The importance of early detection of chronic kidney disease

Francesco Locatelli, Lucia Del Vecchio and Pietro Pozzoni

Department of Nephrology and Dialysis, Ospedale A. Manzoni, Lecco, Italy

Abstract
Despite the absence of precise epidemiological data, we know there are a great many patients in the conservative phase of chronic kidney disease (CKD). The incidence and prevalence of renal replacement therapy (RRT) is increasing worldwide. As well as being a large and growing clinical problem, CKD is of an economic and organizational concern, since RRT consumes a considerable proportion of health care resources. In this context, any medical intervention that may prevent the progression of CKD towards end-stage renal disease (ESRD) is extremely important. Improving the patients’ cardiovascular status is also a major objective in the management of this population, as cardiovascular disease (CVD) is the leading cause of morbidity and mortality for dialysis patients. Several interventions to delay the progressive loss of renal function and/or to prevent the development of CVD are now available. These include low-protein diets; correction of calcium-phosphate disorders and anaemia; blood pressure and proteinuria control; and smoking cessation. Other interventions, such as the administration of lipid-lowering agents, anti-inflammatory drugs, and anti-oxidant agents are emerging as particularly promising therapeutic approaches, although prospective, controlled, randomized clinical trials are needed to demonstrate their clinical usefulness. Intervention in the conservative phase of CKD is likely to be more effective if performed as early as possible in the course of the disease, since it has been widely demonstrated that early and regular nephrology specialist care is associated with decreased morbidity and mortality.

Keywords: cardiovascular disease; chronic kidney disease; referral; renal replacement therapy

Introduction
End-stage renal disease (ESRD) is a considerable social and economic problem worldwide, and one that is increasing. In 1998, the incidence of treated ESRD in Europe ranged from 110 per million population (p.m.p.) in The Netherlands to 192 p.m.p. in Germany [1]. Even higher incidence rates were recorded in the same year in countries outside Europe, such as the USA (>300 p.m.p.) and Japan (>200 p.m.p.) [2]. The prevalence rates of treated ESRD are even more interesting, as they show the actual burden on health care resources. In 1998, the prevalence of treated ESRD in Europe ranged from 498 p.m.p. in the UK to 854 p.m.p. in Italy [1]. Again, Japan and the USA recorded higher rates than European countries, with prevalences of >1400 p.m.p. and almost 1200 p.m.p., respectively [2].

Both incidence and prevalence of treated ESRD are increasing [1]. Reasons for this are likely to be an actual increase in the occurrence of chronic kidney disease (CKD); improved survival from other diseases (so-called competitive risk); and wider acceptance criteria for renal replacement therapy (RRT) – more elderly patients, patients with diabetes, and patients with other severe comorbidities (malignancies, systemic diseases, etc.) are requiring RRT. Data from the Registro Lombardo Dialisi e Trapianto, Italy, show that the percentage of patients starting dialysis aged >65 years almost tripled from 1983 to 1997, from 19.7 to 54% [3]. There were high rates of diabetes and vascular and unknown nephropathies in these patients. Data on ESRD are quite extensive, due to the availability of registries covering a large percentage of patients on RRT. However, epidemiological data regarding CKD in the pre-dialytic phase may be unreliable because of an increasing tendency to extrapolate data obtained from RRT populations. Bearing these limitations in mind, available data indicate that CKD is a significant epidemiological problem even in its conservative phase. The Registro Lombardo Dialisi e Trapianto reported an estimated annual incidence of CKD in Lombardy of 336.6 p.m.p.
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for 1993 [4]. A French epidemiological study of a large urban area indicated an overall annual incidence of CKD of 260 p.m.p., with a striking increase in incidence with age. The incidence in patients aged > 75 years was almost seven times higher than that of patients aged 20–39 years and more than twice that of patients aged 40–59 years [5]. These rates are lower than those from the Lombardy data, probably because more restricted criteria were used in this study to define CKD (serum creatinine concentration (SCr) > 2 mg/dl vs SCr between 1.5 and 3 mg/dl).

The most comprehensive source of epidemiological data on CKD in the pre-dialytic phase is the Third National Health and Nutrition Examination Survey (NHANES III), which collected epidemiological data in the USA from 1988 to 1994. NHANES III reported that 4.98% of the male population and 1.55% of the female population had SCr > 1.5 mg/dl and 0.64 and 0.33%, respectively, had SCr > 2.0 mg/dl. The same report also found that older age and male sex were associated with higher SCr levels. More than 25% of American males aged > 70 years had SCr levels > 1.5 mg/dl [6]. In light of the data, CKD is not only a clinical concern, but also a growing economic and organizational problem, as RRT consumes a considerable proportion of health care resources. Therefore, any early stage medical intervention that may prevent progression of CKD to ESRD is extremely important.

