Current Issues and Future Perspectives of Chronic Renal Failure

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Chronic renal disease is a major health issue in various parts of the world. The number of patients with end-stage renal disease (ESRD) is increasing in both developed and developing countries, greatly expanding the need for chronic dialysis and renal transplantation. In the year 2000, approximately 205,000 and 240,000 patients with ESRD were currently maintained on chronic dialysis in Japan and the United States, respectively, each accounting for roughly 20 and 24% of the estimated world chronic dialysis patients. The current cost for ESRD in Japan and the United States (including about 90,000 transplant recipients in the United States) amounts to approximately US$10 and 15 billion, respectively.

Although some dialysis patients live longer than 5 to 10 yr and are able to work and contribute to the society in which they live, others fare poorly and die within 2 to 3 yr. In addition to mortality, another issue surrounding ESRD is a rapidly aging dialysis population, in part related to the fact that the major proportion of new patients entering dialysis programs comprises people with type 2 diabetes. These problems require the worldwide nephrology community to rededicate itself to the retardation and prevention of the progression of all forms of renal disease. This brief review discusses key issues on ESRD and the prevention strategy of chronic progressive renal disease. We will focus primarily on the issues in Japan and the United States because they represent and illustrate common problems pertaining to ESRD.

Scope of the Problem

Tables 1 and 2 depict some of key numbers of patients with end-stage renal disease (ESRD) in Japan and the United States. We could envision from these numbers that the number of dialysis patients might be reaching its plateau in the United States, although it may still be increasing in Japan. However, because the number of patients with type 2 diabetes seems to be increasing in both countries, the total number may still increase in both countries. In fact, for first time in Japan, diabetes exceeded chronic glomerulonephritis as the primary cause of patients with ESRD entering dialysis programs in 1998. It is expected that the figure will increase further because the total number of cases of diabetes, mostly type 2, now approximately 7 million, will increase in Japan. We should be able to modify several general mechanisms that influence the progression of chronic renal disease; these mechanisms are one of the subjects of this review.

The economic burden of ESRD treatment to patients, their families, the public, and the nation is also enormous. Indeed, the cost is approximately US$10 billion each year in Japan and accounts for approximately 3.5% of total health care cost. Because many patients with ESRD are able to work and contribute the economy as active members of society, this cost may not be entirely lost. The cost could be regarded instead from a different perspective—as for the cost of the care of terminally ill patients.

Nonetheless, it is important to note that chronic dialysis therapy is an expensive medical modality and needs further innovations. The fact that both Japan and the United States lead the world with a sizable fraction of all patients with ESRD reflects in part the health care policies implemented in these countries in the early 1970s, in which costs for dialysis were assumed by the government, with only small costs imposed on the patients as a copay. With such a policy in effect, it has been difficult for health care providers not to enroll any patients in dialysis programs because of ethical and borderline medical reasons. Indeed, a country’s health care policy dictates the practice of health care to a major extent. Several alternatives that might be less expensive are available, such as renal transplantation and chronic ambulatory peritoneal dialysis (PD). Nonetheless, in many poorer parts of the world, these treatment modalities, except perhaps for renal transplantation, may not be widely available as a feasible option.

Another compounding issue of patients with ESRD is the aging population of chronic dialysis patients. This may be in part due to a rising number of type 2 diabetes in both Japan and the United States; thus, most patients will reach ESRD in their 60s and 70s. In fact, the statistics in Japan have shown that two thirds of total dialysis patients are 60 yr or older, and 50% are 65 yr or older; these statistics hold true for the some 30,000 new patients entering dialysis programs each year. These patients are obviously less than optimal candidates for receiving transplants, and they are less likely to receive a kidney from a living related donor (i.e., one of their children). Vascular and other systemic complications, particularly in people with diabetes, make them less qualified candidates for transplantation.

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Table 1. Patients with end-stage renal disease in Japan and the United States

<table>
<thead>
<tr>
<th>Patient</th>
<th>Japan</th>
<th>US</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic dialysis patients</td>
<td>200,000</td>
<td>233,000</td>
</tr>
<tr>
<td>New patients entering ESRD per year</td>
<td>30,000</td>
<td>80,000</td>
</tr>
<tr>
<td>Patients leaving dialysis by death per year</td>
<td>18,000</td>
<td>63,000</td>
</tr>
<tr>
<td>Renal transplantation per year</td>
<td>500–700</td>
<td>12,000</td>
</tr>
<tr>
<td>Patients on peritoneal dialysis</td>
<td>&lt;5%</td>
<td>10%</td>
</tr>
</tbody>
</table>

Data are for 1999 and are based on (1).

