Original Article

Relationship between Anemia and Chronic Complications in Chinese Patients with Type 2 Diabetes Mellitus

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Abstract

Aims: To evaluate the potential association of anemia with micro- and macrovascular complications in Chinese patient with type 2 diabetes mellitus (T2DM).

Methods: A total of 1997 patients with T2DM were included in this cross-sectional study. Patients were defined as anemic, if hemoglobin (Hb) levels were < 13 g/dL in males and < 12 g/dL in females. Data on demographics, anthropometric parameters, and co-morbidities were extracted for each patient.

Results: Twenty two percent of T2DM patients (439/1997) had anemia, and those patients with higher rates of micro- and macrovascular complications had higher rates of anemia. Univariate logistic regression analysis showed that anemia was a risk factor of microvascular complications (OR = 1.83, 95% CI: 1.45 – 2.31; $P < 0.001$) and macrovascular complications (OR = 2.10, 95% CI: 1.63 – 2.71; $P < 0.001$). After adjusting for conventional risk factors, anemia remained positively associated with microvascular complications (OR = 1.52, 95% CI: 1.17 – 1.99), but lost its association with macrovascular complications (OR = 1.01, 95% CI: 0.73 – 1.41). Anemia was also independently associated with diabetic retinopathy, nephropathy, and peripheral neuropathy.

Conclusions: These findings suggest that anemia was related to both micro- and macrovascular complications in Chinese patients with T2DM, but was only an independent risk factor of microvascular complications. Assessment of Hb levels in T2DM patients may help to prevent subsequent diabetic micro- and macrovascular complications.

Keywords: Anemia, Chinese, macrovascular complication, microvascular complication, type 2 diabetes

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Introduction

Anemia is a common complication in patients with diabetes mellitus (DM), particularly in those with overt nephropathy or renal impairment.[1–6] Almost, a quarter of diabetic patients are reported as anemic. Anemia rates among diabetics are estimated to be nearly two- to three fold higher than in individuals without DM, putting these patients at greater risk of complications associated with dysfunctional glomerular filtration and iron storage.[1] In addition, DM patients tend to develop anemia at earlier ages and with greater severity than the general population.[7] In addition to the major causes of general anemia (iron and erythropoietin (EPO) deficiencies and hyporesponsiveness to the actions of EPO), some other physiological factors have been implicated in the development of diabetes-associated anemia, such as deficiencies in vitamin B_{12} and folate.[5,8]

Chronic anemia results in tissue hypoxia, which is known to play a key role in diabetes-associated organ damage. Recent reports have suggested that anemia is an important risk factor for progression to end- stage renal disease (ESRD) in patients with chronic kidney disease, with or without diabetes.[9,10] In addition, a number of studies have suggested that hemoglobin (Hb) levels may be linked to the risk of cardiovascular events in patients with heart failure[11,12] and in the general population.[13,14] Since anemia can lead to artificially low levels of glycosylated hemoglobin (HbA1c), it may result in missed diagnosis of hyperglycemia as well as uninterrupted progression of diabetes-related micro- and macrovascular complications.[4]

Despite the prevalence of diabetes-related anemia and its recognized consequences, very little research has been conducted on the underlying physiological and molecular mechanisms of anemia in diabetic patients. As a result, the relation between anemia and vascular complications in patients with type 2 diabetes mellitus (T2DM) remains unknown. We designed a cross-sectional study to retrospectively investigate the influence of anemia on the occurrence and severity of micro- and macrovascular complications in T2DM patients.

Materials and Methods

Study population

A total of 1997 patients with T2DM were enrolled in this study. All patients were identified from the medical records of the Endocrinology Department of the Shanghai Jiaotong University Affiliated Sixth People's Hospital (China), and had been treated between January 2008 and December 2009. Diagnosis of diabetes was made according to the World Health Organization (WHO)

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criteria (1999 version). Subjects were excluded from the study if they had: type 1 diabetes mellitus; other types of diabetes, such as gestational diabetes; poor general condition; aplastic anemia, hemolytic anemia; severe infection; acute cerebrovascular disease; recent surgery; or severely impaired hepatic function (AST or ALT $> 2 \times$ upper limit of normal).

