

Association between Hemoglobin and Diabetic Peripheral Neuropathy at Different Glycosylated Hemoglobin Levels in Type 2 Diabetes Mellitus Patients

Lingling Zhou

Shanghai Tenth People's Hospital

Xiaojuan Xu

Shanghai Tenth People's Hospital

Hui Sheng

Shanghai Tenth People's Hospital

Shen Qu

Shanghai Tenth People's Hospital

Ran Cui (✉ cuiran1172@163.com)

Shanghai Tenth People's Hospital

Research

Keywords: diabetic peripheral neuropathy, hemoglobin, glycosylated hemoglobin, type 2 diabetes mellitus.

DOI: <https://doi.org/10.21203/rs.3.rs-16650/v2>

License:   This work is licensed under a Creative Commons Attribution 4.0 International License.

[Read Full License](#)

Abstract

Background: To investigate the possible association of diabetic peripheral neuropathy (DPN) and serum hemoglobin levels in type 2 diabetes mellitus (T2DM) patients with different glycosylated hemoglobin levels.

Methods: A total of 995 patients were involved in this retrospective cross-sectional study. Laboratory medical data and electromyography results from the patients were collected. The patients were divided into five groups according to their HbA1c levels (Group 1: HbA1c \leq 7%, Group 2: HbA1c 7% to \leq 8%, Group 3: HbA1c 8% to \leq 9%, Group 4: 9% to \leq 10%, and Group 5: $>$ 10%). Differences in clinical data in the five groups were compared. Analysis of variance (ANOVA) and binary logistic regression analysis were used. All analyses were performed using SPSS 24 (SPSS Inc., Chicago, IL, USA). P value $<$ 0.05 was considered to indicate statistical significance.

Results: A correlation was found between the prevalence of DPN and anemia in both sex groups. Age, BMI, duration of diabetes, ALT, serum creatinine, TC, TG, LDL, FPG, FCP, and hemoglobin A1c differed to a statistically significant extent in different groups. Group 5 showed the highest prevalence of DPN in both sex groups. Hemoglobin levels were higher in Group 5 than in other groups, while composition of anemia was not statistically different. Binary logistic regression showed hemoglobin to be negatively related to the prevalence of DPN in Group 5 in men and in Group 4 in women.

Conclusion: Hemoglobin level was negatively associated with the occurrence of DPN at the HbA1c level of $>$ 10% in men and 9 to 10% in women in T2DM patients. HbA1c must be considered in exploring the correlation between hemoglobin and DPN.

Background

Diabetic peripheral neuropathy (DPN) is one of the most common complications of type 2 diabetes mellitus (T2DM); the prevalence is reported to be around 50% [1, 2]. According to previous studies, the risk factors for DPN are poor glycemic state, long diabetic duration, dyslipidemia, smoking, abusing alcohol, and obesity [3-5]. In few studies, an association was also found between hemoglobin and DPN. Yang et al. found that hemoglobin level in DPN patients was significantly lower than in patients without DPN, and the prevalence of DPN increased as hemoglobin decreased [6]. Wu et al. also found that anemia was an independent risk factor for DPN in T2DM patients [7]. However, to our best knowledge, glycosylated hemoglobin was not considered in the studies that showed a negative relationship between DPN and hemoglobin. Glycosylated hemoglobin is pivotal in the process of developing DPN at various ages [8, 9]. Therefore, glycosylated hemoglobin must be considered as an important factor in the study of the relationship between DPN and hemoglobin.

Diabetic neuropathy affects all peripheral nerves. Thus, diabetic neuropathy can affect all systems and produce global symptoms and syndromes. A patient can have either sensorimotor or autonomic

neuropathy or a combination of these issues Symptoms and syndromes vary depending on the nerve(s) affected. Clinical manifestations are not a reliable means of studying the relationship between DPN and hemoglobin. Nerve conduction study (NCS) is a very important test method for the diagnosis of DPN [10]. NCS is used to evaluate the function, especially the electrical conduction ability, of the motor and sensory nerves of the human body. Nerve conduction velocity (NCV) is a common measurement made during this test. Electromyography (EMG) is a common method of electrodiagnosis of NCV, as it often leads to the identification of motor neuron involvement before clinical evidence can be observed [11]. Thus, NCV may be better than an evaluation of the patient's subjective experience for exploring the relationship between DPN and hemoglobin.

In our cross-sectional study, we divided the subjects into groups with different glycosylated hemoglobin levels. We collected their NCS and hemoglobin data and analyzed the relationships between these two results. This study was different from other studies, as we placed glycosylated hemoglobin within the investigation of the association between DPN and hemoglobin.

