Department of Internal Medicine
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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 on IgA nephropathy
A randomized clinical trial of steroid pulse therapy with or without tonsillectomy, leading the research group by the Ministry of Health, Labour and Welfare, has been published (Nephrol Dial Transplant, 2014). Steroid pulse therapy combined with tonsillectomy had a significant and independent effect on the disappearance of proteinuria over 12 months. Furthermore, a current multicenter study is expected to provide key insights into immunoglobulin A nephropathy.

Studies of low glomerular density in glomerular diseases and of obesity-related glomerulopathy
Our previous studies have shown that low glomerular density is strongly associated with the prognoses of various glomerular diseases. We have reported that obesity-related glomerulopathy (ORG) reflects obesity-induced renal injury and also accompanies a state of renal mass reduction. Both of these factors appear to synergistically contribute to the development of ORG (Nephrol Dial Transplant, 2013). Moreover, we investigated the characteristics of a cohort of Japanese patients with ORG and compared them with cohorts in other countries (Clin Exp Nephrol, 2013). Furthermore, collaborative research to estimate the number of nephrons in Japanese subjects is in progress.

Studies of glomerular epithelial cells (podocytes)
Transgenic mice (NEP25) express human CD25 selectively on podocytes, and injection of a human CD25-targeted recombinant immunotoxin permits selective injury to podocytes. We investigated the mechanisms of podocyte regeneration after glomerular injury using this model (Nephrol Dial Transplant, 2014). Furthermore, we investigated the effect of oxidative stress on podocyte injury, focusing on the Keap1-Nrf2 system, a mas-

ter regulator of the antioxidant response. We demonstrated that Nrf2 activation by genetic Keap1 knockdown attenuated podocyte injury (Nephrol Dial Transplant, 2014).

Studies of CKD mineral and bone disorders

To determine whether normal parathyroid cells have a similar extracellular Ca^{2+} entry system, cells were isolated from normal human parathyroid glands. Normal human parathyroid cells express a dihydropyridine-sensitive Ca^{2+}entry system that may be involved in the $[Ca^{2+}]$o-induced change in $[Ca^{2+}]$i. In a clinical study we clarified that ferric citrate hydrate, a novel iron-based phosphate binder, decreased concentrations of fibroblast growth factor 23.

Studies of peritoneal dialysis

Encapsulating peritoneal sclerosis (EPS) is a serious complication in patients receiving long-term peritoneal dialysis. In a retrospective, observational study, we found that the dialysate-to-plasma ratio of creatinine and the duration of peritonitis were independently associated with EPS. Thus, we conclude that earlier treatment to promote an early recovery from peritoneal dialysis-associated peritonitis could be critical in preventing EPS.

Study of renal transplantation

We examined graft survival in patients who had undergone renal transplantation to determine the significance of caveolin 1 immunoreactivities in the peritubular capillaries.
We compared clinicopathological factors between mismatch and controls. We found that both glomerular hypertrophy and proteinurea were more common in the mismatch group than in the control group.

Studies of polycystic kidney disease

The goals of our research into autosomal dominant polycystic kidney disease (ADPKD) are to investigate the pathophysiology of ADPKD and to develop new therapies. We have reported a functional assay of *PKD1*/*PKD2* genes, described the mechanism of cyst formation, and performed a therapeutic investigation of in-vitro cysts from patients with ADPKD. Currently, research regarding the genetic analysis and the genetic counseling of patients with ADPKD is in progress.

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

We examined the mechanism of the renal protective effects of azilsartan in a rat model of renal failure. Daily urinary sodium excretion was not significant; however, azilsartan tended to suppress plasma aldosterone, daily urinary protein, and norepinephrine excretion compared with vehicle. Our findings suggest that the renal protective effects of azilsartan are due in part to the suppression of aldosterone and the sympathetic nervous system.

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

We examined the relationship between central blood pressure (CBP) and the renin-angio-

tensin-aldosterone system in patients with primary aldosteronism and essential hypertension. The gap between CBP and brachial systolic blood pressure (SBP) increased with the plasma aldosterone concentration in essential hypertension. In primary aldosteronism, the CBP-SBP gap was significantly higher than that in essential hypertension. This study suggests that, even if SBP is well controlled, the kinetics of CBP indicate a different tendency from SBP as the renin-angiotensin-aldosterone system increases and might increase the risk of cardiovascular events.

Association of serum uric acid and observation of kidney tissue in patients with CKD

In patients with CKD, we examined how serum uric acid is associated with pathologic changes in kidney tissue. Elevated serum uric acid levels were strongly associated with interstitial fibrosis and tubular atrophy and weakly associated with hyalinizing arterioles. An increased serum level of uric acid was not associated with glomerular global sclerosis or increased thickness of the arcuate and interlobular arteries. Hyperuricemia is closely associated with the arterioles and tubulointerstitial lesions in patients with CKD.

Publications

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