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Clinical benefits of slowing the progression of renal failure

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Clinical benefits of slowing the progression of renal failure. End-stage renal disease is a social and economic threat worldwide. In this context, any medical intervention that may prevent the progression of chronic kidney disease becomes extremely important. Improving the cardiovascular status is another major objective in the management of this population, because cardiovascular disease is the leading cause of morbidity and mortality among dialysis patients. Moreover, this is only the tip of the iceberg, because many patients die before reaching end-stage renal disease.

Today, several interventions are available to delay the progressive loss of renal function and/or prevent the development of cardiovascular disease, but we are still far from being satisfied. These interventions include low protein diets, correction of calcium-phosphate disorders and anemia, blood pressure and proteinuria control, and smoking cessation. Other interventions, such as the administration of lipid-lowering agents, are emerging as particularly promising therapeutic approaches.

Recently, growing attention has been paid to polytherapeutic approaches to chronic kidney disease, in order to control different causal factors involved in progression and reduce them as much as possible. However, larger prospective, controlled, randomized clinical trials are needed to demonstrate their actual usefulness.

All the interventions are likely to be more effective if performed as early as possible in the course of the disease, because it has been widely demonstrated that early and regular nephrologic care is associated with decreased morbidity and mortality.

End-stage renal disease (ESRD) is a very significant and growing social and economic problem worldwide, and the number of patients requiring renal replacement therapy (RRT) has increased dramatically and partially unexpectedly. In 1984, Eggers et al [1] estimated that 117,200 patients would be receiving RRT by 2000. However, these projections were largely disproved by reality: according to the United States Renal Data System, a total of 378,862 patients were receiving RRT in 2000 in the United States, with a point prevalence rate of 1367 patients per million population [2]. Similarly, although to a lesser extent, the prevalence of ESRD has also significantly increased in European countries and has been paralleled by increased incidence rates worldwide. In this perspective, chronic kidney disease (CKD) does not represent simply a clinical matter, but also a growing economic and organizational problem, because RRT consumes a considerable proportion of health care resources. Therefore, any medical intervention that may prevent the progression of CKD toward ESRD is extremely important. Preventing cardiovascular disease is another important objective. It is well known that patients even with early CKD are at much higher risk of cardiovascular disease in comparison with the general population; cardiovascular disease accounts for 30% of hospitalizations and for more than 50% of deaths in dialysis patients. The prevalence of cardiovascular disease is already high at the beginning of RRT [3, 4], which suggests that the pathogenetic mechanisms have been operating well before. This is also witnessed by the fact that in patients with CKD in the conservative phase at all stages, the occurrence of death is far more common than the need for dialysis [5], which confirms the high burden of cardiovascular disease in this population. For this reason, the management of CKD in the conservative phase should also comprise all available therapeutic options aimed at preventing or reducing the development of cardiac abnormalities and vascular disease.

Key words: chronic kidney disease, cardiovascular disease, end-stage renal disease, hypertension, proteinuria, anemia, hyperphosphatemia, dislipidemia.

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DIET MANAGEMENT

Once considered one of the most important steps in the treatment of CKD, the role of dietary protein restriction in slowing down the progression of CKD has been largely reappraised in recent years. In an Italian multicenter study comparing a low protein diet (0.6 g/kg body weight/day) with a "normal" controlled protein diet (1.0 g/kg body weight/day), the favorable effect of a low protein diet on cumulative renal survival was only of borderline significance ($P < 0.06$) [6]. Similarly, the Modification of Diet in Renal Disease (MDRD) study [7] was unable to demonstrate a significant effect of low protein diets in slowing down the rate of CKD progression. According to an estimate we performed some years ago starting with the results from the MDRD study, the adherence to a low protein diet for nearly 9 years could delay the beginning of RRT of no more than 1 year (Fig. 1)

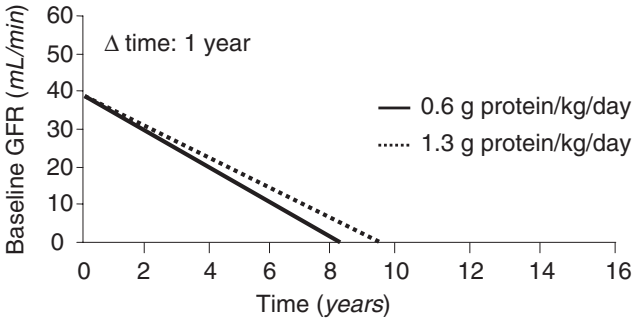

Fig. 1. The effect of the low protein diet in the MDRD Study A: Time to ESRD [8].

