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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.

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)

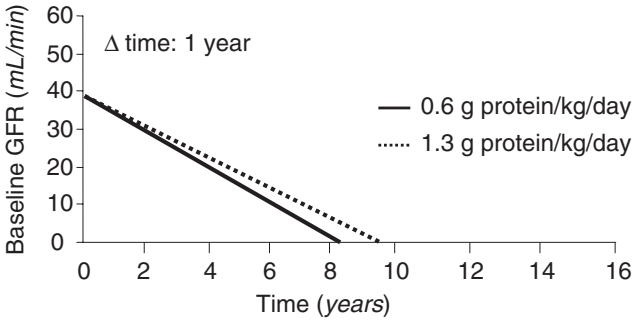

Fig. 1. The effect of the low protein diet in the MDRD Study A: Time to ESRD [8].

[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

<130/80 mm Hg) BP control. Over a median follow-up of 19 months, a similar percentage of patients progressed to ESRD (nearly 20%) in the two groups, suggesting no additional benefit from intensive BP control when patients were already treated with an ACE inhibitor, at least as far as renoprotection was concerned. Indeed, BP reduction is, in any case, of paramount importance to reduce the burden of cardiovascular disease in this population.

It has been hypothesized that complete inhibition of the renin-angiotensin system by dual blockage with ACE inhibitors and ARBs would be most beneficial in the management of progressive CKD than either agent alone. The COOPERATE study [18] seems to confirm that combination treatment safely retards progression compared with monotherapy. After 3 years of follow-up, 11% of the patients on combination treatment reached the combined primary end point of the doubling of serum creatinine from baseline or ESRD compared with 23% of those treated with the two agents alone. These observations are in line with the results of a meta-analysis, which was preliminarily presented at the 2004 American Society Annual Meeting [19]. The authors found a significantly higher antiproteinuric effect of combination therapy compared with ACE inhibitors or ARBs alone (mean proteinuria reduction of 64.6% vs. 37.7%, respectively). However, further studies are still awaited to better confirm this therapeutic option.

USE OF STATINS

On the ground of experimental observations in animal models and human renal biopsies, dislipidemia has been suggested as one of the pathogenetic factors involved in CKD progression. This hypothesis seems to be in line with the results of some clinical studies [20, 21]. In this perspective, the administration of statins could be particularly useful in CKD patients, considering that these agents could reduce the fibrogenic and inflammatory response often observed in many nephropathies. Confirmation of this comes from a number of experimental studies that suggest a direct action of statins in halting extracellular matrix accumulation, overexpression of connective growth factors [22], and tubular-interstitial fibrosis [23].From the clinical point of view, a number of small studies, the results of which have been collected in a meta-analysis [24], seem to suggest an anti-proteinuric effect of statins. Furthermore, these agents may be able to slow down the rate of CKD progression [24]. More recently, Bianchi et al [25] performed a prospective, randomized trial in 56 CKD patients who had received an ACE inhibitor or an ARB for 1 year and were then randomized to receive or not receive atorvastatin while still being administered their previous therapy. Adding the statin caused a significant reduction in proteinuria levels (from 2.2 ± 0.1 g/day to 1.2 ± 1.0 g/day), which remained substantially unmodified in the group of patients not receiving atorvastatine (from 2.0 ± 0.1 g/day to 1.8 ± 1.0 g/day). In addition, creatinine clearance remained stable in those treated with the statin (from 51 ± 1.8 mL/min to 49.8 ± 1.7 mL/min), whereas it progressively decreased in the control group (from 50 ± 1.9 mL/min to 44.2 ± 1.6 mL/min). Larger studies are awaited in this field.

Given the high cardiovascular risk of this population, treatment with statins could also have a role in preventing or reducing the burden of cardiovascular disease. Unfortunately, no prospective, randomized studies have been performed so far in patients with CKD in the conservative phase. However, secondary analyses of large trials performed on both primary and secondary prevention in more heterogeneous populations seem to suggest a positive effect of statins in CKD patients also [26, 27].

CORRECTION OF ANEMIA

Anemia is highly prevalent in CKD patients. This complication is associated not only with a worse quality of life, but also with increased prevalence of cardiovascular disease and higher rates of hospitalization. Hemoglobin levels start to decrease quite early during the course of chronic nephropathies, well before the start of RRT [28]. It is therefore expected that anemia correction, particularly if started early in the conservative phase, could improve the cardiovascular outcome of this population. Small studies have shown that treatment of anemia with erythropoietin is able to reverse some of the functional and morphologic cardiac changes seen in CKD [29]. However, large, randomized, controlled studies [30–32], which were mainly performed in patients already on RRT (and thus with more advanced cardiovascular disease), were unable to demonstrate a major effect of a complete correction of anemia in reducing the risk for hard end points, such as death or major cardiovascular events. Given these considerations, current European Best Practice Guidelines for the management and treatment of anemia in CKD patients suggest to achieve a hemoglobin target of $\geq$11 g/dL [33]. Higher values could be considered for individual patients, taking gender, age, ethnicity, activity, and comorbid conditions into account.