Subjects And Methods

Subjects

A cross-sectional study was performed. Data from patients with T2DM hospitalized in the Department of Endocrinology and Metabolism of Shanghai Tenth People's Hospital (Shanghai, P. R. China) from May 2014 to September 2015 were screened. This study was approved by the ethics committees in the hospital, and informed consent was obtained from the involved participants.

Inclusion and exclusion criteria

Inclusion criteria: 1) T2DM patients; 2) patients with complete hemoglobin, HbA1c, and diabetic peripheral neuropathy data.

Exclusion criteria: 1) acute complications of diabetes including diabetic ketoacidosis and hyperosmolar hyperglycemic coma; 2) a clear history of diseases that affected hemoglobin level, such as hemolytic anemia, aplastic anemia, systematic autoimmune diseases, polycythemia vera, and others; 3) other diseases such as vitamin B12 deficiency, lumbar disc herniation, and neurological disorders capable of affecting NCV; 4) liver failure [12], end-stage renal failure (eGFR < 15 ml/min/1.73 m²), and heart failure [13]; and 5) acute phase of other disease, such as serious infection, or in poor general condition, such as malignant disease.

Finally, detailed data were collected from 995 patients (538 men and 457 women). Based on the degree of glycosylated hemoglobin, the subjects were divided into five groups as follows: Group 1: HbA1c ≤7%, Group 2: HbA1c 7% to ≤8%, Group 3: HbA1c 8% to ≤9%, Group 4: 9% to ≤10%, and Group 5: >10%.

Clinical Measurements and Biochemical Analysis

Information was collected on age, sex, diabetes duration, previous medical history, and current medications. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters-squared (kg/m²). Resting systolic and diastolic blood pressures were measured in a sitting position during medical examinations. Laboratory test results were collected from the electronic medical records, and the methods of measurement were as follows. Overnight fasting blood was collected. Hemoglobin was determined and measured by the cyanide methemoglobin method (Sysmex). Glycosylated hemoglobin (HbA1c) level was measured by high performance liquid chromatography (HPLC), and fasting plasma glucose (FPG) was determined by the glucose oxidase method. Fasting plasma C-peptide (FCP) (Biosource, Nivelles, Belgium) was separately assessed by immune-radiometric assays. Serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), serum creatinine (Cr), and serum uric acid (UA) were analyzed with a routine autoanalyzer (Modular DP analyzer, Roche Diagnostics, Mannheim, Germany). Total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL), and low-density lipoprotein (LDL) were measured by electrochemical luminescence (ELISA). The diagnosis of anemia was made when hemoglobin level was less than 120 g/L in males or 110 g/L in females. Hyperlipidemia was defined as TC greater than 5.2 mmol/l, TG greater than 1.7 mmol/l, or LDL greater than 3.34 mmol/l (according to the reference range provided in the ELISA kits).

Nerve Conduction Study (NCS)

NCS test results were collected from the electronic medical records. All patients were assessed using a Dantec Keypoint 4-channel EMG device (Skovlunde, Denmark) by the same physician or technician. The examinations were performed in a quiet room, and the skin temperature was maintained at or above 31°C. The compound muscle action potential (CMAP) amplitude and conduction velocity (CV) of the motor nerves for the median (right side), ulnar (right side), and common peroneal nerves (both sides) were measured and recorded. Measurements of sensory nerve action potential (SNAP) amplitude and CV were performed using the median (right side), ulnar (right side), and superficial fibular nerve (both sides). The mean of motor nerve amplitude was calculated using the formula: Amplitude motor nerve (mV) = (Amplitude median nerve + Amplitude ulnar nerve + two-sided Amplitude common peroneal nerve)/4. The means of motor nerve CV, sensory nerve amplitude, and sensory nerve CV were calculated using the same method.

Statistical analysis

Data are presented as mean ± SD, and categorical variables are expressed as a percentage. One-way ANOVA or Chi-square (χ^2) tests were used to compare the differences in the five groups. The least significant difference (LSD) test was adopted for post hoc comparisons. Binary logistic regression analysis was used to analyze the association between DPN and hemoglobin, as shown in Table 3. All tests were two-sided, and a P value < 0.05 was considered to indicate statistical significance. All analyses of physiological differences were performed using SPSS 24 (SPSS Inc., Chicago, IL, USA) and stratified by sex.

Results

Demographic, clinical, and biological characteristics of the population in both sexes

In total, 538 men and 457 women were recruited in our study. Age, duration of diabetes, DBP, serum creatinine, TC, LDL, and hemoglobin showed significant differences by sex. BMI, SBP, ALT, TG, FPG and FCP were without statistical significance. Usage of metformin was not found to show any significant difference (Table 1).

