

Is anaemia in patients with diabetes exclusive to diabetic nephropathy?

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ARTICLE POINTS

1 Diabetes is the leading cause of end-stage renal disease in the western world.

2 Renal anaemia is a complication for patients with mild to severe renal failure.

3 The authors questioned the prevalence, predictors and outcomes for people with diabetes and clinical anaemia.

4 From a primary literature search, it is suggested that anaemia in people with diabetes is not exclusive to advanced diabetic nephropathy.

5 Thus, anaemia may be considered as a possible complication for people with diabetes on diagnosis.

KEY WORDS

- Anaemia
- Diabetes
- Nephropathy
- Renal failure
- Evidence base

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Introduction

Diabetes is the leading cause of end-stage renal disease in the western world and significant proportions of patients with diabetes mellitus develop renal complications. Anaemia is a key indicator of renal disease, and may potentially contribute to the pathogenesis of diabetes complications. Early correction of anaemia therefore has the potential to prevent or reverse other complications. This review of the literature examines anaemia in patients with diabetes and seeks to determine whether it is exclusive to diabetic nephropathy.

Diabetes is a leading cause of end-stage renal failure (ESRF). Approximately 20–30% of people with type 1 or type 2 diabetes mellitus will develop overt nephropathy (Krolewski et al, 1985). Although a greater proportion of people with type 1 diabetes subsequently progress to ESRF, 50–60% of people with diabetes receiving renal replacement therapy (RRT) have type 2 diabetes because of the greater prevalence of this type of diabetes in the general population (Cowie et al, 1989).

Renal anaemia is a complication for patients with mild (glomerular filtration rate [GFR] of 60–80 ml/min/1.73m²) to severe (GFR <15 ml/min/1.73m²) renal failure. This is principally because the failing kidney is unable to produce sufficient erythropoietin to stimulate red blood cell production. Delayed diagnosis and treatment of anaemia associated with chronic kidney disease may increase the risk of cardiovascular complications including coronary artery disease, left ventricular disorders and cardiac failure. Early correction of anaemia therefore has the potential to prevent or reverse some cardiovascular morbidity and mortality through reversal of left ventricular hypertrophy (LVH; European Dialysis and Transplant Association, 1999).

Clinical guidelines on screening for renal disease and the prevention of cardiovascular problems are set out in the National Service Framework (NSF) for

diabetes (Department of Health [DoH], 2001). However, while this government paper highlights the importance of early screening for renal disease, the complications of anaemia are not addressed. This omission is surprising as anaemia is recognised as one of the modifiable risk factors for cardiac death amongst patients entering renal replacement programmes (Burton et al, 2000). In contrast, the recent publication of the renal NSF (DoH, 2004) refers to the importance of anaemia correction, management of cardiovascular risk factors and diabetes. These inclusions and omissions have led the authors to question the prevalence, predictors and outcomes for people with diabetes and clinical anaemia.

Search strategy and inclusion criteria

Literature was sought from 1995 to the present day. Articles published only in the English language were included in the review. No restrictions were placed on gender, however, only studies that concentrate on the adult population were included for selection in this review. The review is limited to primary research only. Electronic databases provide a general idea of the volume of literature available in an area. The search was confined to locally available databases such as Medline, the Cochrane Controlled Trials Register and Embase. MeSH (Medical

Subject Heading) terms included the following: 'anaemia & diabetes & renal & RCT's & cohort & prospective & erythropoietin'. The authors also hand-searched readily available journals stored in the practice area, such as *Nephrology*, *Dialysis and Transplantation*; *Nephron*; and *Kidney International*. It was also necessary to contact pharmaceutical companies involved in anaemia-management products to obtain any trials that have been carried out or supported by the companies. The details of such trials may be held on a private database; none were forthcoming.

Results

The 30 articles retrieved were subject to a criterion checklist as described by Crombie (1996) and further validity was ensured by including only those who achieved A, B or C in the 'hierarchy of evidence' tree (see *Table 1*) as described by Sackett and Cook (1994). These ten studies are listed in *Table 2* with the salient points listed in the summary column.

Discussion

It is apparent that anaemia in people with diabetes is a multifaceted problem. Across the five studies that examined the prevalence of anaemia in diabetes patients with and without renal failure, the prevalence of anaemia was found to be 18% of the total population (n=2146). However, in a single-centre study, Thomas et al (2003) demonstrated a prevalence rate of 23%, and Stevens et al (2002), in their multicentre study, identified a prevalence of only 10%. The study by Bosman et al (2001) showed that almost 50% of people with diabetes but without severe renal failure demonstrated anaemia. This was in contrast to the 26 patients in the same study without diabetes, but with reduced GFR consistent with renal failure, who proved to have no evidence of anaemia. In total, the five studies reported a higher prevalence of anaemia in patients with diabetes compared to their counterparts without diabetes. In addition, anaemia was more severe in those with diabetes compared to those without diabetes.

Table 1. Criteria from the 'hierarchy of evidence' tree (Sackett and Cook, 1994)

Criterion	Description
A	RCT (Randomised, controlled trial) Validity and bias addressed. Results identify new knowledge.
B	RuCT (Randomised, uncontrolled trial)/Study/Survey Randomisation method clear, unclear or absent. Bias addressed. Results may or may not identify new knowledge.
C	Study/trial/review Relevant but small numbers (in trials). Not strong on validity or bias. No new knowledge identified.

