Chronic kidney disease (CKD) is a complex, progressive condition that develops slowly in some individuals, but rapidly in others. In addition to the underlying cause of renal failure, the rate of disease progression may be dictated by the presence of CKD risk factors. The principal outcomes of CKD include progressive loss of kidney function leading to end-stage renal disease (ESRD) and the development and progression of cardiovascular disease (CVD).

CKD is a major cause of cardiovascular morbidity and mortality and is considered a significant public health problem that places a burden on global healthcare resources. Notably, the incidence and prevalence of CKD have shown a dramatic increase over the past two decades. It was recently estimated that 11% of adults (19.2 million) in the US alone have early CKD that may progress to ESRD and require renal replacement therapy (RRT), such as dialysis or transplantation. Based on the US Renal Data System (USRDS), a national system that collects, analyses and distributes information about ESRD, it is estimated that the number of individuals receiving RRT will rise to more than 600,000 by 2010.

The observation that small reductions in the decline in renal function early in the disease process can provide marked benefits later, in terms of delaying progression to RRT, suggests that substantial benefits can be gained from the early identification and treatment of individuals at risk. In order to develop effective strategies to identify such individuals and delay or prevent disease progression, a comprehensive understanding of the complex interplay between risk factors influencing the disease process is required.

**Risk Factors for CKD Progression**

A number of primary non-modifiable risk factors for the progression of CKD have been identified, including age, ethnicity, gender and family history. Age was found to be a key predictor of CKD prevalence during an analysis of data from a subpopulation of 15,625 individuals enrolled in the third National Health and Nutrition Examination Survey (NHANES III). This analysis confirmed the frequent occurrence of CKD but also showed that there was a progressive decrease in glomerular filtration rate (GFR) with increasing age. In particular, 10.8% of individuals older than 65 years, but with no evidence of hypertension or diabetes, had CKD stage III or more, confirming age as a key predictor of CKD prevalence.

Gender was also confirmed as a key predictor of CKD prevalence in a similar large meta-analysis of 68 studies involving 11,345 patients with non-diabetic CKD. This analysis found that men experienced a more rapid decline in renal function and worse outcomes than women.

Perhaps more importantly from an interventional viewpoint, a number of independent risk factors have also been identified that may be modified by pharmacotherapy or lifestyle changes to reduce the rate of CKD progression. These modifiable risk factors, which are associated with both impaired renal and cardiac function, include diabetes, hypertension, smoking, inflammation and anaemia.

**Hypertension and Smoking**

In a prospective study of more than 33,000 men, a strong relationship was shown between hypertension and rate of progression to ESRD. In a more recent prospective study, a predominantly Caucasian, community-based cohort of 25,534 men and women showed a similarly significant relationship between the development of CKD and hypertension (stages I–IV, as defined in the sixth report of the Joint National Committee, relative risk 5.7–8.8) and smoking (relative risk 2.6), irrespective of gender. Although the relative risk of CKD was highest in patients with more severe hypertension, overall, the attributable risk of CKD was greatest in patients with stage I hypertension, showing that patients with only modest hypertension comprise the bulk of the CKD burden. Thus, in contrast to the typical approach of only targeting patients with
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stage III or IV hypertension, these findings suggest that optimal treatment of stage I hypertension will have a greater public health impact on reducing CKD.13

Inflammation and CKD

Until recently, consideration of systemic inflammation as a modifiable risk factor for CKD progression received comparatively little attention. Cross-sectional studies show that patients with CKD have a pronounced inflammatory phenotype, including an elevated serum concentration of inflammatory markers, such as C-reactive protein (CRP) and interleukin (IL)-6, and decreased serum albumin levels.10,11

A more recent retrospective analysis of data from 9,250 adults enrolled in NHANES II confirmed systemic inflammation as an independent risk factor for future development of CKD.8 After adjusting for age, race, gender, blood pressure, smoking and body mass index, a graded positive association was observed between increased total white blood cell count and risk of CKD (p<0.001 for trend; relative hazard: highest quartile (Q4) versus lowest quartile (Q1) = 2.34). This relationship remained after additionally adjusting for the presence of diabetes and CVD at baseline. A similarly strong and graded association was observed between decreased serum albumin levels and incident CKD (p=0.02 for trend; relative hazard: Q1 versus Q4 = 2.05).