A correlation was found between the prevalence of DPN and anemia in both sexes. In men, the rate of DPN was 57.1% and that of anemia was 13.8%; the chi-square value was 18.99, and $P < 0.001$. In women, the rate of DPN was 58.2% and that of anemia was 15.0%; the chi-square value was 5.61, and $P = 0.018$. These results indicated that patients with anemia had a higher prevalence of DPN (Figure 1).

Participants were divided into five groups by hemoglobin A1c level. For men, there were 90 participants in Group 1, 97 in Group 2, 109 in Group 3, 76 in Group 4, and 166 in Group 5. For women, there were 98 participants in Group 1, 85 in Group 2, 82 in Group 3, 68 in Group 4, and 124 in Group 5.

Comparisons of each pair of groups are given in Table 2. BMI, diabetic duration, serum creatinine, TC, TG, LDL, FPG, FCP and hemoglobin A1c were statistically different for both sexes. Age and ALT were different only in male participants. The blood pressure indicators, SBP and DBP, were at the same level across all groups for both sexes. The percentage of description of metformin was not found to differ. The prevalence of DPN in the 5 groups were 42.5%, 50.5%, 60.4%, 59.2%, and 67.9% in men, respectively, and 38.4%, 60.0%, 50.0%, 63.2%, and 75.2% in women, respectively. Group 5 had highest prevalence of DPN in both sexes. Hemoglobin was higher in Group 5 compared to other groups, while composition of anemia was not found to be statistically different.

Binary logistic regression between hemoglobin and prevalence of DPN at different hemoglobin A1c levels

Three models were prepared to investigate the correlation between hemoglobin and DPN for different hemoglobin A1c levels. Model 1 included hemoglobin, age, BMI, and duration of diabetes. Model 2 included Model 1, ALT, and serum Cr. Model 3 included Model 2 and hyperlipidemia. No relationship was found between hemoglobin and the prevalence of DPN in any of the hemoglobin A1c levels. Only in Group 5 did hemoglobin show any negative relationship with the prevalence of DPN in men (hemoglobin A1c $>10\%$), and only in Group 4 was this the case in women (hemoglobin A1c 9% to $\leq 10\%$). In all the models, including age, BMI, duration of diabetes, liver and renal function, and lipid profiles, hemoglobin was an important factor for the prevalence of DPN. This correlation was not identified at every hemoglobin A1c level; it was only found in men with hemoglobin A1c $>10\%$ and in women with hemoglobin A1c levels between 9 to $\leq 10\%$.

Discussion

Chi-square test analysis in our retrospective cross-sectional study showed significant correlations between prevalence of DPN and anemia in both sexes. However, binary logistic regression analysis of the relationships between DPN occurrence and other clinical parameters, including age, BMI, diabetic duration, ALT, Cr, and hyperlipidemia, the correlation changed. We found a significant negative correlation between hemoglobin and DPN occurrence in patients with a glycosylated hemoglobin level that was more than 10% in males and between 9% and 10% in females. Similar significant relationships were not found in men or at other glycosylated hemoglobin levels in women. The relationship between hemoglobin and DPN occurrence was in agreement with two previous studies^[6, 7]. Yang et al. found that lower hemoglobin levels were associated with increased prevalence of DPN and higher vibrating perception threshold (VPT)^[6]. Wu et al. found that anemia was an independent risk factor for DPN in T2DM patients. The methods of evaluating DPN were not the same in our study as in the two previous studies. NCS was performed in our study, but VPT was used in Yang's study, and the neuropathy system score (NSS) and neuropathy disability score (NDS) were used in Wu et al.'s study. Regardless of the method used, the results suggested that hemoglobin levels were negatively correlated with DPN. The functions of hemoglobin are to carry oxygen and nutrients, remove free radicals, sustain erythrocytes' normal deformability, and provide antioxidant protection to tissues and organs^[14]. Thus, a low level of hemoglobin is associated with less oxygen, lack of nutrients, decreased or impaired (in anemia patients) erythrocyte deformability, and high oxidative stress status, which are all risk factors for DPN^[1, 15, 16]. Furthermore, bilirubin is a byproduct of normal hemoglobin breakdown that exhibits antioxidant and anti-inflammatory effects on neural tissue. It has been suggested that a low level of serum total bilirubin might be an independent risk factor for DPN in T2DM^[17, 18]. The imbalance between free radicals and antioxidants resulting from low hemoglobin could lead to oxidative stress^[19] and result in endothelial dysfunction, which plays a key role in the development of DPN^[20]. Erythropoietin (EPO) has been reported to have neuroprotective effects in rats with streptozotocin-induced diabetes^[21]. However, no studies have yet shown the relationship between EPO and hemoglobin levels in T2DM patients without overt nephropathy. Therefore, EPO might not be involved in the correlation between hemoglobin and DPN.

