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Dyslipidemia and Blood Indices in the Prognosis of Diabetic Foot Ulcers (DFU)

Jianjian Zhang[1]; Tian Ren[2]; Shouqing Han[3,4]; Yajing Zhao[3,4]*

[1]Department of Internal Medicine, Jinan Second People's Hospital, Jinan, China.

[2]Shandong Ronjun General Hospital, China.

[3]Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China.

[4]Shandong Provincial Key Laboratory of Immunohematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, China.

***Corresponding Author(s): Yajing Zhao**

Department of Hematology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, China.

Tel: 86-531-82169879; Email: zhaoyajing93115@163.com

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Keyword: Diabetic Foot Ulcers; Dyslipidemia; Blood Cells; Infection.

Abstract

Objective: Diabetic foot ulcers (DFU) are major complications of type 2 diabetes, causing a great financial burden to family and society. Our study is to evaluate the risk factors of DFU and the correlation between blood and lipid indices in patients with DFU.

Methods: We enrolled 201 patients with type 2 diabetes without DFU, 53 patients with DFU, and 132 comparative normal controls in a retrospective study.

Results: Our study demonstrated that dyslipidemia and platelet activation are related with infection, severity, and delayed healing of DFU. Platelet indices were correlated with TG and HDL levels in patients with DFU. Patients with infected foot ulcers, with Wagner score over 3, or with non-healing foot ulcers after 1-year follow-up were prone to have higher white blood cell and platelet counts, and lower HDL levels.

Conclusion: Medications of anti-platelet and lipid-lowering drugs might be of great importance in treatments of DFU.

Introduction

Diabetic foot ulcers (DFU) are critical complications of type 2 diabetes, leading to amputation of the limb and even being life threatening, causing a great financial burden on the community [1,2]. Early recognition and management of risk factors, and prevention of the adverse outcomes of DFU is of great importance in improving the life quality of patients with type 2 diabetes [3].

Infection is a major complication of DFU and is associated with poor prognosis. Therefore, management of infection is one of the major strategies in diabetic foot lesions [2]. Platelet-neutrophil interaction promotes inflammatory responses [4]. The systemic inflammatory process leads to changes in white blood cell (WBC) and platelet levels[4,5]. Despite hemostatic and thrombotic effects, platelets are also active participants in the inflammatory response to microbial organisms and foreign substances[6]. Platelet indices such as Mean Platelet Volume (MPV), platelet distribution width (PDW), and plateletcrit (PCT) are indicators of increased platelet activity, and can be considered as indicators for the development and severity of diabetic complications [3,7]. Autologous platelet-rich plasma is used with increasing frequency to treat cutaneous chronic/refractory wounds in clinical practices [8,9]. Furthermore, platelet-derived growth factor can be topically applied in treatment of diabetic

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foot [10,11]. Thus, platelet may play an important role in the pathogenesis and healing of DFU.

Lipids are diverse families of low molecular weight biomolecules that play an essential role in the structure, signaling and energy storage of platelets.[5] Phospholipids are major structural and functional lipids in platelets, which is in common with other mammalian cells. Other lipid types in platelets including steroids, fatty acids, cholesteryl esters, sphingolipids, ceramides, di- and triacylglycerols, performing essential roles in platelet structural maintenance, and signal transduction in activation, inflammation, and hemostasis [5,12].

Platelet-lipid interplay regulates circulatory lipid levels, and intraplatelet lipid repertoire [4]. Platelet activation is associated with significant changes in membrane lipids. Platelets express scavenger receptors for Low-Density Lipoprotein (LDL), through which platelet activation status could be regulated by plasma lipids [13]. Platelets from patients with hyperlipidemia show increased secretion, aggregation, and enhanced superoxide generation. Intraplatelet lipid levels are increased in patients with cardiovascular diseases (CVD), suggesting that platelet-lipid associations may enhance thrombo-inflammatory reaction[12]. Consistently, antiplatelet therapies also influence lipid metabolism [14,15].

