Professor Special Lecture: 146th Regular Meeting of the Medical Society of Toho University

Review Article

Integrated Renal Care from Proteinuria toTransplantation in the Department of Nephrology of Toho University

Ken Sakai

Professor, Department of Nephrology (Omori), School of Medicine, Faculty of Medicine, Toho University

ABSTRACT: Since the advent of hemodialysis, peritoneal dialysis and renal transplantation, these three renal replacement therapies have become common practice in the management of end-stage renal disease. Our department was established in 1980 and has brought together nephrologists, urologists and even pediatric nephrologists who are focused on the treatment of chronic kidney disease using these renal replacement therapies. This review outlines the history of renal replacement therapy and describes the future directions in this area based on the activity in our department, which ranges from management of proteinuria to transplantation for patients at any age.

Toho J Med 1 (4): 57–61, 2015

KEYWORDS: Willem Johan Kolff, chronic kidney disease, low protein diet, dialysis, transplantation

The history of dialysis and the Department of Nephrology

Hemodialysis in the clinical setting was developed by Dr. Willem Johan Kolff in Cleveland Clinic, Cleveland, Ohio, in 1950 (Fig. 1). He was a pioneer in hemodialysis and invented the dialysis machine. His first dialysis machine contained a cellulosic membrane made from sausage skin obtained from a meat shop in Cleveland. His first wish was to treat a young woman in his native country of Holland who suffered from uremia. It was saddening for Dr. Kolff to inform the woman's mother about her daughter's impending death. That was the driving force for him to make a new dialysis machine in order to remove 20 g of urea nitrogen.

The outpatient dialysis clinic was started in Seattle by Dr. Belding H Scribner in 1962. Dr. Scribner, along with a committee of citizens, selected patients who should be treated with dialysis. This is a famous story because death resulting from withholding dialysis was decided by ordinary citizens, and this committee decided whether a patient would live or die. "Life"magazine reported this story (Fig. 2). In fact, a lack of government support meant that the cost of dialysis in those days was very high, so only rich patients could survive. The Seattle dialysis patients survived longer compared with those in Cleveland because Dr. Kolff never selected his patients. The poor survival rate of Cleveland encouraged those physicians to consider transplant as the treatment of choice. Therefore, dialysis and transplantation progressed simultaneously in Cleveland with the same intention to save the patient's life.

The dialysis technique spread worldwide and it also reached Japan. With government support, it became

6–11–1 Omorinishi, Ota, Tokyo 143–8541, Japan
tel: +81-(0)3-3762-4151
e-mail: kensakai@med.toho-u.ac.jp
DOI: 10.14994/tohojmed.2015.r001

Received Nov. 2, 2015
Toho Journal of Medicine 1 (4), Dec. 1, 2015.
ISSN 2189–1990, CODEN: TJMOA2

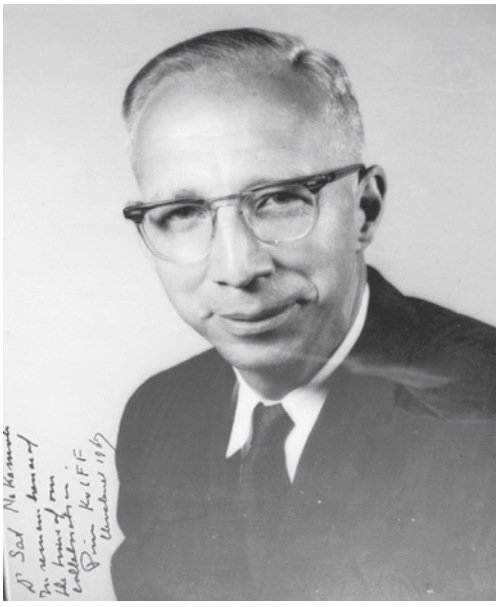

Fig. 1 Willem Johan Kolff (1911-2009) was a pioneer of hemodialysis and the field of artificial organs. He made his major discoveries in dialysis for kidney failure during the Second World War. He immigrated to the US in 1950. During the war, he was in Kampen, where he was active in the resistance against the German occupation. At the same time, Kolff worked to develop the first functioning artificial kidney. He treated his first patient in 1943, and in 1945, he was first able to save a patient's life with hemodialysis treatment. Kolff's work has helped save the lives of millions of acute or chronic renal failure patients. (Photo taken by colleague in Cleveland Clinic)

prevalent in Japan along with intermittent peritoneal dialysis in the 1970s. Toho University Omori Hospital started hemodialysis therapy for use in emergency medicine in 1971. The artificial dialysis center was then opened in 1974. Soon after, the first renal transplantation was performed by our former renal transplant team in 1975. With the aim of treating uremic patients who require dialysis therapy, the Department of Nephrology was established in 1980 and consisted of nephrologists and urologists. That is why nephrologists and urologists in our department continue to work together toward the same purpose with the application of hemodialysis, peritoneal dialysis and renal transplantation.

