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Hemoglobin concentration in men with type 2 diabetes mellitus

Ichiko Harusato, Michiaki Fukui*, Muhei Tanaka, Emi Shiraishi, Takafumi Senmaru, Kazumi Sakabe, Masahiro Yamazaki, Goji Hasegawa, Naoto Nakamura

Department of Endocrinology and Metabolism, Kyoto Prefectural University of Medicine, Graduate School of Medical Science, Kamigyo-ku, Kyoto 602-8566, Japan

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Abstract

Anemia is a common but often overlooked complication of diabetes. We investigated the relationship between hemoglobin concentration and various factors as well as markers of subclinical atherosclerosis in men with type 2 diabetes mellitus. Hemoglobin concentration was measured in 319 men with type 2 diabetes mellitus. We evaluated the relationship between hemoglobin concentration and various factors including age, body mass index, and glycemic control, as well as between hemoglobin concentration and pulse wave velocity or ankle-brachial index (n = 209) and between hemoglobin concentration and carotid intima-media thickness or plaque score (n = 125). Mean hemoglobin concentration was 14.2 ± 0.80 g/dL. Body mass index ($r = 0.340$, $P < .0001$) and estimated glomerular filtration rate ($r = 0.219$, $P = .0011$) were positively associated with hemoglobin concentration, whereas age ($r = -0.388$, $P < .0001$), glycated albumin ($r = -0.148$, $P = .0121$), serum creatinine concentration ($r = -0.206$, $P = .0019$), and log (urinary albumin excretion) ($r = -0.188$, $P = .0010$) were negatively associated with hemoglobin concentration. Multiple regression analysis identified age ($\beta = -0.222$, $P = .0019$), body mass index ($\beta = 0.145$, $P = .0432$), systolic blood pressure ($\beta = 0.214$, $P = .0015$), total cholesterol concentration ($\beta = 0.170$, $P = .0077$), and serum creatinine concentration ($\beta = -0.181$, $P = .0045$) as independent determinants of hemoglobin concentration. No significant association was observed between hemoglobin concentration and serum erythropoietin concentration ($r = -0.079$, $P = .2980$). Negative correlations were found between hemoglobin concentration and pulse wave velocity ($r = -0.289$, $P < .0001$) and between hemoglobin concentration and plaque score ($r = -0.275$, $P = .0024$). In conclusion, hemoglobin concentration was associated with various factors; and decreased hemoglobin concentration was associated with subclinical markers of atherosclerosis in men with type 2 diabetes mellitus.

1. Introduction

Anemia is a common but often overlooked complication of diabetes, reflecting the high prevalence of kidney disease [1,2]. Moreover, patients with diabetes are likely to have anemia than those with other types of chronic kidney disease (CKD). At each stage of kidney disease, prevalence and severity of anemia are increased in diabetic patients compared with those in nondiabetic cohorts [3]. A lot of previous reports have demonstrated the association between anemia and cardiovascular disease (CVD) both in general populations or CKD patients [4-6] and in diabetic patients [7-9]. Cardiovascular disease is the primary cause of mortality and morbidity in patients with type 2 diabetes mellitus [10], and male sex is an independent risk factor for CVD [11].

Several studies have documented abnormalities of hemoglobin concentration in patients with diabetes, although the clinical relevance of these observations remains somewhat elusive. In this study, we investigated the relationship between hemoglobin concentration and various factors including age, body mass index (BMI), blood pressure, serum creatinine concentration, and glycemic control, as well as markers of subclinical atherosclerosis such as pulse wave velocity (PWV), ankle-brachial index (ABI), and intima-media thickness (IMT) and plaque score evaluated by carotid ultrasonography in men with type 2 diabetes mellitus.

* Corresponding author. Tel.: +81 75 251 5505; fax: +81 75 252 3721.
E-mail address: sayarinapm@hotmail.com (M. Fukui).

