

# Unrecognized Anemia in Patients With Diabetes

## A cross-sectional survey

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**OBJECTIVE** — Anemia is common in diabetes, potentially contributing to the pathogenesis of diabetes complications. This study aims to establish the prevalence and independent predictors of anemia in a cross-sectional survey of 820 patients with diabetes in long-term follow-up in a single clinic.

**RESEARCH DESIGN AND METHODS** — A full blood count was obtained in addition to routine blood and urine test results for all patients over a 2-year period to encompass all patterns of review. Predictors of the most recent Hb concentration and anemia were identified using multiple and logistic regression analysis.

**RESULTS** — A total of 190 patients (23%) had unrecognized anemia (Hb <12 g/dl for women and <13 g/dl for men). This prevalence is two to three times higher than for patients with comparable renal impairment and iron stores in the general population. Independent predictors for Hb were transferrin saturation, glomerular filtration rate (GFR), sex, albumin excretion rate, and HbA<sub>1c</sub> level (all  $P < 0.0001$ ). Microalbuminuric patients were >2 times (odds ratio [OR] 2.3) and macroalbuminuric patients >10 times (OR 10.1) as likely to have anemia than normoalbuminuric patients with preserved renal function (GFR >80 ml/min).

**CONCLUSIONS** — Anemia is a common accompaniment to diabetes, particularly in those with albuminuria or reduced renal function. Additional factors present in diabetes may contribute to the development of increased risk for anemia in patients with diabetes.

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Diabetes is the single most common cause of end-stage renal disease (1) and therefore the most common cause of renal anemia. In addition, anemia may be more common in diabetes (2) and develop earlier than in patients with renal impairment from other causes (3). The predominance of damage to renal interstitium, systemic inflammation, and auto-

nomous neuropathy have all been suggested as contributors to anemia in diabetic nephropathy (DN) (3). Like many pathophysiological changes of DN, dysfunction may be apparent before demonstrable changes in the glomerular filtration rate (GFR).

It is unproven whether anemia directly contributes to the acceleration of

complications in DN or to the progression of diabetic renal disease. However, patients with diabetes may be more vulnerable to the effects of anemia because many also have significant cardiovascular disease and hypoxia-induced organ damage. In addition, a number of studies (4–6) have suggested that Hb levels may be linked to the risk of cardiovascular events, hospitalization, and mortality. Against this, there is no conclusive evidence that correcting anemia significantly improves outcomes in patients with failing renal function, apart from quality of life (7).

Because most patients with DN have little overt renal impairment, the majority are supervised by their primary care physician or endocrinologist. However, significant pathology may be present in patients with DN before meeting criteria for referral to a nephrologist (GFR ~30 ml/min) (8). In this population, renal anemia may go unrecognized or untreated. Compounding this, there has been no systematic survey of the prevalence and predictors of anemia in patients with diabetes, particularly in the absence of overt nephropathy (representing the majority of patients). As a precursor to a clinical trial of anemia correction in diabetes, this study aims to establish the predictors of anemia in patients with diabetes.

## RESEARCH DESIGN AND METHODS

This study was designed as a cross-sectional survey of patients in current long-term follow-up in a single diabetes clinic at the Austin and Repatriation Medical Center (ARMC), Australia. The ARMC Diabetes Clinic serves a population of 600,000. The majority of referrals to the clinic are from general practitioners requiring assistance with surveillance and management of the long-term complications of diabetes. Approximately 20% of the patients are referred from other sources, including specialty units within the medical center. None of the participants were shared with nephrological services at the time of testing. “Current long-

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**Abbreviations:** AER, albumin excretion rate; ARMC, Austin and Repatriation Medical Center; DN, diabetic nephropathy; GFR, glomerular filtration rate; NHANES III, Third National Health and Nutrition Examination Survey; TSAT, transferrin saturation; WHO, World Health Organization.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

term follow-up" was defined by the patients having at least three estimations of urinary albumin excretion rate (AER), with at least one AER having been performed within the previous 2 years. A 2-year window was chosen to include the review pattern of all patients currently enrolled in this clinic (i.e., at least biannual follow-up). Using this criterion, 820 patients with diabetes were identified.