Table 2. Major causes of end-stage renal disease in Japan and the United States

<table>
<thead>
<tr>
<th>Cause</th>
<th>Japan (%)</th>
<th>US (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic glomerulonephritis</td>
<td>35</td>
<td>10</td>
</tr>
<tr>
<td>Diabetes</td>
<td>37</td>
<td>45</td>
</tr>
<tr>
<td>Hypertension</td>
<td>5</td>
<td>25</td>
</tr>
</tbody>
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Renal Transplantation

Renal transplantation is the best option available to patients with ESRD. However, cultural and social factors have hampered the increase in renal transplantation in certain parts of the world, including Japan. In fact, in Japan, most renal transplantation procedures have been performed with donations from a living relative, but the number never exceeded 1000 per year. Another donor source of a kidney has been a nonbeating-heart death donor, but again, the number has remained small—less than 300 per year. A transplantation network was created in Japan in 1996 to distribute kidneys and other organs nationwide and to permit better matching. However, the number of renal transplantsations that use kidneys from cadavers has remained less than 200 per year since 1996, and the transplants from living related donors have been about 500 per year.

These figures in Japan are in contrast to those in the United States, where the total number of renal transplants is about 12,000 annually, with slightly more than half of the kidneys taken from cadavers. The United Network for Organ Sharing has played a major role in the growth of a nationwide transplantation program in the United States. However, as organ transplantation becomes more and more available, the shortage of organs has become apparent. The number of registered patients for organ transplantation, including kidney, heart, liver, and other organs, has grown to 60,000 each year, whereas the number of transplantation performed remains approximately 20,000 each year (1). Thus, in the past decades, the gap between those who need transplants and those actually receive organs became larger, with a growing number of patients on the waiting list.

The shortage of organ is a critical issue. Besides humans, there is another possible source of kidney: xenotransplantation, particularly xenotransplantation with pig kidney. In fact, genetic engineering technology has made it possible to manipulate the donor pig to express human genes so that hyperacute rejection may not occur. Nonetheless, a different issue has emerged: the possibility of transfer of unidentified viral genes from donor pig (porcine endogenous retrovirus) to human recipients, which may not be confined to the recipients but may spread to the environment where they live and to other humans (1). Recent incidences of mad cow disease, or a transfer of prion molecules from cow meat to humans, have raised public concern and have increased the fear of such a possibility as real, although careful analyses so far have shown the risk to be quite small (2). The concern has been further aggravated by the effect of genetically modified plants or organisms. Nonetheless, further careful examination of the issue is warranted, as shown by the recent debates with genetically modified foods.

A new potential has recently emerged to create renal function. This is to create a kidney or artificial nephron from human cells. Initial attempts to create artificial nephrons from renal cells seemed encouraging, but so far, no concrete possibility has emerged. Another possibility is the use of human embryonic stem cells, which have the potential to differentiate in vivo, in vitro, or ex vivo into various cell types of the body, including kidney (3). Furthermore, it has been shown that bone marrow stroma cells could be differentiated in vitro into cardiomyocytes, suggesting the possibility that in the future, such cells derived from bone marrow of a patient could be used to replace the damaged heart muscle of the same patient. Transformation in vitro of primitive cell types into nephrons has been shown in vitro in amphibians. Advances in biotechnology and genetic engineering have extraordinary potential in the new century.

Peritoneal Dialysis

Chronic ambulatory PD and other PD modalities may provide a less expensive means to treat patients with ESRD who require chronic regular dialysis. There are certain advantages in PD over hemodialysis (HD), but PD has not been widely used in Japan; in fact, PD has been used in less than 5% of patients with ESRD. Why? There are several medical and nonmedical reasons. Some patients will be placed on PD purely for medical reasons. However, when there is no particular reason to choose either HD or PD, many patients will be placed on HD. One of the main reasons is the fact that 70 to 80% of patients will not be able to be on a chronic dialysis program more than 5 yr as a result of loss of peritoneal function. This is particularly true in Japan, where the majority of patients will be maintained on HD longer than 10 yr. In fact, 25% of HD patients in Japan are on HD longer than 10 yr.