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2. Subjects and methods

2.1. Patients

Hemoglobin concentration was measured in 319 men with type 2 diabetes mellitus recruited from the outpatient clinic of the Kyoto Prefectural University of Medicine. We evaluated the relationship between hemoglobin concentration and various factors including age, BMI, blood pressure, glycemic control, serum lipid concentration, serum creatinine, current treatment of diabetes, and presence of CVD. The relationship between serum erythropoietin concentration and hemoglobin concentration or reticulocyte count was investigated in 175 men. Moreover, the relationships between hemoglobin concentration and PWV or ABI (n = 209) and between hemoglobin concentration and carotid IMT or plaque score (n = 125) were investigated additionally.

2.2. Clinical and biochemical assessment

Type 2 diabetes mellitus was diagnosed according to the "Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus" [12]. Retinopathy was graded as follows: no diabetic retinopathy (NDR), simple diabetic retinopathy (SDR), and proliferative diabetic retinopathy (PDR). Nephropathy was graded as follows: normoalbuminuria, urinary albumin excretion less than 30 mg/g Cr; microalbuminuria, 30 to 300 mg/g Cr; or macroalbuminuria, more than 300 mg/g Cr. Glomerular filtration rate (GFR) was estimated from the Modification of Diet in Renal Disease equation for Japanese patients [13]. Sitting blood pressure was measured after a 5-minute rest. *Cardiovascular disease* was defined as a previous myocardial or cerebral infarction based on the clinical history or physical examination. Subjects were classified as nonsmokers, past smokers, or current smokers according to a self-administered questionnaire.

Patients were excluded if they were taking any medications known to affect hemoglobin concentration (eg, erythropoietin). In addition, patients with advanced renal dysfunction (serum creatinine >2.0 mg/dL) were also excluded. Furthermore, patients with malignant disease, liver cirrhosis, thyroid disorders, hematologic disease, or infectious disease were excluded from this study. Approval for the study was obtained from the local Research Ethics Committee, and informed consent was obtained from all participants.

Blood samples were obtained in the morning. Hemoglobin concentrations were analyzed within 4 hours of blood drawing using a SYSMEX XE-2100 autoanalyzer (Sysmex, Kobe, Japan). Glycated albumin was determined by an enzymatic method using albumin-specific proteinase, ketoamine oxidase, and an albumin assay reagent (Lucica GA-L; Asahi Kasei Pharma, Tokyo, Japan). Serum erythropoietin concentration was determined by an erythropoietin assay (Recombigen Erythropoietin RIA Kit; Mitsubishi Chemical Medience, Tokyo, Japan), performed according to the manufacturer's instructions. Serum total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride concentrations were assessed using standard enzymatic methods. Urinary albumin and creatinine concentration were determined in an early morning spot urine. Urinary albumin excretion was measured with an immunoturbidimetric assay. A mean value for urinary albumin excretion was determined from 3 urine collections.

2.3. Measurement of PWV and ABI

Brachial-ankle (ba) PWV and ABI were measured by an automatic waveform analyzer (model BP-203RPEII; Colin, Komaki, Japan), which simultaneously measures pulse volumes in the brachial and ankle arteries using an oscillometric method together with bilateral arm and ankle blood pressure. Subjects were examined in the supine position after 5 minutes of bed rest. The baPWV was calculated by time phase as distance/time (in centimeters per second). The time delay between the arrival of the pulse wave at the brachium and ankle at each side was measured automatically by gating the pulse wave to the peak of the R wave of the electrocardiogram. The distance between the brachium and ankle at each side was estimated based on body height and was adjusted for average Japanese body composition. Details of the method have been described elsewhere [14]. After bilateral determination of baPWV, the higher value was taken as representative for each subject. The ABI was calculated bilaterally as the ratio of systolic pressure in the ankle to systolic pressure in the arm, with the lower value considered representative for each subject.

