

Department of Internal Medicine

Division of Kidney and Hypertension

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General Summary

Our major fields of research are nephrology, hypertension, and uric acid metabolism. Published achievements and recent reports are summarized here.

Research Activities

Nephrology

1. Glomerulonephritis

Recently, steroid pulse therapy has been recommended as a treatment for patients with progressive immunoglobulin A nephropathy. We demonstrated that steroid pulse therapy significantly decreases the severity of proteinuria. In addition, tonsillectomy, in combination with steroid pulse therapy, can induce clinical remission in patients with immunoglobulin A nephropathy.

We generated and analyzed inducible and podocyte-specific vascular endothelial growth factor transgenic mice using the Tet-On system. Our results indicate that dysregulation of vascular endothelial growth factor expression leads to the alteration of glomerular capillary formation via dysfunction of both endothelial and mesangial cells.

Metanephros transplantation significantly reduced vascular Ca and Pi content. Von Kossa staining of the media of the thoracic aorta indicated that metanephros transplantation suppresses the progression of vascular calcification.

2. Dialysis and kidney transplantation

We evaluated the clinical value of combined therapy with peritoneal dialysis and hemodialysis and found that it is a useful way of controlling body fluids and that peritoneal function can be maintained over a long period of treatment time (*Clinical Nephrology*, 2010). Moreover, we evaluated peritoneal histology. In addition, we studied vascular calcification in patients with end-stage renal disease (*Clinical Nephrology*, 2010).

We studied acute humoral rejection and attempted to perform ABO-incompatible renal transplantation and husband-to-wife renal transplantation. In transplant glomerulopathy, glomerular expression of plasmalemmal vesicle-associated protein 1 is positively correlated with the severity of transplant glomerulopathy and proteinuria (*American Journal of Transplantation*, 2008). We found an association between peritubular capillary endothelial c-Jun activation and interstitial fibrosis in chronic antibody-mediated rejection.

Hypertension

A study of awareness of home blood pressure (BP) measurement among practitioners who deal with hypertension was a main research project in 2010. This study was unique in that it focused specifically on home BP measurement. Because the guidelines released by the Japanese Society of Hypertension in 2008 are the only guidelines to include home-based BP, we believe highlighting the importance of home-based BP measurement is important. The study has been completed and was submitted to the journal *Blood Pressure*.

In patients with chronic kidney disease, T-type calcium channels can be overexpressed in the kidney. In addition, blocking of T-type calcium channels leads to inhibition of Rho-kinase activity and renal interstitial. We extended this result to further investigate the cardiorenal continuum by introducing 5/6 nephrectomized rats. We are now analyzing laboratory and histological findings.

Uric acid metabolism

We investigated the hypouricemic effect of a novel synthesized xanthine oxidase inhibitor, topiroxostat, in patients who have hyperuricemia with and without gout. Topiroxostat showed dose responsiveness in its ability to lower serum levels of uric acid, and doses of both 80 mg and 120 mg produced significantly greater increases in estimated glomerular filtration rate than did placebo.

Publications

Gheisari Y, Yokoo T, Matsumoto K, Fukui A, Sugimoto N, Ohashi T, Kawamura T, Hosoya T, Kobayashi E. A thermoreversible polymer mediates controlled release of GDNF to enhance kidney regeneration. *Artif Organs* 2010; **34**: 642-7.

Terawaki H, Takada Y¹, Era S¹, Funakoshi Y², Nakayama K³, Nakayama M³, Ogura M, Ito S³, Hosoya T¹ (Gifu Univ, ²Funakoshi Clin, ³Tohoku Univ). The redox state of albumin and serious cardiovascular incidence in hemodialysis patients. *Ther Apher Dial* 2010; **14**: 465-71.

Terawaki H, Yokoyama K, Yamada Y, Maruyama Y, Iida R, Hanaoka K, Yamamoto H, Obata T, Hosoya T. Low-grade endotoxemia is contributing to chronic inflammation in hemodialysis patients: examination with the novel lipopolysaccharide detection method. *Ther Apher Dial* 2010; **14**: 477-82.