### Determination of variables

At each routine visit, standard indices were recorded from blood testing, including creatinine, urea, albumin, fasting blood glucose, fasting lipid profile, HbA<sub>1c</sub>, and C-reactive protein. Urinary creatinine, urea, albumin, and protein were obtained from a 24-h collection. In addition, a full blood count and transferrin saturation (TSAT) and ferritin levels were obtained. Results obtained outside the outpatient setting (e.g., hospitalized patients or in an emergency setting) were excluded. Where more than one blood test had been performed during the 2-year period, the most recent test that included a full blood count was used for analysis. The most recent (prior) routine results for patients who later died or were referred to a nephrologist during the 2-year survey period were included in the analysis. Creatinine clearance was estimated using the MDRD-6 formula (9). AER was derived from 24-h urinary albumin measurement, categorically defined from the three most recent AER measurements. Macroalbuminuria was defined as two of three AER measurements >200  $\mu\text{g}/\text{min}$ . Microalbuminuria was defined as two of three AER measurements >20  $\mu\text{g}/\text{min}$ . Normoalbuminuria was defined by two of three AER measurements <20  $\mu\text{g}/\text{min}$ . In addition, clinical data, including anthropomorphic measurements, age, race, sex, BMI, type and duration of diabetes, and length of follow-up, were obtained from patient records for all patients.

### Anemia definitions

Hb, the major outcome variable, was primarily handled as a continuous variable. Hb was also recoded as a binary outcome for estimating the risks for anemia (expressed as adjusted odds ratios [ORs]). Two binary definitions of anemia were used: 1) Hb  $\leq 11$  g/dl (irrespective of sex), a level that guidelines suggest benefits from the correction of anemia (10); and 2)

Hb <13 g/dl in men and <12 g/dl in women, a sex-specific definition used by the World Health Organization (WHO) (11).

### Subgroup analysis

Half (50%) of the patients from the clinic population were randomly selected to have an isotopic GFR measured using <sup>99</sup>Tc-labeled DTPA (diethylenetriamine-pentaacetic acid). GFR was corrected for body surface area, and the Brochner-Mortensen correction was applied. In a randomly selected subgroup of 330 patients (40%), a clinical history detailing the presence or absence of specific diabetes complications and treatment modalities was also obtained.

### Statistical methods

Continuous data are expressed as mean  $\pm$  SEM except where specified. Differences in continuous variables were compared using Student's *t* tests (two groups) or one-way ANOVA (three or more groups, where subgroups were compared using Fisher's protected least significant difference post hoc test). Differences in categorical variables were compared using  $\chi^2$  analysis. Pearson correlation was used to analyze univariate associations between continuous variables. Multivariate analysis utilized multiple regression and ANCOVA to model the independent predictors of Hb. For the two definitions of anemia, logistic regression was used to analyze associations between independent predictors (where the  $\beta$  coefficients for the subgroup variables were expressed as ORs with 95% CIs).

## RESULTS

### Outpatient population

A total of 820 patients with diabetes were in current long-term follow-up in our center. The study included 458 men (56%) and 362 women who had been followed-up for a median of 4.8 years (range 1–28). The mean age was  $62.2 \pm 0.5$  years (range 17–88). Of the women in our population, 71% were aged >55 years and were therefore likely to be amenorrhoeic. Over 95% of patients were of Caucasian descent, and the study included no African-American patients. The mean duration of diabetes was 16 years, with a median of 6 years spent in the ARMC clinic, attending at a median frequency of every 4 months. The major-

ity of participants had type 2 diabetes (80%), of whom 46% were receiving insulin. Sixty-one percent of patients in the clinic had normoalbuminuria, 27% microalbuminuria, and 12% macroalbuminuria. Only 5% of patients had heavy proteinuria (>1 g/24 h). The mean HbA<sub>1c</sub> was 7.9% in both men and women.

In the subgroup of patients with clinical data, 69% received antihypertensive treatment, the majority (82%) with an ACE inhibitor. Forty percent of patients had documented vascular disease (32% having a history of ischemic heart disease, 10% cerebrovascular disease, and 12% peripheral vascular disease). Forty-four percent of patients were current or ex-smokers. Thirty-seven percent had retinopathy (32% background and 5% proliferative).