2.4. Ultrasonographic measurement of carotid IMT and plaque score

B-mode ultrasonographic imaging of the carotid artery was performed using a high-resolution, real-time ultrasonograph with a 7.5-MHz transducer. Examination and image analysis were performed by trained sonographers kept unaware of other data. The IMT was measured in the far wall of the vessel as the distance from the leading edge of intima-adventitia interface. The average measurement was taken as the mean IMT. We defined a *plaque* as a visually distinct area with an IMT greater than that of neighboring sites. The plaque score was determined as the sum of the maximum thickness of all plaques measured in millimeters on the near and far wall of the vessels.

2.5. Statistical analysis

Means and frequencies of potential confounding variables were calculated as appropriate. Unpaired Student *t* tests or analyses of variance were conducted to assess statistical significance of differences between groups using Stat View software (version 5.0; SAS Institute, Cary, NC). Because urinary albumin excretion and serum erythropoietin concentration showed skewed distributions, logarithmic (log) transformations were carried out before performing correlation analyses. The relationships between hemoglobin concentration and age, BMI, blood pressure, glycemic

control, serum lipid concentration, serum erythropoietin concentration, and other variables were examined by Pearson correlation analyses. Multiple linear regression analysis was performed to assess the combined influence of variables on hemoglobin concentration. To examine the effects of various factors on hemoglobin concentration, the following factors were considered as independent variables: age, duration of diabetes, BMI, glycated albumin, systolic blood pressure, serum total cholesterol concentration, and serum creatinine concentration. All continuous variables are presented as the mean ± SD. A P value < .05 was considered statistically significant.

3. Results

Clinical characteristics of 319 men with type 2 diabetes mellitus enrolled in this study are shown in Table 1. Mean age and hemoglobin concentration were 63.5 ± 11.1 years and 14.2 ± 0.80 g/dL, respectively.

The relationships between hemoglobin concentration and other variables are shown in Table 2. Body mass index, systolic blood pressure, diastolic blood pressure, serum total cholesterol concentration and triglyceride concentration, and estimated GFR were positively associated with hemoglobin concentration, whereas age, duration of diabetes, glycated albumin, serum creatinine concentration, and log (urinary albumin excretion) were negatively associated with hemoglobin concentration. Multiple regression analysis identified age, BMI, systolic blood pressure, total cholesterol concentration, and serum creatinine concentration as independent determinants of hemoglobin concentration (Table 3).

Table 1
Clinical characteristics of patients with type 2 diabetes mellitus

n	319
Age (y)	63.5 ± 11.1
Age at onset (y)	50.1 ± 12.1
Duration of diabetes (y)	13.3 ± 11.2
BMI (kg/m^2)	23.2 ± 3.1
Systolic blood pressure (mm Hg)	134 ± 15
Diastolic blood pressure (mm Hg)	78 ± 10
Hemoglobin A_{1c} (%)	7.1 ± 1.1
Glycated albumin (%)	20.0 ± 4.4
Hemoglobin (g/dL)	14.4 ± 1.4
Erythropoietin (mU/mL)	24.2 ± 10.8
Reticulocyte count (10^{10}/L)	4.9 ± 1.9
Total cholesterol (mg/dL)	194 ± 32
Triglyceride (mg/dL)	135 ± 90
HDL cholesterol (mg/dL)	52 ± 14
Smoking (none/past/current)	70/147/102
Nephropathy (normo-/micro-/macroalbuminuria)	191/196/32
Retinopathy (NDR/SDR/PDR)	239/38/42
Current treatment (diet/OHA/insulin)	33/217/69
CVD (−/+)	271/48
Estimated GFR (mL/[min 1.73 m^2])	68.6 ± 17.8
Urinary albumin excretion rate (mg/g Cr)	161 ± 540

Data are mean ± SD or number of patients. OHA indicates oral hypoglycemic agents; Cr, creatinine.

