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Epidemiology of cardiovascular risk in patients with chronic kidney disease

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Abstract

Background. Chronic kidney disease (CKD) patients are highly prone to cardiovascular disease for a number of reasons. At the time of starting renal replacement treatment, their cardiovascular condition is already severely compromised, suggesting that cardiovascular risk factors begin to operate very early in the progression of CKD. Moreover, those patients reaching end-stage renal disease without cardiovascular abnormalities have a high probability of developing *de novo* cardiovascular disease.

Methods. In this review, we analyse the prevalence of the major cardiovascular risk factors in CKD patients and their importance as contributors to the excess cardiovascular disease in this population. We also describe and discuss the main results obtained in the management of these risk factors in terms of preventing cardiovascular morbidity and mortality.

Results. Hypertension plays a major role in determining cardiac damage at all stages of CKD, including the dialytic phase. Anaemia is a major determinant of the development of left ventricular hypertrophy and therefore its correction can be expected to improve cardiovascular status and long-term survival, but this needs to be done before changes in cardiac structure become well established. Calcium–phosphate disorders are increasingly acknowledged to be cardiovascular risk factors in CKD, yet their medical control is still far from being satisfactory. Dyslipidaemia is particularly frequent in CKD patients, but the benefit of lipid-lowering treatments still has to be proven. Finally, CKD is associated with newly recognized risk factors for atherosclerosis, although their importance as cardiovascular risk factors is still controversial.

Conclusions. Nephrologists should attempt to give optimal treatment for well-established cardiovascular risk factors, even if this generally fails to prevent the excess cardiovascular disease of CKD patients. Increasing attention is now being paid to newly recognized CKD-related risk factors for atherosclerosis, although their real importance is still under debate and, before therapeutic prescriptions can be applied to CKD patients, further studies in these new fields are needed.

Keywords: anaemia; cardiovascular disease; chronic kidney disease; dyslipidaemia; end-stage renal disease; hyperphosphataemia; hypertension

Introduction

Chronic kidney disease (CKD) patients, particularly those with end-stage renal disease (ESRD), are at much higher risk of cardiovascular disease than the general population. Cardiovascular disease is by far the leading cause of morbidity and mortality in dialysis patients, accounting for almost 40% of hospitalizations [1] and almost 50% of deaths [1,2] and, after stratification for age, race and gender, the cardiovascular mortality rate in ESRD patients is ~10–20 times that in the general population [3]. It is therefore not surprising that CKD has recently been called a 'vasculopathic state' [4]. In order to prevent or at least delay the development of cardiac abnormalities, understanding the determinants of cardiovascular disease and preparing interventions aimed at correcting them is vitally important in the management of CKD patients.

Cardiovascular conditions in end-stage renal disease

There is growing evidence that the prevalence of cardiovascular disease among CKD patients is already

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high by the time renal replacement treatment (RRT) is begun [1,5,6]. This is extremely important as it has been widely shown that the cardiovascular status at the beginning of dialysis greatly affects patient outcomes [6]. The results of a number of studies suggest that factors leading to the development of cardiovascular abnormalities begin to operate very early in the progression of CKD, well before the patients reach ESRD. In a community-based cohort, Culleton *et al*. [7] showed that the prevalence of all the major traditional cardiovascular risk factors other than smoking (including hypertension, diabetes, hypercholesterolaemia and overweight) was significantly higher in patients with even mild renal failure (serum creatinine >1.5 mg/dl) than in those with normal renal function, suggesting that they are associated even with the earliest stages of CKD (Table 1). This may be because CKD promotes or enhances the development of such risk factors and/or because CKD and cardiovascular disease may in many cases share the same risk factors (it should be remembered that diabetes mellitus and hypertensive nephroangiosclerosis are now the leading causes of ESRD in many countries). However, a series of CKD-specific haemodynamic and metabolic risk factors (Table 1) can further increase a patient's cardiovascular risk from the earliest stages of the disease [2]. It is therefore not surprising that the Hypertension Detection and Follow-up Program (HDFP) study [8] found that hypertensive patients with baseline serum creatinine levels of >1.7 mg/dl had a 2.22 times higher 8-year mortality rate than all other patients, even after adjustment for other cardiovascular risk factors. More recently, in a secondary analysis of the Hypertension Optimal Treatment (HOT) study data relating to 18 597 hypertensive patients [9], the risk ratios for major cardiovascular events and for cardiovascular and overall mortality (adjusted for achieved diastolic and systolic blood pressure, age, gender, smoking habits, previous cardiovascular disease, diabetes and total serum cholesterol) were all significantly increased ($P < 0.001$) in patients with an estimated creatinine clearance of ≤ 60 ml/min. In conclusion, given the multiplicity of CKD-related cardiovascular risk factors, and the fact that they tend to develop very early in the progression of the disease, it is extremely important to treat them as early as possible in the course of CKD, before the progressive changes in cardiac structure and function become irreversible [10].