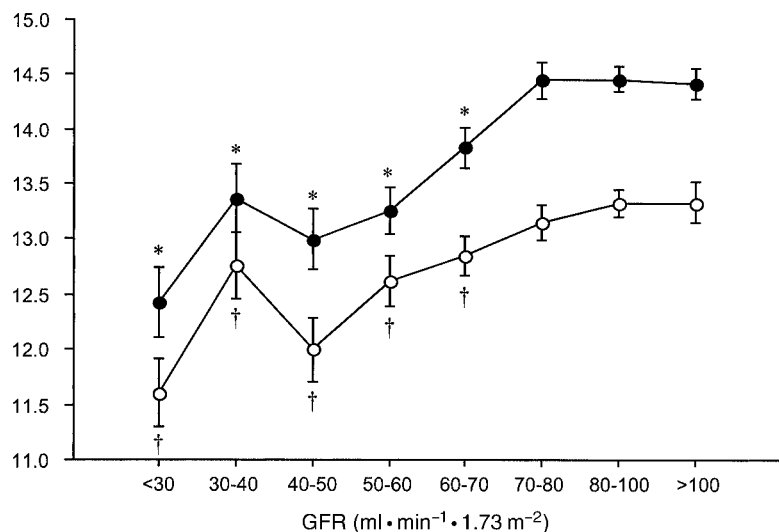
Using the MDRD-6 equation (9), the mean estimated GFR was  $75.7 \pm 1.3$   $\text{ml} \cdot \text{min}^{-1} \cdot 1.73$   $\text{m}^{-2}$  for men and  $72.1 \pm 1.4$   $\text{ml} \cdot \text{min}^{-1} \cdot 1.73$   $\text{m}^{-2}$  for women ( $P < 0.08$ ). Thirty percent of male and female patients had an estimated GFR <60  $\text{ml} \cdot \text{min}^{-1} \cdot 1.73$   $\text{m}^{-2}$ , including 102 patients with normoalbuminuria (12% of all survey patients), consistent with our previous series (12). Almost half of patients in the survey (49%) had both a GFR >60  $\text{ml} \cdot \text{min}^{-1} \cdot 1.73$   $\text{m}^{-2}$  and normoalbuminuria.

### Predictors of Hb level

The mean Hb was  $139.3 \pm 0.3$  g/l for men and  $129.0 \pm 0.7$  g/l for women ( $P < 0.0001$ ). Multiple regression revealed five independent predictors of Hb, including GFR, sex, AER, HbA<sub>1c</sub>, and iron stores (all  $P < 0.0001$ ). These five variables explained ~42% of the Hb variance in the entire clinic population. While sex was an important determinant of raw Hb levels, represented by divergent reference ranges in the general population (13), the most powerful predictors were TSAT and GFR, accounting for 22 and 10% of the variance in Hb, respectively. Similar results could be obtained in multivariate analysis using either MDRD-estimated GFR or DTPA-GFR (data not shown).

### Hb level and GFR

The association between GFR and Hb was essentially continuous at lower levels of GFR. Compared with patients with a GFR 80–100  $\text{ml} \cdot \text{min}^{-1} \cdot 1.73$   $\text{m}^{-2}$ , Hb was significantly lower in all patients with a GFR <70  $\text{ml} \cdot \text{min}^{-1} \cdot 1.73$   $\text{m}^{-2}$  in both



**Figure 1**—Differences in raw Hb at declining levels of GFR. Stratification by sex revealed parallel trends in men (○) and women (●). Hb was significantly lower compared with patients with GFR 80–100 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> within all subgroups <70 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> (*P* < 0.05 within \*male or †female subgroups).

men (*P* < 0.0001) and women (*P* < 0.0001). Stratification by sex revealed parallel trends in men and women (Fig. 1). There was no significant difference in Hb between patients with a GFR 80–100 and >100 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> in either men or women. By contrast, Hb was significantly lower when compared with patients with GFR 80–100 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> in all subgroups <70 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> (*P* < 0.05 within all male and female subgroups with GFR <70 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>). Notably, both men and women with a GFR between 30 and 40 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> appeared to have a Hb that was reduced to a lesser degree than many other subgroups with GFR <70 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>. The five variables associated with raw Hb remained independent predictors when analysis was restricted to patients with a GFR >60 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup> (*n* = 568), while only GFR was no longer significantly associated with anemia at levels of renal function >80 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>.