To the best of our knowledge, this is the only study stratifying glycosylated hemoglobin (HbA1c) level to analyze the correlation between hemoglobin and DPN prevalence. The concentration of HbA1c was influenced primarily by hemoglobin. Clinical studies have shown that anemia due to iron deficiency can cause an increase of HbA1c; inversely, anemia due to other causes may lead to a decreased HbA1c value^[22]. Anemia has been shown to be associated with a shorter erythrocyte life span, reduced hemoglobin concentration, and compensatory hyperplasia^[23]. All these factors can cause significant changes in the production of HbA1c. Thus, it is necessary to treat glycosylated hemoglobin as a distinct factor when exploring the relationship between hemoglobin and DPN. In our study, we found that this relationship existed only for HbA1c at the level from 9% to 10% or more than 10%. No correlation was found in either of the lower (HbA1c <9%) HbA1c groups. Thus, anemia should be considered as a chronic complication of T2DM^[24]. Glycosylated hemoglobin played an important role in the relationship between hemoglobin and DPN. When patients had relatively low HbA1c levels (<9%), the correlation between

hemoglobin and DPN could not be statistically detected (Table 3). Similar results have been found in other studies^[25]. For patients with severely inadequate glycemic control (HbA1c >9%), the relationship between hemoglobin and DPN was close enough to be assessed statistically (Table 3). Based on these results, HbA1c must be considered in exploring the correlation between hemoglobin and DPN.

Interestingly, the outcome of sex in this relationship was different from a result reported in a previous study. Yang et al. found an inverse association of DPN with hemoglobin, which was stronger in males than in females^[6]. In Wu et al.'s study, sex was not introduced as a variable of difference^[7]. Different HbA1c levels might be an explanation for this discrepancy. In Yang et al.'s study, HbA1c levels in the involved patients were 9.40 ± 2.48 (without DPN) and 10.10 ± 2.67 (with DPN), respectively, which had statistical significance ($P < 0.001$). However, we grouped HbA1c and came to different results. More studies should be performed to elucidate this discrepancy.

This study had some limitations. First, our study was a retrospective cross-sectional study. Thus, cause-and-effect relationships could not be established. Second, since these observations were made as part of a cross-sectional study, the exact pathophysiologic processes involved could not be elucidated; experiments in vitro or in vivo should be performed. Third, several other confounding parameters affecting DPN were not excluded, such as insufficient serum folic acid and vitamin B12 deficiency. Finally, the data used were collected from only one hospital, so selection bias and information bias could not be avoided. In future work, we will involve additional hospitals, in order to collect information from more patients to comprehensively investigate the relationship between hemoglobin and DPN.

In conclusion, hemoglobin level was negatively associated with the occurrence of DPN at a HbA1c level of >10% in men and 9 to 10% in women T2DM patients. Large prospective investigations are warranted to establish causal associations between hemoglobin and DPN. In clinical settings, physicians should examine electromyography in T2DM patients with low hemoglobin levels. The potential for a positive effect of treatment of anemia on DPN also needs to be investigated to achieve greater certainty in the future.

Conclusion

To sum up, hemoglobin level was negatively associated with the occurrence of DPN at the HbA1c level of >10% in men and 9 to 10% in women in T2DM patients. HbA1c must be considered in exploring the correlation between hemoglobin and DPN.

Declarations

This study was approved by the ethics committees in the hospital, and informed consent was obtained from the involved participants.

Consent for publication

Not applicable

Availability of data and materials

The datasets analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Funding

This study was supported by the National Natural Science Foundation of China (NSFC 81500650) and the Shanghai Tenth People's Hospital Climbing Plan for Distinguished Young Scholars (2018SYPDRC049).

Authors' contributions

ZLL and XXJ did the data acquisition, analysis job, and drafted the work. SH and QS interpreted the patient data. CR substantively revised it. All authors read and approved the final manuscript.

Acknowledgements

Not applicable.