A significant percentage of CKD patients starting RRT are therefore already affected by cardiovascular abnormalities, but it must also be remembered that ESRD patients with no clinical or echocardiographic signs of cardiovascular impairment are at high risk of developing *de novo* cardiovascular disease. In addition to the detrimental consequences of pre-existing cardiovascular risk factors, possibly exacerbated by the start of dialysis and the loss of residual renal function, it is likely that the uraemic state *per se* (with the accumulation of potential cardiodepressant toxins and the acceleration of inflammatory and oxidant processes) and factors related to the dialytic treatment itself (Table 1) significantly contribute to the onset of cardiovascular abnormalities. One study found that the cumulative incidence of *de novo* ischaemic heart disease was 8% after 1 year, and had increased to 15% by the end of the second year, among patients undergoing peritoneal dialysis [11], whereas another study in haemodialysis patients found a cumulative incidence of 12 and 18% at the end of the first and second year, respectively [12]. In a prospective study of 432 dialysis patients, *de novo* ischaemic heart disease occurred in 9% of the patients who had no ischaemic signs at the start of dialysis [13], and a recent analysis of a large cohort of 3120 incident dialysis patients who were free of cardiovascular disease at the time of admission to RRT showed that 6.3% developed *de novo* cardiovascular disease (defined as coronary artery disease, myocardial infarction or heart failure), with an incidence of 4.42 *de novo* cardiovascular events per 100 patient-years [14]. The same study interestingly showed that treatment modality (haemodialysis or peritoneal dialysis) did not significantly affect the risk of developing *de novo* cardiovascular disease [14].

Cardiovascular risk factors in chronic kidney disease

Hypertension

Hypertension is a frequent finding at all stages of CKD. Although its prevalence varies widely depending on the nature of the underlying renal disease, it increases nearly linearly as renal function falls, and so the vast majority of patients with significant renal failure present high blood pressure [15]. The many pathogenic

Table 1. Multiple risk factors for cardiovascular disease in CKD patients

Traditional risk factors	Risk factors specific to CKD	Risk factors related to dialysis
Hypertension	Haemodynamic overload (plasma volume expansion, arterio-venous fistula)	Intra- and inter-dialytic changes in cardiac filling
Diabetes	Anaemia	Fluctuations in blood pressure
Dyslipidaemia	Calcium–phosphate disorders	Fluctuations in serum electrolyte levels
Smoking	Electrolyte imbalances	Bioincompatibility of membranes
Overweight	Chronic inflammation	Dialysate impurity
Hyperhomocysteinaemia	Oxidative stress	
	Hypercatabolism	
	Uraemic state	

mechanisms leading to CKD-related hypertension include the expansion of the extracellular volume (experimental and clinical evidence suggests that this may be the main cause of renal hypertension), increased sympathetic activity, an inappropriately increased activation of the renin–angiotensin system, altered endothelial function, high parathyroid hormone levels and the frequent administration of erythropoietin.