#### AER and Hb level

Although multiple regression analysis revealed AER was independently associated with Hb (*P* < 0.0001), AER only explained an additional 2% of the variance after accounting for GFR and sex. The association between AER and Hb was similar across the sexes, without any evidence of statistical interaction (*P* = 0.54). In

both men and women, Hb was lowest in the patients with macroalbuminuria, regardless of GFR (Fig. 2).

#### Other predictors for Hb level

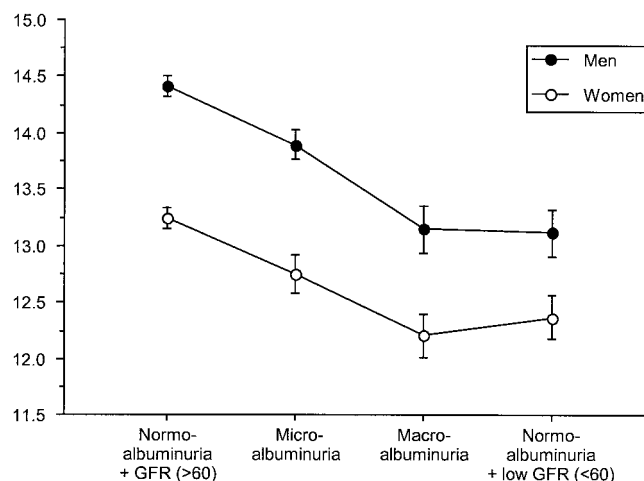
HbA<sub>1c</sub> was associated with Hb (*P* < 0.0001), although this association proved to be weak (~2% Hb variance). Hb levels were significantly lower in patients with a history of ACE inhibitor use (*P* < 0.0001), blood pressure therapy of any kind (*P* < 0.0001), any degree of retinopathy (*P* = 0.02), or smoking (*P* < 0.02). However, all of these associations were

eliminated after adjusting for GFR using ANCOVA. Systolic blood pressure also showed a weak inverse association with Hb (*r* = -0.15, *P* < 0.01), but again this was eliminated after adjusting for GFR and sex. Although inflammation may influence anemia, no independent association was found between C-reactive protein and Hb concentration. In addition, age, BMI, and type of diabetes were not associated with Hb.

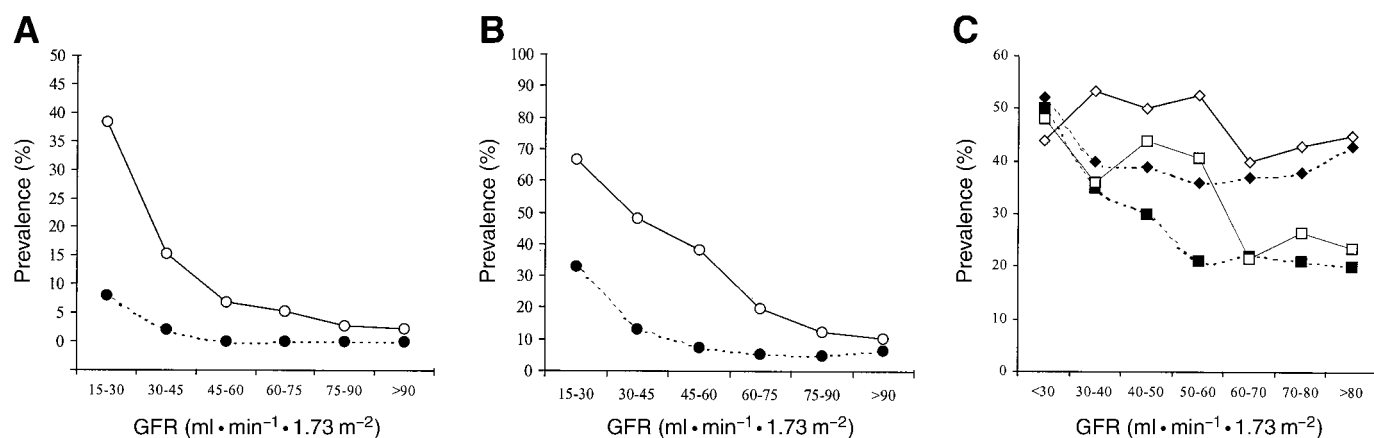
#### Predictors and prevalence of anemia

Figure 3 shows estimates of the prevalence of anemia, using both definitions, at different levels of GFR in the present study's diabetic population, as compared with estimates for the population derived from the Third National Health and Nutrition Examination Survey (NHANES III) (2). Notably, at all levels of GFR, patients with diabetes were more likely to have anemia.

