Impact of diabetes on haemoglobin levels in renal disease

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Abstract

Aims/hypothesis Anaemia is a common complication of renal impairment. It has been suggested that renal failure secondary to diabetes is associated with more severe anaemia, but this has not been clearly substantiated in the published literature. To clarify this, we undertook a single centre, retrospective study to identify the impact of diabetes on anaemia associated with renal impairment.

Materials and methods Information on clinical, biochemical and haematological parameters of 2,052 stable ambulatory patients attending a single tertiary referral renal unit was collected. The impact of diabetic kidney disease on haemoglobin levels at all degrees of renal impairment was studied by comparison with patients with non-diabetic kidney disease after correcting for other commonly associated variables that influence anaemia in patients with renal impairment.

Results Linear regression analysis showed lower haemoglobin in patients with diabetic kidney disease ($p < 0.01$). At chronic kidney disease (CKD) stages 3, 4 and 5, mean haemoglobin levels in patients with diabetic kidney disease compared with those in patients with non-diabetic kidney disease were 129.5 vs 136.9 g/l ($p < 0.001$), 120.5 vs 126.9 g/l ($p < 0.001$) and 107.1 vs 115.9 g/l ($p < 0.01$), respectively. At CKD stage 4 and 5 the two groups were comparable for ferritin, plasma intact parathyroid hormone levels, ACE inhibitor use and length of follow-up by a nephrologist.

Conclusions/interpretation Diabetic kidney disease is associated with lower haemoglobin in comparison with non-diabetic kidney disease, especially at GFR < 60 ml/min.

Keywords Anaemia · Diabetes · Diabetic nephropathy · Erythropoietin

Abbreviations

ACEI ACE inhibitor
CKD chronic kidney disease
PTH parathyroid hormone

Introduction

WHO estimates that there will be 221 million diabetic patients worldwide by 2010, rising from an estimated 151 million in 2000 [1]. Diabetes continues to be the most common cause for end-stage renal disease in the western world [2–4]. The increasing incidence of diabetes and improved longevity due to better management of such patients is likely to further increase the workload for diabetologists and nephrologists from this disease group. Patients with diabetic kidney disease continue to have a poor prognosis, with mortality being 70 to 100 times that of a matched population [5]. The excess cardiovascular mortality associated with diabetes and chronic renal failure is well recognised [6].

Anaemia is one of many modifiable factors that influence the morbidity and mortality associated with renal impairment. A common perception within the renal and diabetic community is that anaemia associated with diabetic kidney disease tends to be more severe when compared with anaemia in patients who have other causes of renal

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impairment. Preview of medical literature does not substantiate this conclusively, hence we set out to test this hypothesis formally in a large UK renal unit. A definitive answer to this question is especially relevant, because if the perception is confirmed, effective and proven treatment in the form of recombinant human erythropoietin is already available.

Subjects and methods

Selection and classification of participants All ambulatory patients under active follow-up by the Richard Bright Renal Unit at Bristol, UK between 1 January 2004 and 31 June 2004 were assessed for inclusion. The renal unit is the regional nephrology referral centre with a catchment population of 1.3 million. The PROTON database used by the unit was interrogated for clinical and laboratory information and if required additional data were obtained from case notes. The data were collected retrospectively and none of the patients had blood tests performed solely for the purpose of inclusion in the study. Patients were included if they had a minimum of 6 months of follow-up and two or more estimations of renal and haematological parameters. Exclusion criteria included clinical history of recent blood loss, recent in-patient admission, current or previous history of cytotoxic therapy, current or previous erythropoietin therapy, current or recent intravenous iron therapy, recent history of blood transfusion, patients on renal replacement therapy, diagnosis of rapidly progressive glomerulonephritis, patients with acute renal failure and patients with current history of malignancy including haematological malignancies (Fig. 1).

Patients were classed as having diabetic nephropathy either by renal histology or if they had the full range of clinical features (including diabetic retinopathy, proteinuria, hypertension and drug controlled type 1 or 2 diabetes) associated with absence of any clinical features capable of providing an alternative explanation of renal impairment. Of the 336 patients categorised as having diabetic nephropathy, 29 patients had this proven by renal biopsy; in the remainder diagnosis was on the basis of the full range of clinical criteria. Patients with either (1) diabetes plus another cause for renal failure or (2) diabetic nephropathy with a second pathology as determined by renal histology were excluded from the analysis. All other patients with no current or previous history of diabetes (as defined by the WHO criteria) were included in the category of non-diabetic renal disease.