Blood pressure control is of paramount importance in slowing the progression of CKD towards ESRD [16,17] and decreasing cardiovascular risk in these patients. However, the relationship between hypertension and outcome in dialysis patients has been a controversial issue for many years because CKD patients are likely to have been exposed to hypertension for a long time, and long-term hypertension is a well known cause of cardiac failure, followed by reduced blood pressure (the so-called 'reverse causality'). In other words, the results of cross-sectional observational studies in which patients are categorized by blood pressure levels may be misleading. Some recent studies have found a negative effect of low blood pressure on the survival rates of dialysis patients, and an apparently consistent positive effect of high blood pressure [18–21], but the results of other studies with longer follow-ups have shown a clear relationship between higher blood pressure values and a worse cardiovascular outcome in ESRD patients. A 2.2-fold increase in the risk of cardiovascular death has been observed in patients with a mean pre-dialysis blood pressure of >98 mmHg in comparison with those whose blood pressure was <98 mmHg [22] and, in a Canadian cohort of 432 dialysis patients, Foley *et al*. [23] found that, although lower blood pressure levels were associated with significantly increased mortality, each 10 mmHg increase in mean arterial pressure was independently associated with a progressive increase in concentric left ventricular hypertrophy (LVH) and the development of *de novo* heart failure and ischaemic heart disease. It is therefore likely that hypertension plays a major role in determining cardiac damage also in dialysis patients (mainly due to the development of LVH), who should therefore be monitored and treated accordingly in order to keep their blood pressure as low as possible while taking into account individual patient characteristics. In other words, adequate blood pressure control should be a major objective in the management of patients with CKD in both the earliest and latest stages.

During the earlier stages of CKD, drugs blocking the renin–angiotensin system [angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor antagonists] are the first-choice antihypertensive agents because they are more effective in slowing the progression of renal failure than other antihypertensive drugs at the same apparent level of blood pressure control [24].There is, however, no proof that any class of antihypertensive drugs is superior to another in preventing cardiovascular disease in dialysis patients if blood pressure is adequately controlled. However, the results of the HOPE study, which showed that the ACE inhibitors led to a better prognosis in patients at high cardiovascular risk than other antihypertensive drugs [25], make the elective use of ACE inhibitors advisable also in dialysis patients, or at least in those with clinical or echocardiographic signs of cardiovascular disease.

Anaemia

Anaemia, which is thought to make a substantial contribution to the development of cardiac abnormalities in CKD patients, is a very frequent complication. A number of observational studies have shown that it inversely correlates with residual renal function, yet its prevalence is already high during the earlier stages of CKD [26–31].

LVH is also very frequent among CKD patients. Approximately 70% of patients starting dialysis have echocardiographically detected LVH [32], and changes in cardiac structure tend to progress during dialysis treatment [33]. The Canadian Multi-Center Study of Renal Anemia [28] in patients with various stages of CKD found that the prevalence of LVH progressively increased with declining renal function from the 30% prevalence at an early CKD stage (creatinine clearance 50–75 ml/min). A recent echocardiographic analysis of 334 CKD patients with creatinine clearance levels of 15–35 ml/min enrolled in the CREATE (Cardiovascular Reduction Early Anaemia Treatment with Epoetin beta) study [34] showed that 21% had concentric and 29% eccentric LVH, 22% had left ventricular dilation, and only 29% had a normal echocardiogram. It is worth noting that the prevalence of LVH varies widely in different geographical areas, being highest in Northern Europe and lowest in Asia [35]. The high prevalence of LVH among CKD patients is very important because it is an independent risk factor for mortality later during dialysis [36]. The significant association between anaemia and LVH in both dialysis patients and patients with early CKD suggests that anaemia is primarily implicated in the development of LVH in CKD [28,37–39] and also explains why it has a significantly negative impact on prognosis. Large-scale studies have indeed shown an inverse relationship between haematocrit levels and mortality and morbidity in dialysis patients [40–43], and similar results have been obtained in CKD patients [27,30].