It is clear that it is critically important that further research be performed that is focused on the function of the peritoneum and the mechanisms of the decline in peritoneal membrane functions during PD therapy. In addition, new, innovative PD fluids must be developed. The major focus on research in this regard seems to be on vascular proliferation, which results in a rapid decrease in effective osmotic gradient and perhaps in encapsulating sclerosing peritonitis, which is a serious and long-term complication of chronic ambulatory PD.

Another reason HD is preferred in Japan may be patient
preference. Many patients understandably prefer to be treated under the close supervision and care of nurses and doctors in a dialysis clinic near to their home or workplace. And another important factor in PD is its cost in Japan. The current medical reimbursement policy in Japan will pay around US$40,000 to 50,000 per year to the dialysis provider per patient either on HD or PD. This reimbursement for HD will cover costs for the dialysis machines and supplies, as well as costs for the hospitals, clinics, doctors, and allied health professionals. In contrast, the majority of the money reimbursed for PD will go to the companies that provide PD fluids; thus, there is little incentive for doctors, hospitals, and dialysis clinics to place patients on PD unless there are clear medical contraindications for HD.

Complications of Chronic Dialysis

Although retarding the progression of chronic renal disease is crucial to the treatment of ESRD, prevention and management of various complications of chronic dialysis patients are also of critical importance in maintaining the quality of life of these patients. Although there are many complications that are particular to chronic dialysis patients, including vascular disease, peritonitis (for PD), bone disease, dialysis amyloidosis, and malnutrition, a recent proposal of the possible role of carbonyl stress as an underlying biochemical mechanism for some of these complications is of particular importance (4). This carbonyl stress hypothesis suggests that through continuous oxidative as well as nonoxidative stresses, several carbonyl compounds will be generated in quantities so massive (compared with any other medical condition, including diabetes) that extraordinary amounts of glycation end products will accumulate, thus modifying proteins throughout the body. This is a new and attractive hypothesis with a solid scientific, experimental, and clinical basis, and thus, it warrants further investigation and development.

Control of Hypertension

Although choices of dialysis modalities, availability of transplantation, and access to transplantation vary from one country to another, there are more general strategies available to intervene in progressive chronic renal disease and to prevent it from reaching its end stage.

It has been well established that proper control of hypertension is essential for the treatment of chronic renal disease. It has been known for many years that hypertension accelerates the progression of renal disease, and hypertension may be further aggravated by renal parenchymal damage, thus forming a vicious cycle. Adequate control of hypertension with any antihypertensive agents will be effective in retarding the progression of chronic renal disease. However, available data in the laboratory animals, as well as in patients with chronic renal disease of any origin, have indicated that angiotensin blockade by angiotensin-converting enzyme inhibitors (ACEI) is superior compared with other antihypertensive agents. In fact, administration of ACEI to even normotensive subjects with chronic renal disease may be warranted; this class of drugs could thus be regarded as “renal pills.” ACEI has been widely used in patients with chronic renal disease, and their use may only be limited by the possibility of their side effects (e.g., cough, hyperkalemia). Indeed, many doctors tend to avoid ACEI in patients with advanced renal failure because of the possibility of hyperkalemia, which requires frequent monitoring.

More recent observations in patients with chronic renal disease strongly indicate that there is a real possibility that the continuous application of angiotensin blockade by ACEI may in fact completely retard the progression of chronic renal disease (5). Moreover, the glomerular pathology in patients with type 1 diabetes who receive pancreas transplantation may revert to normal over the course of years—observations that suggest that the glomerular lesions in type 1 diabetes (6), and thus by inference in glomerular sclerosis of many other chronic renal diseases, could be in principle reversible. These clinical data strongly indicate and justify aggressive management of progressive chronic renal disease.

