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Anemia complicating type 2 diabetes: Prevalence, risk factors and prognosis

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ABSTRACT

Aims: To determine the prevalence, risk factors and prognosis of anemia in representative community-based patients with type 2 diabetes.
Methods: Data from the Fremantle Diabetes Study Phase II (FDS2; n = 1551, mean age 65.7 years, 51.9% males) and Busselton Diabetes Study (BDS; n = 186, mean age 70.2 years, 50.0% males) cohorts, and from 186 matched BDS participants without diabetes, were analyzed. The prevalence of anemia (hemoglobin ≤130 g/L males, ≤120 g/L females) was determined in each sample. In FDS2, associates of anemia were assessed using multiple logistic regression and Cox proportional hazards modeling identified predictors of death during 4.3 ± 1.2 years post-recruitment.
Results: The prevalence of anemia at baseline was 11.5% in FDS2 participants, 17.8% in BDS type 2 patients and 5.4% in BDS participants without diabetes. In FDS2, 163 of 178 patients with anemia (91.6%) had at least one other risk factor (serum vitamin B_{12} < 140 pmol/L, serum ferritin <30 μg/L and/or transferrin saturation < 20%, serum testosterone <10 nmol/L (males), glitazone therapy, estimated glomerular filtration rate (eGFR) <60 mL/min 1.73 m^2, malignancy, hemoglobinopathy). More anemic than non-anemic FDS2 patients died (28.7% *versus* 8.0%; $P < 0.001$). After adjustment for other independent predictors (age as time-scale, male sex, Aboriginality, marital status, smoking, eGFR), anemia was associated with a 57% increase in mortality ($P = 0.015$).
Conclusions: Type 2 diabetes at least doubles the risk of anemia but other mostly modifiable risk factors are usually present. Anemia is associated with an increased risk of death after adjustment for other predictors.
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1. Introduction

Anemia has been considered a frequent and unrecognized co-morbidity in diabetes[1] but estimates of its prevalence vary widely. In the Predialysis Survey on Anemia Management (PRESAM) involving patients with advanced nephropathy,[2] diabetes did not increase the risk of anemia, but other studies from a variety of countries have shown that between 14% and 45% of patients with diabetes are anemic.[3–8] Notwithstanding the PRESAM data, this discrepancy may reflect differences in the proportions with renal impairment since the prevalence in outpatients with normal renal function (estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2) has been estimated at only 10%.[9]

An apparent diabetes-specific risk of anemia has been attributed to reduced responsiveness to erythropoietin (EPO).[10] There are, however, other factors that could contribute to depressed erythrocyte production and accelerated destruction in diabetes including chronic inflammation, oxidative stress, advanced glycation, microangiopathy, male hypogonadism and metformin-associated depressed serum vitamin B_{12} concentrations.[1,11] Whatever the cause, the consequences of anemia complicating diabetes appear adverse, including evidence of increased all-cause and cardiovascular mortality.[6,12]

Evaluation of available data relating to the prevalence, causes and consequences of anemia in type 2 diabetes is complicated by several factors. First, most relevant studies have involved selected[2] or referred[3,7–9,12,13] patients, with the possibility that more have complications such as renal impairment that would lead to an overestimation of anemia prevalence. Second, even in population-based studies,[6] only a limited number of risk factors for anemia and its sequelae have been included in multivariable analyses, which may result in model specification bias and thus incorrect estimates of the influence of the independent variables, including anemia itself in the case of prognostic outcomes.

Conflicts of interest: The authors have no conflicts of interest to declare.

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In light of these considerations, the aim of this study was to investigate the association between type 2 diabetes, anemia and mortality in well-characterized, community-based samples.

2. Patients and methods

2.1. Patients

The prevalence of anemia was ascertained from two population-based observational studies conducted in the state of Western Australia (WA): the Fremantle Diabetes Study Phase II (FDS2)[14] and the Busselton Diabetes Study (BDS).[15] The FDS2 is a longitudinal study of 1732 patients including 1551 (89.5%) with type 2 diabetes (mean ± SD age 65.7 ± 11.6 years, 51.9% males) from an urban population of 157,000. Patients were recruited between 2008 and 2011 from 4639 people who were resident in the catchment area and had a confirmed diabetes diagnosis. Non-participants were a mean of 0.6 years younger than participants but their sex distribution and categorization by diabetes type were similar. The BDS is a cohort study that involved 186 patients with type 2 diabetes (aged 70.2 ± 10.2 years, 50.0% males) and 186 age- and sex-matched participants without diabetes recruited between 2008 and 2010 from the 31,000 people living in the rural shire of Busselton. The BDS participants were identified from involvement in prior Busselton Health Surveys[16] supplemented by health professional referral, word-of-mouth and advertising.[15]

The FDS2 was approved by the Human Research Ethics Committee of the Southern Metropolitan Area Health Service and the BDS by the University of WA Human Research Ethics Committee, and written informed consent was obtained from all participants.