As anaemia is an important and potentially modifiable risk factor for the development of LVH in CKD patients, correcting it can be expected to improve their cardiovascular status and long-term survival. Although small and not randomized, some studies have demonstrated that at least a partial regression of LVH is possible in early CKD after the partial correction of anaemia with recombinant human erythropoietin [44,45]. However, the multicentre Canadian Normalization of Haemoglobin Study [46] of 146 haemodialysis patients found that complete anaemia correction failed to induce any significant regression of well-established LVH. Taken together, these results clearly indicate that anaemia treatment seems to have a more beneficial effect on LVH regression if it is given as early as

possible during the course of CKD (and in any case before patients have reached ESRD). This is probably because long-term exposure to a series of co-morbid conditions other than anaemia-induced chronic volume and pressure overload leads to the development of myocardial fibrosis, calcium deposition, increased left ventricular stiffness and atherosclerosis, all of which are factors preventing the reversibility of well-established LVH.

The treatment of renal anaemia is in any case recommended in all CKD patients because it has been demonstrated to have beneficial effects not only on cardiovascular status [45–47], but also on patient outcome and well-being [47,48]. The debate on what the target haematocrit level should be in these patients is still open: it is not clear whether they should be maintained in a partially anaemic state, as suggested by the current guidelines [49,50], or whether normalizing haemoglobin concentrations leads to additional cardiac advantages and improved outcomes. A target haemoglobin level of 11–12 g/dl (haematocrit 33–36%) is currently recommended in all patients, as higher levels have not been demonstrated to increase survival [51]. However, a slight, non-statistically significant association between higher achieved haemoglobin levels and higher LVH regression rates was reported in the Canadian Normalization of Haemoglobin Study [46]. It is known that the normalization of anaemia can significantly improve the quality of life and physical function of selected categories of patients, particularly younger patients without severe cardiovascular disease [46,52,53]. The best strategy for the management of renal anaemia therefore probably consists of tailoring the target haemoglobin concentration to individual patient characteristics such as age, gender, modality of dialysis, the presence of co-morbid conditions, and the length of time on dialytic and recombinant human erythropoietin treatment [54].

Calcium–phosphate disorders

There is recent growing evidence that CKD-related calcium–phosphate disorders, particularly high serum phosphorus levels, are not only implicated in the pathogenesis of bone disease (renal osteodystrophy), but also significantly contribute to the high rates of cardiovascular mortality among CKD patients. In a large-scale study of 6047 haemodialysis patients, higher hyperphosphataemia levels were found to be significantly associated with an increased risk of death, even after adjusting for pre-existing medical conditions, the delivered dialysis dose, estimates of nutritional status and estimates of non-compliance [55]. These results, which have been confirmed and even extended by another study [56], clearly demonstrate that hyperphosphataemia directly contributes to the excessive mortality of CKD patients, in whom it recently has been defined as a 'silent killer' [57]. The exact mechanisms by which hyperphosphataemia leads to increased mortality have not yet been completely clarified, but they probably involve the calcification (due to increased calcium–phosphate product and/or secondary hyperparathyroidism) of coronary plaques, cardiac valves and myocardial tissue [57], and a relationship to inflammation has also been recently reported. The association with increased cardiovascular mortality further underlines the importance of adequately controlling hyperphosphataemia, and suggests that nephrologists should radically change their perception of its level of danger: the prevention of death due to cardiovascular disease is far more important than the prevention of bone disease.

Despite the increasing importance of calcium–phosphate disorders, their medical control is still far from being satisfactory, as documented by the still considerably high occurrence of parathyroidectomy, which provides indirect proof of an inability to effectively counteract the development of secondary hyperparathyroidism by means of diet and drugs [58]. Any improvement in the management of these disorders requires the establishment of adequate dialysis, and giving more emphasis to the use of aluminium- and calcium-free phosphate binders, while bearing in mind the long-term side effects of aluminium administration and the fact that high doses of calcium salts can increase cardiovascular tissue calcification. The use of the newly introduced drugs for controlling hyperphosphataemia can be expected to reduce the burden of this complication.