Diabetic complications and co-morbidities

Upon admission, all patients underwent a comprehensive assessment of diabetes-related complications and risk factors. Diabetic retinopathy (DR) was assessed by professional ophthalmologists, and classified according to the International Clinical Diabetic Retinopathy Scales.[15] Diabetic nephropathy (DN) was classified according to albuminuria urine test results in at least two out of three consecutive 24-hour urine collections: normoalbuminuria (< 30 mg/24 h), microalbuminuria (30 – 300 mg/24 h), or macroalbuminuria (> 300 mg/24 h). Diabetic peripheral neuropathy (DPN) was diagnosed either by electromyogram (EMG) findings, the presence of typical symptoms and compatible findings from neurological examinations, or a history of treatment for neuropathy. Coronary heart disease (CHD) was considered to be present if the patient had an ischemic history or electrocardiographic signal perturbations that are typical of ischemia, such as T waves spiking before ST elevation. Cerebrovascular disease (CVD) was diagnosed based on the presence of either transient ischemic attack or strokes. Peripheral atherosclerosis (PA) was defined by the presence of plaque on the wall of carotid or lower limb arteries using ultrasonography. DR, DN and DPN were considered as diabetic microvascular complications, while CHD, CVD and PA were considered as diabetic macrovascular complications.

Anthropometric parameters and demographic information

The patient gender, age and duration of T2DM were obtained through patient self-reporting. The patient height, body weight, and blood pressure were measured on the day of admission. Body mass index (BMI) was calculated as kg/m^2. Hypertension was defined as either blood pressure $\geq 140/90$ mmHg or current antihypertensive treatment. Dyslipidaemia was defined according to the American National Cholesterol Education Program (Adult Treatment Panel III): elevated total cholesterol (TC ≥ 6.1 mmol/L) and/or triacylglycerol (TG ≥ 2.26 mmol/L), or an elevated low density lipoprotein cholesterol (LDL-C ≥ 4.14 mmol/L), or a depressed high density lipoprotein cholesterol (HDL-C < 1.0 mmol/L).[16] Fasting blood samples were drawn before breakfast on the second day of hospitalization for measurements of fasting plasma glucose (FPG), HbA1c, glycated albumin (GA), TC, TG, HDL-C, and LDL-C. The 2 hour postprandial glucose (2hPG) level was measured from blood drawn after a mixed meal. Plasma glucose concentration was measured by the glucose oxidase method in an automated Biochemistry Analyzer (Beckman Coulter, Brea, CA, USA). Serum lipid indices and creatinine (Cr) were measured by enzymatic procedures using the 7600–020 autoanalyzer by Hitachi (Tokyo, Japan). The GFR was measured by radionuclide renal dynamic imaging (modified Gate's method), after intravenous injection of ^{99}mTc-diethylene-triamine-pentaacetic acid (^{99}mTc-DTPA). The imaging study was carried out using a Siemens Signature e.cam SPECT (General Electric Medical Systems, Waukesha, WI, USA). HbA1c was measured by high performance liquid chromatography using the HLC-723G7 autoanalyzer by Tosoh (Tokyo, Japan). GA was measured by an enzymatic method using a liquid enzymatic assay kit (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan). The 24 hour urine albumin level was measured by nephelometry with the N antiserum to human albumin assay kit and a BN II analyzer (Dade Behring, Deerfield, IL, USA). Hypersensitive C-reactive protein (CRP) was examined by nephelometry with the Vista CardioPhase^R high sensitivity CRP kit (Dade Behring, Tokyo, Japan). Hb was measured using the XE-5000 automated blood analyzer by Sysmex Corp (Kobe, Japan).