Preventing cardiovascular disease (CVD) in CKD patients is another major objective. It is well known that, even in the early stages of CKD, patients are at much higher risk of CVD than the general population. CVD accounts for 30% of hospital admissions and for > 50% of deaths in patients on dialysis. There is already a high prevalence of CVD among patients with CKD at the start of RRT [7,8], suggesting that even at this stage patients have reached, or are at least close to reaching, near-terminal cardiac failure as well as renal failure. Indeed, it has been widely demonstrated that cardiovascular (CV) status at the beginning of dialysis strongly affects the outcome of patients [9] and is the main factor affecting morbidity and mortality in these patients. Therefore, interventions aimed at preventing cardiac abnormalities, such as adequate antihypertensive treatment, anaemia correction, limitation of saline and volume overload, and control of calcium-phosphate metabolism and dyslipidaemia, are crucial in the management of these patients, especially if they are started as early as possible in the course of CKD. Furthermore, given the very high morbidity and mortality of patients on RRT, a great effort should also be made to delay the progression of CKD to ESRD for as long as possible. The efficacy of some therapeutic approaches, such as low-protein diets, correction of metabolic disorders, control of blood pressure (BP) and proteinuria, and stopping smoking, has already been proven. Other interventions, such as the administration of statins, anti-inflammatory agents, and anti-oxidants, are still being evaluated.

Dietary management

The efficacy of dietary protein restriction in slowing progression of CKD is still controversial, despite a large number of studies over the last decades. Several large-scale randomized clinical studies reported minor benefits of low-protein diets but failed to demonstrate a major effect. In an Italian multicentre study, the effect of a low-protein diet (0.6 g/kg body weight/day) on cumulative renal survival was only of borderline significance ($P < 0.06$) compared with a ‘normal’ controlled protein diet (1.0 g/kg body weight/day) [10]. In the Modification of Diet in Renal Disease (MDRD) study [11], the mean decline in glomerular filtration rate (GFR) was $-3.6$ ml/min/year and $-4.03$ ml/min/year in patients who had been assigned to receive either a usual protein diet (1.3 g/kg/day) or a low-protein diet (0.58 g/kg/day), respectively. Assuming that the rate of progression from chronic renal insufficiency (CRI) to ESRD is linear, and that compliance and effect of treatment are constant over time, the time to ESRD (defined as a GFR of < 5 ml/min) can be expected to be 9.33 and 8.33 years, respectively. Adherence for nearly 9 years to a low-protein diet, which may be very demanding on patients and their families and may increase the risk of malnutrition, only delayed the start of RRT by up to 1 year [12]. A recent meta-analysis showed that a restricted protein intake was associated with a 39% reduction in the relative risk of death or need for RRT compared with normal protein intake ($P = 0.006$) [13]. However, because low-protein diets decrease serum-urea levels, and the decision to start RRT is often based on these levels, patients with a reduced protein intake would be expected to start RRT later than patients with higher protein intake. Therefore, it is difficult to understand from the data whether low-protein diets effectively reduce the progression of CKD or simply provide better metabolic control, which in any case is of major importance for phosphate control.

Correction of calcium-phosphate disorders

Disturbances of calcium-phosphate metabolism certainly play a key role in CKD. Indeed, over the past few years, evidence has accumulated 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 patients with CKD. A study of 6047 patients receiving haemodialysis for at least 1 year found that higher degrees of phosphataemia 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 of non-compliance [14]. These findings, confirmed and even extended by a subsequent study [15], clearly suggest that hyperphosphataemia contributes directly to the excessive mortality rate of ESRD patients,
probably through calcified coronary plaques and the calcification of cardiac valves and myocardial tissue due to increased calcium-phosphate product and/or secondary hyperparathyroidism [16]. In this context, it is appropriate to define hyperphosphataemia as a ‘silent killer’ [16]. The relationship between hyperphosphataemia and increased mortality highlights the importance of adequate control of hyperphosphataemia. A radical change in the nephrologist’s perception of the danger of hyperphosphataemia is needed: it is far more important to avoid death from cardiac calcification than to prevent renal osteodystrophy.