Dyslipidemia

Lipid abnormalities are more frequent in CKD patients than in the general population, although their prevalence varies widely depending on the cause and stage of CKD [59]. CKD-related lipid disorders mainly consist of increased serum triglyceride levels (due to an enhanced production and accumulation of triglyceride-rich lipoproteins, such as very low-density lipoproteins and intermediate-density lipoproteins), low high-density lipoprotein cholesterol levels, increased amounts of small low-density lipoproteins, increased plasma concentrations of lipoprotein(a), and a number of qualitative changes in apolipoprotein(b) that impair the metabolism of several lipoprotein classes and thus ultimately contribute to progressive atherosclerosis. The results of some recent studies [60,61] suggest that these complex changes in lipid profiles may significantly contribute to the high cardiovascular mortality and morbidity of CKD patients. However, the contribution of lipid abnormalities to the development of cardiovascular disease in CKD patients is still not completely understood, mainly because dyslipidaemia interferes with a number of non-traditional cardiovascular risk factors, particularly the activated acute-phase response. The European Joint Task Force and the National Cholesterol Education Program expert panel have issued guidelines for the general population aimed at lowering the cardiovascular risk related to dyslipidaemia, according to which serum low-density lipoprotein cholesterol levels should be kept below 160 mg/dl and serum triglyceride levels below 500 mg/dl. These guide-

lines should also be applied to dialysis patients, mainly because of their very high risk for the development and progression of atherosclerosis and cardiovascular disease. However, as the pathogenesis of atherosclerosis in dialysis patients is different from that in the general population, and given that the benefit of using lipid-lowering drugs has not yet been demonstrated in such patients, the results of some ongoing large-scale intervention trials, such as the 4D trial (Determination of Cardiovascular End-points in NIDDM Dialysis Patients) [62], should be awaited before target levels and lipid-lowering pharmacological treatments can be definitely recommended for dialysis patients.

Emerging cardiovascular risk factors

In addition to the classical cardiovascular risk factors, newly recognized risk factors for the development of atherosclerosis have been recently identified in the general population and, interestingly, all of them seem to be associated with CKD. For example, there is growing evidence that inflammation probably plays a key role in the initiation and progression of the atherosclerotic process, and atherosclerosis has been consequently defined as 'an inflammatory disease' [63]. A high percentage of CKD patients (particularly ESRD patients) have serological evidence of an activated inflammatory response [64–67] due to multiple potential causes, including the decreased renal clearance of pro-inflammatory cytokines, co-morbidities, the accumulation of advanced glycation end-products, and other factors related to the dialytic procedure (such as vascular access infections, membrane bioincompatibility, contaminated dialysate) [68]. Uraemia is considered at present to be a state of activated acute-phase response. In this context, high serum concentrations of markers of systemic inflammation (including C-reactive protein and interleukin-6) have been associated with atherosclerosis [66,67] and increased cardiovascular mortality in ESRD patients [64,65,69–71]. However, as it is very difficult to distinguish whether chronic inflammation is a cause or a consequence of cardiovascular disease, the real role of inflammation in the development of cardiovascular abnormalities in CKD patients is still an open question, and no treatments for the management of chronic inflammation in CKD are currently recognized [68]. Nevertheless, the potential link between inflammation and cardiovascular disease has led to increased attention being paid to all of the factors that can maintain or enhance inflammation in CKD patients, as is documented by the current debate concerning the role of dialysis biocompatibility as a means of improving patient outcomes.

Hyperhomocysteinaemia, which is now widely recognized as an independent predictor of cardiovascular disease in the general population, is present from the earliest stages of CKD, increases inversely with the reduction in renal function and is prevalent in $>85\%$ of ESRD patients [72]. Given the potential pro-atherogenic role of hyperhomocysteinaemia, a number of attempts have been made to lower plasma homocysteine levels in CKD patients by means of high doses of folic acid supplementation, alone or in combination with vitamin B_6 and B_{12} [73]. However, although these therapies are effective in partially reducing plasma homocysteine levels in many cases, the clinical impact of this reduction on cardiovascular morbidity and mortality still needs to be assessed in randomized trials.