Anemia definitions

The presence of anemia was defined as Hb < 13 g/dL in males and < 12 g/dL in females, as recommended by the WHO.[17] Anemic patients were divided into two groups: anemia-1 (Hb > 11 g/dL) and anemia-2 (Hb ≤ 11 g/dL). Hb was primarily handled as a continuous variable and recoded as a binary outcome for estimating the prevalence of anemia.

Statistical analysis

All analyses were performed using SPSS statistical software (ver. 16.0; SPSS Inc., Chicago, IL, USA). Numerical variables with normal distribution were expressed as mean ± SD, while those with non-normal distribution were expressed as median (quartile). The one-way ANOVA and Student's *t* tests were used to compare means of normally distributed variables. The Mann-Whitney U test was used for non-normally distributed variables. The Chi-squared (c^2) test was used to analyze categorical variables. Binary logistic regression analyses were used to estimate the odds ratios (ORs) with 95% confidence intervals (CIs) for vascular complications after adjusting for other clinical and biochemical variables.

Results

A total of 1997 type 2 diabetic patients were analyzed in this study; among them 1141 (57.1%) were males and 856 (42.9%) were females. The mean age was 59.67 ± 12.26 years, and the mean duration of diabetes was 8.06 ± 6.71 years. The overall prevalence of anemia was 22.0% (439/1997). Among the male patients, 19.1% (218/1141) were anemic, and 25.8% (221/856) of the female patients were anemic. Macrovascular complications were diagnosed in 69.6% of the total patient population. Microvascular complications were diagnosed in 62.7% of the total patient population, and included retinopathy (29.7%), nephropathy (24.5%) and peripheral neuropathy (42.9%). The prevalence of both macrovascular and microvascular complications was significantly higher in patients with anemia than in non-anemic patients (macrovascular: 80.4% *vs.* 66.6%; microvascular: 76.8% *vs.* 60.2%).

Table 1 summarizes the demographic, anthropometric, and metabolic characteristics of the study population stratified by the diagnoses of macro- and microvascular complications. Patients with macro- or microvascular complications were older with longer disease duration, higher rate of hypertension, history of dyslipidemia and anemia, higher level of albuminuria, elevated CRP, lower Hb, and lower GFR. According to the status of glycemic control, patients with microvascular complications tended to present with higher HbA1c and GA levels, but these levels were not significantly different from those observed in patients with macrovascular complications (both, $P > 0.05$). Compared to T2DM anemic patients with no vascular complications, the prevalence of anemia was significantly higher in patients with microvascular complications (14.1% *vs.* 26.4%, $P < 0.001$) and in those with

Table 1. Clinical characteristics of the patients stratified by diagnoses of macro- and microvascular complications.