Nephritis, nephrotic syndrome and low protein diet therapy

Dr. Kiyofumi Hirata (Fig. 3) moved to Toho University from Keio University in the 1970s. He became the first professor of the nephrology division in 1979. His work in Keio University was focused on the treatment of glomerulonephritis based on biopsy findings. There was no established method of immunofluorescence; light and electron microscopy were the only available tools, along with the patient's history. After immunofluorescence became available, most of mesangial proliferative nephritis became known as immunoglobulin A (IgA) nephropathy, which is also called Berger's disease. Immunosuppressants used nowadays were not available at that time. Azathioprine, cyclophosphamide and corticosteroid were the only medications for nephrotic syndrome. The mean duration of hospitalization was 3 months for patients with nephrotic syndrome. Dr. Sonoo Mizuiri also joined the department in the 1970s. Her excellent work contributed our department and nephrology society in diabetic nephropathy, peritoneal dialysis and transplant.[1–4] She became the second professor of Nephrology. She still works in Hiroshima prefecture.

The primary work of Prof. Hirata after his move to Toho University was low protein diet therapy for non-dialysis chronic kidney disease (CKD) patients. The concept was that a low protein diet with sufficient energy intake could slow the deterioration in renal function. Even today, he is famous as a pioneer of low protein diet therapy in CKD. He has written many articles and books. Unfortunately, he passed away from reactivated tuberculosis after retirement.

Transplantation

In 1986, Prof. Hirata invited another professor, Dr. Akira Hasegawa, from Kiyose Children's Hospital. Prof. Hasegawa was famous for his work in pediatric renal transplantation. He had graduated from Keio University and worked in urology. The number of transplants increased dramatically after the arrival of Prof. Hasegawa. He made the wishes of children come true: going to elementary school, graduating from university, starting a career, getting married and even having babies. Their wishes would not have been realized if their condition was managed by dialysis alone. This policy has continued after the appointment of Prof. Seiichiro Shishido, the present chairman of pediatric transplantation.

In 1989, Prof. Hasegawa, Dr. Takehiro Ohara and Dr. Atsushi Aikawa (present chairman of the department) operated on a woman who had systemic lupus erythematosus (SLE) requiring hemodialysis. That was the first year in

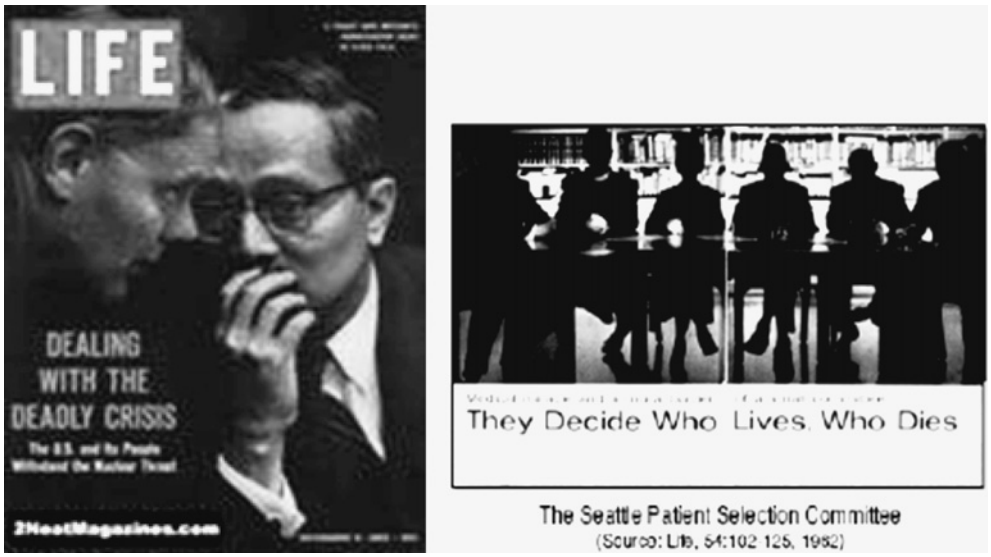

Fig. 2 Cover of "Life" on November 9, 1962. The magazine reported on the Seattle patient selection committee, which decided who lives and who dies.