Various findings suggest that CKD is a pro-oxidant state, as shown by the increase in a number of oxidative stress markers in CKD patients [74]. Although a number of factors directly related to CKD (e.g. age and diabetes), uraemia (e.g. inflammation and hyperhomocysteinaemia) or dialysis (e.g. bioincompatible membranes and endotoxin-contaminated dialysate) potentially contribute toward the development of an imbalance between antioxidant defence mechanisms and excessive generation of oxidants, the exact mechanisms leading to the genesis of oxidative stress in CKD patients are not known. The increasing importance given to oxidative stress in the context of CKD arises from the fact that it has been suggested to contribute to the pathogenesis of a number of important complications, including cardiovascular disease. Markers of oxidative stress have been correlated with impaired endothelial function or the presence of carotid plaques and intima media thickness in some studies [75–77], but the results of other studies are conflicting [78]. Moreover, only one cross-sectional study has so far found a positive association between oxidative stress markers and cardiovascular disease in haemodialysis patients [79], and no prospective epidemiological studies have yet evaluated this association at earlier stages of CKD. Although there is no striking evidence that increased oxidative stress contributes to the increased cardiovascular morbidity and mortality of CKD patients, various interventional trials have used antioxidant manoeuvres aimed at reducing cardiovascular disease by reducing the oxidative status; however, the majority of them have investigated the effects on laboratory parameters. The Secondary Prevention with Antioxidants of Cardiovascular Disease in End-Stage Renal Disease (SPACE) trial is the only study that has so far demonstrated an improvement in cardiovascular outcomes in haemodialysis patients with a history of cardiovascular disease given daily oral vitamin E supplementation [80]. However, given that vitamin E may have pharmacological activities other than its redox function and that the SPACE trial did not determine the effects of vitamin E supplementation on oxidative status, it is not clear whether the positive results were really due to an effective reduction in oxidative stress, not least because of the relatively short duration of the trial (median follow-up 519 days). As a whole, these results provide no definite evidence of the clinical benefit of antioxidant manoeuvres in reducing cardiovascular disease in CKD patients, and so no practical recommendations can be given until the results of further studies are available.

Conclusion

Cardiovascular disease is the leading cause of morbidity and mortality in CKD patients. The significant prevalence of patients starting RRT with signs of well-established cardiovascular abnormalities is indirect proof that cardiovascular risk factors are present from the early stages of CKD. In this context, the early detection and treatment of modifiable risk factors must be seen as a primary challenge for the nephrologist in the everyday management of CKD patients. Particular care must be taken to give optimal treatment for the most important cardiovascular risk factors active in CKD patients, i.e. hypertension, anaemia, calcium–phosphate disorders and lipid abnormalities. In addition to the classical cardiovascular risk factors, CKD is also associated with newly recognized risk factors for the development of atherosclerosis, including chronic inflammation, hyperhomocysteinaemia and oxidative stress. However, although various hypotheses and preliminary data suggest that these factors may play an important role in the development of cardiovascular disease among CKD patients, their importance as cardiovascular risk factors is still controversial. Furthermore, the clinical impact of interventions aimed at correcting these factors still has to be assessed: the results of ongoing investigations are awaited with much interest, but it is too early to make any therapeutic recommendations. Nevertheless, it is known that, despite the high prevalence of traditional cardiovascular risk factors in CKD patients, their predictive value in terms of cardiovascular outcome is not as strong as in the general population, and that the management of well-established risk factors such as hypertension, anaemia, hyperparathyroidism and dyslipidaemia, in addition to often being inadequate, fails to prevent the excess of cardiovascular events in CKD patients. Accordingly, the management of cardiovascular risk of patients with CKD in the new millennium urgently needs adjunctive pharmacological therapies with different targets from those of more conventional approaches.

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