

A Retrospective Study Assessing the Risk Factors of Type 2 Diabetes Mellitus Linked to Diabetic Foot Ulcer Incidence in Jiaxing, China

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Abstract

Objective: Diabetic foot (DF) is one of the common serious complications of diabetes, which is an important cause of death and disability, and is associated with diabetic vascular disease and diabetic neuropathy. The purpose of this study was to assess the incidence and risk factors for diabetic foot among a diabetic population.

Methods: The study was a retrospective cohort review. The population studied was 348 male examinees of type 2 diabetes mellitus (DM), in which age-matched equal examinees (174 patients each) were with diabetic foot (DF Group) and with no indication of diabetic foot (non-DF group), hospitalized in the same year at The First Hospital of Jiaxing, China. Medical records were reviewed to collect clinical profile, including duration of disease, smoking, previous diabetic foot incidence, and medication (such as metformin). Categorical data between groups were analyzed using chi-square test (χ^2). Unconditional logistic regression analysis was used for multi-factor analysis to identify the risk factors of diabetic foot.

Results: Comparing the baseline data of DF Group and non-DF Group, age, course of disease, LDL-C and use of metformin showed no significant difference ($P > 0.05$). The results of the logistic regression analysis showed that smoking history ($OR=1.88, P=0.020$), previous diabetic foot history ($OR=2.290, P=0.016$), Hcy ($OR=1.194, p \leq 0.001$) were independent risk factors for diabetic foot disease, and HgB ($OR=0.984, P=0.021$) was the protective factor of diabetic foot disease in male subjects. Age ($OR=0.985, P=0.304$), course of disease ($OR=1.048, P=0.233$), history of metformin use ($OR=0.851, P=0.509$), HbA1c ($OR=1.302, P=0.059$), LDL-C ($OR=0.936, P=0.698$), Creatinine ($OR=1.010, P=0.326$), and ALB ($OR=0.943, P=0.084$) were not significantly correlated with diabetic foot disease.

Conclusions: Smoking, previous diabetic foot history, and homocysteine are independent risk factors for diabetic foot disease. HgB is the protective factor of diabetic foot disease in male patients.

Introduction

Diabetic foot (DF) is one of the common serious complications of diabetes, which is an important cause of death and disability, and is associated with diabetic neuropathy and diabetic vascular disease(2020). Nontraumatic lower limb amputation is a serious complication of both diabetic neuropathy and peripheral vascular disease. On an average, 50% of non-traumatic amputees are from diabetic population. The annual mortality rate of diabetic foot ulcer patients is 14.4%. Even after amputation, the mortality rate of DF is up to 40% despite providing routine treatment(2018). Smoking, fluctuation in blood glucose level, and chronic kidney disease have been confirmed as some of the diabetic foot risk factors(Qiang 2016a). Further search for other risk factors for DF, especially simple indicators, and the intervention of risk factors is particularly important.

Homocysteine (Hcy), a sulfur-containing amino acid, is an essential metabolic intermediate in methionine metabolism. The sulfhydryl group of homocysteine is a reactive group that can participate in redox reaction and causes oxidative stress. It is generally accepted that homocysteine promotes

atherosclerosis(Borowska 2017) and it is a risk factor for cardiovascular disease and stroke(Vadini 2019). Earlier studies have shown that homocysteine is a risk factor for DF in type 2 diabetic patients. (Bruce and Young 2008; Gazzaruso 2012; Qiang 2016b) Current evidence suggests that metformin reduces the absorption of vitamin B12, which, in turn, leads to increase in the risk of B12 deficiency and giant cell anemia. Vitamin B12 deficiency may also lead to elevated levels of homocysteine.(Orlenko 2018) The relationship between metformin, homocysteine, and DF is not well studied. Given the importance to diabetic complications and lack of definitive risk factors for DF, our present study aimed to assess the risk factors for DF in men based on metformin treatment, smoking and other clinical factors.