Starting from the experimental observation that hypoxia could worse kidney damage, it has been hypothesized that anemia correction may have favorable effects in slowing down the progression of CKD. However, evidence on this issue is still very limited. Preliminary observations were obtained in small and/or retrospective studies [34, 35]. More recently, secondary analyses of two trials aimed at testing the effect of anemia normalization on mortality were not able to demonstrate any effect of the progression of CKD [31, 32]. However, in one of the two studies [31], the analysis was performed only in a limited number of patients who were in the conservative

phase (72 out of 416). Moreover, diastolic BP values at the end of follow-up were higher in patients assigned to the higher hemoglobin target, possibly confounding the analysis. The other study [32], which was performed on 155 CKD patients not on RTT, suffered from the limitation that only a few patients reached the hemoglobin target, which led to an insufficient split of hemoglobin values between the two groups and thus reduced statistical power. More recently, a Greek randomized study found a significant reduction in the risk of developing ESRD or death in those who were put to a hemoglobin target higher than 13 g/dL compared with the control group (treatment with erythropoietin only in the case of a drop of hemoglobin below 9 g/dL) [36]. However, the particular high number of patients reaching the end point during a median follow-up of only 22.5 months imposes caution in the interpretation of these results.

CORRECTION OF CALCIUM-PHOSPHATE DISORDERS

Disturbances of calcium-phosphate metabolism play a key role in CKD, making an important contribution to the development of osteodistrophy. In the past few years, evidence has increased about the fact that elevated levels of serum phosphorus and subsequent secondary hyperparathyroidism not only cause bone disease, but also significantly contribute to the high morbidity and mortality of CKD patients. In a study of 6047 patients receiving hemodialysis for at least 1 year, higher levels of phosphatemia were associated with increased risk of death, even after adjustment for pre-existing medical conditions, delivered dose of dialysis, and estimates of nutritional status and noncompliance [37]. More recently, the same authors analyzed data from 40,538 hemodialysis patients and confirmed an increased relative risk of death in those with serum phosphorus concentrations >5.0 mg/dL [38]. Higher adjusted serum calcium concentrations were also associated with an increased risk of death.

Even if the exact pathogenetic mechanisms explaining these associations are still unknown, it is now quite clear that calcium-phosphate disorders contribute to vascular and tissue calcifications, especially those involving coronary arteries, cardiac valves, and myocardial tissue. In this context, the definition of hyperphosphoremia as a "silent killer" seems to be appropriate. Given these considerations, adequate control of phosphate and parathyroid hormone (PTH) levels is extremely important in CKD patients. Unfortunately, the therapeutic tools now available are still unsatisfactory and laden by a number of side effects. This is testified by the low percentage of patients that, according to the results of the DOOPSstudy, reach target values of calcium, phosphate, and PTH recommended by current guidelines. We hope that calcimimetics and new vitamin D analogues could be of better help.

SMOKING CESSATION

The potential mechanisms of smoking-related nephrotoxicity are many, including both acute and chronic pathways. Smoking patients with type 1 or type 2 diabetes are at higher risk of developing microalbuminuria followed byproteinuria (i.e., overt diabetic nephropathy). Moreover, they have an accelerated progression of diabetic nephropathy toward ESRD in comparison with nonsmoking diabetics [39]. The adverse effects of smoking on CKD progression have been also shown in nondiabetic renal diseases [40]. These data, taken together with the increased cardiovascular risk related to smoking, suggest that cessation of smoking has to be taken into consideration by physicians as a primary goal in the management of CKD patients.

THE IMPORTANCE OF EARLY REFERRAL TO NEPHROLOGISTS

All the interventions available today in the conservative phase of CKD are likely to be more effective if performed as early as possible in the course of the disease. The detrimental effects of late referral have been widely highlighted, both in terms of higher morbidity and higher mortality. An early referral to nephrologic care, in addition to its beneficial effects for patient health, could also lead to significant advantages in terms of cost savings for society [41].

Despite this evidence, late referral is a widespread problem in all countries, and no decreases in its rate have been registered in recent years. However, a hypothetical increase in the referral rate to nephrologists would not be free from organizational problems. Given the high and increasing prevalence of CKD patients, the evaluation of the cost-effectiveness of screening programs of groups at higher risk of developing progressive CKD (e.g., elderly patients with diabetes or hypertension) and the development of new models of health care delivery, the involvement of nephrologists and other physicians and non-physicians in an integrated way will be an inevitable strategy for the future.

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