Glomerular filtration rate was estimated using the modified four variable Modification of Diet in Renal Disease formula [7]. Patients were grouped according to the National Kidney Federation/Disease Outcomes Quality

Initiative Chronic Kidney Disease (CKD) stages 1 to 5 based on estimated GFR [8]. Current and prior drug history was evaluated from the database. Subjects were included as being on ACE inhibitor (ACEI) therapy if drugs from that class had been prescribed for a minimum of 3 months prior to their last recorded haemoglobin level. Length of follow-up was defined as time from original referral to the renal service. Even though two or more urine dipstick results were available for all patients, uniformly quantified data on proteinuria were not available and hence we were unable to analyse the influence of this variable on haemoglobin levels.

Statistical methods Data were analysed using GraphPad Prism for Windows version 4.0 (GraphPad Software, San Diego, CA, USA). After parameters were tested for

Fig. 1 Flow-chart of patients included and excluded in both categories according to chronic kidney disease (CKD) stage. Asterisk: Inter-current illness includes suspected or proven gastro-intestinal or extra-gastro-intestinal blood loss. EPO, erythropoietin

distribution, the appropriate parametric and non-parametric tests were used for analysis. Linear regression analysis was used to determine the difference in slope of haemoglobin between patients with diabetic and those with non-diabetic kidney disease. Unless stated otherwise, values are expressed as means with 95% CIs, and the criterion for statistical significance was taken as a two-tailed p value <0.05 .

Results

Baseline characteristics Patient characteristics are shown in Table 1. As expected, there were considerably more patients with type 2 diabetes than type 1 diabetes in the diabetic nephropathy group. At all CKD stages, GFR in patients with diabetic and non-diabetic kidney disease was comparable. There was no significant difference in GFR between patients with type 1 and type 2 diabetes or upon individual comparison of each diabetes type with non-diabetic patients at all CKD stages (data not shown). The study population was predominantly ($>97\%$) white, in keeping with the demographics of the region. There was no difference in ethnicity between the diabetic and non-diabetic groups of patients.

Haemoglobin levels Figure 2 denotes the linear regression analysis of haemoglobin (with 95% CI) against GFR in patients with diabetic vs those with non-diabetic kidney

Fig. 2 Linear regression analysis of haemoglobin (Hb) versus GFR in patients with diabetic kidney disease (dotted line) vs non-diabetic kidney disease (continuous line). Broken thin lines denote 95% CI limits for each slope. $p<0.01$ for comparison of the two slopes

disease. The difference between the two slopes is statistically significant ($p<0.01$). Mean haemoglobin levels with 95% CI at each CKD stage for both groups of patients are listed in Table 2. The haemoglobin levels in diabetic patients tended to be lower at CKD stage 2 than in non-diabetic patients, with significantly lower levels at GFR <60 ml/min. This relationship is sustained up to CKD stage 5 renal impairment. Although we observed a trend towards lower haemoglobin in diabetic stage 2 CKD patients, this was a relatively smaller group in comparison with the non-diabetic patients. These results should therefore be interpreted with caution. There is no internationally agreed threshold of haemoglobin level to define anaemia in patients with renal disease. However, most clinicians worldwide tend to react with investigations or interventions at a level of less than 110 g/l in such patients. Hence, we have presented data comparing numbers and percentages of diabetic and non-diabetic patients with haemoglobin <110 g/l at various stages of kidney disease in Table 3.