If the presence of anemia is defined categorically as an Hb level ≤11 g/dl, then 56 patients were anemic (7%), including 33 women and 23 men (Fig. 4A). In logistic regression analysis, TSAT and GFR were the only significant predictors for anemia of this magnitude (all *P* < 0.0001). When patients were stratified according to GFR and AER subgroups, after adjusting for TSAT, logistic regression revealed that compared with normoalbuminuric patients with a GFR >80 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>, patients with persistent microalbuminuria (*n* = 222) had 4 times the risk of anemia (OR 4.0, 95% CI



**Figure 2**—Complex association between Hb level and GFR, sex, and AER. Subgroups were stratified according to overt macroalbuminuria, persistent microalbuminuria, normoalbuminuria with low GFR (<60 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>), and normoalbuminuria without low GFR (>60 ml·min<sup>-1</sup>·1.73 m<sup>-2</sup>).



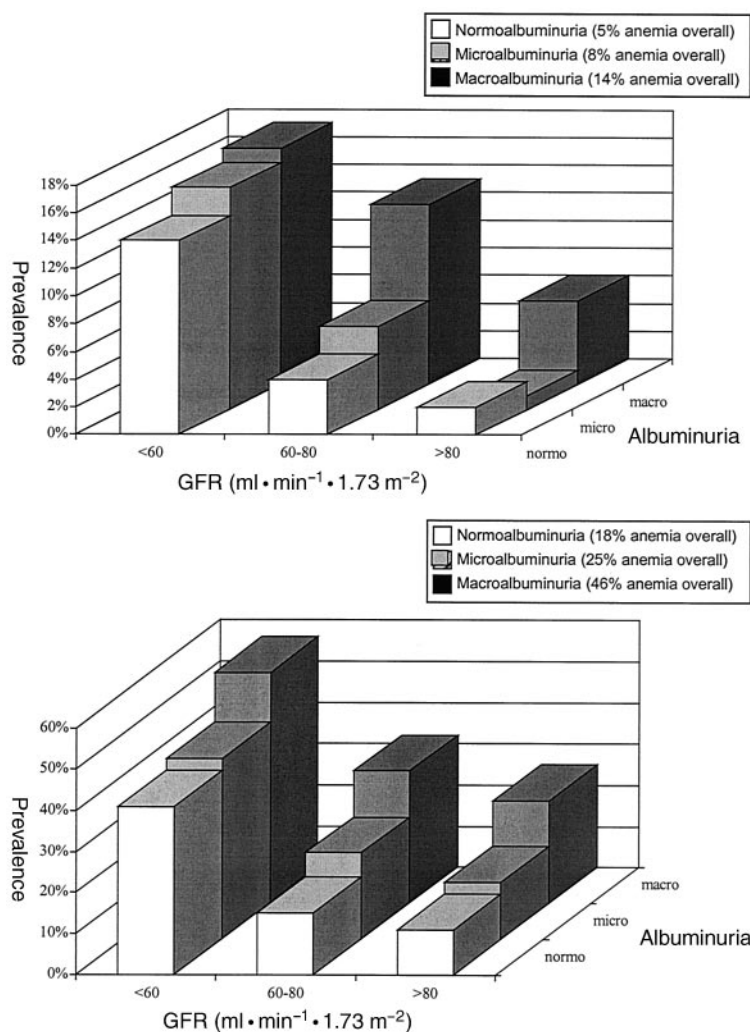
**Figure 3**—The prevalence of anemia (A and B) and reduced iron indices (C) in the diabetic population (○) compared with the general population (●, NHANES III). A: Hb  $\leq 11$  g/dl; B: WHO criteria (men Hb  $< 13$  g/dl, women Hb  $< 12$  g/dl). C: TSAT  $< 20\%$  (squares, men; diamonds, women). NHANES data reprinted with permission (2).