Diabetes and CKD

Type 2 diabetes is one of the fastest growing epidemics worldwide. The number of individuals diagnosed with type 2 diabetes was estimated at 124 million in 1997, a number expected to reach 221 million by 2010.15 Significantly, the presence of diabetes has a considerable impact on the progression of CKD. Nephropathy, a major complication of diabetes associated with poor glycaemic control, occurs in approximately one-third of type 2 diabetic patients and is the single most important cause of ESRD in both the US and Europe.16,17 For example, approximately 24% of all patients in Europe beginning dialysis had diabetes in 1999.18

Large, pivotal intervention trials provide evidence of a causal relationship between diabetes and CKD, showing that intensive glycaemic control in both type 1 and type 2 diabetic patients prevents the development and slows the progression of diabetic kidney disease by 25–50%.19–20 Despite this, however, there is little awareness of the risk of CKD development and progression associated with diabetes.17,21

This situation in patients with CKD is compounded further in that CVD develops earlier and is more prevalent and more severe when diabetes is also present. In fact, in CKD patients with diabetes there is an approximate three-fold increase in the incidence of cardiovascular events and cardiovascular-related mortality compared with non-diabetic patients with CKD.22

Anaemia, Diabetes and CKD

The compounding effect of diabetes on adverse clinical outcomes in patients with CKD is exacerbated further by anaemia.23 Anaemia occurs more frequently (two- to three-fold greater incidence), earlier and with greater severity in patients with both CKD and diabetes compared

Figure 1: Kaplan–Meier Curves Showing the Cumulative Incidence of ESRD by Quartile of Baseline Haemoglobin (Hb) in Patients with Type 2 Diabetes and Nephropathy26

Figure 2: Mean Rate of Decline in Creatinine Clearance in Patients with CKD (Stages I–IV, Pre-ESRD/pre-dialysis) Receiving Either Epoetin or No Epoetin

ESRD = end-stage renal disease, Hb = haemoglobin, Q = quartile.
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Mean rate of decline in creatinine clearance (ml/min/1.73m²/month)

0.0 No epoetin (n=42)
0.2
0.4
0.6
0.8
1.0
1.2

p<0.01 epoetin versus no epoetin

ESRD = end-stage renal disease.
Source: Jungers et al. (2001).45

CKD = chronic kidney disease.
with patients with CKD alone. This is particularly relevant as studies in patients with diabetic nephropathy show that the degree of anaemia further exacerbates the rate of CKD progression, i.e. the greater the degree of anaemia in these patients, the more rapid the progression to ESRD and RRT (see Figure 1).

Despite the strong relationship between anaemia in diabetes and adverse clinical outcomes in patients with CKD, there is still a general lack of awareness among physicians about anaemia and its implications for CKD patients with diabetes. In fact, up to 66% of such patients can have unrecognised anaemia.

**Anaemia – An Underestimated Risk Factor for CKD Progression**

Numerous studies suggest that anaemia together with diabetes presents a substantial risk for CKD progression. However, it is particularly notable that, although anaemia was reported to be an independent risk factor for the progression of both CKD and CVD nearly a decade ago, its importance as such is still underestimated by physicians and patients alike.

The assertion that anaemia represents an independent risk factor for CKD is based, in part, on data from NHANES III (1988–1994, n=19,215 nationally representative subjects). Here, a continuous relationship was observed in both men and women between low haemoglobin (Hb) levels and renal impairment, a relationship that was evident even at modest reductions in renal function.