Materials And Methods

Research design

This study was carried out on 348 diabetic patients admitted in Department of Endocrinology, The First Hospital of Jiaying from January 2012 to June 2019 .The enrolled diabetic patients were divided into two groups. DF Group: 174 men of type 2 DM with DF. Non-DF Group (control): 174 patients without diabetic foot selected according to age (inter-group gap <4 years) and course (inter-group gap <2 years) with 1:1 matching design. Both groups had no significant difference in age and course of disease ($P > 0.05$). To carry out this study, verbal consent was obtained from the patients. The ethical committee of The First Hospital of Jiaying approved this study.

Inclusion criteria: Patients with type 2 DM, diabetic foot Wagner ulcer grade 1 to 5.

Exclusion criteria: Type 1 DM, urinary tract infection, diabetic foot Wagner ulcer grade 0, complications with systemic lupus erythematosus, chronic glomerulonephritis, acute nephritis, severe liver dysfunction, Henoch-Schonlein purpura of lower extremity skin, ulcers caused by squamous cell carcinoma of lower extremity and other malignant tumors.

Data collection

The medical records were retrospective reviewed. The following relevant clinical data were collected, counted and analyzed: age, course of disease, smoking, past history of diabetic foot, metformin use, homocysteine (Hcy), hemoglobin (Hgb), glycosylated hemoglobin (HbA1c), creatinine, low density lipoprotein cholesterol (LDL-C), serum albumin (ALB), etc. Fasting blood samples were collected on the first day morning after admission and immediately sent to the laboratory in our hospital through the Taikang pneumatic tube transport system. The biochemical indices were tested on the DDP module of Roche Modular P800 biochemical analyzer, USA. Homocysteine assay kit (cyclic enzyme method) was obtained from Jiaying Botai Biological Technology Development Co., Ltd. The reference value range of homocysteine in our hospital is (15~20 μ mol/L); Glycosylated hemoglobin was determined using Bio-Rad D10 blood hemoglobin analyzer, CA, USA. The detection method is high pressure liquid chromatography.

DF was evaluated and graded according to Wagner classification (Level 0: Risk factors for foot ulcers, No ulcers; Level 1: Superficial ulcers in the skin, No clinical infection; Grade 2: Ulcers reach tendons, bones, ligaments and joints, No abscess or bone infection; Grade 3: Ulcer with deep abscess and osteomyelitis; Level 4: Localized gangrene; Level 5: Large or all gangrene).

Metformin usage refers to continuous use for at least three or more months in the first half of the year of diabetes (Dose: ≥ 0.75 g/ day). The smoking history refers to present the smoker of ≥ 1 year with average daily numbers ≥ 5 or former smoker who quit smoking in less than 10 years. History of DF refers to the Wagner ulcer grade 1 before the patient was hospitalized.

Statistical analysis

Statistical analysis was performed with SPSS 16.0 (SPSS Inc., Chicago, USA). Data were expressed as mean \pm SD. *t*-test was used for the comparison of quantitative variables between two groups. Categorical data between groups were analysed using chi-square test (χ^2). Unconditional logistic regression analysis was used for multi-factor analysis. A P value <0.05 is considered significant.

Results

A total of 348 diabetic patients were involved in this study. There was no significant difference in age, course of disease, LDL-C, and metformin use between the two groups ($P>0.05$), DF group and non-DF group. There were significant differences observed in smoking history, previous history of diabetic foot, Hcy, HbA1c, HgB, Creatinine, and ALB ($P<0.05$). See table 1 for details.

Risk factor analysis for diabetic foot

Logistic regression analysis showed that smoking history ($OR=1.88$, $P=0.020$), and previous history of diabetic foot disease ($ORP=2.290$, $P=0.016$), Hcy ($OR = 1.194$, $p\leq 0.001$) were independent risk factors for diabetic foot and HgB ($OR = 0.984$, $P=0.021$) was a protective factor for diabetic foot. Age ($OR=0.985$, $P=0.304$), course of disease ($ORP=1.048$, $P=0.233$), metformin history ($ORP=0.851$, $P=0.509$), HbA1c ($OR = 1.302$, $P=0.059$), LDL-C ($OR = 0.936$, $P=0.698$), Creatinine ($OR = 1.010$, $P=0.326$), ALB ($OR = 0.943$, $P=0.084$) and other indicators were not significantly associated with diabetic foot. See table 2 for details.