2.2. Methods

In FDS2, each participant was assessed at baseline and invited to biennial reviews over six years, with questionnaire follow-up in alternate years. In BDS, patients were assessed only at baseline. All FDS2/BDS face-to-face assessments comprised a comprehensive questionnaire, physical examination and fasting laboratory tests.[14] Dietary details were obtained using a validated questionnaire.[17] Ethnic background was based on self-selection, country/countries of birth and parents' birth, language(s) spoken at home and country of grandparents' birth. Laboratory testing in FDS2/BDS was carried out in the same nationally-accredited facility. All participants were considered to have anemia if they had a hemoglobin ≤130 g/L in males and ≤120 g/L in females based on WHO criteria.[18]

In addition to usual-care tests, baseline serum vitamin B_{12} concentrations were assayed for each FDS2 participant and serum iron, transferrin and ferritin were assayed in anemic FDS2 patients. Serum iron was measured by the Ferrene-S colorimetric method, transferrin by turbidimetric immunoassay and ferritin by chemiluminescent immunoassay (Architect ci8200, Abbott Diagnostics, Macquarie Park, New South Wales, Australia). Between-day coefficients of variation were 2.3% and 1.7% at serum transferrins of 17.5 and 42.3 μmol/L, respectively, and 6.25% and 6.1% at serum ferritins of 35 and 396 μg/L, respectively.

Complications in FDS2 participants were ascertained using data obtained at assessments, supplemented by information from the WA Data Linkage System[19] that includes all hospitalizations (public and private) and death registrations from 1970 to end-December 2012. For BDS, only data collected at study assessments were used. Cardiovascular complications were based on self-reported or documented myocardial infarction or stroke, with peripheral arterial disease (PAD) defined as an ankle:brachial index ≤0.90 or a diabetes-related lower extremity amputation. Microalbuminuria and macroalbuminuria were defined as a urinary albumin:creatinine ratio (ACR) ≥3.0 and ≥30.0 mg/mmol, respectively, on an early morning urine sample, neuropathy as a score of >2/8 on the Michigan Neuropathy Screening Instrument clinical portion,[20] and any retinopathy in either/both eyes on non-mydriatic photography. The eGFR was calculated from the serum creatinine.[21]

2.3. Statistical analysis

The package IBM SPSS Statistics 22 (IBM Corporation, Armonk, NY, USA) was used for statistical analysis. Data are presented as proportions, mean ± SD, geometric mean (SD range), or, for variables which did not conform to a normal or log-normal distribution, median and [inter-quartile range]. For independent samples, two-way comparisons of proportions were by Fisher's exact test, for normally-distributed variables by Student's *t*-test, and for non-normally-distributed variables by Mann–Whitney U-test. Bivariate associates of anemia with $P < 0.20$ were considered for entry into a multiple logistic regression model which used forward conditional stepwise entry (entry $P < 0.05$, removal $P > 0.10$) to identify independent associates of anemia at baseline in FDS2. For analysis of predictors of all-cause death in FDS2, bivariate baseline associates were first determined. Cox proportional hazards modeling, with age as the time scale and left truncation at study entry, employed due to the presence of covariates strongly associated with age,[22] was used to determine independent predictors of all-cause death in FDS2 excluding anemia using interactive forward conditional modeling. After adjustment for the most parsimonious model, anemia as a continuous variable or as quintiles was entered.

3. Results

3.1. Prevalence of anemia

Of 1551 FDS2 participants, 1548 (99.8%) had a hemoglobin concentration available at baseline. All of the 186 BDS controls without diabetes and all but one of the 186 BDS patients with type 2 diabetes had a hemoglobin concentration at baseline. The prevalence of anemia in FDS2 participants was 11.5% (95% CI 10.0%–13.2%). In BDS, the prevalence of anemia was 17.8% in the sample with diabetes and 5.4% in the matched group without diabetes (see Table 1). To allow comparability between FDS2 and BDS, a sample of 186 FDS2 patients with type 2 diabetes and age, sex and diabetes duration matched to those of the BDS patients with type 2 diabetes was selected. The prevalence of anemia in this subset was 10.2%, similar to that in the FDS2 sample as a whole but significantly lower than that in BDS type 2 participants ($P = 0.049$; see Table 1).

3.2. Associates of anemia in FDS2

The characteristics of the FDS2 groups categorized by anemia status at study entry are shown in Table 2. Anemic patients were older at study entry, less likely to be married/in a stable *de facto* relationship and more likely to be Indigenous, than those who were not anemic.

Table 1
Prevalence of anemia in BDS participants with type 2 diabetes and without diabetes, and in a subset of FDS2 patients matched with the BDS patients with type 2 diabetes for age, sex and diabetes duration.

Study	BDS no diabetes	BDS type 2 diabetes	FDS2 type 2 diabetes
Number	186	185	186
Age (years)	70.3 ± 10.1	70.2 ± 10.2	70.3 ± 10.2
Sex (% males)	50.0	50.3	50.0
Diabetes duration (years)		8.5 [4.9–13.8]	8.5 [5.0–13.6]
Anemia (%)	5.4 (2.8–10.0)	17.8 (12.8–24.3)	10.2 (6.4–15.7)

Data are number, percentages (95% confidence intervals), mean ± SD or median [inter-quartile range].

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