Fig. 3 Prof. Kiyofumi Hirata, the first chairman of nephrology at Toho University Omori Hospital, dedicated his life's work to chronic kidney disease patients by developing a low protein diet. (Photo taken by colleague in Department of Nephrology)

which ABO incompatible renal transplantation in Japan was performed, where the patient received a kidney from a donor with a different blood type. Before the procedure, plasma apheresis and splenectomy were performed. This patient also had an IgA deficiency due to plasma cell class switch abnormalities that were probably caused by SLE. She experienced frequent anal abscesses as a result of IgA deficiency. Interestingly, her IgA level returned to normal after successful renal transplantation. After 26 years, her graft function remains good (serum creatinin: SCr 0.9mg/dl) and lupus nephritis has not recurred, setting a world record for graft survival in ABO incompatible renal transplantation (Fig. 4). ABO incompatible kidney transplantation is now common worldwide—a procedure that originated from Japan,[5] here in Toho University.

Recurrence of glomerulonephritis after transplantation is another interest for physicians in the field of nephrology.[6–8] Including SLE, as described in the case above, IgA nephropathy, focal segmental glomerulosclerosis and hemolytic uremic syndrome frequently reoccur even after transplantation. The natural progression of these conditions and regression while under immunosuppressant treatment led us to develop a treatment strategy for native glomerulonephritis.

Donor health is also an important issue in living donor renal transplantation. Living donors are the primary source of kidneys in Japan, and further study is needed in this area in order to develop a strategy to protect their life and kidney.[9]

Nutritional therapy for non-dialysis CKD patients

As described above, renal nutritional therapy remains the main field of study in this department. Profs. Hirata and Mizuiri have spent a considerable amount of time do-

Fig. 4 The woman next to Prof. Aikawa had systemic lupus erythematosus (SLE) requiring hemodialysis and received a kidney transplant from her mother in 1989. She has the record of longest graft survival in ABO blood incompatible renal transplantation in Japan.
(We have obtained a written permission from the patient of this photo taken by colleague in Department of Nephrology)

ing research in this area. Dr. Yasushi Ohashi, an associate professor, is a young investigator who is staying in the Cleveland Clinic for a period of time to study the body composition of CKD patients. As the CKD stage increases with time, their total body water content decreases, especially intracellular fluid. Such fluid imbalance (the shrinkage of the intracellular fluid compartment may be due to muscle wasting) might be related to malnutrition and poor patient outcome. Dr. Ohashi has reported this in many articles.[10, 11] In cooperation with the Department of Nutrition, we will continue to work on a low protein diet to delay the progression of CKD patients and to maintain their nutritional status.

Summary

Under the direction of Prof. Aikawa, the number of transplants has increased to 800 cases in our department. In Japan, the order of choice of renal replacement therapy has changed: first is hemodialysis, with transplantation in the second position, and third is peritoneal dialysis. Hemodialysis patients with cardiovascular disease are now the target of a national study. Drs. Hiroki Hase and Nobuhiko Joki in the Department of Nephrology in Ohashi Medical Center have extensively reported their work in this field.[12] Renal issues ranging from proteinuria to transplantation as well as complications involving patients at any age are our concern, and we will carry on study, practice and education to tackle these challenges.