The predictors of anaemia in this patient population are difficult to define. In the studies by Cotroneo et al (2000), Winkler et al (1999), and Bosman et al (2001), the main conclusions pointed to diminished erythropoietin production and reduced GFR.

It is well documented that erythropoietin deficiency occurs in patients with advancing renal failure, but very little evidence is available examining erythropoietin deficiency in diabetes.

Studies by Winkler et al (1999), Cotroneo et al (2000) and Bosman et al (2001) demonstrated diminished erythropoietin production as a predictor of anaemia in patients with diabetes and without overt nephropathy. While none of the studies characterised the mechanisms for the failure of erythropoietin production, a major contributing factor may be autonomic neuropathy in the presence of damaged erythropoietin-producing fibroblasts in the renal cortex.

GFR is a predictor of anaemia for patients with and without diabetes. All the studies correlated that lower GFR levels predict the onset of anaemia by means of lower haemoglobin concentrations. While the evidence from this review demonstrates that anaemia is more severe in those with diabetes than in their counterparts without diabetes, continuing renal failure seems to determine the severity of anaemia – regardless of the cause of chronic renal failure (Thomas et al, 2003).

The main outcome of anaemia in patients with diabetes and renal failure is

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1 In total, five studies reported a higher prevalence of anaemia in patients with diabetes compared to their counterparts without diabetes.

2 The predictors of anaemia in this patient population are difficult to define. In three of the studies, the main conclusions pointed to diminished erythropoietin production and reduced GFR.

3 Very little evidence is available examining erythropoietin deficiency in diabetes.

a deterioration in kidney function and cardiac failure. Silverberg et al (2003) demonstrated stabilisation in kidney function and an improvement in cardiac function following the correction of anaemia in diabetes patients with severe congestive cardiac failure.

In addition, Ueda et al (2003) and Toto et al (2003) suggest that the progression of kidney failure may be retarded as a clinical outcome of anaemia correction.

This review has demonstrated that the presence of diabetes-associated complications may exacerbate anaemia in people with diabetes. Early correction of

anaemia is particularly important in people with diabetes, as it occurs prematurely and with greater severity than in the non-diabetic patient group with similar levels of renal impairment. Early intervention with erythropoietin therapy may reduce anaemia-induced organ damage, such as cardiac ischaemia, and retard the progression of kidney failure.

The cost effectiveness of erythropoietin therapy for patients with mild renal failure has not been evaluated. However, it is important to consider the potential benefits of interventions that

Table 2. A summary of the ten papers selected after validity checking

Author	Date	Title	Study design	Sample size	Summary of study
Bosman DR, et al	2001	Anemia with erythropoietin deficiency occurs early in diabetic nephropathy	Cohort study	53	Anaemia associated with erythropoietin (EPO) can occur early in diabetic nephropathy, before the onset of advanced renal failure, but is found not to occur in non-diabetic renal disease of similar severity.
Cotroneo P, et al	2000	Blunted erythropoietin response to anaemia in patients with type 1 diabetes	Survey	13	The majority of type 1 diabetes patients who had anaemia also had low EPO levels. Autonomic neuropathy appears to play a role.
Ishimura E, et al	1998	Diabetes mellitus increases the severity of anemia in non-dialyzed patients with renal failure	Clinical trial	40	Indicated that higher serum creatinine levels and the presence of diabetes were independent risk factors for anaemia.
Silverberg DS, et al	2003	The effect of correction of anaemia in diabetic and non-diabetics with severe resistant congestive heart failure and chronic renal failure by subcutaneous erythropoietin and intravenous iron	Clinical trial	179	Correction of anaemia in both patients with and without diabetes improved cardiac function and stabilised renal function.
Stevens P, et al	2003	Anaemia in patients with diabetes: unrecognised, undetected and untreated?	Survey	1054	Anaemia has a significant impact on the quality of life of patients with diabetes.
Thomas MC, et al	2003	Unrecognised anaemia in patients with diabetes: a cross-sectional survey	Cross-sectional survey	820	The prevalence of anaemia is 2–3 times higher for patients with diabetes. Predictors of anaemia include: transferrin saturation, glomerular filtration rate, albumin excretion rate.
Toto RD	2003	Anaemia and outcomes in patients with type 2 diabetes mellitus and nephropathy: lessons from the RENAAL trial	Multivariate	1513	Prevention or correction of anaemia reduces the incidence of end-stage renal disease and congestive heart failure in patients with type 2 diabetes.
Ueda H, et al	2003	Factors affecting progression of renal failure in patients with type 2 diabetes	Observational	85	In patients with type 2 diabetes and renal failure hypo-albuminaemia, anaemia, and high blood pressure predict rapid progression of renal failure.
Winkler AS, et al	1999	Erythropoietin depletion and anaemia in diabetes mellitus	Control trial	33	Supports autonomic neuropathy as a cause of anaemia with EPO depletion.
Yun YS, et al	1999	Reduced erythropoietin responsiveness to anemia in diabetic patients before advanced diabetic neuropathy	Case-control	70	Indicates the presence of anaemia in patients with diabetes but without advanced diabetic neuropathy. May reflect early renal interstitial damage.

prolong survival, improve quality of life and reduce the need for dialysis or transplantation. Recognising and treating anaemia in this patient population before the onset of renal failure may improve outcomes with respect to mortality risks associated with the person with diabetes.

Conclusion

The limited evidence from this review suggests that people with diabetes may suffer from anaemia without diabetic nephropathy. Thus, anaemia may be considered a possible complication for people with diabetes on diagnosis. ■

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