Table 2
Correlation between hemoglobin concentration and other variables

	r	P
Age	−0.388	<.0001
Duration of diabetes	−0.287	<.0001
BMI	0.340	<.0001
Glycated albumin	−0.148	.0121
Systolic blood pressure	0.186	.0017
Diastolic blood pressure	0.389	<.0001
Total cholesterol	0.224	.0001
Triglyceride	0.214	.0003
HDL cholesterol	0.002	.9726
Serum creatinine	−0.206	.0019
Estimated GFR	0.219	.0011
Log (urinary albumin excretion)	−0.188	.0010

No significant association was observed between hemoglobin concentration and serum erythropoietin concentration (Fig. 1A), and positive correlation was found between serum erythropoietin concentration and reticulocyte count (Fig. 1B). Negative correlations were found between hemoglobin concentration and PWV (Fig. 2A) and between hemoglobin concentration and plaque score (Fig. 2B). No significant correlations were found between hemoglobin concentration and IMT (r = −0.126, P = .1616) and between hemoglobin concentration and ABI (r = 0.053, P = .4309).

Hemoglobin concentration was significantly lower in patients with macroalbuminuria (13.5 ± 1.2 g/dL) than microalbuminuria (14.1 ± 1.5 g/dL, P = .0143) and normoalbuminuria (14.5 ± 1.2 g/dL, P = .0005), whereas hemoglobin concentrations did not differ based on the severity of diabetic retinopathy (14.6 ± 1.7, 14.0 ± 1.6, and 14.0 ± 3.1g/dL for patients with NDR, SDR, and PDR, respectively). Hemoglobin concentration was lower in patients with CVD than without (13.8 ± 1.7 vs 14.5 ± 1.3 g/dL, P = .0015). Hemoglobin concentration did not differ according to smoking status (14.7 ± 1.3, 14.2 ± 1.3, and 14.4 ± 1.4 g/dL for current smokers, past smokers, and nonsmokers, respectively).

4. Discussion

In this study, we investigated the relationship between hemoglobin concentration and various factors including age,

Table 3
Multiple regression analysis on hemoglobin concentration

	β	P
Age	−0.222	.0019
Duration of diabetes	−0.126	.0721
BMI	0.145	.0432
Glycated albumin	−0.088	.1737
Systolic blood pressure	0.214	.0015
Total cholesterol	0.170	.0077
Serum creatinine	−0.181	.0045

R^2 = 0.284 (P < .0001).

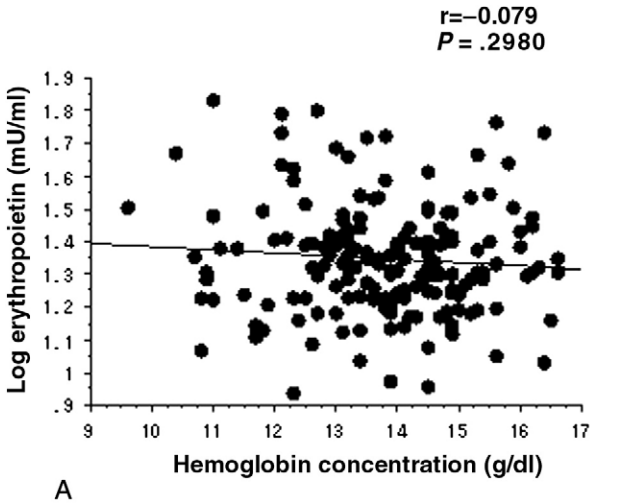

Fig. 1. Correlations between hemoglobin concentration and serum erythropoietin concentration (A) and between serum erythropoietin concentration and reticulocyte count (B) in men with type 2 diabetes mellitus.

