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Anaemia in diabetic patients with chronic kidney disease — prevalence and predictors

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Abstract *Aims/hypothesis:* We investigated the relationship between haemoglobin (Hb) and diabetes in patients with renal disease. *Subjects, materials and methods:* All adult patients with stable chronic kidney disease attending renal or diabetic outpatient clinics in a six-month period were identified. Patients' notes and electronic patient records were used to build a comprehensive biochemical and clinical database. Results were analysed for the predictors of Hb, the severity of anaemia in both groups and the relative impact of diabetes on haemoglobin and anaemia. *Results:* The study group consisted of 468 patients, of whom 204 had diabetes and 264 did not. At every level of renal function haemoglobin levels were lower by an average of 10 g/l in subjects with diabetes than in those without. Likewise, anaemia was found to occur at an earlier stage of chronic kidney disease (and to be of greater severity) in diabetic patients. Independent predictors of haemoglobin included female sex, diabetes, renal function and serum albumin, with diabetes and renal function being the greatest predictors. Multiple logistic regression showed that patients with diabetes had an odds

ratio of 4 for being anaemic. Had we used an estimated GFR of less than 60 ml/min to trigger investigation of anaemia, we would have detected 85% of anaemic patients. *Conclusions/interpretation:* Anaemia is frequently found in diabetic patients with renal disease, occurs earlier and is more severe than in similar but non-diabetic subjects. In contrast to previous publications, our findings suggest that anaemia is prevalent at the earliest stages of chronic kidney disease. We advocate an estimated GFR threshold of <60 ml/min to trigger investigation for anaemia in diabetic subjects.

Keywords Anaemia · Chronic kidney disease · Diabetes · Nephropathy

Abbreviations ACEI/ARBs: ACE inhibitors/angiotensin II receptor blockers · CKD: chronic kidney disease · CRP: C-reactive protein · eGFR: estimated GFR · Hb: haemoglobin · K/DOQI: Kidney Disease Outcomes Quality Initiative · MDRD: Modification of Diet in Renal Disease · rHuEPO: recombinant human erythropoietin

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Introduction

Anaemia associated with chronic kidney disease has substantial clinical and public health importance in terms of morbidity, mortality and quality of life, but relatively little is known about its epidemiology [1]. Patients with renal insufficiency have reduced haemoglobin levels, mostly as a result of decreased production of erythropoietin due to tubulointerstitial damage. However, the relationship between the degree of renal insufficiency and the magnitude of reduction in haemoglobin is not precisely defined [1]. There is an increasing realisation of the importance of early detection and screening of mild to moderate chronic renal failure (most often defined by formulae manipulating serum creatinine values). Few large-scale studies have assessed the relationship between renal function and haemoglobin, particularly including categories of milder renal impairment [2].

World Health Organization statistics identify around 150 million people with diabetes mellitus worldwide and suggest that this figure may double by 2025 [3]. Diabetes mellitus is the single most common cause of end-stage renal disease and consequently the most common cause of renal anaemia [3]. Patients with diabetes mellitus are also twice as likely to have anaemia as those with renal impairment from other causes [4]. Furthermore, declining haemoglobin levels may be observed before changes in renal function [5]. This 'early' anaemia is thought to be mainly caused by a relative resistance or absolute deficiency of erythropoietin production by the kidney [6–8]. It is yet unproven whether anaemia directly contributes to the acceleration of complications in diabetic nephropathy or to the progression of diabetic small vessel disease. Nevertheless, patients with diabetes may be more vulnerable to the effects of anaemia, since many also have significant cardiovascular disease and hypoxia-induced organ damage [9].

The aim of this study was to determine the relationship between the degree of renal insufficiency and the magnitude of anaemia in diabetic patients and to determine whether anaemia exists in patients who have diabetic nephropathy but not severe renal functional impairment. Therefore we chose to compare a group of diabetic patients with mild to moderate chronic kidney disease with a group of patients with non-diabetic renal disease of comparable severity.

