp).

Monitoring of body water composition by the simultaneous use of bioelectrical impedance analysis and Crit-LineR during hemodialysis. *Clin Exp Nephrol.* 2014 Feb 12. Epub ahead of print.

Kobayashi S, Ogura M, Hosoya T. Acute neutropenia associated with initiation of febuxostat therapy for hyperuricaemia in patients with chronic kidney disease. *J Clin Pharm Ther.* 2013; **38:** 258-61.

Tsuboi N, Utsunomiya Y, Hosoya T. Obesity-related glomerulopathy and the nephron complement. *Nephrol Dial Transplant.* 2013; **28** Suppl4: iv108-13.

Terawaki H[1], Yamagishi S[2], Funakoshi Y[3], Matsuyama Y[4], Terada T[1], Nakayama K[5], Ogura M, Hosoya T, Ito S[5], Era S[4], Nakayama M[1] ([1]Fukushima Med Univ, [2]Kurume Univ, [3]Funakoshi Clin, [4]Gifu Univ, [5]Tohoku Univ). Pigment epithelium-derived factor as a new predictor of mortality among chronic kidney disease patients treated with hemodialysis. *Ther Apher Dial.* 2013; **17:** 625-30.

Miyazaki Y, Shimizu A, Ichikawa I[1], Hosoya T, Pastan I[2], Matsusaka T[1] ([1]Tokai Univ, [2]Nat Cancer Inst). Mice are unable to endogenously regenerate podocytes during the repair of immunotoxin-induced glomerular injury. *Nephrol Dial Transplant.* 2014; **29:** 1005-12. Epub 2013 Dec 8.

Stiburkova B[1], Sebesta I[1], Ichida K[2], Nakamura M[2], Hulkova H[1], Krylov V[3], Kryspinova L, Jahnova H[1] ([1]Charles Univ, [2]Tokyo Univ Pharm Life Sci, [3]Univ Coll London). Novel allelic variants and evidence for a prevalent mutation in URAT1 causing renal hypouricemia: biochemical, genetics and functional analysis. *Eur J Hum Genet.* 2013; **21:** 1067-73.

Zeniya M, Nakano M, Saeki C, Yokoyama K, Ishikawa T[1], Takaguchi K[2], Takahashi H ([1]Saiseikai Niigata Daini Hosp, [2]Kagawa Pref Central Hosp). Usefulness of combined application of double-filtration plasmapheresis and twice-daily injections of interferon-β in hemodialysis patients with hepatitis C virus genotype 1b infection and a high viral load. *Hepatol Res.* 2014; **44:** E257-60. Epub 2013 Sep 17.

Kuriyama S, Yokoyama K, Hara Y, Sugano N, Yokoo T, Hosoya T. Effect of aliskiren in chronic kidney disease patients with refractory hypertension undergoing hemodialysis: a randomized controlled multicenter study. *Clin Exp Nephrol.* 2014; **18:** 821-30. Epub 2013 Nov 20.

Ito I[1], Waku T[2], Aoki M[1], Abe R[3], Nagai Y[3], Watanabe T[1], Nakajima Y[1], Ohkido I, Yokoyama K, Miyachi H[4], Shimizu T[2], Murayama A[1], Kishimoto H[1], Nagasawa K[3], Yanagisawa J[1] ([1]Univ Tsukuba, [2]Univ Tokyo, [3]Tokyo Univ Agric Technol, [4]Okayama Univ). A nonclassical vitamin D receptor pathway suppresses renal fibrosis. *J Clin Invest.* 2013; **123:** 4579-94.

Matsuo H[1], Nakayama A[1], Sakiyama M[1], Chiba T[1], Shimizu S[1], Kawamura Y[1], Nakashima H[1], Nakamura T[1,2], Takada Y[1], Oikawa Y[3], Takada T[4], Nakaoka H[5], Abe J[1], Inoue H[1], Wakai K[6], Kawai S[6], Guang Y[6,7], Nakagawa H[6], Ito T[1], Niwa K[3], Yamamoto K[8], Sakurai Y[1], Suzuki H[1], Hosoya T, Ichida K[9], Shimizu T[10], Shinomiya N[1] ([1]Nat Defense Med Coll, [2]RIKEN, [3]Toho Univ, [4]Univ Tokyo, [5]Nat Inst Genet, [6]Nagoya Univ, [7]Seinan Jogakuin Univ, [8]Kyushu Univ, [9]Tokyo Univ Pharma Life Sci, [10]Midorigaoka Hosp). ABCG2 dysfunction causes hyperuricemia due to both renal urate underexcretion and renal urate overload. *Sci Rep.* 2014; **4:** 3755.

