Chronic Kidney Diseases – Recent Advances in Clinical and Basic Research
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Preface

Chronic kidney disease (CKD) is a growing worldwide public health problem resulting from the increasing number of patients with diabetes and hypertension as well as from the aging of the population. In addition, the pathology associated with CKD appears to become more complex with age, and because of that, the most important task the Japanese Society for Dialysis Therapy has been charged with is approaching dialysis therapy with a view to the future. I would like to improve the prognosis of patients with CKD by undertaking effective measures to prevent and control complications in the elderly from the ground up and by promoting home care. Returning the fruits of the Society’s activities to the public through such shifts in thinking in regard to CKD management and dialysis therapy as well as contributing to Japan and the world through the medium of dialysis medicine are missions of the Japanese Society for Dialysis Therapy.


Yamashita and Sakurai show the removal characteristics of on-line pre-dilution hemodiafiltration (HDF) compared with those of hemodialysis (HD) using super high-flux dialyzers. A higher reduction rate of α₁-microglobulin was more easily achieved by employing on-line pre-dilution HDF rather than HD with super high-flux dialyzers. HDF with a large amount of fluid exchange and a large amount of albumin loss is worth trying as long as albumin loss is controlled in a measured manner.

Mineshima describes the past, present and future of the dialyzer. For a long time, regenerated cellulose had been widely used from the beginning of dialysis therapy. Cellulose triacetate membrane has a higher performance because of the lower thickness of the membrane. Many types of synthetic membranes, such as polysulfone, polyethersulfone and polyester polymer alloy, have asymmetrical structures. Recently, many types of high-flux dialyzers with high-performance
membranes and a high internal filtration/backfiltration flow rate have been introduced.

Inaba shows that increased calcium load lowers bone turnover by suppressing parathyroid function, resulting in the formation of adynamic bone disease. Adynamic bone disease is also major risk factor for ectopic calcification including the vascular wall by diminishing the capacity of bone to absorb the surplus calcium and phosphate in circulation. Therefore, it is recognized that the maintenance of bone turnover within the normal range might be most important to protect against the development of vascular calcification and to attenuate the load of phosphate and calcium, particularly in HD patients.

Nakanishi et al. studied the deregulation of several iron transport systems of polymorphonuclear leukocytes and the effect of TNF-α on human umbilical vein endothelial cells or polymorphonuclear leukocytes obtained from HD patients and controls. In regard to bacterial infection, the availability of iron to these intracellular pathogens is critical for their growth. In particular, iron accumulation in cells and endosomes may accelerate the spread of infection. Oxidative stress is caused by iron sequestration in vascular cells and macrophages as well as by the derangement of iron metabolism in mitochondria, and the observed increase in hepcidin and TNF-α may accelerate these crucial steps of oxidative stress in vascular disease.

Masakane et al. show that home HD (HHD) is one of the best choices for improving the quality of life and survival rate of dialysis patients because a longer and more frequent dialysis program is used to achieve adequate dialysis. There were 461 dialysis patients treated with HHD as of the end of 2013, which accounted for only 0.1% of all dialysis patients in Japan. In order to achieve a successful HHD program in Japan, there are several issues to be resolved.

Shigematsu et al. describe that lanthanum carbonate is the most powerful calcium-noncontaining phosphate binder used for hyperphosphatemia. In this article, they discuss the efficacy and safety of lanthanum carbonate and how it was effective for treating hyperphosphatemia in dialysis patients. Lanthanum carbonate was able to decrease serum fibroblast growth factor (FGF) 23 levels, suggesting a good influence on the cardiovascular system of dialysis patients. No negative effects of lanthanum carbonate on bone metabolism or bone morphometry have been reported.

Tsuchiya et al. report the role of the Klotho/FGF23 axis in CKD. Klotho and FGF23 have been reported to be being involved in CKD-mineral bone disorder. Klotho functions as a cofactor of FGF receptors and has been reported to cause FGF23 action. FGF23, in cooperation with Klotho, inhibits phosphate reabsorption and vitamin D production in the kidney. Blood Klotho and FGF23 levels have been reported to increase from the early stages of CKD, and they are
receiving attention as new surrogate markers reported to be related to life expectancy. In this review, they summarize and outline the pathophysiology of Klotho and FGF23 in CKD-mineral bone disorder as well as important points that are starting to influence clinical practice.

Kawanishi and Nitta show the cell sheet-based tissue engineering technique for mesothelial cell injury. Previous cell sheet engineering research has made it possible to transplant cells that retain their function, and stacking different types of cells in cell sheet layers has also become possible. Mesothelial cell transplantation, as a means of achieving peritoneal regeneration, needs to be performed under conditions in which the surface area of the visceral peritoneum is large and the area of mesothelial cell damage is small. In this article, they explain cell sheet engineering as a technology for transplanting cells with a variety of intact intercellular adhesion and cell membrane molecules as well as its application to peritoneal regeneration.