Recent introduction of angiotensin (AT) receptor blockade is of potential interest because this class of drugs will specifically block the action of angiotensin via its type 1 receptor (AT1R) through which most of angiotensin actions on BP and vasculature and on aldosterone production are brought about. In this scenario, it is expected that blockade of AT1R will render type 2 receptor (AT2R) unopposed to elevated endogenous AT. Because the AT action via AT2R is thought to be associated with vasodilation, lowering of BP, and dilation of both glomerular afferent and efferent arterioles, AT1R blockade may be theoretically superior to ACEI in the management of chronic renal disease (7). However, most of the available data suggest that there is little difference in the action of ACEI versus AT1R blockers. Nonetheless, some interesting data suggest that they act differently in vivo on the renal function in rats with chronic renal failure, as well as in patients with chronic heart failure (7). Further studies are warranted to investigate this issue.

Dietary Protein Intake

It has been well documented in laboratory animal models that a low-protein diet is an effective way to retard the progression of renal disease. Clinical data seem to support this notion, but efforts at conducting high-quality clinical investigations are hampered by the difficulties in implementing such treatment modalities. Just imagine how effectively one can control, maintain, and monitor daily dietary protein intake in many patients who have different dietary habits and family conditions, in addition to differences in lifestyle and culture. Thus, it is not the question of its efficacy, but rather the question of implementation and practice that governs dietary protein intake.

Yet another interesting potential is the mechanism or mechanisms by which a low-protein diet can bring about the retardation of progression of chronic renal disease. In this regard, the answer has yet to be found; thus, further research is warranted to elucidate the pathophysiologic, molecular, and cellular mechanisms involved.
Molecular Biology and Genetic Engineering

As in any other area of biomedical research, basic research is the key to the future because it will provide new insights for the mechanisms, and thus the possibilities, for the future prevention and treatment of any disease. In this regard, advances in molecular and genetic engineering have drastically and fundamentally changed our research approaches and technological possibilities. Indeed, we have gained great insight into the potential causal molecular mechanism, in addition to or in relation to the hemodynamic mechanisms, of progression of chronic renal disease (e.g., involvements of transforming growth factor beta and other cytokines and growth factors) by molecular and genetic analyses, gene transfer, and other technologies. Data in genetically engineered animals have also provided invaluable insight into the structure and function of kidney in health and disease.

Nonetheless, the major obstacle in research in nephrology has been the lack of a clear target molecule against which new innovative pharmaceuticals should be developed. Moreover, there is a lack of proper animal models for chronic progressive renal disease and in vitro systems by which the effects of any new drugs could be tested with fairly established clinical relevance.

One of the research tools widely used is the cloning of genes specific to an organ, a tissue, or a cell type. In this respect, in the past, such attempts have been unsuccessful in kidney research. However, we have successfully cloned several new genes that are specifically or abundantly expressed in human glomerular mesangial cells. One such gene is a new member of serine protease inhibitor family, called megisin (mesangial serine protease inhibitor) (8). It is predominantly expressed in human mesangial cells and is upregulated at the gene and protein levels in mesangial cells of patients with proliferative IgA nephritis. The human genomic clone of megisin has been obtained, and the sites in its 5′-upstream portion have been identified that are regulated by specific nuclear factors. Homologs in rats and mice have been cloned, and studies in experimental models are under way. Furthermore, human megisin transgenic mice clearly indicate the pathophysiologic role of megisin. This kind of experimental approach will certainly provide us with exciting new dimensions in our understanding of the new therapeutic potentials for chronic renal disease.

Conclusions

The development and advancement of both science and technology in the 20th century have changed the fields of life science and health care in a way far beyond our imagination a hundred years ago. Chronic dialysis therapy is one such medical therapy, which began in the second half of the 1900s. However, the economic burden and suffering of patients and their families clearly indicate the need for improvements and the need for new alternative solutions. Renal transplantation is obviously a feasible alternative, but the organ shortage has become apparent, as has the lack of effective and affordable immunosuppressants with few adverse effects.

Both laboratory and clinical investigations will continue to advance our knowledge and understanding of health and disease, and in the new century, we hope that nephrologists have various new options so that eventually almost no patients with renal disease will reach the end stage and require dialysis therapy. Although research and developments will continue in renal disease, ESRD, dialysis, and complications of chronic dialysis, new innovative developments are within sight; these include, as outlined in this brief review, embryonic stem cells to create a new kidney or new nephrons, and new agents targeted on specific kidney genes to prevent the progression of renal disease. These represent challenges for all nephrologists.

By the midpoint of the new century, we hope that nephrologists will rarely see patients with ESRD.

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