[8]. However, we have to balance this with the fact that these diets are very demanding on patients and their families and could expose to the risk of malnutrition. Dietary counseling remains a fundamental step in the management of CKD patients, who have to be taught to assume a hyposodic diet with controlled protein and phosphate intake and adequate caloric content, especially in the more advanced phases of CKD (when the risk of malnutrition is higher).

BLOOD PRESSURE AND PROTEINURIA CONTROL

Not only is hypertension an important presenting feature of CKD but, together with proteinuria, it is a major factor contributing to its progression. As a consequence, effective anti-hypertensive therapy is the cornerstone of treatment in CKD patients, excepting the possible treatment of primary disease.

Over the last decade, a number of trials have been performed to assess the degree of blood pressure (BP) reduction needed to achieve renoprotection. In the MDRD study, aside from randomization to two different dietary protein intakes, patients were also randomized to a usual BP control or to a stricter BP control [7]. In study A (baseline GFR 25–55 mL/min), the mean decline in GFR was faster in the first 4 months of follow-up and slower thereafter in the strictthan in the usual BP group, while in patients with more advanced CKD, the decline of GFR was linear and did not differ significantly between the two BP groups. The patients with higher levels of baseline proteinuria received greater benefits from being assigned to a low BP target. According to the estimate mentioned previously [8], a stricter control of BP could delay the time to ESRD by 1.24 years over a period of 9.4 years compared with the usual BP target of those years. Very recently, Sarnak et al [9] published the results of the long-term follow-up of this study. After a median of 5.9 years, ESRD developed in 62% of the participants in the low target BP group and in 70% of the patients in the usual BP group, indicating a significant reduced risk for kidney failure with the low BP target (after controlling for covariates, hazard ratioof 0.68; confidence interval, 0.57–0.82). This effect was similar during follow-up, without any difference between intervals during or after the randomized trial. As expected, the risk reduction tended to be larger in patients with more severe proteinuria.

The African American Study of Kidney Disease and Hypertension study [10] was designed afterwards to assess the impact of two BP goals (102–107 mm Hg and ≤92 mm Hg, respectively) and three different drug regimens (ramipril, amlodipine, and metoprolole) on the progression of hypertensive nephrosclerosis in African Americans. However, in this specific population, a lower BP control did not result in a better outcome compared with the usual control. These negative findings could be partially explained by the fact that the selected patients had only mild proteinuria or that they were predominately African Americans.

Given the clear relationship between urinary protein excretion and BP levels, any anti-hypertensive therapy has the potential to decrease proteinuria and CKD progression. However, some agents are probably capable of reducing CKD progression, because they also halt other pathogenetic mechanisms involved in glomerular and tubular-interstitial renal damage; this is particularly true for drugs blocking the renin-angiotensin system, as demonstrated by a number of clinical trials [11–13]. These findings were confirmed by a meta-analysis of 11 randomized trials comparing the efficacy of antihypertensive regimens including those in patients with nondiabetic renal disease. After adjustment for changes in BP, the relative risk in the angiotensin-converting enzyme (ACE) inhibitor group compared with standard antihypertensive therapy was 0.69 for ESRD and 0.70 for the combined end point of the doubling of baseline serum creatinine or ESRD [14].

In patients with type 2 diabetic nephropathy, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan study [15] and the Irbesartan Diabetic Nephropathy Trial [16] have shown that angiotensin receptor blockers (ARBs) are able to slow down the progression of nephropathy at least partly independently of their capacity to lower BP.

In the majority of these studies, systolic BP and diastolic BP values achieved with the experimental treatment were lower than those obtained during standard anti-hypertensive therapy. This has raised the controversy whether these drugs are really superior to other antihypertensive agents when recommended BP values are achieved. Very recently, Ruggenenti et al [17] published the results of the REIN-2 study. This was a multicenter, randomized, controlled trial of 338 patients with nondiabetic proteinuric nephropathies receiving ACE inhibitors, who were randomized to conventional (diastolic BP < 90 mm Hg) or intensive (systolic BP/diastolic BP

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