Subjects, materials and methods

Study population

All adult (>18 years) patients attending either the Renal and/or Diabetic Outpatient departments at Guy's Hospital, London from October 2004 to March 2005 were considered for this analysis. Inclusion criteria for the study were ambulatory patients without erythropoietin or a blood transfusion in the 3 months preceding the study, and with stable kidney function ranging from chronic kidney disease (CKD) stages 1–5, as well as valid blood tests during the specified time periods. Patients were excluded if they had had an acute illness within the last 2 weeks, if there was inadequate clinical or biochemical information on the patient, if the patient was on chemotherapy or immunosuppressants and if patients had had a blood transfusion or had been on exogenous recombinant human erythropoietin (rHuEPO) within the last 3 months. Patients with macrocytic (vitamin B12 and folate deficiency) or microcytic anaemia (iron deficiency) were also excluded.

Data on the following were collected using Electronic Patient Record and medical notes: demographic characteristics, laboratory parameters, levels of proteinuria and medication status with emphasis on ACE inhibitors/angiotensin II receptor blockers (ACEI/ARBs). A database was constructed on Microsoft Excel 2003.

Definitions, variables and patient categories

The following variables were considered: age, sex, weight, haemoglobin (Hb), haematinics, diabetes status, serum albumin, serum creatinine, estimated GFR (eGFR), C-reactive protein (CRP), parathyroid hormone, and ACEI/ARB treatment. Proteinuria was quantified in the nephrology clinic by dipstick test from spot urine samples given on freshly voided specimens in the clinic (nil, trace, +1 to +4).

Diabetes was defined according to WHO criteria: symptoms of diabetes mellitus plus random plasma glucose concentration ≥ 11.1 mmol/l or fasting plasma glucose concentration ≥ 7.0 mmol/l or 2-h plasma glucose concentration ≥ 11.1 mmol/l after a 75-g glucose load [10, 11]. Estimated GFR values were calculated using the simplified Modification of Diet in Renal Disease (MDRD) formula ($186 \times [\text{serum creatinine in mg/dl}^{-1.154}] \times [\text{age in years}^{-0.203}]$ multiplied by 0.742 for women) [12]. Participants were further classified on the basis of eGFR values for CKD stages from the Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines: ≥ 90 (CKD1), 60–89 (CKD2), 30–59 (CKD3), 15–29 (CKD4) and <15 (CKD5) $\text{ml min}^{-1} 1.73 \text{ m}^{-2}$ [13]. Participants were also categorised as having anaemia based on the K/DOQI definition (Hb <120 g/l for men and post-menopausal women [>50 years old] and <110 g/l for pre-menopausal women [≤ 50 years old]) [14].

Statistical analysis

Statistical analyses were performed using Microsoft Excel and StatView for Windows version 5.0.1 (SAS Institute, Cary, NC, USA). Descriptive analyses were used for the demographic characteristics. Comparison of groups with parametric data was achieved using unpaired *t* tests while non-parametric data were compared with the Mann–Whitney *U* test. Groups involving nominal variables were compared by the chi-square test. To assess thresholds to trigger screening for anaemia, we calculated sensitivities, specificities, and positive and negative predictive values. Correlations of haemoglobin with single variables were examined using univariate regression analyses; calculation of Spearman's rank correlation coefficients and significance was by Fisher's *r* to *z* test. To determine which variables were independently predictive of haemoglobin, a multiple regression analysis was constructed on the basis of two models. The first model incorporated variables with the greatest univariate correlation with haemoglobin, namely diabetes, female sex, age, CRP, serum albumin and eGFR (in preference to serum creatinine). The second model additionally incorporated the effect from ferritin and ACEI/ARB therapy. Odds of anaemia as predicted from the diabetes status were calculated using multiple logistic regression adjusted for all the other variables. For all analyses, *p* values of less than 0.05 were taken as denoting statistical significance.