Other characteristics affecting haemoglobin levels Table 4 shows the other recognised factors that influence haemoglobin levels in patients with renal impairment. Information on plasma intact parathyroid hormone (PTH) levels and

Table 1 Patient characteristics

	Diabetic kidney disease ($n=303$)	Non-diabetic kidney disease ($n=1,749$)	p value
Age	61.4 (59.0–63.7)	60.3 (59.2–61.4)	0.89
Sex (male %)	55.7	54.8	0.8
Type 2 diabetes (%)	74.5		
CKD 1			
n	13	130	
GFR (ml/min)	102.4 (93.0–111.8)	108.1 (104.7–111.5)	0.30
CKD 2			
n	28	337	
GFR (ml/min)	72.9 (70.0–75.7)	73.0 (72.1–73.9)	0.94
CKD 3			
n	105	637	
GFR (ml/min)	42.3 (40.6–44.1)	43.0 (42.3–43.7)	0.67
CKD 4			
n	117	461	
GFR (ml/min)	21.5 (20.7–22.3)	22.0 (21.3–22.7)	0.61
CKD 5			
n	40	184	
GFR (ml/min)	11.2 (10.5–12.0)	10.8 (10.4–11.2)	0.37

Table 2 Haemoglobin in diabetic vs non-diabetic patients at various CKD stages

	Haemoglobin (g/l) in patients with diabetic kidney disease	Haemoglobin (g/l) in patients with non-diabetic kidney disease	p value
CKD 1	135.5 (126.2–144.8)	134.8 (132.8–136.9)	NS
CKD 2	135.9 (124.8–142.0)	138.9 (137.4–140.4)	0.09
CKD 3	129.5 (126.5–132.4)	136.9 (135.7–138.0)	<0.001
CKD 4	120.5 (117.6–123.4)	126.9 (125.5–128.4)	<0.001
CKD 5	107.1 (103.4–110.8)	115.9 (113.7–118.1)	<0.01

Table 3 Number of patients with haemoglobin <110 g/l in diabetic vs non-diabetic patients at various CKD stages

	Patients with diabetic nephropathy, <i>n</i> (%)	Patients with non-diabetic kidney disease, <i>n</i> (%)	<i>p</i> value
CKD 1	1 (8)	3 (2.3)	NS
CKD 2	1 (3.5)	9 (2.6)	NS
CKD 3	11 (10.4)	21 (3.2)	0.01
CKD 4	25 (21.3)	33 (7.1)	<0.01
CKD 5	34 (85)	37 (20.1)	<0.01

ferritin was available for 149/157 (94.9%) diabetic patients and 606/645 (93.9%) non-diabetic patients with moderate to advanced renal impairment (CKD stages 4 and 5). We were unable to obtain the same information in a substantial number of patients from the other CKD groups. This is not unexpected, as routine surveillance for secondary complications of chronic renal impairment is undertaken only in patients with advanced renal impairment. Data on use of ACEIs and length of follow-up were available for all 2,052 patients, and no difference was found in either parameter between the diabetic and non-diabetic patients at all CKD stages (data not shown). As shown in Table 4, in patients with GFR <30 ml/min there was no significant difference in ferritin levels, Pth levels, ACEI use or length of follow-up.

Discussion

The association between declining renal function and anaemia is well recognised [9]. The relationship between anaemia, diabetes and renal impairment has also been investigated in several small studies [10–12]. The Kidney Early Evaluation Study also reported diabetes to be independently correlated with anaemia in persons with moderate reduction in kidney function [13]. This study, however, is limited in as far as it was a targeted study with participant self-reporting being the major means of data gathering.

With regard to the question of whether anaemia in diabetic nephropathy is more severe than that seen in patients with

non-diabetic kidney disease, two single centre studies with limited patient numbers have suggested that anaemia tends to occur earlier and is more severe in patients with diabetic nephropathy than in an equivalent non-diabetic patient group. Thus Bosman et al. [14] compared 27 patients with type 1 diabetes and diabetic nephropathy with 26 patients with glomerulonephritis. They reported that anaemia was more likely in diabetic patients and that serum erythropoietin levels were comparable in the two groups. This study included only patients with relatively well preserved renal function (creatinine <180 µmol/l). A similar study by Ishimura et al. [15] demonstrated that 19 patients with type 2 diabetes had comparable erythropoietin levels, but significantly lower haemoglobin when compared with 21 patients with equivalent non-diabetic renal impairment.