In our study, we collected the platelet indices and lipid levels in patients with type 2 diabetes, and further investigated the role of blood and lipid indices on the severity and prognosis of DFU. Our study aims to distinguish the sensitive laboratory indicators for patients with type 2 diabetes who have high risk of developing DFU, and to look for methods in prevention of the development and worsening of DFU.

Methods

Patients' characteristics

In our study, we included 201 patients with type 2 diabetes without DFU (126 men and 75 women; 33-88 years old; median age, 61 years), 53 patients with DFU (33 men and 20 women; 40-84 years old; median age, 66 years), and 132 age and gender-matched normal controls (93 men and 39 women; 25-89 years old; median age, 62 years) between January 2019 and June 2020 at Qilu hospital and Jinan Second People's Hospital. Follow-ups were initiated at the date of sample collection and ended in July 2021 or at the date of death. Patients were excluded if they had active infectious diseases other than foot ulcers, hematological disorders, malignancies, and autoimmune diseases. This study was performed in accordance with the ethical guidelines and was approved by the ethics committees of the two hospitals. Informed consents were obtained from all participants before participation in the study.

Analysis of blood indices and lipid levels

Peripheral blood samples were obtained from patients with or without DFU, and normal controls. WBC count, neutrophil count, lymphocyte count, platelet count, MPV, PDW, and PCT were measured routinely by using Beckman Coulter LH 780 hematology analyzer (Beckman Coulter, Brea, CA, USA) according to the manufacturer's instructions. Lipid levels including triglyceride (TG), cholesterol, LDL, and high-density lipoprotein (HDL) were collected as part of routine clinical practice.

Statistical analysis

Statistical analysis was performed using SPSS version 20 software. All data were expressed as means ± SEM or medians with interquartile ranges. The continuous variables were compared using Student t-test, Kruskal Wallis test, or Mann-Whitney test. Categorical variables were compared using the Chi-square test. Correlations were analyzed using multivariate logistic regression analysis. *P* values < 0.05 were statistically significant.

Results

Evaluation of blood indices and lipid levels in diabetes

We compared the blood indices and lipid levels among patients with type 2 diabetes without DFU, patients with DFU, and normal controls **(Table 1)**. Platelet count, WBC count, and neutrophil count were higher in patients with DFU, compared to those in patients without DFU, and normal controls **(Figure 1A, E, F)**. Patients with DFU had higher levels of PCT compared to patients without DFU, and normal controls **(Figure 1B)**. Lower PDW levels were observed in patients with type 2 diabetes compared to those in normal controls **(Figure 1C)**. Patients without DFU had higher MPV levels than normal controls, while MPV in patients with DFU did not significantly differ from that of normal controls **(Figure 1D)**. Furthermore, lymphocyte count was lower in patients with DFU, and thus the levels of Neutrophil to Lymphocyte Ratio (NLR) and Platelet to Lymphocyte Ratio (PLR) were higher in patients with DFU, compared to those in patients without DFU, and normal controls (Figure 1G-I). Patients with DFU possessed lower cholesterol and TG levels compared to patients without DFU **(Figure 1J, K)**. Higher HDL levels were observed in normal controls than those in patients with type 2 diabetes **(Figure 1L)**.

Blood and lipid indices in foot ulcers with bacterial infection

One of the important factors related to the severity of DFU is infection on foot ulcers. Patients with DFU had poor vascular circulation and were painless, thus making them prone to injury and delayed recovery. Patients with DFU enrolled in the hospitals were routinely given a bacteria culture of secretion to guide anti-bacterial treatment. We divided the patients into bacteria positive and bacteria negative groups according to the bacteria culturing results. There were 64.2% of patients with DFU positive in bacteria culturing. It was shown that platelet count, WBC count, neutrophil count, PCT levels, and PLR levels were significantly higher in patients positive in bacteria culturing compared to those in patients negative in bacteria culturing on foot ulcers. More patients were smoking in the bacteria positive group. HDL levels were significantly lower in patients with bacterial infection than those in patients without bacterial infection. We didn't observe an obvious difference in other lipid levels between the two groups of patients **(Table 2)**.