**Blood pressure and proteinuria control**

Other than treatment of the primary disease, control of BP and proteinuria are the only interventions to date that have definitively demonstrated the ability to slow the progression of CKD. Results from the MDRD study showed that patients assigned to target mean arterial pressures of 92 and 107 mmHg had a decline in GFR of −3.56 and −4.10 ml/min/year, respectively. It was calculated that this strict control of BP could delay time to ESRD by 1.24 years over a period of 9.4 years (9.43 vs 8.19 years) [12]. The MDRD study also indicated that patients with higher levels of proteinuria had faster declines in GFR and that the beneficial effect of lowering BP on the progression of CKD was associated with the severity of baseline proteinuria [17]. For this reason, proteinuria level should always be taken into account when defining the target BP for patients with CKD. Reduction of proteinuria as a means of slowing CKD progression is also becoming recognized as important in normotensive patients.

Thus, the role of BP control in slowing the progression of CKD is well established. However, some antihypertensive drugs themselves display renoprotective effects that appear to be partially independent of the BP control they provide. Several clinical trials have shown that drugs blocking the renin–angiotensin system (angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists) are more effective in reducing CKD progression than other antihypertensive drugs, and that this renoprotective effect could be partially independent of an increased BP control (Figure 1) [12,18]. A recent meta-analysis of 11 randomized trials compared the efficacy of antihypertensive regimens with and without ACE inhibitors in 1860 patients with non-diabetic renal disease. After adjustment for changes in BP during follow-up, the relative risk in the ACE inhibitor group was 0.69 for ESRD and 0.70 for the combined endpoint of the doubling of baseline SCr or development of ESRD [19].

Type 2 diabetes is the leading cause of ESRD in many countries. Two large randomized controlled clinical trials, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study [20] and the Irbesartan Diabetic Nephropathy Trial (IDNT) [21], have highlighted that angiotensin II receptor antagonists are renoprotective in patients with type 2 diabetes. These drugs seem to be able to slow the progression of diabetic nephropathy, to some degree independently of their capacity to lower BP [20,21]. However, current guidelines recommend a target BP of 120/80 mmHg rather than the 140/90 mmHg achieved in the majority of trials so far. Superiority of ACE inhibitors or angiotensin II receptor antagonists over other antihypertensive drugs in slowing the progression of CKD has not been demonstrated at this lower BP level. Prospective, controlled, randomized trials are needed to answer this important question, even if the answer turns out to be that it is difficult to reach this BP level in CKD patients without using ACE inhibitors or angiotensin II receptor antagonists.

**Correction of anaemia**

Anaemia is highly prevalent in patients with CKD and is a major problem. It is associated with reduced

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**Fig. 1.** (a) Estimate of the effect of mean arterial pressures (MAP) of 107 (usual BP) and 92 mmHg (low BP) in delaying the progression of CRI in patients in the Modification of Diet in Renal Disease (MDRD) Study A. The mean baseline GFR was 38.6 ml/min. Patients with a MAP of 107 mmHg had a higher decline in GFR (−4.1 ml/min/year) compared with patients with a MAP of 92 mmHg (GFR of −3.5 ml/min/year). Strict BP control delayed the beginning of RRT by 1.24 years (9.43 vs 8.19) [12]. (b) Estimate of the effect of ACE inhibitors compared with placebo in delaying the need for RRT in patients in the AIPRI Study. Patients taking benazepril had a lower decline in GFR (−3.38 ml/min/year) than placebo (−4.95 ml/min/year). This produced an estimated delay in the beginning of RRT of 3.85 years over a period of 11.3 years (11.32 vs 7.47) [12].
Cessation of smoking

Over the last few years, smoking has emerged as an important risk factor for the progression of CKD [26]. The potential mechanisms of smoking-related nephrotoxicity are many, including both acute and chronic pathways. There is now evidence that smokers with type 1 or type 2 diabetes are at higher risk of developing microalbuminuria, of progressing to develop gross proteinuria (i.e. overt diabetic nephropathy) and, above all, of accelerated progression of diabetic nephropathy towards ESRD than non-smokers with diabetes [27]. The adverse effects of smoking on the progression of CKD have also been shown in non-diabetic renal disease [28]. Although large prospective trials investigating this issue are still lacking, the data suggest that smoking is probably a major risk factor for patients with CKD both with and without diabetes. Hence, physicians now see stopping smoking as a primary goal in the management of patients with CKD.