	Macrovascular complication			Microvascular complication		
	Absent	Present	*p*	Absent	Present	*p*
Total, n	607	1390		722	1275	
Sex, M/F	357/250	784/606	> 0.05	427/295	714/561	< 0.001‡
Age, years	50.07 ± 11.31	63.87 ± 10.12	< 0.001‡	56.90 ± 12.14	61.24 ± 12.06	< 0.001‡
Duration, years	5.0 (1.0~10.0)	9.0 (4.0 ~ 13.0)	< 0.001‡	4.0 (0.5 ~ 9.0)	10.0 (4.0 ~ 13.0)	< 0.001‡
BMI, kg/m²	24.93 ± 3.52	24.70 ± 3.51	> 0.05	24.61 ± 3.28	24.86 ± 3.64	> 0.05
Hypertension, % of patients	43.2	64.6	< 0.001‡	48.6	63.5	< 0.001‡
SBP, mmHg	126.23 ± 15.48	133.60 ± 17.70	< 0.001‡	126.81 ± 15.59	133.91 ± 17.83	< 0.001‡
DBP, mmHg	79.77 ± 9.50	79.52 ± 9.79	> 0.05	78.71 ± 8.88	80.09 ± 10.1	0.002†
Dyslipidemia, % of patients	45.6	58.3	< 0.001‡	44.9	59.8	< 0.001‡
TC, mmol/L	4.47 (3.90 ~ 5.22)	4.68 (4.06 ~ 5.47)	< 0.001‡	4.55 (3.96 ~ 5.28)	4.65 (4.04 ~ 5.42)	0.044†
TG, mmol/L	1.48 (1.01 ~ 2.35)	1.51 (1.04 ~ 2.17)	> 0.05	1.46 (1.0 ~ 2.12)	1.53 (1.04 ~ 2.23)	0.035†
HDL-C, mmol/L	1.09 (0.94 ~ 1.25)	1.05 (0.91 ~ 1.25)	0.03†	1.10 (0.98 ~ 1.28)	1.04 (0.9 ~ 1.24)	< 0.001‡
LDL-C, mmol/L	2.92 (2.42 ~ 3.54)	3.19 (2.59 ~ 3.89)	< 0.001‡	3.07 (2.46 ~ 3.74)	3.18 (2.57 ~ 3.84)	0.033†
FPG, mmol/L	8.60 ± 2.82	8.19 ± 2.85	0.004†	8.13 ± 2.53	8.42 ± 3.0	0.033†
2hPG, mmol/L	13.96 ± 4.54	14.10 ± 4.74	> 0.05	13.78 ± 4.51	14.21 ± 4.76	> 0.05
HbA1c, %	8.79 ± 2.25	8.97 ± 2.32	> 0.05	8.46 ± 2.13	9.17 ± 2.35	< 0.001‡
GA, %	24.72 ± 7.44	25.50 ± 8.16	> 0.05	23.67 ± 7.16	26.15 ± 8.23	< 0.001‡
Anemia, % of patients	14.2	25.4	< 0.001‡	14.1	26.4	< 0.001‡
Hb, g/dL	13.81 ± 1.54	13.26 ± 1.58	< 0.001‡	13.73 ± 1.37	13.25 ± 1.67	< 0.001‡
CRP, mg/L	0.92 (0.44 ~ 2.30)	1.10 (0.54 ~ 2.76)	0.001†	0.98 (0.47 ~ 2.18)	1.12 (0.53 ~ 2.87)	0.001†
Albuminuria, mg/24 h	9.65 (5.70 ~ 22.87)	11.71 (5.65 ~ 34.71)	< 0.001‡	7.72 (5.02 ~ 12.83)	16.53 (6.69 ~ 63.80)	< 0.001‡
GFR, mL/min	104.09 ± 23. 36	87.63 ± 24.37	< 0.001‡	98.31 ± 22.46	89.08±26.19	< 0.001‡

BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; TC: total cholesterol; TG: triglyceride; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol; FPG: fasting plasma glucose; 2hPG: 2 h postprandial glucose; HbA1c: glycosylated hemoglobin; GA: glycated albumin; Hb: hemoglobin; CRP: C-reactive protein; GFR: glomerular filtration rate.
Data are presented as mean ± SD or mean (quartile). † $P < 0.05$, ‡ $P < 0.001$. The *t*-test was used to compare means of normally distributed variables, and the Mann-Whitney U test was used for non-normally distributed variables. The Chi-squared (c^2) test was used to analyze categorical variables.

Table 2. Results of Logistic regression after ajusting conventional diabetes–related factors.

	Microvascular		Macrovascular	
Items	***P*–value**	**OR (95% CI of OR)**	***P*–value**	**OR (95% CI of OR)**
Sex	0.568	0.94 (0.75–1.17)	< 0.001‡	0.53 (0.41–0.69)
Age	0.130	1.01 (0.99–1.02)	< 0.001‡	1.13 (1.11–1.15)
Diabetic duration	< 0.001‡	1.07 (1.06–1.10)	< 0.001‡	1.06 (1.03–1.08)
BMI	0.039†	1.04 (1.01–1.07)	0.948	1.00 (0.96–1.04)
Blood pressure	0.002†	1.43 (1.14–1.80)	0.119	1.24 (0.95–1.62)
HbA1c	< 0.001‡	1.11 (1.06–1.16)	0.392	0.98 (0.93–1.03)
CRP	0.816	1.00 (0.99–1.01)	0.110	1.02 (0.99–1.04)
Serum lipid status	0.362	1.11 (0.89–1.39)	0.395	1.12 (0.86–1.47)
GFR	0.287	0.997 (0.992–1.002)	0.668	1.00 (0.99–1.01)
Anemia	< 0.001‡	2.71 (1.58–4.67)	0.907	1.04 (0.57–1.89)
† $P < 0.05$; ‡ $P < 0.001$				