Table 1 Demographic and laboratory parameters

Variable (mean±SD)	Diabetic (n=204)	Non-diabetic (n=264)	<i>p</i>
Male:Female [<i>n</i> (%)]	130 (63.7%):74 (36.3%)	159 (60.2%):105 (39.8%)	NS
Mean age (years±SD)	63.0±13.6	52.8±16.6	<0.001
Mean weight (kg±SD)	87.4±21.0	78.0±17.5	<0.001
Median (IQR) creatinine (µmol/l)	137 (128)	135 (118)	NS
Mean eGFR (ml/min±SD)	50.0±28.8	51.2±28.8	NS
Mean Hb (g/l±SD)	123±19	133±17	<0.001
Mean MCV (fl±SD)	87.3±6.4	89.5±5.8	<0.005
Median (IQR) ferritin (µg/l)	91 (121)	71 (125)	NS
Median (IQR) CRP (mg/l)	7 (11.5)	6 (5)	NS
Mean albumin (g/l±SD)	36.1±4.5	37.7±4.9	<0.001
ACEI/ARB therapy (<i>n</i> , %)	144, 71	125, 47	<0.001
Mean PTH (pmol/l±SD)	202±200	220±230	NS
Mean HbA _{1c} (%±SD)	7.6±1.5	—	—

Parametric data are represented as mean±SD while non-parametric data are shown as median (interquartile range, IQR). Comparison between diabetic and non-diabetic patients is made using the unpaired *t* test and Mann–Whitney test for parametric and non-parametric data, respectively

Hb Haemoglobin concentration, *MCV* mean corpuscular volume, *CRP* C-reactive protein, *eGFR* estimated glomerular filtration rate, *ACEI/ARB* angiotensin converting enzyme inhibitors/angiotensin II receptor blockers, *PTH* parathyroid hormone concentration

Results

Demographic data

There were 501 subjects in the study, of whom 33 were excluded as mentioned above. Of the remaining 468 participants, 264 had diabetes and 204 did not. The vast majority of the diabetic cohort had type 2 diabetes (88.7%), therefore the diabetic population was considered together without separating type 1 from type 2. As the proportion of black people was equal and small in both groups (10.8:10.6%), this racial variance was ignored with respect to application of estimated GFR formulae. The characteristics of the studied group are summarised in Tables 1 and 2. As expected, the majority of patients (77.5%) in the diabetic group had underlying diabetic nephropathy (ranging from microalbuminuria to overt diabetic nephropathy), while the rest (22.5%) had other renal diagnoses in the context of diabetes. The proportions of patients in each CKD group were comparable. Due to the small number of

patients with CKD stages 1 and 5 in each group, they were considered together with CKD stages 2 and 4, respectively, as shown in Table 3.

Anaemia prevalence by level of renal function and diabetes status

In all CKD stages, including normal and mildly impaired renal function, anaemia prevalence was significantly greater and mean haemoglobin level was lower in patients with diabetes than in non-diabetic patients (Table 3, Fig. 1). Overall, there was a mean difference of approximately 10 g/l at each CKD stage. The mean eGFR did not differ between patients with and without diabetes at the individual CKD stages. There was a significant linear relationship between haemoglobin levels and eGFR, both in diabetic and in non-diabetic patients (Fig. 2).

Of the 264 subjects without diabetes, 44 had anaemia (17%). Four of these subjects had serum creatinine values of <120 µmol/l and four had an eGFR of >60 ml/min. In the group with diabetes, 83 of 204 patients were anaemic (41%), of whom 13 had a serum creatinine of <100 µmol/l and 13 had eGFR values >60 ml/min. Using these and adjacent thresholds for triggering screening for anaemia in diabetic and non-diabetic patients, we calculated the sensitivity, specificity, and positive and negative predictive values of these cut off points (Table 4).

Potential determinants of Hb level in diabetic vs nondiabetic patients

Univariate analyses for predictors of haemoglobin level are presented in Table 5. A two-stage multiple regression analysis was then performed as detailed in methods above

Table 2 Underlying renal pathology

Renal pathology	Diabetic (n=204) (%)	Non-diabetic (n=264) (%)
Diabetic nephropathy	158 (77.5%)	0
Chronic glomerulonephritis	19 (9.3%)	53 (20.1%)
Adult polycystic kidney disease	0	20 (7.6%)
Autoimmune and vasculitis	5 (2.5%)	33 (12.5%)
Reflux nephropathy/obstruction/pyelonephritis	9 (4.4%)	48 (18.2%)
Hypertension/miscellaneous/unknown	13 (6.4%)	110 (41.7%)

The underlying renal pathology was identified from studying patient records

Table 3 Mean haemoglobin values and prevalence of anaemia (K/DOQI definition) in various stages of chronic kidney disease (CKD)