References

- [1] ALBERS J W, POP-BUSUI R. Diabetic neuropathy: mechanisms, emerging treatments, and subtypes [J]. *Curr Neurol Neurosci Rep*, 2014, 14(8): 473.
- [2] LU B, YANG Z, WANG M, et al. High prevalence of diabetic neuropathy in population-based patients diagnosed with type 2 diabetes in the Shanghai downtown [J]. *Diabetes Res Clin Pract*, 2010, 88(3): 289-94.
- [3] SUGIMOTO K, MURAKAWA Y, SIMA A A. Diabetic neuropathy—a continuing enigma [J]. *Diabetes Metab Res Rev*, 2000, 16(6): 408-33.
- [4] TESFAYE S, CHATURVEDI N, EATON S E, et al. Vascular risk factors and diabetic neuropathy [J]. *N Engl J Med*, 2005, 352(4): 341-50.
- [5] ZIEGLER D, RATHMANN W, DICKHAUS T, et al. Prevalence of polyneuropathy in pre-diabetes and diabetes is associated with abdominal obesity and macroangiopathy: the MONICA/KORA Augsburg Surveys S2 and S3 [J]. *Diabetes care*, 2008, 31(3): 464-9.

- [6] YANG J, YAN P J, WAN Q, et al. Association between Hemoglobin Levels and Diabetic Peripheral Neuropathy in Patients with Type 2 Diabetes: A Cross-Sectional Study Using Electronic Health Records [J]. *Journal of diabetes research*, 2017, 2017(2835981).
- [7] WU F, JING Y, TANG X, et al. Anemia: an independent risk factor of diabetic peripheral neuropathy in type 2 diabetic patients [J]. *Acta Diabetol*, 2017, 54(10): 925-31.
- [8] JAISWAL M, DIVERS J, DABELEA D, et al. Prevalence of and Risk Factors for Diabetic Peripheral Neuropathy in Youth With Type 1 and Type 2 Diabetes: SEARCH for Diabetes in Youth Study [J]. *Diabetes care*, 2017, 40(9): 1226-32.
- [9] SU J B, ZHAO L H, ZHANG X L, et al. HbA1c variability and diabetic peripheral neuropathy in type 2 diabetic patients [J]. *Cardiovasc Diabetol*, 2018, 17(1): 47.
- [10] PERKINS B, BRIL V. Electrophysiologic testing in diabetic neuropathy [J]. *Handb Clin Neurol*, 2014, 126(235-48).
- [11] KANE N M, OWARE A. Nerve conduction and electromyography studies [J]. *J Neurol*, 2012, 259(7): 1502-8.
- [12] THIERRY, ARTZNER, BAPTISTE, et al. Liver transplantation for critically ill cirrhotic patients: Overview and pragmatic proposals [J].
- [13] CHAPLIN S. Chronic heart failure in adults: diagnosis and management. [J]. *Prescriber*, 2019, 30(1): 16-8.
- [14] SIEMS W G, SOMMERBURG O, GRUNE T. Erythrocyte free radical and energy metabolism [J]. *Clin Nephrol*, 2000, 53(1 Suppl): S9-17.
- [15] JAVED S, ALAM U, MALIK R A. Burning through the pain: treatments for diabetic neuropathy [J]. *Diabetes Obes Metab*, 2015, 17(12): 1115-25.
- [16] POPEL A S, JOHNSON P C. Microcirculation and Hemorheology [J]. *Annu Rev Fluid Mech*, 2005, 37(43-69).
- [17] KIM E S, LEE S W, MO E Y, et al. Inverse association between serum total bilirubin levels and diabetic peripheral neuropathy in patients with type 2 diabetes [J]. *Endocrine*, 2015, 50(2): 405-12.
- [18] CHUNG J O, CHO D H, CHUNG D J, et al. Physiological serum bilirubin concentrations are inversely associated with the prevalence of cardiovascular autonomic neuropathy in patients with Type 2 diabetes [J]. *Diabet Med*, 2014, 31(2): 185-91.
- [19] REEDER B, WILSON M. Hemoglobin and Myoglobin Associated Oxidative Stress: from Molecular Mechanisms to Disease States [J]. *Current Medicinal Chemistry*, 12(23): 2741-51.

- [20] LI Q R, WANG Z, ZHOU W, et al. Epalrestat protects against diabetic peripheral neuropathy by alleviating oxidative stress and inhibiting polyol pathway [J]. *Neural Regen Res*, 2016, 11(2): 345-51.
- [21] ROBERTO B, BELGIN B, MICHAEL B, et al. Erythropoietin both protects from and reverses experimental diabetic neuropathy [J]. *Proceedings of the National Academy of Sciences of the United States of America*, 2004, 101(3): 823-8.
- [22] ENGLISH E, IDRIS I, SMITH G, et al. The effect of anaemia and abnormalities of erythrocyte indices on HbA1c analysis: a systematic review [J]. *Diabetologia*, 2015, 58(7): 1409-21.
- [23] GALLAGHER E J, LE ROITH D, BLOOMGARDEN Z. Review of hemoglobin A(1c) in the management of diabetes [J]. *J Diabetes*, 2009, 1(1): 9-17.
- [24] THOMAS M, TSALAMANDRIS C, MACISAAC R, et al. Anaemia in diabetes: an emerging complication of microvascular disease [J]. *Curr Diabetes Rev*, 2005, 1(1): 107-26.
- [25] ISMAIL-BEIGI F, CRAVEN T, BANERJI M A, et al. Effect of intensive treatment of hyperglycaemia on microvascular outcomes in type 2 diabetes: an analysis of the ACCORD randomised trial [J]. *Lancet*, 2010, 376(9739): 419-30.