macrovascular complications (14.2% *vs.* 25.4%, $P < 0.001$).

Logistic regression analysis of variables associated with micro- or macrovascular complications was performed. Univariate logistic regression analysis showed that anemia was related to both microvascular complications (OR = 1.83, 95% CI: 1.45 – 2.31; $P < 0.001$) and macrovascular complications (OR = 2.10, 95% CI: 1.63 – 2.71; $P < 0.001$). However, after adjustment for age, the association with macrovascular complications was lost (OR = 1.11, 95% CI: 0.82 – 1.50). Further adjustment for sex, diabetic duration, BMI, blood pressure, HbA1c, plasma lipid status, GFR and CRP was made, and anemia remained positively associated with microvascular complications (OR = 2.71, 95% CI: 1.58 – 4.67), (Table 2).

The relationship between anemia and subtype of microvascular complication was examined. The prevalence of anemia was much higher in patients with DR (27.3% *vs.* non-DR: 19.7%, $P < 0.001$), DN (35% *vs.* non-DN: 17%, $P < 0.001$), and DPN (28.1% *vs.* non-DPN: 17.4%, $P < 0.001$).

We performed logistic regression analysis of variables associated with each subtype of microvascular complication measured at the last clinical assessment. Univariate logistic regression analysis showed that patients with anemia had a higher risk of developing DN (OR = 2.15, 95% CI: 1.40 – 3.32; $P < 0.001$), DR (OR = 2.16, 95% CI: 1.41 – 3.31; $P < 0.001$), and DPN (OR = 1.85, 95% CI:

Table 3. Results of Logistic regression on each microvascular complication after adjusting conventional diabetes–related factors.

	DN		DR		DPN	
Items	***P*-value**	**OR (95% CI of OR)**	***P*-value**	**OR (95% CI of OR)**	***P*-value**	**OR (95% CI of OR)**
Sex	0.011†	0.72 (0.55–0.93)	0.257	1.15 (0.91–1.45)	0.533	0.93 (0.75–1.16)
Age	0.036†	0.98 (0.97–0.99)	< 0.001‡	0.96 (0.95–0.97)	< 0.001‡	1.03 (1.02–1.04)
Diabetic duration	< 0.001‡	1.04 (1.02–1.06)	< 0.001‡	1.10 (1.08–1.12)	< 0.001‡	1.06 (1.04–1.08)
BMI	< 0.001‡	1.09 (1.05–1.13)	0.262	0.98 (0.95–1.02)	0.079	1.03 (0.99–1.06)
Blood pressure	< 0.001‡	2.42 (1.81–3.23)	0.004†	1.45 (1.13–1.87)	0.879	0.98 (0.78–1.24)
HbA1c	0.333	1.03 (0.97–1.08)	0.019†	1.06 (1.01–1.16)	< 0.001‡	1.14 (1.09–1.19)
CRP	0.001†	1.02 (1.01–1.04)	0.816	1.00 (0.99–1.11)	0.502	1.01 (0.99–1.02)
Serum lipid status	< 0.001‡	1.75 (1.35–2.29)	0.399	0.90 (0.71–1.15)	0.730	0.96 (0.77–1.20)
GFR	< 0.001‡	0.987 (0.98–0.99)	0.07	0.99 (0.98–1.00)	0.436	0.998 (0.99–1.00)
Anemia	0.001†	2.15 (1.40–3.32)	< 0.001‡	2.16 (1.41–3.31)	0.005†	1.85 (1.20–2.85)

1.20 – 2.85; $P = 0.005$). After further adjustment for sex, diabetic duration, BMI, blood pressure, HbA1c, GFR and plasma lipid status, anemia remained positively associated with DR (OR = 1.43, 95% CI: 1.09 – 1.88), DN (OR = 1.91, 95% CI: 1.43 – 2.55), and DPN (OR = 1.40, 95% CI: 1.08 – 1.81), (Table 3).