References

1) Mizuiri S, Ohashi Y, Hemmi H, Arita M, Yamada K, Aoki T, et al. Effects of new peritoneal dialysis solutions, pyridoxamine and AT1 receptor blocker, on TGF-β1 and VEGF expression in rat peritoneal mesothelial cells. Am J Nephrol. 2009; 30: 295-302.
2) Mizuiri S, Hemmi H, Arita M, Tai R, Hattori Y, Muto A, et al. Effluent markers related to epithelial mesenchymal transition with adjusted values for effluent cancer antigen 125 in peritoneal dialysis patients. Int J Nephrol. 2011; 2011: 261040.
3) Mizuiri S, Aoki T, Hemmi H, Arita M, Sakai K, Aikawa A. Urinary angiotensin-converting enzyme 2 in patients with CKD. Nephrology (Carlton). 2011; 16: 567-72.
4) Mizuiri S, Hemmi H, Arita M, Aoki T, Ohashi Y, Miyagi M, et al. Increased ACE and decreased ACE2 expression in kidneys from patients with IgA nephropathy. Nephron Clin Pract. 2011; 117: c57-66.
5) Aikawa A, Kawamura T, Shishido S, Saito K, Takahashi K; ABO-Incompatible Transplantation Committee members. ABO-incompatible living-donor pediatric kidney transplantation in Japan. Clinics (Sao Paulo). 2014; 69: 22-7.
6) Sakai K, Saneshige M, Takasu J, Yanagisawa T, Aoki Y, Kawamura T, et al. Clinical remission and pathological progression after tonsillectomy in a renal transplant patient with recurrent IgA nephropathy. Clin Transplant. 2009; 23 (supple 20): 44-8.
7) Sakai K, Takasu J, Nihei H, Yonekura T, Aoiki Y, Kawamura T, et al. Protocol biopsies for focal segmental glomerulosclerosis treated with plasma exchange and rituximab in a transplant patient. Clin Transplant. 2010; 24 (Supple 22): 60-5.
8) Shishido S, Satou H, Muramatsu M, Hamasaki Y, Ishikura K, Hataya H, et al. Combination of pulse methylprednisolone infusions with cyclosporine-based immunosuppression is safe and effective to treat recurrent focal segmental glomerulosclerosis after pediatric kidney transplantation. Clin Transplant. 2013; 27: E 143-50.
9) Ohashi Y, Thomas G, Nurko S, Stephany B, Fatica R, Chiesa A, et al. Association of metabolic syndrome with kidney function and histology in living kidney donors. Am J Transplant. 2013; 13: 2342-51.
10) Ohashi Y, Otani T, Tai R, Okada T, Tanaka K, Tanaka Y, et al. Associations of proteinuria, fluid volume imbalance, and body mass index with circadian ambulatory blood pressure in chronic kidney disease patients. Kidney Blood Press Res. 2012; 36: 231-41.
11) Ohashi Y, Tai R, Aoki T, Mizuiri S, Ogura T, Tanaka Y, et al. The associations of malnutrition and aging with fluid volume imbalance between intra- and extracellular water in patients with chronic kidney disease. J Nutr Health Aging. 2015; DOI:10.1007/s12603-015-0480-5
12) Joki N, Hase H, Nakamura R, Yamaguchi T. Onset of coronary artery disease prior to initiation of haemodialysis in patients with end-stage renal disease. Nephrol Dial Transplant. 1997; 12: 718-23.

Ken Sakai, Professor Curriculum vitae

March	1986	Graduated from Toho University and National Examination for Medical Practitioners
June	1986	Resident, Toho University Omori Medical Center
June	1987	Resident, Kawasaki Municipal Ida Hospital
July	1989	Assistant, Department of Nephrology, School of Medicine, Faculty of Medicine, Toho University
July	1990	Physician, Kawasaki Municipal Ida Hospital
Dec.	1991	Board Certified Member of the Japanese Society of Internal Medicine
July	1992	Assistant, Department of Nephrology, School of Medicine, Faculty of Medicine, Toho University
Dec.	1993	Clinical Research fellow, Department of Nephrology and Hypertension, Cleveland Clinic (Cleveland, Ohio, USA)
Jan.	1996	Assistant, Department of Nephrology, School of Medicine, Faculty of Medicine, Toho University
June	1999	Board Certified Senior Member of the Japanese Society for Dialysis Therapy
Nov.	1999	Doctor of Philosophy (PhD), Toho University
April	2002	Board Certified Senior Member of the Japanese Society of Nephrology
April	2004	Lecturer, Department of Nephrology, School of Medicine, Faculty of Medicine, Toho University
May	2007	Director of Department of Internal Medicine and Dialysis Treatment Center, Saiseikai Yokohamashi Nanbu Hospital
Nov.	2008	Associate Professor, Department of Nephrology, School of Medicine, Faculty of Medicine, Toho University
Nov.	2011-present	Professor, Department of Nephrology, Toho University Omori Medical Center

Major Research Interests

Nephrology in Comprehensive medical care for chronic nephritis, peritoneal dialysis, hemodialysis and kidney transplant

Professional and Society Memberships (including Community Activities)

Board member of Society for Kidney Transplant Pathology
Councilor and board member of committee for promotion of renal transplantation of Japanese Society of Nephrology
Board member of the Japan Society for Transplantation
Councilor of the Japanese Society of Dialysis Therapy (Committee for medical specialist system, chairperson of curriculum committee; member of working group for Guideline for Renal Anemia in Chronic Kidney Disease)