To our knowledge, this is the first large study comparing haemoglobin in patients with diabetic vs patients with non-diabetic renal impairment. This study for the first time also controls for other common contributing factors associated with anaemia in patients with renal impairment, e.g. ACEI use [16, 17], secondary hyperparathyroidism [18–20] and iron deficiency.

The finding of lower haemoglobin in diabetic patients could have been due to: (1) relative deficiency of erythropoietin in patients with diabetes [14]; (2) autonomic neuropathy associated with diabetes interfering with anaemia-sensing by the erythropoietin-producing cells in the kidney [21–23]; (3) a lower baseline level but appropriate erythropoietin response to hypoxia in patients with diabetic autonomic neuropathy [24]; (4) damage to the erythropoietin-producing peri-tubular fibroblasts in patients with diabetes [25]; and finally (5) chronic inflammation associated with diabetes [26–28] contributing to erythropoietin hypo-responsiveness. The retrospective nature of our study prevented measurement and analysis of serum erythropoietin levels or inflammatory markers like C-reactive protein in our cohort of patients. It should also be noted that up to 5% of patients with type 1 diabetes have associated coeliac disease [29], which may contribute to anaemia. Since less than 25% of our diabetic patients were type 1, and ferritin levels were comparable, it is likely that even after correction for the projected incidence of coeliac disease, the haemoglobin levels were significantly lower in the diabetic than in the non-diabetic group.

Table 4 Comparison of other factors that affect haemoglobin in diabetic vs non-diabetic patients in CKD stages 4 and 5

	Diabetic kidney disease (<i>n</i> =157)	Non-diabetic kidney disease (<i>n</i> =645)	<i>p</i> value
Ferritin (pmol/l)	212.3 ^a (206.2–218.4)	215.7 ^a (213.2–218.1)	0.46 ^b
Parathyroid hormone (ng/l)	21.30 ^a (18.0–24.6)	20.40 ^a (18.5–22.3)	0.13 ^b
Patients on ACEI (%)	58	55	0.39
Length of follow-up (months)	33.5 ^a (30.5–36.6)	29 ^a (26.9–31.1)	0.67 ^b

^a Median values

^b Mann–Whitney *U* test

Possible weaknesses of the study are the retrospective study design and the inherent selection bias due to enrolment of only patients attending a tertiary referral renal service. Typically only patients with proteinuria±renal impairment and diabetes are referred to and followed up by nephrologists. Hence patients at the severe end of the diabetic nephropathy spectrum will be overrepresented. However, this bias will also be apparent in the non-diabetic renal impairment group, because regular follow-up is more likely in patients with more advanced renal impairment, where anticipatory intervention by nephrologists may be beneficial. Only a small number of patients with diabetes had diabetic nephropathy confirmed by renal histology. A clinical quartet of proteinuria, retinopathy, hypertension and diabetes±renal impairment are universally accepted as being diagnostic of diabetic kidney disease/diabetic nephropathy [30], and these features have been used previously to define disease [31]. While some studies have suggested a high incidence of non-diabetic kidney disease in patients with diabetes and proteinuria [32], others have not been able to replicate these findings [33]. The inclusion of retinopathy in our definition of diabetic nephropathy further strengthens the likelihood of this being the underlying pathology [34]. As uniformly quantified proteinuria data were not available, we were unable to assess the impact of this variable on haemoglobin levels.

In spite of the above-mentioned shortcomings, our study concludes that patients with diabetic kidney disease have significantly lower haemoglobin levels than patients with non-diabetic kidney disease. This relationship is not explained by differences in other common contributory factors to anaemia associated with renal impairment, implicating the presence of diabetes as an independent risk factor. A heightened awareness of this finding will help tighten surveillance for anaemia in patients with diabetes in general and diabetic patients with renal impairment in particular. Anaemia in patients with renal impairment contributes to considerable cardiovascular morbidity and mortality [35, 36] and in diabetic patients may speed progression to end-stage renal failure [37, 38]. Since proven, safe and effective treatment for anaemia associated with renal impairment is already widely available in the form of recombinant human erythropoietin, prospective trials of early erythropoietin intervention in patients with diabetic kidney disease are urgently required. Earlier correction of anaemia in this subset of patients may slow progression of renal impairment, reduce cardiovascular morbidity and improve patient survival.

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