Emerging therapeutic approaches

On the basis of several experimental models, as well as observations from human renal biopsies, dyslipidaemia accompanying CKD has been claimed to hasten the progression of CKD [29]. This hypothesis has been confirmed in prospective studies [30–32]. Administration of statins or other lipid-lowering agents may be particularly useful here since, in addition to their beneficial effects on the serum lipid profile, these agents may also influence the inflammatory and fibrogenic responses that are common in many forms of progressive CKD. Indeed, there is growing evidence that inflammatory events, particularly in the tubulo-interstitial compartment, play a critical role in the non-immunological progression of CKD. Inhibiting the inflammatory component of cellular events may therefore be another way of slowing the progression of CKD. In this context, it is worth noting that the renoprotection achieved by ACE inhibitors or angiotensin II receptor antagonists can also be explained, at least in part, by their ability to block the pro-inflammatory actions of angiotensin II. Pharmacological interventions aimed more specifically at inhibiting intrarenal inflammatory events are therefore likely to further slow the progression of CKD. Indeed, the potential therapeutic role of several anti-inflammatory drugs, including steroids, non-steroidal anti-inflammatory drugs, cyclooxygenase-2 (COX-2) inhibitors, macrophage-inhibiting devices (anti-macrophage serum, systemic X-irradiation, essential fatty acid-deficient diets, gamma lactone) and myco-phenolate mofetil, even for non-immune-mediated CKD, have been investigated in several experimental studies. Positive inhibitory effects on the progression of interstitial fibrosis have been shown for all of these treatments [33]. However, prospective, controlled, randomized clinical trials are needed to demonstrate the clinical usefulness of these drugs in the treatment of CKD.

Oxidative stress, which results from an imbalance between antioxidant defence mechanisms and excessive generation of oxidants, is clearly increased in CKD, as evidenced by the increase in several indicators of oxidative stress in these patients. Although these changes are more pronounced in patients undergoing haemodialysis, there is evidence that they begin in the earliest stages of CKD. Increased oxidative stress in CKD has been claimed to contribute to the pathogenesis of several important aspects of CKD, such as dialysis-related amyloidosis, malnutrition, low response to rHuEPO therapy and, most importantly, hypertension and atherosclerosis, thus leading to increased CV risk. Increased oxidative stress in CKD may therefore contribute to the increased morbidity and possibly the mortality of these patients, although prospective epidemiological studies to confirm this are still lacking. This suggests a potential role for antioxidants in patients with CKD. A number of trials have investigated the effects of antioxidant supplementation with vitamin E [34–37], vitamin C [38]...
or melatonin [39] on several experimental or clinical outcomes, with interesting results. With the objective of clarifying the potential benefits of antioxidant therapy on the outcome of CKD, larger, prospective, controlled trials are desirable in the near future.

The importance of early referral to a nephrologist

All interventions now available in the conservative phase of CKD are likely to be more effective if performed as early as possible in the course of the disease; in other words, if patients are referred to the nephrologist early. The consequences of late referral have been documented, both in terms of higher morbidity [40] and higher mortality [41,42]. In a recent, large, retrospective study of 1057 French patients, who started dialysis between 1989 and 1998, 5-year survival was found to be significantly lower in patients who had been referred <6 months (57.8 ± 4.2%), or 6 months to 3 years (65.3 ± 3.9%) prior to start of dialysis in comparison with those who had been referred earlier, between 3 and 6 years (77.1 ± 3.7%, P < 0.01) or >6 years (65.3 ± 3.9%, P < 0.001) prior to start of dialysis [43]. A recent economic evaluation based on USA and Canadian data over a 5-year period showed that an early referral to nephrology specialist care, in addition to its beneficial effects for patient health, could also lead to significant advantages in terms of health care costs [44].

Taken together, there is now striking evidence that early and regular nephrology specialist care in the pre-dialytic phase of CKD is associated with decreased morbidity, decreased short-term mortality, improved long-term survival on dialysis, and decreased costs. Despite this evidence, the epidemiological data indicate that late referral has not decreased in recent years. There is no barrier to referral to nephrology specialist care in most countries, which suggests that the problem is to a large degree cultural, i.e. there is a widespread lack of awareness of the potential benefits of early and regular management by a nephrologist. However, it is also important to consider the effect on resources of a widespread shift to early referral. As the prevalence of CKD is high and rising, evaluation of the cost-effectiveness of screening programmes for groups at high risk of developing progressive CKD (e.g. elderly patients with diabetes or hypertension) and the development of new models of health care delivery, integrating care from nephrologists and other physicians and other healthcare professionals, will inevitably be needed in the future. However, stressing the vital importance of early detection of CKD and the subsequent early referral of patients to regular nephrology specialist care is probably the most urgent challenge for nephrologists today. We can no longer ignore the fact that late referral to a nephrologist leads to ‘loss of chance for the patient, loss of money for the society’ [45].

References

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