Otani H¹, Kikuya M¹, Hara A¹, Terata S¹, Ohkubo T¹, Kondo T¹, Hirose T¹, Obara T¹, Metoki H¹, Inoue R¹, Asayama K¹, Kanno A¹, Terawaki H, Nakayama M¹, Totsune K¹, Hoshi H¹, Satoh H¹, Izumi S¹, Imai Y¹ (Tohoku Univ). Association of kidney dysfunction with silent lacunar infarcts and white matter hyperintensity in the general population: the Ohasama study. *Cerebrovasc Dis* 2010; **30**: 43-50.

Terawaki H, Nakao M, Nakayama K¹, Nakayama M¹, Kimura A, Takane K, Mitome J,

Hamaguchi A, Ogura M, Yokoyama K, Ito S, Hosoya T (Tohoku Univ). Peritoneal clearance and transport of methylglyoxal. *Nephrol Dial Transplant* 2011; **26**: 754-5.

Okonogi H, Utsunomiya Y, Miyazaki Y, Koike K, Hirano K, Tsuboi N, Suzuki T, Hara Y, Ogura M, Hosoya T, Kawamura T. A predictive clinical grading system for immunoglobulin a nephropathy by combining proteinuria and estimated glomerular filtration rate. *Nephron Clin Pract* 2011; **118**: c292-300.

Yokoyama K, Urashima M, Ohkido I, Kono T, Yoshida T, Muramatsu M, Niu T, Hosoya T. L-type voltage-dependent calcium channel alpha subunit 1C is a novel candidate gene associated with secondary hyperparathyroidism: an application of haplotype-based analysis for multiple linked single nucleotide polymorphisms. *Nephron Clin Pract* 2010; **115**: c237-43.

Utsunomiya Y, Hara Y, Ito H, Okonogi H, Miyazaki Y, Hashimoto Y (Univ Toyama), Hosoya T. Effects of probenecid on the pharmacokinetics of mizoribine and co-administration of the two drugs in patients with nephrotic syndrome. *Int J Clin Pharmacol Ther* 2010; **48**: 751-5.

Matsuo N, Yokoyama K, Maruyama Y, Ueda Y, Yoshida H, Tanno Y, Yamamoto R, Terawaki H, Ikeda M, Hanaoka K, Yamamoto H, Ogura M, Watanabe S, Kimura Y, Hosoya T. Clinical impact of a combined therapy of peritoneal dialysis

and hemodialysis. *Clin Nephrol* 2010; **74**: 209-16.

Ohkido I, Yokoyama K, Kagami S, Hosoya T. The hypothesis that bone turnover influences FGF23 secretion. *Kidney Int* 2010; **77**: 743.

Yoshida H, Yokoyama K, Yaginuma T, Ohkido I, Yamamoto H, Utsunomiya Y, Kawakami M (Seirei Sukura Citizen Hosp), Hosoya T. Difference in coronary artery intima and media calcification in autopsied patients with chronic kidney disease. *Clin Nephrol* 2011; **75**: 1-7.

Mitome J, Yamamoto H, Maruyama Y, Kobayashi A, Yaginuma T, Matsuo N, Tanno Y, Hayakawa H, Miyazaki Y, Yokoyama K, Utsunomiya Y, Yamaguchi Y, Hosoya T. Successful treatment of recurrent focal segmental glomerulosclerosis combined with calcineurin inhibitor nephrotoxicity four yr after kidney transplantation. *Clin Transplant* 2010; **24 Suppl 22**: 48-53.

Kanno A, Metoki H, Kikuya M, Terawaki H,

Hara A¹, Hashimoto T¹, Asayama K¹, Inoue R¹, Shishido Y¹, Nakayama M¹, Totsune K¹, Ohkubo T¹, Imai Y¹ (Tohoku Univ). Usefulness of assessing masked and white-coat hypertension by ambulatory blood pressure monitoring for determining prevalent risk of chronic kidney disease: the Ohasama study. *Hypertens Res* 2010; **33**: 1192-8.

Reviews and Books

Terawaki H, Era S (Gifu Univ), Nakayama M, Hosoya T. Decrease in reduced-form albumin among chronic kidney disease patients: new insights in cardiovascular complications. *Ther Apher Dial* 2011; **15**: 156-60. Epub 2011 Jan 25.

Yokoo T, Yanagita M. Stem cell therapy against oxidative stress and hypoxia. In: Miyata T, Eckardt KU, Nangaku M, editors. *Studies in renal disorders*. New York: Springer; 2011. p. 673-88.