Tables

	Men (n = 538)	Women (n = 457)	P value
Age (years)	61.2 ± 10.8	64.2 ± 10.0	<0.001
BMI (kg/m ²)	24.7 ± 3.4	24.9 ± 3.7	0.359
Duration of diabetes (months)	126.1 ± 93.9	148.0 ± 97.0	<0.001
SBP (mmHg)	136.3 ± 19.7	138.1 ± 21.3	0.252
DBP (mmHg)	76.4 ± 11.9	73.1 ± 11.2	<0.001
ALT (U/L)	22.3 ± 19.7	19.9 ± 18.6	0.056
Cr (µmol/L)	83.6 ± 47.0	64.0 ± 26.1	<0.001
TC (mmol/L)	4.3 ± 1.1	4.8 ± 1.3	<0.001
TG (mmol/L)	1.8 ± 1.5	1.8 ± 1.2	0.427
LDL (mmol/L)	2.6 ± 0.9	2.8 ± 1.1	<0.001
FPG (mmol/L)	8.7 ± 3.3	8.5 ± 3.2	0.369
FCP (ng/mL)	2.0 ± 1.3	2.2 ± 1.7	0.139
Hemoglobin A1c (%)	9.2 ± 2.2	8.9 ± 2.1	0.043
Metformin treatment (%)	35.7	30.6	0.086
Hemoglobin (g/L)	136.7 ± 16.0	122.5 ± 13.1	<0.001
BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, ALT: alanine aminotransferase, Cr: serum creatinine, TC: total cholesterol, TG: triglycerides, LDL: low density lipid; FPG: fasting plasma glucose, FCP: fasting C-peptide.			

Table 1
Demographic, clinical, and biological characteristics of the study participants

	Men (n = 538)					Women (n = 457)				
	Group 1	Group 2	Group 3	Group 4	Group 5	Group 1	Group 2	Group 3	Group 4	Group 5
	(n = 90)	(n = 97)	(n = 109)	(n = 76)	(n = 166)	(n = 98)	(n = 85)	(n = 82)	(n = 68)	(n = 124)
Age (years)	61.3 ± 9.7	63.8 ± 9.1	61.8 ± 10.2	61.5 ± 12.2	59.4 ± 11.2 ^b	65.3 ± 9.7	63.7 ± 9.8	64.5 ± 9.1	64.6 ± 10.0	63.2 ± 10.9
BMI (kg/m ²)	25.0 ± 3.5	25.2 ± 3.1	24.7 ± 3.1	25.0 ± 3.5	24.1 ± 3.6 ^{a,b}	25.4 ± 4.3	25.2 ± 3.5	25.3 ± 4.1	24.9 ± 2.9	24.1 ± 3.4 ^{a,b,c}
Duration of diabetes (months)	115.6 ± 87.7	146.6 ± 86.0 ^a	148.7 ± 86.8 ^a	132.9 ± 97.4	102.6 ± 98.6 ^{b,c,d}	116.1 ± 87.0	159.4 ± 99.8 ^a	154.0 ± 90.8 ^a	185.7 ± 94.6 ^{a,c}	139.9 ± 99.1 ^d
SBP (mmHg)	134.6 ± 21.7	137.2 ± 20.4	139.2 ± 18.6	138.0 ± 20.3	133.8 ± 18.8	138.1 ± 20.2	140.4 ± 17.8	137.8 ± 24.1	139.8 ± 22.6	135.2 ± 21.5
DBP (mmHg)	74.7 ± 11.9	75.4 ± 12.3	77.3 ± 11.2	75.2 ± 12.9	78.1 ± 11.6	72.3 ± 11.1	75.0 ± 10.7	71.7 ± 12.1	73.2 ± 11.7	73.1 ± 11.0
ALT (U/L)	20.5 ± 12.7	18.7 ± 11.3	23.0 ± 23.9	25.8 ± 25.9 ^b	23.1 ± 20.3	17.8 ± 13.0	21.9 ± 22.1	20.5 ± 12.2	18.1 ± 11.2	21.0 ± 25.3
Cr (μmol/L)	99.0 ± 96.4	84.5 ± 27.5 ^a	84.1 ± 30.5 ^a	78.6 ± 25.9 ^a	76.6 ± 27.1 ^a	69.6 ± 27.9	62.8 ± 25.1	62.8 ± 22.0	65.9 ± 33.7	59.9 ± 22.3 ^a
TC (mmol/L)	4.1 ± 1.0	4.1 ± 1.0	4.3 ± 1.1	4.2 ± 1.0	4.8 ± 1.1 ^{a,b,c,d}	4.5 ± 1.3	4.5 ± 1.0	4.6 ± 1.0	4.9 ± 1.2	5.2 ± 1.5 ^{a,b,c}
TG (mmol/L)	1.9 ± 2.2	1.5 ± 0.9	1.8 ± 1.2	1.8 ± 1.4	1.9 ± 1.6 ^b	1.6 ± 0.9	1.7 ± 0.8	2.0 ± 1.2 ^{a,b}	2.1 ± 1.6 ^{a,b}	1.9 ± 1.4
LDL (mmol/L)	2.3 ± 0.8	2.4 ± 0.8	2.5 ± 0.9 ^a	2.4 ± 0.8	2.9 ± 1.0 ^{a,b,c,d}	2.6 ± 1.1	2.7 ± 0.9	2.7 ± 0.9	2.9 ± 1.0	3.2 ± 1.3 ^{a,b,c,d}

BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, ALT: alanine aminotransferase, Cr: serum creatinine, TC: total cholesterol, TG: triglycerides, FPG: fasting plasma glucose, FCP: fasting C-peptide, DPN: diabetic peripheral neuropathy. Group 1: HbA1c ≤ 7%, Group 2: HbA1c 7% to ≤ 8%, Group 3: HbA1c 8% to ≤ 9%, Group 4: 9% to ≤ 10%, and Group 5: >10%. ^a compared to Group 1, *P* < 0.05; ^b compared to Group 2, *P* < 0.05; ^c compared to Group 3, *P* < 0.05; ^d compared to Group 4, *P* < 0.05.

	Men (n = 538)					Women (n = 457)				
FPG (mmol/L)	6.2 ± 1.5	7.5 ± 2.1 ^a	8.1 ± 2.5 ^a	9.6 ± 3.3 ^{a,b,c}	10.9 ± 3.7 ^{a,b,c,d}	6.2 ± 1.2	7.5 ± 2.4 ^a	8.3 ± 2.7 ^a	8.9 ± 3.1 ^{a,b}	11.0 ± 3.5 ^{a,b,c,d}
FCP (ng/mL)	2.4 ± 1.5	2.2 ± 1.3	2.1 ± 1.3	2.1 ± 1.2	1.7 ± 1.1 ^{a,b,c,d}	2.5 ± 1.1	2.3 ± 1.3	2.3 ± 1.4	2.3 ± 2.7	1.8 ± 1.7 ^{a,b}
Hemoglobin A1c (%)	6.4 ± 0.4	7.5 ± 0.3 ^a	8.5 ± 0.3 ^{a,b}	9.5 ± 0.3 ^{a,b,c}	11.8 ± 1.5 ^{a,b,c,d}	6.4 ± 0.4	7.6 ± 0.3 ^a	8.5 ± 0.3 ^{a,b}	9.5 ± 0.3 ^{a,b,c}	11.6 ± 1.4 ^{a,b,c,d}
Metformin treatment (%)	40.9	41.2	34.9	35.5	30.1	27.3	35.2	28.9	39.7	27.0
DPN (%)	42.5	50.5	60.4	59.2	67.9 ^a	38.4	60.0	50.0	63.2 ^a	75.2 ^{a,c}
Hemoglobin (g/L)	133.8 ± 16.5	135.4 ± 15.4	135.9 ± 16.5	135.9 ± 15.4	139.9 ± 16.1 ^{a,b,c}	120.7 ± 12.6	119.2 ± 14.1	123.8 ± 12.0 ^b	122.7 ± 11.3	125.3 ± 13.9 ^{a,b}
Anemia (%)	13.3	16.5	15.7	10.5	12.1	18.4	18.2	12.0	16.2	11.1
BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, ALT: alanine aminotransferase, Cr: serum creatinine, TC: total cholesterol, TG: triglycerides, FPG: fasting plasma glucose, FCP: fasting C-peptide, DPN: diabetic peripheral neuropathy. Group 1: HbA1c ≤ 7%, Group 2: HbA1c 7% to ≤ 8%, Group 3: HbA1c 8% to ≤ 9%, Group 4: 9% to ≤ 10%, and Group 5: >10%. ^a compared to Group 1, <i>P</i> < 0.05; ^b compared to Group 2, <i>P</i> < 0.05; ^c compared to Group 3, <i>P</i> < 0.05; ^d compared to Group 4, <i>P</i> < 0.05.										

