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The future of renoprotection

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The future of renoprotection. Chronic kidney diseases are emerging as a global threat to human health. Renal replacement therapy by dialysis or renal transplantation prolongs survival in patients with end-stage renal disease (ESRD) and, in most cases, provides a good quality of life. In all wealthy countries, new patients on dialysis outnumber those who die, and the group of patients on renal replacement therapy is growing. The provision of adequate treatment to all is absorbing a large proportion of the health care budget and is being looked at with concern by policymakers. Because rationing of dialysis or deciding that some patients cannot be treated is out of the question, clinicians should be looking for ways to prevent the need for dialysis in as many patients as possible. Simple and inexpensive treatments are plausible and possibly effective. There is robust experimental evidence that proteinuria is responsible for interstitial inflammation and subsequent fibrosis, which thereby contributes to progressive renal function loss. Clinical studies and clinicopathologic correlations in patients with progressive nephropathies indicate that observations in experimental models are relevant to understanding human disease. Researchers have identified an important correlation between urinary protein excretion and rate of glomerular filtration rate decline in patients with diabetic and nondiabetic chronic nephropathy. Renoprotection is a strategy that aims to interrupt or reverse this process. The current therapeutic approach for proteinuric chronic nephropathies is based on blockade of the renin-angiotensin system with angiotensin converting-enzyme inhibitors and/or angiotensin-receptor blockers that limit proteinuria, and reduce glomerular filtration rate decline and risk of ESRD more effectively than other antihypertensive treatments. Full remission of the disease, however, is seldom obtained, particularly when pharmacologic intervention is started late. For those who do not respond, treatment procedures to achieve remission and/or regression must include a multimodel strategy to implement renoprotection. The role of lifestyle changes, including smoking cessation, should not be overlooked. A more concerted, strategic, and multisectorial approach, underpinned by solid research evidence, is essential to help reverse the increasing incidence of these chronic diseases, not just for a few beneficiaries, but equitably and on a global scale.

Resumen

Las enfermedades renales crónicas se han constituido en una seria amenaza global a la salud. La diálisis y el trasplante renal prolongan la vida de los pacientes con insuficiencia renal crónica (IRC) y en su mayor parte, proveen de una buena calidad de vida. En los países desarrollados el número de pacientes nuevos en diálisis sobrepasa al de los que fallecen, por lo que el número de pacientes en diálisis va en aumento. Es motivo de preocupación el que la provisión de un tratamiento adecuado a todo aquel que lo necesita, este consumiendo un elevado porcentaje de los presupuestos destinados a la atención de la salud. Dado de que está fuera de consideración el racionar o el decidir que pacientes no reciban tratamiento dialítico, debemos de buscar las medidas necesarias que prevengan el uso de diálisis en tantos pacientes como sea posible. Es factible y posible el utilizar tratamientos sencillos y de bajo costo. Existe una sólida evidencia experimental de que la proteinuria es responsable de la inflamación y subsiguiente fibrosis del intersticio renal, contribuyendo de esta forma al deterioro de la función renal. Estudios clínicos realizados en pacientes con nefropatías progresivas, indican que las observaciones hechas en animales de experimentación son relevantes al estudio de la enfermedad en humanos. Se ha encontrado una importante correlación entre la proteinuria y la disminución en la velocidad de filtración glomerular, tanto en pacientes con nefropatía diabética como no diabética. La renoprotección es una estrategia dirigida a interrumpir o revertir este proceso. El tratamiento actual de las nefropatías crónicas se basa en el concepto de que la utilización del bloqueo del sistema renina angiotensina con inhibidores de la ECA y/o bloqueadores del receptor de la angiotensina, disminuye la proteinuria, la perdida de la filtración glomerular y el riesgo de IRC, en forma más efectiva que otros fármacos antihipertensivos. Sin embargo, rara vez se obtiene una remisión total, especialmente si el tratamiento se inicia en forma tardía. En individuos que no respondan a dicha terapia, se debe de utilizar una estrategia de protección renal múltiple. Cambios en los hábitos de vida del individuo, incluyendo el abandono del tabaco, no deben de ser pasados por alto. Un abordaje concertado, multifactorial y estratégico, sustentado por una sólida evidencia científica, es indispensable para revertir el incremento en la incidencia de estas enfermedades crónicas, no solo para el beneficio de unos cuantos, sino en una forma globaly equitativa.

Key words: renoprotection, proteinuria, renin-angiotensin system blockade, chronic kidney disease.