A further study in a Canadian cohort of patients with CKD also showed that, for any given level of kidney function, the risk of progression to RRT increased with the severity of anaemia. Most importantly, this latter study found that the prevalence of anaemia (defined according to World Health Organization (WHO) criteria as Hb <13.5g/dl) was not only higher with advanced renal disease, but that 25% of patients had anaemia at a relatively early stage of kidney disease (i.e. GFR >50ml/min).

**Left Ventricular Hypertrophy**

Complementing these studies, other investigators observed that anaemia also contributed to the development of left ventricular hypertrophy (LVH) and chronic heart failure. Each 0.5g/dl decrease in Hb concentration was independently associated with a 32% increase in LV growth, i.e. an increase in LV mass. Given this, it is perhaps not surprising that LVH is typically found in approximately 50% of patients with CKD and 75% of patients with ESRD.

Clinical trials demonstrating the reno- and cardioprotective effects of treating anaemia with recombinant human erythropoietin (epoetin) also suggest that anaemia is an independent risk factor for the progression of CKD. It is well established that epoetin is highly effective for the treatment of anaemia in patients with CKD, improves quality of life and reduces the risk of morbidity and mortality from CVD.

A retrospective analysis of data from a clinical trial in predominantly non-diabetic patients with CKD (stages I–IV, pre-ESRD/pre-dialysis) found that while the rate of decline in mean creatinine clearance was unchanged in moderately anaemic patients who did not receive epoetin, the rate of decline decreased significantly in severely anaemic patients who received epoetin (p<0.01 versus no epoetin) (see Figure 2). Furthermore, in a study in children with pre-dialysis chronic renal failure, long-term administration of epoetin (mean 31 months) was associated with a delayed deterioration in renal function.

Moreover, this improvement was reflected in a significant delay of approximately six months in the delay of approximately one-third of type 2 diabetic patients and is the single most important cause of ESRD in both the US and Europe.
initiation of dialysis in patients receiving epoetin compared with those who did not (16.3 versus 10.6 months, respectively; p<0.01).

A similar study, also in non-diabetic pre-dialysis patients, showed that correction of anaemia using epoetin was associated with a significant improvement in cumulative renal survival compared with no epoetin therapy (p=0.0003). The fact that clinical factors known to modify renal function, such as blood pressure, angiotensin-converting enzyme (ACE) inhibitor therapy and amount of dietary protein, were rigorously controlled for led the authors of this study to conclude that anaemia per se is a key factor in CKD progression. In addition, in patients with moderate CKD, mild anaemia (mean Hb 10.4g/dl) and congestive heart failure, correction of anaemia using epoetin was associated with significant improvements in GFR, functional status and cardiac function.

The beneficial effect of initiating epoetin pre-dialysis, in terms of hard clinical outcomes, is supported further by observational data from the Health Care Financing Administration (HFCA). In this analysis, mortality risk was reduced by up to 40% in patients who received epoetin compared with those who did not.

These findings have since been confirmed in a recent prospective trial in non-diabetic pre-dialysis patients with non-severe anaemia (Hb level 9.0–11.6g/dl) randomised to early or deferred treatment with epoetin. Here, the early use of epoetin was associated with a 60% risk reduction for initiation of RRT and death. The increased risk of anaemia-related cardiovascular events in patients with CKD is exacerbated if diabetes is also present. However, it remains unclear whether correction of anaemia in early diabetic nephropathy will have any impact on cardiovascular morbidity and mortality. It is anticipated, however, that on-going trials such as the Individualised Risk-profiling In DiabEtes Mellitus (IRIDIEM) and the Anaemia CORrection in Diabetes (ACORD) studies will clarify the benefits of anaemia correction with regard to cardiovascular risk.

In summary, regular monitoring and prompt intervention to control key modifiable risk factors is important for the prevention of CKD progression and for the long-term clinical outcome of patients with renal anaemia.
Risk Factors in the Progression of Chronic Kidney Disease

References


