

Department of Internal Medicine

Division of Kidney and Hypertension

Tatsuo Hosoya, *Professor and Chairperson*
Tetsuya Kawamura, *Associate Professor*
Keitaro Yokoyama, *Associate Professor*
Yoichi Miyazaki, *Assistant Professor*
Masato Ikeda, *Assistant Professor*
Takashi Yokoo, *Assistant Professor*
Ichiro Ohkido, *Assistant Professor*

Iwao Ohno, *Professor*
Yasunori Utsunomiya, *Associate Professor*
Makoto Ogura, *Associate Professor*
Kazushige Hanaoka, *Assistant Professor*
Hiroshi Hayakawa, *Assistant Professor*
Nobuo Tsuboi, *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

Clinical studies of immunoglobulin nephropathy

We retrospectively analyzed the prognosis of immunoglobulin nephropathy, led a research group of the Ministry of Health, Labour and Welfare, and published a new clinicopathologic classification for predicting long-term renal outcomes. A manuscript describing a randomized clinical trial of steroid pulse therapy with or without tonsillectomy is under peer review. Furthermore, we studied the prognostic factors for steroid-treated immunoglobulin nephropathy and concluded that the achievement of proteinuria <0.4 g/day at 1 year could be a therapeutic indicator for a favorable renal outcome.

Clinical studies of low glomerular density in various glomerular diseases

Our previous studies showed that low glomerular density is strongly associated with the prognosis of various glomerular diseases. Moreover, we reported that low glomerular density with glomerulomegaly was the most characteristic finding in obesity-related glomerulopathy. To collect supporting evidence, we are investigating the distribution of glomerular density in different cortical zones of the human kidney. Furthermore, collaborative research about estimating the number of nephrons in Japanese subjects is in progress.

Experimental study on glomerular epithelial cells

Transgenic mice (NEP25) express human CD25 selectively on podocytes, and injection of a human CD25-targeted recombinant immunotoxin (LMB2) permits selective injury of glomerular epithelial cells (GECs). With this model we are investigating

the mechanisms of GEC regeneration after glomerular injury. Furthermore, we are investigating the role of oxidative stress in GEC injury, with a focus on the Keap1-Nrf2 system, a master regulator of the antioxidant response.

Studies of patients with CKD

In clinical research we found that higher levels of 1,25-dihydroxyvitamin D may be associated with better kidney function in patients with type 2 diabetes and that this association was modified by vitamin D receptor gene polymorphisms. We investigated the effect of cinacalcet on serum levels of calcium and phosphorus in patients undergoing hemodialysis with or without a high parathyroid hormone level to control serum levels of calcium and phosphorus. We concluded that administration of cinacalcet to patients with or without high parathyroid hormone levels facilitates the control of calcium and phosphorus levels. Moreover, we found that serum levels of the sphingolipid sphingosine 1-phosphate decreased significantly in all patients after 6 months of treatment with cinacalcet. In basic research, we analyzed the relation between bone and vascular injury in CKD and evaluated the enzyme klotho. In addition, we found that the serum creatinine level was lower in patients undergoing hemodialysis than in healthy persons. The serum phosphorus level was independently associated with the serum soluble α -klotho level.

Studies of patients undergoing peritoneal dialysis

Encapsulating peritoneal sclerosis is a severe complication of long-term peritoneal dialysis (PD) and has a high mortality rate. We used a laparoscopic approach to evaluate peritoneal injury in patients undergoing PD. We found that PD peritonitis is a risk factor for encapsulating peritoneal sclerosis, and we hypothesized that the bacterial species causing PD peritonitis would change depending on the neutral-pH PD solution.

Studies of renal transplantation

We showed an association between peritubular capillary endothelial c-Jun activation and interstitial fibrosis in chronic antibody-mediated rejection.

Studies of patients with polycystic kidney disease

We investigated the mechanism by which the intracellular Ca^{2+} concentration changes with drug administration or with changes in the extracellular Ca^{2+} concentration. Calcium oscillations may be associated with the function of renal tubular epithelial cells.

Clinical study on hypertensive patients with CKD

The Jikei Optimal Antihypertensive Treatment (JOINT) study is a large-scale prospective interventional observational study investigating the effect of a fixed-dose combination of losartan and hydrochlorothiazide in patients with CKD. The study, which had a total of 280 subjects, has been completed. The main results were published in *Clinical and Experimental Nephrology*. Additionally, we performed an extensional observation on the relationship between uric acid and its associates as a subanalysis of the JOINT study. The results were submitted to the English version of *Internal Medicine*.

Central blood pressure and activity of the renin-angiotensin-aldosterone system

We examined the relationship between central blood pressure (CBP) and the activity of the renin-angiotensin-aldosterone system (RAS) in patients with primary aldosteronism and in patients with essential hypertension. The gap between CBP and brachial systolic blood pressure (SBP) increased with the plasma aldosterone concentration in patients with essential hypertension. Although patients with primary aldosteronism did not demonstrate this tendency, the CBP-SBP gap in these patients was significantly higher than that in patients with essential hypertension, and this gap decreased with adrenalectomy or eplerenone treatment in patients with primary aldosteronism. This study suggests that, in primary aldosteronism, the regulation of the RAS is impaired by oversecretion of aldosterone and by the increase in CBP by a mechanism independent of the serum RAS, such as elevated organ RAS and inflammation. Furthermore, even if the SBP is controlled normally, the kinetics of the CBP indicate a different tendency from SBP as the RAS increases and might increase the risk of cardiovascular events.

Publications

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