Patients with chronic kidney disease (CKD) have a high burden of cardiovascular (CV) morbidity and strategies to modulate CV risks are needed in this population. Anaemia has been recognised as a frequent complication of diabetic nephropathy, appearing earlier than in non-diabetic renal disease. Recent data suggest that anaemia is a potentially modifiable risk factor and its correction could improve outcome in CKD patients. The potential benefit of erythropoietin treatment in patients with diabetic renal disease is also emerging.

Aetiology of Anaemia in Diabetic Nephropathy

In type I diabetic patients, a series of observations have documented very convincingly that the onset of anaemia occurs early. Bosman et al. compared 27 type I diabetic patients with diabetic nephropathy and an average serum creatinine concentration of 96 umol/L (maximum 160 umol/L) with 26 non-diabetic patients with glomerulonephritis and persistent proteinuria. Thirteen of the 27 diabetic patients were anaemic (haemoglobin 10.6 ± 0.9 g/dL), but none of the patients with glomerulonephritis (haemoglobin 13.7 ± 1.4 g/dL, P<0.005) was. When the erythropoietin concentration in the diabetic patients was compared with reference values measured in patients with microcytic anaemia (mostly caused by iron deficiency), it became obvious that the erythropoietin concentrations were clearly inappropriate to the low haemoglobin concentrations. The authors proposed the interesting hypothesis that the inadequate secretion of erythropoietin in response to anaemia was due to autonomic polyneuropathy causing efferent sympathetic denervation. This idea was based on animal studies showing that renal denervation interferes with erythropoietin secretion and that anaemia may occur in patients with primary failure of the autonomic nervous system. When these were combined with damaged erythropoietin-producing fibroblasts in the renal cortex, early development of anaemia will result in the patients with diabetes. Other confounding factors are iron deficiency and therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Resistance to erythropoietin, on the other hand, has not been demonstrated in diabetic patients.

Consequences of Anaemia in Patients with Diabetes

Diabetes and anaemia are each associated with significant morbidity and mortality. While the contribution of anaemia to the development of diabetic complications is not completely understood, it is imperative that both be managed to limit negative outcomes. Patients with diabetes are two to four times more likely to have heart disease or suffer a stroke than non-diabetics, and approximately 75% of patients with diabetes die of CV-related causes. Anaemia is associated with a greater incidence of left ventricular hypertrophy, de novo or recurrent cardiac failure, and increased cardiac-related hospitalisations and deaths.

Beneficial Effects of Anaemia Management

In studies in which investigators explored the connections between diabetic neuropathy and anaemia, the haemoglobin levels of patients with diabetes improved with erythropoietin administration. Rarick and colleagues showed that the administration of erythropoietin improves haematocrit values and quality of life in patients with diabetes, anaemia and clinically normal renal function. Although this study was too small to determine the causes of early anaemia in patients with diabetes, it provided preliminary evidence...
of the need for early anaemia screening and treatment in patients with diabetes.

In the The Anaemia CORrection in Diabetes (ACORD) Study\textsuperscript{16}, one hundred seventy-two patients with type 1 or 2 diabetes mellitus, mild to moderate anaemia, and stage 1 to 3 chronic kidney disease were randomly assigned to attain a target haemoglobin level of either 13 to 15 g/dL (group 1) or 10.5 to 11.5 g/dL (group 2). The primary end point was change in left ventricular mass index (LVMI). Secondary end points included echocardiographic variables, renal function, quality of life, and safety. Median haemoglobin level and left ventricular mass index (LVMI) were similar in groups 1 and 2 (haemoglobin 11.9 and 11.7 g/dL; LVMI, 113.5 and 112.3 g/m\(^2\), respectively). At study end, haemoglobin levels were 13.5 g/dL in group 1 and 12.1 g/dL in group 2 (P < 0.001). No significant differences were observed in median LVMI at month 15 between study groups (group 1, 112.3 g/m\(^2\); group 2, 116.5 g/m\(^2\)). Multivariate analysis showed a non-significant decrease in LVMI (P = 0.15) in group 1 versus group 2.

Anaemia correction had no effects on the rate of decrease in creatinine clearance, but resulted in significantly improved quality of life in group 1 (P = 0.04).

The Trial to Reduce Cardiovascular Events with Aranesp (darbepoetin alpha) Therapy (TREAT) is a randomised controlled trial designed to determine the impact of anaemia correction on mortality and non-fatal cardiovascular events in patients with type 2 diabetes and stage 3-4 nephropathy\textsuperscript{17}. 4000 patients will be randomised in a 1:1 manner to achieve a target haemoglobin of 13 g/dL or ≥9 g/dL with darbepoetin alpha therapy. Placebo will be given for a haemoglobin of >9 g/dL in the low-haemoglobin group. TREAT, when completed, will provide data that are critical to the management of cardiovascular risk in this high-risk population.

Whether anaemia correction may be beneficial to the progression of diabetic nephropathy remains unknown. One study demonstrated that the reversal of anaemia by recombinant erythropoietin was able to slow down the progression of chronic renal disease but this effect is less prominent in diabetics compared to non-diabetic patients\textsuperscript{20}. In another open uncontrolled study in which 179 patients with chronic heart failure were treated with recombinant erythropoietin and iron to maintain a target haemoglobin of 12.5 g/dL throughout the study, the mean serum creatinine and creatinine clearance (assessed with the Cockcroft-Gault formula) did not change significantly in either group during the study, whereas the mean rate of fall in creatinine clearance in the period before the study (untreated anaemia) was >1 ml/min/month in both groups\textsuperscript{21}.

Diabetic kidney disease is an increasingly common clinical entity. Despite the considerable advances, many issues including the prevalence, pathophysiology and consequences of anaemia in diabetic patients remain unsettled. Further prospective and controlled studies are urgently needed to clarify these issues.

References