Blood and lipid indices in delayed healing of DFU

In our 1-year follow-up, 20 patients healed and lived without foot ulcers, and 26 patients still suffered from foot ulcers, among which, 9 patients received amputation. Two patients died and 5 patients were lost of follow-up. We analyzed the influence factors for the prognosis of DFU. Patients with unhealed foot ulcers possessed higher WBC and neutrophil levels, and lower PLR levels compared to patients with healed foot ulcers. For lipid indices, higher TG levels and lower HDL levels were observed in patients with nonhealing foot ulcers **(Table 3)**. Smoking rate was higher in patients with nonhealing foot ulcers although the difference was not significant (P = 0.077).

High WBC count was associated with the severity of DFU

We grouped the severity of foot ulcers using Wagner-Meggitt classification [16]. Patients whose Wagner scores lower than 3 had decreased WBC and neutrophil levels, which is in accordance with the patients who were in bacteria negative group or had better healing ulcers after treatments. Interestingly, male patients turned to have higher Wagner scores **(Table 4)**.

Correlation of blood indices and lipid levels in patients with DFU

We analyzed the correlation of the platelet indices and lipid levels in patients with DFU **(Supplemental table 1)**. Platelet count was positively correlated with PCT and TG levels. Negative correlation was found in PCT and HDL levels. Among lipid indices, cholesterol was significantly correlated with TG, LDL, and HDL levels. No significant associations were found in LDL with platelet indices.

Anti-thrombotic or lipid-lowering interventions were not found to influence the prognosis of DFU

Among the patients with DFU we enrolled, 69.8% of them had comorbidities with metabolic syndromes such as hypertension (n = 31), atherosclerosis (n = 15), or hyperlipidemia. These patients received anti-thrombotic and anti-lipid medications besides regular treatments for type 2 diabetes. We investigated the influence of aspirin, clopidogrel, cilostazol, statins, and the regular anti-diabetic treatments such as insulin and metformin, on the severity and prognosis of DFU. No significant influence was found of these anti-thrombotic and anti-lipid drugs on the Wagner score, amputation rate, and the healing of foot ulceration (Supplemental table 2-4). However, among the regular anti-diabetic treatments, insulin was found to promote higher Wagner scores in these patients (Supplemental table 2). Metformin treatment did not have influences on prognosis of DFU.

Table 1: Baseline characteristics of patients with type 2 diabetes and normal controls.

Variables	T2DM	DFU	Normal	*P* values
Age (Years) (mean ± SE)	60.25 ± 0.60	63.92 ± 1.33	61.29 ± 0.55	0.073
Gender (male, %)	126 (62.7)	33 (62.3)	93 (70.5)	0.306
Platelet count (×10^9/L) (mean ± SE)	220.98 ± 3.44	285.53 ± 1.33	229.11 ± 3.48	< 0.0001****
WBC (×10^9/L) (median, IQR)	5.91 (2.35)	7.81 (5.55)	6.12 (1.46)	< 0.0001****
Neutrophils (×10^9/L) (median, IQR)	3.5 (1.59)	5.57 (4.52)	3.55 (1.42)	< 0.0001****
Lymphocytes (×10^9/L) (median, IQR)	1.73 (0.84)	1.44 (0.78)	1.90 (0.76)	< 0.0001****
MPV (mean ± SE)	9.81 ± 0.08	9.51 ± 0.16	9.49 ± 0.07	0.016*
PCT (mean ± SE)	0.22 ± 0.01	0.27 ± 0.11	0.22 ± 0.03	< 0.0001****
PDW (mean ± SE)	14.88 ± 0.15	15.10 ± 0.23	15.60 ± 0.12	0.003**
NLR (median, IQR)	1.95 (1.07)	3.75 (3.67)	1.84 (0.95)	< 0.0001****
PLR (median, IQR)	119.19 (63.16)	180.74 (165.97)	115.86 (49.14)	< 0.0001****
Cholesterol (mean ± SE)	4.63 ± 0.09	4.07 ± 0.13	4.51 ± 0.08	0.007**
TG (mean ± SE)	1.96 ± 0.13	1.31 ± 0.08	1.28 ± 0.06	< 0.0001****
LDL (mean ± SE) (mean ± SE)	2.51± 0.07	2.35 ± 0.10	2.56 ± 0.07	0.335
HDL (mean ± SE)	1.18 ± 0.30	1.06 ± 1.22	1.36 ± 0.04	< 0.0001****