CKD stage	Diabetes status	n (%)	Hb (g/l) (mean±SD)	p (Hb)	eGFR (ml/min) (mean±SD)	p (eGFR)	Anaemia prevalence n (%)	p (anaemia prevalence)
CKD 1 and 2 (n=172)	Diabetic	76 (44%)	132±17	<0.002	82±17	NS	13 (17%)	<0.01
	Non-diabetic	96 (56%)	140±15		83±16		4 (4%)	
CKD 3 (n=156)	Diabetic	65 (42%)	121±17	<0.0001	43±9	NS	33 (51%)	<0.0001
	Non-diabetic	91 (58%)	135±17		44±9		12 (13%)	
CKD 4 and 5 (n=140)	Diabetic	63 (45%)	115±17	<0.001	19±7	NS	37 (59%)	<0.05
	Non-diabetic	77 (55%)	124±13		19±7		28 (36%)	

Patients (n=468, of whom 204 had diabetes) were divided into stages of CKD based on estimated glomerular filtration rate (eGFR).

Haemoglobin levels obtained from laboratory measurements were compared between diabetic and non-diabetic subjects in each CKD stage
Hb Haemoglobin concentration

(Table 6). The first model (age, diabetes, female sex, eGFR, serum albumin and CRP) predicted 39% of the variance in haemoglobin, with eGFR and diabetes being the greatest predictors. The second model (as above but also including CRP and ACEI/ARB therapy) was predictive of 35% of the variance in haemoglobin, with diabetes as the greatest determinant. Multiple logistic regression analysis was used to determine the impact of diabetes on the likelihood of anaemia. This analysis factored contributions from age, female sex, eGFR, ACEI/ARB therapy, CRP, albumin and ferritin (data not shown). Diabetes status conferred an odds ratio for having anaemia of 4 (95% CI 1.8 to 7.1, $p<0.0005$)

independently of other factors. In this analysis, the odds ratio of having anaemia with every 1 unit drop in eGFR was 1.02 (95% CI 1.01 to 1.04, $p<0.001$). Splitting patients with diabetes into those who had diabetic nephropathy and those without diabetic nephropathy failed to reveal differences between haemoglobin values or frequency of anaemia. Indeed, logistic regression analysis demonstrated that diabetic nephropathy in itself is not an independent risk factor for the development of anaemia.

Fig. 1 Mean haemoglobin in different chronic kidney disease (CKD) groups in diabetic and non-diabetic patients with renal disease. 468 patients with (n=204) and without (n=264) diabetes, classified according to stage of CKD, were studied. Mean haemoglobin values (Hb) were compared at different CKD stages. Due to the small number of patients with CKD stages 1 and 5 in each group, these were considered together with CKD stages 2 and 4, respectively. Triangles, non-diabetic patients; circles, diabetic patients. Error bars: standard deviations. All p values compare diabetic with non-diabetic patients in the same CKD group. *** $p<0.001$; † $p<0.002$; # $p<0.0001$

Fig. 2 Linear regression showing the relationship between renal function and haemoglobin (Hb). Four hundred sixty-eight subjects with renal disease, divided into those with (n=204) and without (n=264) diabetes mellitus, were studied. Estimated glomerular filtration rate (eGFR) using the MDRD formula was calculated for each patient and linear regression analysis was carried out to investigate the relationship between eGFR and mean Hb. Regression lines (solid line, diabetic subjects; dashed line, non-diabetic subjects) also reflect the tendency of the diabetic group to have lower Hb levels than non-diabetic subjects, given a similar level of renal function. Filled circles, diabetic patients; open circles, non-diabetic patients. $r^2=0.19$ for diabetic patients and 0.16 for non-diabetic subjects

Table 4 Thresholds for triggering anaemia screening

Cohort	Parameter	Threshold	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Non-diabetic	Serum creatinine	>120 $\mu\text{mol/l}$	91	48	26	96
		>130 $\mu\text{mol/l}$	90	51	34	96
	eGFR	<60 ml/min	91	42	24	96
		<50 ml/min	89	53	27	96
Diabetic	Serum creatinine	>100 $\mu\text{mol/l}$	84	39	49	79
		>110 $\mu\text{mol/l}$	77	51	52	77
	eGFR	<60 ml/min	84	52	55	83
		<50 ml/min	72	60	55	76