The frequency of each chronic vascular complication is presented in Figure 1 according to the severity of anemia. The frequencies of macro- and microvascular complications were found to increase with increasing severity of anemia. Moreover, the frequencies of microvascular complication subtypes (DN, DR, and DPN) also increased with increasing anemia severity (all, $P < 0.001$).

The relationship between the severity of anemia and the severity of microvascular complications was examined. The prevalence of diabetic nephropathy with macroalbuminuria and of proliferative diabetic retinopathy was much higher among patients in the more severe anemia group (anemia II) than in the non-anemic group (DN: 27.5% *vs*. 4.0% and PDR: 9.2% *vs*. 1.5%), (Figure 2, a, b).

Discussion

In this large-scale cross-sectional study involving 1997 Chinese patients with T2DM, anemia was correlated with both micro- and macrovascular complications of diabetes by univariate logistic regression analysis. However, anemia was only independently associated with the microvascular complications. In addition, anemia was correlated with each of the microvascular subtypes (DN, DR and DPN) evaluated in our study.

In this study, anemia was independently associated with DN. Forty-four percent of the T2DM patients with anemia also had albuminuria, compared to only 23% of the non-anemic patients. Moreover, the prevalence of macroalbuminuria was nearly 4-fold higher in the anemic patients. Previous studies have shown that a reduced hemoglobin concentration, even within the 'normal' range, distinguishes patients at increased risk of developing ESRD.[9,10,18] It is possible that anemia decreases oxygen delivery to the kidney tissue, thereby causing the detrimental hypoxic state.

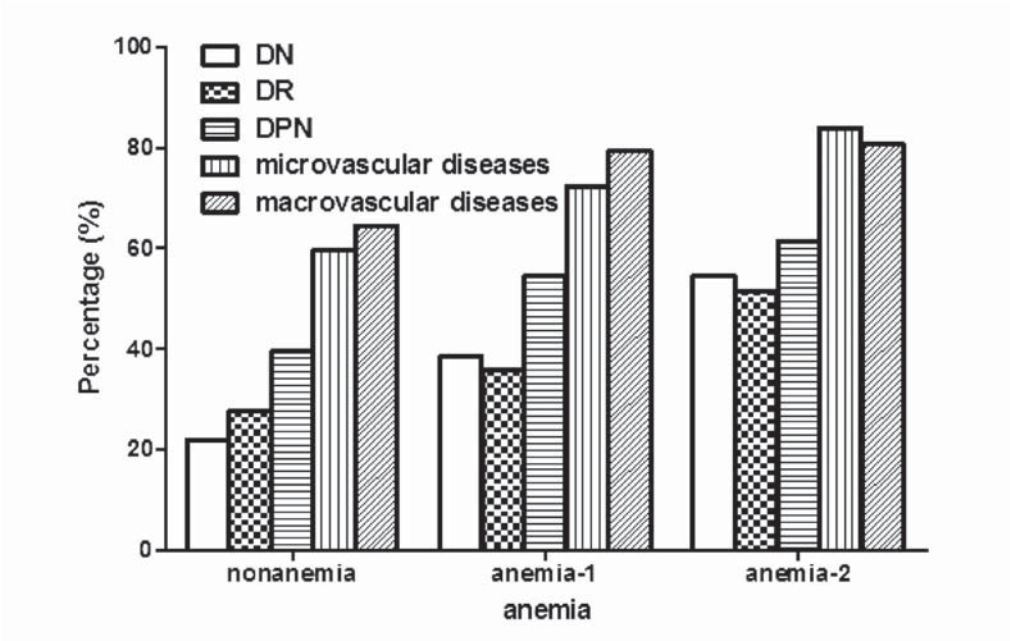

Figure 1. Prevalence of vascular diseases among T2DM patients stratified by anemia severity. Anemia-1: Hb >11 g/dL; Anemia-2: Hb ≤11 g/dL. Macrovascular disease is shown by solid black bars. Microvascular diseases are shown by white bars with thick black hatches. Microvascular subtypes include peripheral neuropathy, retinopathy, and nephropathy.