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THE BURDEN OF CHRONIC RENAL DISEASES

Chronic kidney diseases are emerging as a global threat to human health [1]. During the last decade, the dialysis population has been growing at an average of 7% per year. There are now approximately 1.1 million people worldwide on renal replacement therapy (RRT) and, according to reliable estimates, the number of patients on maintenance dialysis will double in 10 years (Fig. 1). The

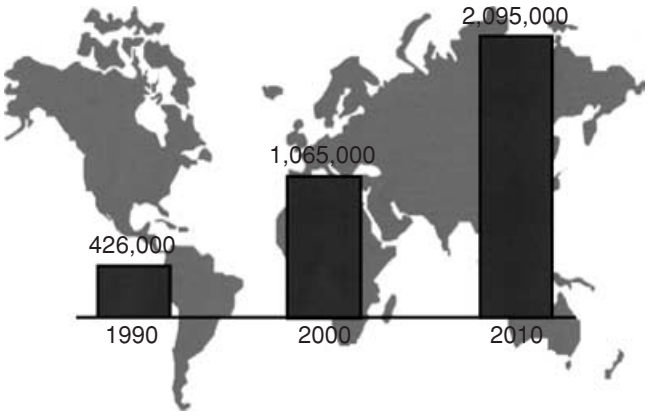

Fig. 1. Global maintenance dialysis population from 1990 to 2010 (modified from [2]).

total cumulative cost for RRT in the next decade will exceed US $1 trillion [2], a surprising figure from any point of view. In the United States, the total Medicare cost for dialysis and transplantation was US $12.7 billion in 1999 and is expected to exceed US $28.3 billion in 2010. Although this sum is 6% of the total Medicare budget, it serves only 0.7% of the Medicare population. In the European Union, the percentage of the health care expenditure absorbed by RRT programs ranges from 0.7% to 1.8%, whereas patients with end-stage renal disease (ESRD) are 0.025% to 0.06% of the total population. Continuing provision of adequate facilities, equipment, and manpower to assist the growing number of patients with ESRD will pose a substantial burden on health care resources in all developed countries in the near future. Thus, the cost and complexity of RRT put it out of reach for low-income countries, which are struggling to provide preventive and therapeutic measures for communicable diseases such as malaria, tuberculosis, acquired immune deficiency syndrome, and tropical disease infections, and have to assign their meager budget to sanitation, vaccine, nutrition, and other basic needs.

Contemporary treatment for ESRD is so costly that there is little chance that the vast majority of the world's population will have access to it. Less-privileged countries simply cannot establish programs for regular RRT for all patients with chronic kidney disease because of its prohibitive cost [3].

How might the global burden of chronic kidney disease be diminished in the future? At the present, there are no definitive cures for most acquired kidney diseases, and there is no reasonable expectation that gene therapy will be available soon enough to treat genetic forms of kidney diseases, such as polycystic kidney disease. Renal transplantation is limited by organ shortage [4], a worldwide problem that is not likely to be resolved by xenotransplantation in the near or immediate future. The best we can do at the present time is to concentrate our efforts on the prevention of progression of renal diseases.

MECHANISMS OF RENAL DISEASE PROGRESSION

During the last 20 years, research in animals and people has helped our understanding of the mechanisms by which chronic kidney diseases progresses and has indicated possible preventive methods. A large number of studies established that progressive deterioration of renal function is the result of compensatory glomerular hemodynamic changes in response to nephron loss. In a widely used experimental model of renal mass reduction, the remaining nephrons undergo hypertrophy, reduced arteriolar resistance, and increased glomerular blood flow [5]. There is a lot of experimental and clinical evidence that pharmacologic inhibition of renin-angiotensin system with angiotensin-converting enzyme (ACE) inhibitors or with angiotensin II subtype 1 receptor antagonists (ARB) slow the progression of renal failure. In vivo, angiotensin II enhances the vascular tone of both afferent and efferent glomerular arterioles and modulates intraglomerular capillary pressure and glomerular filtration rate (GFR) [6]. Aside from these glomerular hemodynamic effects of angiotensin II, other studies have revealed several nonhemodynamic effects of angiotensin II that may also be important. These findings have suggested that angiotensin II may alter permselective properties of the glomerular capillary barrier by mediating contraction of the foot processes, ultimately changing slit-diaphragm architecture and allowing proteins to escape more easily into the urinary space [7]. Abnormal protein trafficking through the glomerular capillary wall might contribute to progression of renal disease. Indeed, recent data are in support of the possibility that the excessive protein load of podocytes can be a factor underlying progressive injury of these glomerular cells and through their release of transforming growth factor $\beta 1$, ultimately allowing myofibroblast differentiation of mesangial cells [8]. Moreover, excessive protein reabsorption by proximal tubuli provides further intrinsic toxicity to this nephron segment. Thus, both in vitro and in vivo, protein overload causes increased production of vasoactive and inflammatory mediators such as endothelin-1, monocyte chemoattractant protein-1, normal T cell expressed and secreted, a chemotactic cytokine for monocytes and memory T cells, and osteopontin [9]. The activation of a variety of molecules, such as cytokines, growth factors, and vasoactive substances, may result in abnormal accumulation of extracellular matrix collagen, fibronectin, and other components that are responsible for interstitial fibrosis. Proinflammatory mediators promote local recruitment of macrophages and lymphocytes [10], which, in turn, can stimulate the transformation of interstitial cells into myofibroblasts. Proximal tubular epithelial cells can interact with interstitial fibroblast to promote fibrogenesis via release of profibrogenic molecules [11].

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