Four hundred sixty-eight patients (204 diabetic) with kidney disease were selected. Sensitivities, specificities, positive predictive values (PPV) and negative predictive values (NPV) were calculated for different thresholds of serum creatinine and estimated glomerular filtration rate (eGFR) to trigger screening for anaemia

Discussion

In this study we evaluated the prevalence of anaemia in relation to diabetes status across a broad range of kidney function, starting from near-normal up to end-stage renal disease. Statistically significant differences in the haemoglobin values and prevalence of anaemia existed between participants with and without diabetes independent of other variables. Moreover, this difference was observed at all levels of kidney function (CKD 1 to CKD 5). This contrasts with similar recent large-scale population studies, which showed statistically significant differences in haemoglobin levels only in moderate renal impairment (CKD 3) [15], so our finding has potentially important implications for anaemia screening in diabetic populations.

Independent predictors of haemoglobin across all ranges of kidney function were found to be female sex, eGFR, diabetes, serum albumin and CRP, although the last of these was a weak predictor. The most powerful predictors of haemoglobin were diabetes mellitus and renal function. Indeed, the presence of diabetes conferred a four-fold increased risk of being anaemic. Age and serum ferritin were not found to be independently predictive of haemoglobin levels despite significant correlations on univariate analysis. This negative finding should be interpreted with caution with respect to age, as age and sex are used to calculate eGFR in the MDRD formula and are therefore potential mathematical confounders when considering independent determinants of haemoglobin or anaemia. ACEI/ARBs have been suggested to have a negative impact on haemoglobin levels, and although a higher proportion of the diabetic population was

on ACEI and/or ARBs than the non-diabetic population (71.3 vs. 47.3%), these drugs did not appear to be independently linked to lower haemoglobin values in these patients.

To our knowledge, only three recent large-scale population studies have examined the relationship between anaemia and renal function with regard to diabetes status [9, 15, 16]. The present study differs from these in terms of the definitions of anaemia and CKD, as well as in demographic constitution (mainly race and sex) and the use of a non-diabetic comparator group. In the present study, anaemia was more common and haemoglobin was significantly lower among diabetic patients in all CKD stages including 1 and 2 than among non-diabetic subjects. By contrast, in the KEEP study, anaemia prevalence in diabetic patients was significantly greater only for CKD stages 2 and 3 (haemoglobin values were lower among diabetic patients only in CKD stage 3) [15].

In (non-diabetic) renal disease, erythropoietin depletion and anaemia are not normally present until glomerular filtration is less than approximately 20 to 40 ml min⁻¹ 1.73 m⁻², which corresponds to serum creatinine between 177 and 300 $\mu\text{mol/l}$ [17, 18]. However, both this study and others have demonstrated a linear relationship between Hb and eGFR even at what would be considered normal renal function onwards (see Fig. 2) [9, 15, 16, 19]. Indeed, a large proportion of anaemic subjects in the present study had near-normal renal function.

Why does anaemia preferentially develop in diabetic patients even before overt diabetic nephropathy? The relationship between diabetes and anaemia has been related

Table 5 Predictors of haemoglobin, univariate analysis

Diabetes status	Age	Female sex	Ferritin	CRP	Serum albumin	Serum creatinine	eGFR	ACEI/ARB therapy
Diabetes	-0.23**	-0.21*	0.01 ¥	-0.22*	0.47***	-0.37***	0.43***	0.002 ¥
No diabetes	-0.075 ¥	-0.28***	0.02 ¥	-0.11 ¥	0.33***	-0.35***	0.40***	0.009 ¥

Biochemical parameters were obtained from electronic patient records for 468 patients with kidney disease, split into those with ($n=204$) and without ($n=264$) diabetes mellitus. Univariate correlation analyses were carried out between biochemical parameters and haemoglobin (Hb) levels for each group. Statistically significant ($p<0.05$) correlations (Spearman's rank correlation coefficient) are presented CRP C-reactive protein, eGFR, estimated glomerular filtration rate, ACEI/ARB angiotensin converting enzyme inhibitor/angiotensin II receptor blocker