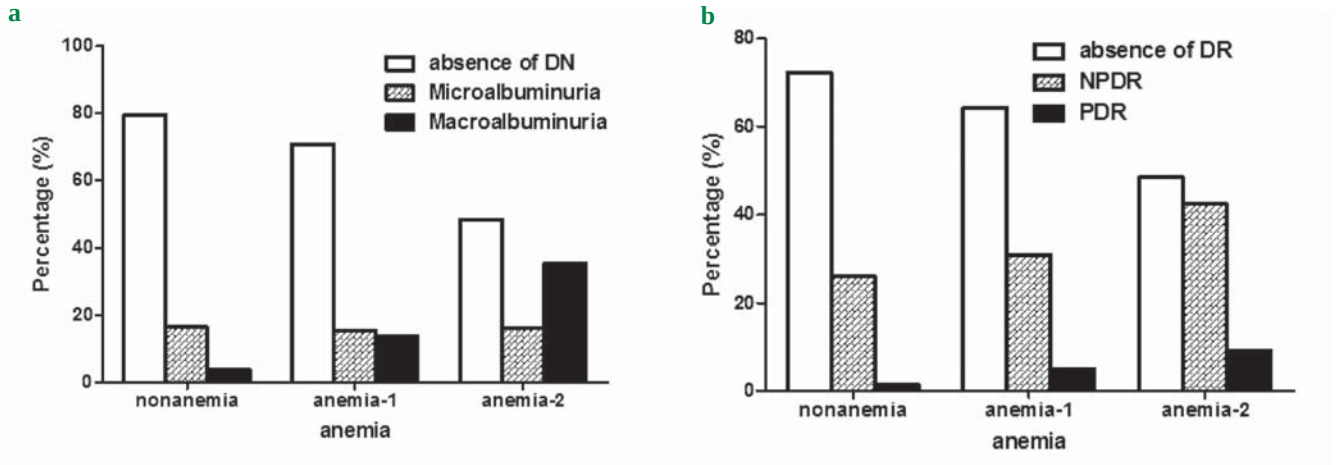

Figure 2. Relationships between the severity of anemia and the severity of microvascular complications; **a)** Prevalence of microalbuminuria and macroalbuminuria according to groups of anemia and compared to normoalbuminia ($P < 0.001$ by c^2 test); **b)** Prevalence of nonproliferative and proliferative diabetic retinopathy according to groups of anemia and compared to absence of DR ($P < 0.001$ by c^2 test).

In a study of anemic patients with renal insufficiency of varying origin, EPO-stimulated increases in Hb were associated with slower progression of nephropathy.[19] In addition, some prospective clinical studies of patients with advanced nephropathy have revealed delayed deterioration of renal function in anemic patients successfully treated with exogenous EPO.[20,21]

Another principal finding of the current study is that anemia was independently associated with DR. Moreover, despite the potential effects of DN on anemia, we were able to demonstrate an association of anemia with DR after the inclusion of GFR as a covariate in the regression analysis. The prevalence of PDR was found to be significantly increased with increasing severity of anemia. Finally, Hb levels were significantly lower in patients with DR than in those without DR. These findings are consistent with those of Early Treatment Diabetic Retinopathy Study (ETDRS), which was a large prospective study aimed at identifying the factors responsible for DR progression to high-risk proliferative retinopathy. The ETDRS found that low hematocrit was an independent risk factor for development of high risk PDR and visual impairment.[22] Similarly, a large cross-sectional study by another group showed that DR rates were two-fold higher in patients with mild anemia (Hb < 12 g/dL), with a significantly higher prevalence of severe retinopathy, compared to subjects with DR and Hb > 12 g/dL.[23] Taken together, these results suggest that subjects with low Hb levels tend to have an increased risk of retinopathy, especially of the severe form. In addition, a few small studies have demonstrated that correction of anemia in patients with diabetes may be associated with a reduction in the presence of macular hard exudates and edema.[24–27]