Table 2

Demographic, clinical, and biological characteristics of the patients in groups with different glycosylated hemoglobin levels

	Group 1		Group 2		Group 3		Group 4		Group 5	
	≤ 7%		7% to ≤ 8%		8% to ≤ 9%		9% to ≤ 10%		> 10%	
	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>	β (95% CI)	<i>P</i>
Men										
Model 1	0.975 (0.945 '1.007)	0.125	0.993 (0.963 '1.024)	0.649	0.977 (0.946 '1.009)	0.160	0.982 (0.946 '1.019)	0.339	0.960 (0.932 '0.989)	0.007
Model 2	0.975 (0.941 '1.010)	0.161	0.999 (0.967 '1.032)	0.937	0.988 (0.954 '1.023)	0.501	0.980 (0.943 '1.019)	0.315	0.961 (0.932 '0.991)	0.011
Model 3	0.975 (0.941 '1.010)	0.160	1.004 (0.971 '1.038)	0.826	0.985 (0.949 '1.022)	0.418	0.982 (0.944 '1.021)	0.349	0.959 (0.930 '0.990)	0.009
Women										
Model 1	1.007 (0.966 '1.049)	0.742	0.988 (0.949 '1.029)	0.564	0.978 (0.940 '1.017)	0.263	0.935 (0.880 '0.992)	0.027	0.994 (0.962 '1.027)	0.727
Model 2	1.011 (0.965 '1.059)	0.647	1.001 (0.960 '1.045)	0.947	0.984 (0.945 '1.025)	0.447	0.918 (0.857 '0.984)	0.016	0.988 (0.954 '1.023)	0.500
Model 3	1.010 (0.964 '1.059)	0.669	1.003 (0.960 '1.048)	0.887	0.984 (0.944 '1.025)	0.431	0.906 (0.833 '0.985)	0.021	0.987 (0.952 '1.022)	0.452
Model 1: hemoglobin, age, BMI and diabetic duration										
Model 2: Model 1 + ALT and Cr										
Model 3: Model 2 + hyperlipidemia										

Table 3

Binary logistic regression between hemoglobin and prevalence of DPN in different hemoglobin A1c levels

Figures

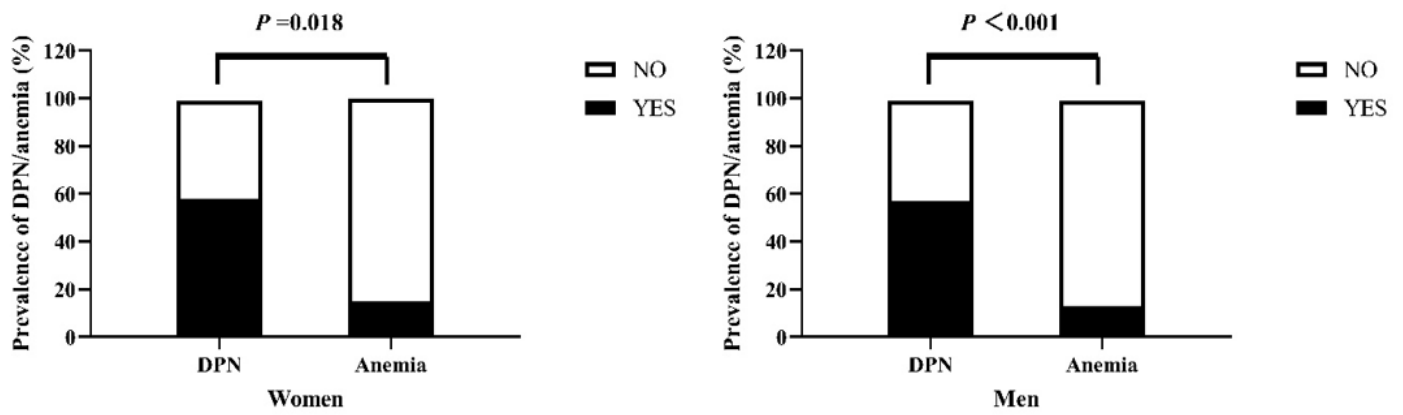


Figure 1

Correlation between prevalence of DPN and anemia in both sexes. Pearson Chi-square test was performed to assess the correlation between DPN and anemia. In men, the rate of DPN was 57.1% and that of anemia was 13.8%. The Chi-square was 18.99, and $P \leq 0.001$. In women, the rate of DPN was 58.2% and that of anemia was 15.0%. The Chi-square was 5.61, and $P = 0.018$.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- [STROBEchecklistcrosssectional.pdf](#)