* $p<0.01$, ** $p<0.001$, *** $p<0.0001$, ¥ not statistically significant

Table 6 Predictors of haemoglobin, multiple regression analysis

Model	Regression coefficient (adjusted r^2)	p
One	0.39	<0.0001
Age	0.02	NS
Female sex	-0.26	<0.0001
eGFR	0.35	<0.0001
Diabetes	-0.29	<0.0001
Albumin	0.26	<0.0001
CRP	-0.09	0.03
Two	0.35	<0.0001
Age	0.001	NS
Female sex	-0.23	<0.0001
eGFR	0.30	<0.0001
Diabetes	-0.31	<0.0001
Albumin	0.23	0.0001
CRP	-0.12	<0.05
ACEI/ARB	0.02	NS
Ferritin	0.03	NS

Biochemical parameters were obtained from electronic patient records for 468 patients with kidney disease, split into those with ($n=204$) and without ($n=264$) diabetes mellitus. A two-step model was devised to determine independent predictors of haemoglobin. The first model contained: diabetes, female sex, age, CRP, serum albumin and eGFR (in preference to serum creatinine); the second model additionally incorporated the effect of ferritin and ACEI/ARB therapy

CRP C-reactive protein, eGFR estimated glomerular filtration rate, ACEI/ARB angiotensin converting enzyme inhibitor/angiotensin II receptor blocker

to advancing kidney damage involving the tubulointerstitial compartment and leading to relative deficiency of and/or resistance to erythropoietin [6–8, 20, 21] and uraemia. It has recently become clear that the failure to increase circulating erythropoietin levels in response to falling haemoglobin levels is the dominant factor in the genesis of anaemia associated with diabetic nephropathy as it is with CKD [19, 22, 23]. Most importantly, failure to increase synthesis of erythropoietin in response to anaemia appears to be more extreme than that seen in other renal (and particularly glomerular) diseases [4]. There are many other reasons that causally link diabetes and anaemia (comprehensive review, see [24]).

Additionally, anaemia identifies patients with increased risk of mortality and morbidity [24–28] and progression of diabetic complications [29]. Despite this, there are as yet no separate guidelines for anaemia screening in diabetics. On the other hand, diabetic subjects have been treated in the same way as non-diabetic subjects with CKD, as it is not yet clear whether we should use a different haemoglobin target in diabetic patients. There is no solid evidence to support the notion that correction of anaemia significantly improves clinical outcomes in diabetic patients with CKD, apart from quality of life [30], but this in itself may be very significant from the patients' perspective. For most of the renal interventional studies, there was a substantial degree of renal impairment at the time of rHuEPO intervention.

Similar studies need to be done at a much earlier stage of CKD to see if the potential benefits of rHuEPO are also evident, or even more obvious.

The present study has several limitations: erythropoietin levels were not measured in any of the subjects to differentiate between erythropoietin deficiency and resistance. Additionally, the form of the data restricted the possibilities of dissecting out underlying patho-mechanisms in detail; also formal quantification of autonomic function in the diabetic subjects was not available, making it impossible to elucidate any impact of autonomic neuropathy on the cause of anaemia in diabetic subjects.

Nevertheless, our findings show that across a broad range of kidney function extending from near-normal to ESRD, diabetes was independently correlated with anaemia in a large group of patients with renal disease (even at an early stage). Diabetic subjects had lower haemoglobin values than their non-diabetic counterparts for the same level of renal function, and anaemia occurred in diabetic patients at earlier stages of CKD than in nondiabetic patients. These findings have implications with regard to screening for anaemia in otherwise healthy, ambulant diabetic outpatients. We advocate a renal function threshold value of eGFR <60 ml/min (which would detect 85% of anaemic patients and involve a positive anaemia result in 55% of patients screened) or serum creatinine of >100 $\mu\text{mol/l}$ (which would detect 84% of anaemic patients and return a positive anaemia result in 49% of those screened). Anaemia, whether as a complication of diabetes mellitus, or as a potential risk for progression to diabetic complications, remains under-evaluated, under-recognised and under-treated. We therefore recommend early screening, even at near-normal GFR, and more aggressive management of diabetic anaemia with a view to improving quality of life and ultimate outcome for patients affected.

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