Discussion

Within the aged population, the incidence of diabetes has been gradually increased, and the chronic complications associated with diabetes also increased significantly. DF is one of the serious complications of diabetes. The First Hospital of Jiaying has a multidisciplinary cooperative treatment team for treating DF. The patients with DF have been well treated and so the numbers of patients with diabetic foot visiting our hospital have been increased greatly. So, we have enough patients in our hospital to provide samples for this study and carry out a lot of research on DF.

The early prevention of DF risk factors is the key to reduce the death and disability of diabetic foot. Our previous studies suggest that homocysteine is a risk factor for DF(Qiang 2016b), but we did not include smoking, history of DF, etc., in previous studies. Recent studies reported that metformin can cause vitamin B12 absorption disorders, vitamin B12 deficiency, folic acid deficiency, and leads to elevated homocysteine level which may aggravate diabetic peripheral neuropathy. On the other hand, metformin administration is believed to improve diabetic peripheral neuropathy by reducing blood sugar level. Diabetic peripheral neuropathy is an important cause of DF (2020), so metformin is worth further exploration. Real and co-workers discussed the relationship between homocysteine and diabetic foot, but did not compare the course of disease, age and sex.(González et al. 2010) The age and course of DF patients are different from that of normal diabetic patients. This study analyzed the risk factors of diabetic foot in male diabetic foot patients, matched the age and course of disease, analyzed the risk factors of diabetic foot, and understood the influencing factors of diabetic foot excluding the factors age, course and sex.

Homocysteine is not only a risk factor for cardiovascular and cerebrovascular diseases(Naveed and Bokhari 2015; Vadini 2019). This study further confirmed that homocysteine is a risk factor for diabetic foot and is in consistent with previous studies(Qiang 2016b). It is believed that homocysteine can lead to endothelial dysfunction.(Austin et al. 2004) It can directly damage and destroy vascular endothelial cells by oxidative stress, promoting lipid peroxidation, inhibiting nitric oxide synthesis, inducing cell necrosis and apoptosis. In addition, it also promotes proliferation of vascular smooth muscle cells, damage platelets and coagulation-fibrinolysis balance, resulting in vascular endothelial damage, accelerate the progress of atherosclerosis and thrombosis. It is believed that homocysteine can lead to arteriosclerosis and occlusion through direct cytotoxicity,(Lahiri et al. 2013; Tripathi 2015) and then cause ischemic and hypoxic injury of nerve, and damage nerve cells directly through endoplasmic reticulum stress(Lehotský et al. 2016). Our study suggests that metformin is not a risk factor for DF and that metformin ($OR = 0.851$, $POR = 0.509$) has no direct correlation with diabetic foot. Metformin can cause vitamin B12 deficiency and may affect the metabolism of homocysteine, but the latest study also suggests that metformin treatment can reduce the level of homocysteine(Zhang 2019). Homocysteine is not only affected by drugs, but also associated with abdominal obesity and insulin resistance. Metformin treatment reduces homocysteine by reducing insulin resistance.

This study suggests that smoking history ($OR = .1.88$, $POR = .0.020$), previous history of DF disease ($OR = .2.290$, $POR = .0.016$) are risk factors for DF and are consistent with current view(2020). Of all the risk factors, the history of DF was the most correlated and the risk was the highest. After the rehabilitation of DF patients, how to prevent the recurrence of DF is particularly important.

This study suggests that hemoglobin is negatively correlated with the occurrence and development of diabetic foot ($OR = 0.984$, $POR = 0.021$). Hemoglobin is the protective factor of DF; and anemia is the risk factor of DF. The role of hemoglobin in the occurrence and development of DF cannot be ignored. Hemoglobin is the protein responsible for oxygen transport in the body. Anemia often causes local

ischemia and hypoxia, exacerbates the occurrence and development of diabetic foot. Hemoglobin is directly related to the prognosis of DF(Costa 2017).