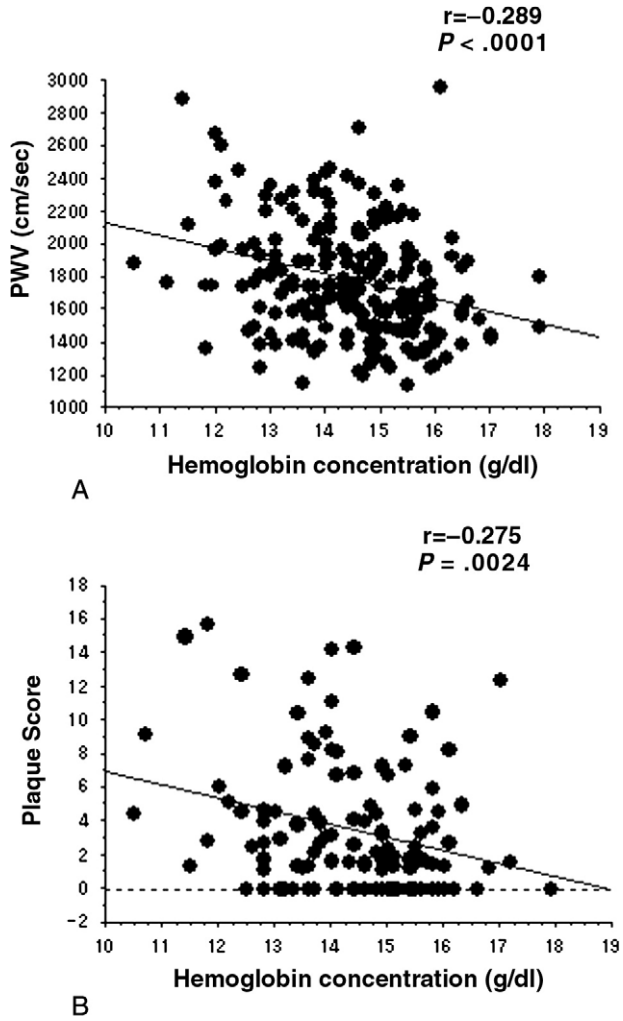

Fig. 2. Correlations between hemoglobin concentration and PWV (A) and between hemoglobin concentration and plaque score (B) in men with type 2 diabetes mellitus.

BMI, blood pressure, glycemic control, serum lipid concentration, PWV, ABI, IMT, and plaque score in men with type 2 diabetes mellitus. Body mass index, systolic blood pressure, diastolic blood pressure, serum total cholesterol and triglyceride concentration, and estimated GFR were positively associated with hemoglobin concentration, whereas age, duration of diabetes, glycated albumin, serum creatinine concentration, and log (urinary albumin excretion) were negatively associated with hemoglobin concentration. Multiple regression analysis identified age, BMI, systolic blood pressure, total cholesterol concentration, and serum creatinine concentration as independent determinants of hemoglobin concentration. Moreover, negative correlations were found between hemoglobin concentration and PWV and between hemoglobin concentration and plaque score evaluated by carotid ultrasonography.

Anemia is a common finding in patients with CKD [15]. Diabetes, as the most common cause of CKD, is therefore the most common cause of renal anemia [3]. Serum creatinine concentration and log (urinary albumin excretion) were negatively associated with hemoglobin concentration in our study. In addition, anemia is more common in patients with diabetic nephropathy than in patients with other renal disease. The Third National Health and Nutrition Examination Survey found that patients with diabetes were nearly twice as likely to have anemia as subjects without diabetes but with a similar degree of renal impairment [3]. Craig et al [16] reported that all diabetic patients even without nephropathy had an ongoing and significant decrease in hemoglobin concentration. Early dysfunction in renal tubules, which are the primary sites of erythropoietin production, has been reported in patients with diabetes before the onset of microalbuminuria [17]. Inadequate erythropoietin responses in diabetes can be caused by low levels of erythropoietin, functional erythropoietin deficiency, and/or erythropoietin resistance [16,18]. In the present study, positive correlation was found between serum erythropoietin concentration and reticulocyte count;

however, no significant association was found between hemoglobin concentration and serum erythropoietin concentration. Moreover, multiple linear regression analysis, if we would add serum erythropoietin concentration as a covariate, did not determine serum erythropoietin concentration as a determinant of hemoglobin concentration ($\beta = -0.059$, $P = .4573$).