Hosoya T, Ohno I, Nomura S[1], Hisatome I[2], Uchida S[3], Fujimori S[3], Yamamoto T[4], Hara S[5] ([1]Suzuka Kaisei Hosp, [2]Tottori Univ, [3]Teikyo Univ, [4]Hyogo Coll Med, [5]Toranomon Hosp). Effects of topiroxostat on the serum urate levels and urinary albumin excretion in hyperuricemic stage 3 chronic kidney disease patients with or without gout. *Clin Exp Nephrol.* 2014 Jan 22. Epub ahead of print.

Nakao M, Yokoyama K, Yamamoto I, Matsuo N, Tanno Y, Ohkido I, Hayakawa H, Ikeda M, Yamamoto H, Hosoya T. Risk factors for encapsulating peritoneal sclerosis in long-term peritoneal dialysis: a retrospective observational study. *Ther Apher Dial.* 2014; **18:** 68-73.

Hosoya T, Kimura K[1], Itoh S[2], Inaba M[3], Uchida S[4], Tomino Y[5], Makino H[6], Matsuo S[7], Yamamoto T[8], Ohno I, Shibagaki Y[1], Iimuro S[9], Imai N[1], Kuwabara M[10], Hayakawa H ([1]St. Marianna Univ Sch Med, [2]Tohoku Univ, [3]Osaka City Univ, [4]Teikyo Univ, [5]Juntendo Univ, [6]Okayama Univ, [7]Nagoya Univ, [8]Hyogo Coll Med, [9]Univ Tokyo Hosp, [10]Toranomon Hosp). The effect of febuxostat to prevent a further reduction in renal function of patients with hyperuricemia who have never had gout and are complicated by chronic kidney disease stage 3: study protocol for a multicenter randomized controlled study. *Trials.* 2014; **15:** 26.

Miyazaki Y, Shimizu A[1], Pastan I[2], Taguchi K[3], Naganuma E[3], Suzuki T[3], Hosoya T, Yokoo T, Saito A[4], Miyata T[3], Yamamoto M[3], Matsusaka T[1] ([1]Tokai Univ, [2]NIH, [3]Tohoku Univ, [4]Niigata Univ). Keap1 inhibition attenuates glomerulosclerosis. *Nephrol Dial Transplant.* 2014; **29:** 783-91. Epub 2014 Feb 11.

Kurashige M[1], Hanaoka K, Imamura M[1], Udagawa T, Kawaguchi Y[2], Hasegawa T[2], Hosoya T, Yokoo T, Maeda S[1] ([1]RIKEN, [2]Kanagawa Pref Shiomidai Hosp). A comprehensive search for mutations in the PKD1 and PKD2 in Japanese subjects with autosomal dominant polycystic kidney disease. *Clin Genet*. 2014 Mar 10. Epub ahead of print.

Yokoyama K, Akiba T[1], Fukagawa M[2], Nakayama M[3], Sawada K[4], Kumagai Y[5], Chertow GM[6], Hirakata H[7] ([1]Tokyo Women's Med Univ, [2]Tokai Univ, [3]Fukushima Med Univ, [4]Akita Univ, [5]Kitasato Univ, [6]Stanford Univ, [7]Jpn Red Cross Fukuoka Hosp). A randomized trial of JTT-751 versus sevelamer hydrochloride in patients on hemodialysis. *Nephrol Dial*

Transplant. 2014; **29:** 1053–60. Epub 2013 Dec 26.

Yokoyama K, Hirakata H[1], Akiba T[2], Fukagawa M[3], Nakayama M[4], Sawada K[5], Kumagai Y[6], Block GA[7] ([1]Jpn Red Cross Fukuoka Hosp, [2]Tokyo Women's Med Univ, [3]Tokai Univ, [4]Fukushima Med Univ, [5]Akita Univ, [6]Kitasato Univ, [7]Denver Nephrologists). Ferric itrate hydrate for the treatment of hyperphosphatemia in nondialysis-dependent CKD. *Clin J Am Soc Nephrol.* 2014; **9:** 543–52.