Ogawa and Nitta report the hyporesponsiveness to erythropoiesis-stimulating agents (ESAs) in dialysis patients. Hyporesponsiveness to ESAs is defined as a continual need for higher than 300 IU/kg/week doses of epoetin or 1.5 mg/kg/week doses of darbepoetin. ESA hyporesponsiveness contributes to morbidity, mortality, and the health-care economic burden of dialysis patients. The most common causes of ESA resistance are absolute or functional iron deficiency and inflammation. Maintaining adequate iron stores is clearly accepted as the most important strategy for reducing the ESA requirement and for enhancing ESA efficacy. This article summarizes the common causes of ESA hyporesponsiveness and the proposed therapeutic interventions.

Kawanishi et al. describe the perspectives on encapsulation peritoneal sclerosis (EPS) in CAPD patients. The mortality rate for EPS has been high, primarily due to complications related to bowel obstruction. Currently, there is a consensus on therapy; however, treatment with corticosteroids and tamoxifen should be administered in a timely manner. The final therapeutic option for EPS is surgical enterolysis (adhesiolysis). Moreover, a biocompatible peritoneal dialysis (PD) solution has become available for patients worldwide and may further reduce peritoneal deterioration and EPS risk.

Abe and Okada describe the clinical efficacy and safety of dipeptidyl peptidase-4 (DPP-4)-inhibitors for CKD patients. All of the currently available DPP-4 inhibitors can be used in CKD patients, and their use is increasing. Numerous clinical trials have shown that DPP-4 inhibitors provide effective and consistent glycemic control, with a good tolerability profile but without severe hypoglycemia or weight gain. Moreover, DPP-4 inhibitors reduce the levels of glycated albumin, which is a better indicator of glycemic control than glycated hemoglobin, without causing hypoglycemia in dialysis patients.
Nakamoto reports the results of a nationwide statistical survey of PD registry in Japan at the end of 2012. There were 9,514 PD patients at the end of 2012 (3.1%), indicating 128 fewer than in the 2011 survey (9,642 patients). There were 347 non-PD+catheter patients, and 175 patients were started on PD in 2012 but were switched to another therapy in the same year. The sum of these 522 patients and of the total number of PD patients was 10,036 (522 + 9,514). The number of PD-only patients was 7,322 (80.4%), and the number of PD+HD patients was 1,788 (19.6%). Around 40% of PD patients were using icodextrin, which was a much higher percentage than that found in other countries.

Takura reports the cost-effectiveness of HD in Japan. The incremental cost-effectiveness ratio of HDF to HD was 20,589 ΔUS$/Δquality-adjusted life years (QALY). After stratification for primary disease, the cost-effectiveness for diabetic nephropathy was 88,774 ± 27,801 US$/QALY in 1 month and 97,416 ± 36,156 US$/QALY in 36 months. These results suggest that the HDF is a cost-effective therapy. Furthermore, the incremental cost-effectiveness ratio after 36 months of observation increased mainly among diabetic nephropathy patients.

Tsuchida et al. present vascular access for long-term HD/HDF therapy in Japan. Of 105 patients with an arteriovenous fistula, only 20 had an arteriovenous graft (AVG) (16.0%), whereas of the 774 patients who had been on dialysis treatment for less than 20 years, 91 had an AVG (11.7%), which indicated that the percentage of patients with an AVG increased with dialysis vintage. Arteriovenous fistula was the main vascular access used for patients who had been on dialysis treatment for over 20 years, which is very rare, even on a global scale. However, switching to an AVG is unavoidable in cases of vein deterioration due to long-term dialysis use. Access by an AVG is expected to increase further in long-term patients in the future.

Naganuma and Takemoto describe the new aspects of cerebrovascular disease in dialysis patients. Compared with those in the general population, strokes in dialysis patients are characterized by a higher incidence of hypertensive intracerebral hemorrhage. Recent studies on dialysis cohorts have shown that asymptomatic cerebrovascular diseases, including silent cerebral infarction, white matter hyperintensities, and cerebral microbleeds, are related to future onset of stroke, cognitive impairment, and dementia. Other studies have shown that the prevalence of white matter hyperintensities and cerebral microbleeds is significantly higher in dialysis patients than in healthy subjects.

Tomo shows that rigorous standards have been established for the purification of dialysis fluid, which is becoming ever more widely practiced in Japan. The effects of dialysis fluid purification include prevention of micro-inflammation, preservation of residual renal function, improvement of nutritional status, and resolution of resistance to ESAs. Dialysis fluid that does not contain acetate
has become available, and there have been reports of decreased micro-inflammation, etc. with this innovation.

Nitta and Ogawa summarize the pathogenesis, evaluation and management of vascular calcification in dialysis patients. There are two types of vascular calcification: intimal and medial calcification. The transformation of vascular smooth muscle cells into osteoblast-like cells seems to be a key element in the pathogenesis of medial calcification in the presence of calcium and phosphate deposition. Vascular calcification causes increased arterial stiffness by medial calcification and is followed by left ventricular hypertrophy and decreased coronary artery perfusion as well as myocardial ischemia by intimal calcification. This review summarizes the pathophysiology, diagnostic procedures and therapeutic implications of vascular calcification in end-stage renal disease patients.

We hope that you will enjoy the wide range of papers presented in this volume.

*Kosaku Nitta, Tokyo
President of the Japanese Society for Dialysis Therapy*