In our study, the prevalence of anemia was much higher in patients with DPN than in those without DPN, and logistic regression showed that anemia was a risk factor of DPN after adjusting for conventional diabetes-related risk factors. Furthermore, the correlation between anemia and peripheral neuropathy remained significant after the inclusion of GFR as a covariate in the final model. Anemia-induced hypoxia is known to accelerate nerve injury in diabetes. For example, in patients with asymmetrical peripheral vascular disease, nerve function is more severely impaired in the more ischemic leg.[28] Similarly, anemic DN patients have been reported to show evidence of more severe diabetic neuropathy than their non-anemic DN counterparts.[29]

Although there is no clear evidence indicating that anemia causes direct vascular injury, some studies have demonstrated that anemia may modulate the activity of molecular signaling pathways that lead to progressive organ damage. For instance, hypoxia influences a wide range of mitogenic- and fibrogenic-related factors and modifies the expression of genes involved in angiogenesis and capillary permeability, vasomotor response, glycolysis, matrix metabolism, and cell survival.[30] Each of these pathways can lead to characteristic diabetic complications. In addition, anemia is associated with a reduction in both the number of red blood cells and antioxidant potential of erythrocytes,[31] which may further complicate the diabetic state.

In our T2DM population, the prevalence of macrovascular disease was significantly higher in patients with anemia than those without anemia. Furthermore, anemia was associated with macrovascular disease by univariate logistic regression analysis, indicating that anemia increased the risk of developing macrovascular disease in T2DM patients. However, after adjustment for age, the association between anemia and macrovascular disease lost statistical significance. These findings were not completely consistent with previous studies,[11,13,32–35] which have reported that anemia is an independent risk factor of macrovascular disease. One study showed that anemia was a potent adverse risk factor for new-onset heart failure,[34] while another showed that anemia was a prognostic marker for poor outcomes in patients with established cardiac dysfunction.[36] It was suggested that the increased prevalence of anemia in diabetes patients may contribute to their worse prognosis of heart failure, compared to non-diabetic patients.[37] Although, anemia does not cause atherosclerosis, it is conceivable that tissue hypoxia associated with atherosclerotic (macrovascular) disease is accentuated by a reduction in the oxygen-carrying capacity of the blood, or by an increase in cardiac workload, and stimulation of the sympathetic nerve activity associated with anemia. According to our findings, there is no association between anemia and macrovascular disease that might be related to the cross-sectional design of our study. It is possible that unknown factors confounded the results. Otherwise, age was found to be related to anemia in our T2DM patients, which may have impacted our age-adjusted correlation analysis between anemia and macrovascular complications.

Findings from our study suggest that anemia evaluation should

be considered for inclusion in the routine management of T2DM patients and anemia should be treated to minimize the risk of micro- and macrovascular complications. Moreover, patients who are diagnosed with T2DM and anemia may benefit from more thorough examinations to detect diabetes-associated micro- and macrovascular complications. Early detection and treatment of each chronic vascular complication will undoubtedly enhance the life quality of T2DM patients. Due to the inherent limitations of the cross-sectional study design, our results simply showed that anemia is associated with diabetic micro- and macrovascular complications. However, direct role in the development or progression of diabetic complications remains to be clearly established; future prospective randomized controlled trials will be useful in this regard.

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Conflict of Interest

The authors declare that they have no conflict of interest.

Authors' Contribution

Bin-Bin He and Miao Xu contributed equally to the work and should be considered co-first authors

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