Iida R, Yokoyama K, Ohkido I, Tabei I, Takeyama H, Suzuki A[1], Shibasaki T[1], Matsuba D, Suda N, Hosoya T ([1]Keio Univ). Detection of dihydropyridine- and voltage-sensitive intracellular Ca^{2+} signals in normal human parathyroid cells. *J Physiol Sci.* 2013; **63:** 235–40.

Tomioka NH[1], Nakamura M[2], Doshi M[1], Deguchi Y[1], Ichida K[2], Morisaki T[3], Hosoyamada M[1] ([1]Teikyo Univ, [2]Tokyo Univ Pharm Life Sci, [3]Nat Cereb Cardiovasc Ctr Res Inst). Ependymal cells of the mouse brain express urate transporter 1 (URAT1). *Fluids Barriers CNS.* 2013; **10:** 31.

Sakiyama M[1], Matsuo H[1], Shimizu S[1], Chiba T[1], Nakayama A[1], Takada Y[1], Nakamura T[1], Takada T[2], Morita E[3], Naito M[3], Wakai K[3], Inoue H[1], Tatsukawa S[1], Sato J[1], Shimono K[4], Makino T[5], Satoh J[1], Suzuki H[2], Kanai Y[6], Hamajima N[3], Sakurai Y[1], Ichida K[7], Shimizu T[8], Shinomiya N[1] ([1]Nat Defense Med Coll, [2]Univ Tokyo Hosp, [3]Nagoya Univ, [4]Toho Univ, [5]Nagoya City Univ, [6]Osaka Univ, [7]Tokyo Univ Pharmacy Life Sci, [8]Midorigaoka Hosp). Common variant of leucine-rich repeat-containing 16A (LRRC16A) gene is associated with gout susceptibility. *Hum Cell.* 2014; **27:** 1–4.

Nakayama A[1], Matsuo H[1], Shimizu T[2], Ogata H[1], Takada Y[1], Nakashima H[1], Nakamura T[1], Shimizu S[1], Chiba T[1], Sakiyama M[1], Ushiyama C[3], Takada T[4], Inoue K[5], Kawai S[6], Hishida A[6], Wakai K[6], Hamajima N[6], Ichida K[5], Sakurai Y[1], Kato Y[2], Shimizu T[7], Shinomiya N[1] ([1]Nat Defense Med Coll, [2]Kanazawa Univ, [3]Toho Univ, [4]Univ Tokyo, [5]Tokyo Univ Pharm Life Sci, [6]Nagoya Univ, [7]Midorigaoka Hosp). Common missense variant of monocarboxylate transporter 9 (MCT9/SLC16A9) gene is associated with renal overload gout, but not with all gout susceptibility. *Hum Cell.* 2013; **26:** 133–6.

Ohno I, Hayashi H[1], Aonuma K[2], Horio M[3], Kashihara N[4], Okada H[5], Komatsu Y[6], Tamura S[7], Awai K[8], Yamashita Y[9], Kuwatsuru R[10], Hirayama A[11], Saito Y[12], Murohara T[13], Tamaki N[14], Sato A[2], Takayama T[11], Imai E[13], Yasuda Y[13], Koya D[15], Tsubakihara Y[3], Horie S[16], Korogi Y[17], Narumi Y[18], Hayakawa K[19], Daida H[10], Node K[20], Kubota I[21] ([1]Nippon Med Sch, [2]Univ Tsukuba, [3]Osaka Univ, [4]Kawasaki Med Sch, [5]Saitama Med Univ, [6]St. Luke's Int Hosp, [7]Univ Miyazaki, [8]Hiroshima Univ, [9]Kumamoto Univ, [10]Juntendo Univ, [11]Nihon Univ, [12]Nara Med Univ, [13]Nagoya Univ, [14]Hokkaido Univ, [15]Kanazawa Med Univ, [16]Teikyo Univ, [17]Univ Occup Environment Health, [18]Osaka Med Coll, [19]Kyoto City Hosp, [20]Saga Univ, [21]Yamagata Univ); Japanese Society of Nephrology, Japan Radiological Society, and Japanese Circulation Society Science Advisory and Coordinating Committee. Guidelines on the use of iodinated contrast media in patients with kidney disease 2012. digest version: JSN, JRS, and JCS Joint Working Group. *Clin Exp Nephrol.* 2013; **17:** 441–79.