1.1–15.9,  $P < 0.05$ ) and patients with persistent macroalbuminuria ( $n = 94$ ) had  $>12$  times the risk of anemia (12.9, 3.3–51.3,  $P < 0.001$ ). Subjects with normoalbuminuria but impaired renal function ( $\text{GFR} < 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ,  $n = 222$ ) had almost 11 times the risk of anemia (10.9, 2.4–44.2,  $P < 0.001$ ), i.e., a similar risk to patients with macroalbuminuria.

If the presence of anemia was defined categorically using the WHO sex-specific criteria (11), then 190 patients with diabetes were anemic (23%), including 85 women and 105 men (Fig. 4B). Using this definition, TSAT, GFR (both  $P < 0.0001$ ), and AER ( $P < 0.01$ ) remained the main predictors of anemia. In this definition, again after adjusting for TSAT and compared with normoalbuminuric patients with a  $\text{GFR} > 80 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , patients with microalbuminuria had  $>2$  times the risk of anemia (OR 2.3, 95% CI 1.2–4.5,  $P < 0.02$ ) and patients with macroalbuminuria had  $>10$  times the risk of anemia (10.1, 4.8–21.0,  $P < 0.0001$ ). Subjects with a normal AER but impaired renal function ( $\text{GFR} < 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ) had six times the risk of anemia (5.9, 2.8–12.4,  $P < 0.0001$ ). Nearly half (46%) of patients with macroalbuminuria had anemia, irrespective of GFR.

### Iron status

Fifty percent of patients with a Hb  $< 11$  g/dl and 43% of patients with WHO-defined anemia had insufficient iron stores to support erythropoiesis (TSAT  $< 20\%$ ), most of whom were women. This



**Figure 4**—Prevalence of anemia stratified according to AER (normo-, micro-, and macroalbuminuria) and GFR ( $< 60$ , 60–80, and  $> 80 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ ). Anemia was defined as Hb  $\leq 11$  g/dl (A) and WHO criteria (men  $< 13$  g/dl, women  $< 12$  g/dl) (B).



was particularly marked once renal function fell below  $60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , where there was a striking increase in the prevalence of low iron stores compared with the general (NHANES III) population (Fig. 3C) (14). All four iron variables (TIBC, log ferritin, serum iron, and TSAT) were strongly associated with Hb on multivariate analysis ( $P < 0.0001$ ), much more so than sex or renal function. In an additive regression model, serum iron explained an additional 15% of the variance in Hb, while TSAT explained an additional 18%. Notably, there was no significant sex difference in the prevalence of anemia (Hb  $< 11 \text{ g/dl}$ ) after adjusting for either serum iron or TSAT (on logistic regression).

**CONCLUSIONS** — Anemia is a common accompaniment to diabetes, particularly in patients with albuminuria or reduced renal function. The estimated prevalence of anemia depends on essentially arbitrary criteria used to define the presence or absence of anemia. Nonetheless, studies in patients with renal impairment suggest that deleterious effects begin with Hb  $\leq 11 \text{ g/dl}$ , meaning that 7% of patients with diabetes may benefit from intervention according to current guidelines (10). By contrast, the WHO guidelines recommend an investigation of anemia when the Hb concentration is  $< 12 \text{ g/dl}$  in women and  $< 13 \text{ g/dl}$  in men (11). Using this definition, nearly one in four patients with diabetes (23%) have anemia warranting evaluation.

Although other smaller studies have suggested that the prevalence of anemia is increased in diabetes, these surveys have generally selected patients with overt nephropathy (15). In contrast, the PRESAM (Predialysis Survey on Anemia Management) failed to show a difference between patients with and without diabetes (16). However, PRESAM only included pre-end-stage patients with advanced nephropathy. Our study represents the first comprehensive cross-sectional survey of an established diabetes clinic, including patients with both occult and overt renal disease. In addition, approximately half of the patients with diabetes in this study had both normoalbuminuria and a GFR  $> 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$ , potentially making this survey more representative of the overall population with diabetes. For both sexes, the risk of anemia in patients with diabetes is approximately two to

three times that of a general population with the same level of GFR and similar iron stores (Fig. 3). This is consistent with NHANES data showing an adjusted OR of 1.7 for anemia in diabetes (2). Notably, the prevalence of anemia was increased by diabetes, even in patients with preserved renal function.