This study suggested that age ($OR = 0.985, P = 0.304$), course of disease ($OR = 1.048, P = 0.233$), HbA1c ($OR = 1.302, P = 0.059$), LDL-C ($OR = 0.936, P = 0.698$), creatinine ($OR = 1.010, P = 0.326$), and ALB ($OR = 0.943, P = 0.084$) were not significantly correlated with DF. The occurrence of DF is closely related to the poor control(2020) of blood sugar, but our hospital did not suggest that glycosylated hemoglobin is related to DF, and the occurrence is affected by long-term chronic hyperglycemia. Glycosylated hemoglobin represents blood sugar for nearly 2 ~ 3 months.

Conclusions

Smoking history, previous diabetic foot history, and homocysteine are independent risk factors for DF disease. HgB is the protective factor of DF disease in male patients. This study suggests that metformin is not a risk factor for DF and has no direct correlation with DF. Thus, our retrospective study reflects that the usage of metformin to reduce blood sugar levels is safe in DM patients. We are planning for more prospective studies on metformin and DF in DM patients to validate our findings further.

Abbreviations

DF: Diabetic foot); DM: diabetes mellitus; Hcy: Homocysteine; HgB: hemoglobin; HbA1c: glycosylated hemoglobin; LDL-C: low density lipoprotein cholesterol; ALB: serum albumin.

Declarations

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Authors' contributions

Qiang Zhou interpreted the data and drafted the manuscript. Yichuan Shao contributed to the study conceptualization and the discussion of results. Minjie Mao contributed to the study design and data analysis. Danlu Yu contributed to the data interpretation and the discussion of results. Shengjie Tang contributed to the study design, data interpretation and the discussion of results. Yinling Yang and Chenggao Xu contributed to the data interpretation, discussion of results and revising the manuscript. All authors read and approved the final manuscript.

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Availability of data and materials

The data used to support the findings of this study are available from the corresponding author upon request.

Ethics approval and consent to participate

The study was approved by the ethical committee of the First Hospital of Jiaxing

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1: Comparison of test indexes between two groups

	DF-group	non-DF-group	P value
Number of cases	174	174	
Age (years)	67.71±8.35	67.53±8.25	0.842
Course (years)	12.23±3.13	11.82±3.24	0.235
Smoking (Yes/No)	87/87	59/115	0.003
History of metformin use (yes/no)	79/95	90/84	0.283
Previous history of diabetic foot disease (yes/no)	19/155	37/137	0.013
Hcy (umol/L)	20.52±6.54	17.09±3.05	0.000
HbA1c(%)	8.31±0.81	8.11±0.96	0.036
HgB (g/L)	105.83±18.48	110.36±17.78	0.021
LDL-C (mmol/L)	3.13±0.74	3.06±0.75	0.378
Creatinine (umol/L)	87.47±17.31	82.86±14.91	0.008
ALB (g/L)	33.96±3.64	35.11±3.72	0.004

Table 2: Regression analysis logistic diabetic foot

Indicators	β	SE	Wald	OR value	CI 95 per cent	P value
Age	-0.015	0.015	1.058	0.985	0.957~1.014	0.304
Course	0.047	0.039	1.424	1.048	0.970~1.132	0.233
Past history of diabetic foot disease	0.828	0.345	5.772	2.290	1.165~4.500	0.016
History of smoking	0.592	0.255	5.406	1.808	1.097~2.977	0.020
Metformin	-0.161	0.244	0.437	0.851	0.527~1.373	0.509
HCY	0.177	0.040	19.402	1.194	1.103~1.292	0.000
HbA1c	0.264	0.140	3.570	1.302	0.990~1.713	0.059
HgB	-0.016	0.007	5.312	0.984	0.971~0.998	0.021
LDL-C	-0.067	0.172	0.150	0.936	0.668~1.310	0.698
Creatinine	0.009	0.010	0.963	1.010	0.991~1.029	0.326
ALB	-0.059	0.034	2.982	0.943	0.881~1.008	0.084
Constant	-2.147	2.312	0.862	0.117	...	0.353