The etiology of anemia in patients with diabetes is thought to be multifactorial. The Third National Health and Nutrition Examination Survey revealed that inflammation, nutritional deficiencies, concomitant autoimmune disease, drugs, and hormonal changes will be the causes of anemia in addition to diabetic nephropathy [3]. Bhatia et al [19] demonstrated that men with type 2 diabetes mellitus tend to have normocytic normochronic anemia and that their hematocrit level was inversely related to serum C-reactive protein concentration, an index of systemic inflammation. Body mass index, blood pressure, serum total cholesterol, and triglyceride concentration were positively associated with hemoglobin concentration; and glycated albumin was negatively associated with hemoglobin concentration in this study. Johns and Peterson [20] reported that erythrocyte factors and plasma protein factors contribute to the increased viscosity seen in the blood of diabetic patients. In addition, red cells from diabetic patients aggregate more readily than those obtained from normal controls. Abnormalities in red cell deformability could be expected to decrease red cell survival. Erythrocyte survival studies performed with radioactive sodium chromate (^{51}Cr)-labeled red cells documented a 13% decrease in red cell survival when patients were hyperglycemic [21].

Age was negatively associated with hemoglobin concentration in this study. Serum testosterone declines in older men. Beginning at approximately 25 years of age, serum testosterone concentration steadily declines by a mean of 1.0% per year [22]. Bhatia et al [19] also demonstrated that men with type 2 diabetes mellitus have normocytic normochronic anemia and that their hematocrit level was positively related to calculated free testosterone. Testosterone is known to stimulate erythropoiesis in the bone marrow and increase erythrocyte. Moreover, testosterone is also known to increase 2,3-diphosphoglycerate, which is a matrix of erythrocyte membrane and which facilitates the unloading of oxygen from hemoglobin into the tissues by decreasing the oxygen affinity for hemoglobin [23]. Thus, low serum testosterone may affect erythrocyte production and its survival. Men with diabetes have significantly lower serum concentrations of endogenous androgens than nondiabetic men [24,25], which might be one of the factors for the high prevalence of anemia in patients with diabetes [26].

Previous studies have demonstrated the association between anemia and CVD both in general populations [4-6] and in diabetic patients [7-9]. Although anemia itself may not cause atherosclerosis, it is conceivable that tissue hypoxia associated with atherosclerotic disease is accentuated by a reduction in the oxygen-carrying capacity of blood or by an increase in cardiac work and stimulation of sympathetic activity associated with anemia [20]. The progression of CVD is the primary cause of mortality, and anemia is a powerful risk factor of death from CVD in patients with diabetes [7-9]. Although several studies have previously shown the association between hemoglobin concentration and subclinical atherosclerosis markers in patients with CVD or hypertension, there are few studies concerning the association between hemoglobin concentration and subclinical atherosclerosis markers in patients with type 2 diabetes mellitus. Negative correlation was found between hemoglobin concentration and PWV, a simple, noninvasive way to quantitate atherosclerosis in this study, which was also applicable in multiple regression analysis (data not shown). Moreover, hemoglobin concentration was lower in patients with CVD than without. In general, we pay little attention to hemoglobin concentration as a factor for progression of atherosclerosis in diabetic patients. Anemia is common among diabetic patients but is an often overlooked complication, although anemia can be a modifiable risk factor. Therefore, it is of clinical significance to clarify the role of hemoglobin concentration in the development and progression of atherosclerosis.

Limitations of our study include a cross-sectional design. There are no data of serum testosterone concentration and associations with hemoglobin concentration, PWV, and plaque score, which make the findings of the study weak in view of underlying mechanisms and causality. Furthermore, results in this study may not be applicable to the general population or to patients with type 2 diabetes mellitus in a primary care clinic because patients in an outpatient clinic in a university hospital are selected patients. Large prospective trials and intervention studies are needed to better assess the association between hemoglobin concentration and various factors and between hemoglobin concentration and atherosclerosis in men with type 2 diabetes mellitus.

In conclusion, hemoglobin concentration was associated with various factors; and decreased hemoglobin concentration was associated with subclinical markers of atherosclerosis in men with type 2 diabetes mellitus.

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