While GFR and iron stores remain the strongest predictors of Hb, they do not explain the increased prevalence of anemia in patients with diabetes (Fig. 3). This study raises the possibility that additional factors (such as albuminuria and dysglycemia) also contribute to anemia in diabetes. It is well established that tubulointerstitial injury occurs independently and in advance of declining GFR in DN (17,18). The severity of this early injury correlates far better with AER than with GFR (18). In our study, AER was a significant additional predictor of Hb level and anemia, independent of renal function. This was particularly marked in patients with macroalbuminuria, regardless of GFR. However, proteinuria itself does not appear to be the causal factor, as patients with persistent proteinuria from nondiabetic etiology have less anemia than diabetic patients (3). It appears more likely that proteinuria is a marker of tubulointerstitial injury in diabetes (18), perhaps more so than nondiabetic conditions associated with proteinuria considered to be primarily glomerular in origin.

It has been suggested that the widespread use of ACE inhibitors may contribute to anemia in patients with diabetes (3,19), although recent evidence has found no link between ACE inhibitor use and Hb levels (20). In support of these findings, we were unable to find any association between ACE inhibitor use and Hb after correcting for differences in GFR. Previous studies have found a correlation with polyneuropathy and the development of anemia in diabetes (21). Polyneuropathy may also be closely correlated with other diabetes complications, including nephropathy, making it difficult to separate cause from effect. To this end, the incidence of vascular disease, while associated with a lower Hb level on univariate analysis, was no longer correlated after correcting for differences in GFR.

This study clearly illustrates the importance of iron stores in the development and progression of anemia in patients with diabetes. While failing renal function is associated with spontaneous

decrease in protein intake, dietary intake of protein is reported to be similar in patients with or without nephropathy (22). Transferrinuria, particularly in patients with impaired renal function and proteinuria, may also contribute to iron deficiency. Autoimmune gastritis in type 1 diabetes has been associated with iron deficiency (23), although in our survey there was no appreciable difference in Hb between type 1 and type 2 diabetes. Infection with *Helicobacter pylori*, the major risk factor for atrophic gastritis, may be more common in patients with diabetes and more often associated with the presence of endoscopic lesions and chronic gastritis (24). Nutritional regimens associated with reduced protein and increased fiber and carbohydrate, frequent blood testing, and self-measurement of glucose may contribute to iron depletion. In opposition to this, there was poor correlation between the total number of blood tests performed during the survey period and the Hb level ( $r = -0.07$ ), as well as no association with Hb after adjusting for GFR ( $P = 0.16$ ).

The vast majority of patients in a diabetes clinic will never be referred to a nephrologist. Most will die of vascular disease or comorbid illness before reaching end-stage renal disease. This study demonstrates that anemia is an early and common complication of diabetes. Those patients at greatest risk of anemia can be readily identified. In our population, 60% of patients with anemia warranting investigation had GFR  $< 60 \text{ ml} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}$  and nearly half (46%) of patients with macroalbuminuria had anemia (Fig. 4B). It remains to be established that identification and correction of anemia will benefit patients with diabetes. Certainly anemia in chronic kidney disease identifies patients at increased risk for progressive renal disease (6), hospitalization, and premature death (25). In patients with ischemic complications of diabetes (who constitute 40% of our population), the correction of anemia may be particularly important. In addition, normalization of Hb may prevent progressive left ventricular dilatation in patients with normal left ventricular volumes (26) and improve some dimensions of quality of life, including physical activity (7). Notably, physical activity remains one of the most efficacious interventions for the management of diabetes (27). As the risk of anemia is strongly associated with GFR in our

study, it seems likely that supplementation with erythropoietin could correct anemia, particularly in the patients with anemia and adequate iron stores. However, potential benefits need to be balanced against the risks of adverse arterial effects and the complications of erythropoietin use, including hypertension and pure red cell aplasia. These issues should be clarified as results from upcoming controlled studies in patients with diabetes become available. Meanwhile, this survey should encourage heightened awareness of the potential impact of anemia in the diabetic population.

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