WBC: White Blood Cell; **MPV:** Mean Platelet Volume; **PCT:** Plateletcrit; **PDW:** Platelet Distribution Width; **NLR:** Neutrophil To Lymphocyte Ratio; **PLR:** Platelet To Lymphocyte Ratio; **TG:** Triglyceride; **LDL:** Low-Density Lipoprotein; **HDL:** High-Density Lipoprotein.
*P < 0.05, **P < 0.01, ****P < 0.0001

Table 2: Baseline characteristics in patients with or without bacterial infection on DFU.

Variables	Bacteria negative (n = 19)	Bacteria positive (n = 34)	*P* values
Age (Years) (mean ± SE)	65.53 ± 2.54	63.79 ± 1.51	0.534
Gender (male, %)	13 (68.4)	20 (58.8)	0.489
Smoking (number)	10	13	0.042*
Platelet count (×10^9/L) (mean ± SE)	243.2 ± 17.13	311.9 ± 17.57	0.013*
WBC (×10^9/L) (median, IQR)	6.45 (3.90)	8.68 (6.65)	0.014*
Neutrophils (×10^9/L) (median, IQR)	4.79 (3.79)	6.27 (6.66)	0.006**
Lymphocytes (×10^9/L) (median, IQR)	1.44 (1.04)	1.44 (0.68)	0.476
MPV (mean ± SE)	9.91 ± 0.21	9.32 ± 0.21	0.076
PCT (mean ± SE)	0.24 ± 0.017	0.29 ± 0.015	0.043*
PDW (mean ± SE)	15.34 ± 0.32	14.96 ± 0.32	0.44
NLR (median, IQR)	3.55 (3.06)	4.39 (6.27)	0.057
PLR (median, IQR)	136.63 (122.37)	199.04 (181.43)	0.043*
Cholesterol (mean ± SE)	4.27 ± 0.23	3.97 ± 0.15	0.255
TG (mean ± SE)	1.29 ± 0.12	1.33 ± 0.11	0.794
LDL (mean ± SE)	2.41 ± 0.18	2.32 ± 0.12	0.65
HDL (mean ± SE)	1.20 ± 0.08	0.99 ± 0.05	0.022*

WBC: White Blood Cell; **MPV:** Mean Platelet Volume; **PCT:** Plateletcrit; **PDW:** Platelet Distribution Width; **NLR:** Neutrophil To Lymphocyte Ratio; **PLR:** Platelet To Lymphocyte Ratio; **TG:** Triglyceride; **LDL:** Low-Density Lipoprotein; **HDL:** High-Density Lipoprotein.
*P < 0.05, **P < 0.01

Table 3: Clinical characteristics for different prognostic outcomes of patients with DFU.

Variables	Heal (n = 20)	Not heal (n = 26)	*P* values
Age (Years) (mean ± SE)	65.53 ± 2.54	63.79 ± 1.51	0.518
Gender (male, %)	17 (65.4)	12 (60)	0.708
Smoking (number)	10	13	0.077
Platelet count (×10^9/L) (mean ± SE)	277.7 ± 23.53	282.6 ± 19.7	0.874
WBC (×10^9/L) (median, IQR)	7.07 (3.32)	7.92 (7.35)	0.031*
Neutrophils (×10^9/L) (median, IQR)	5.14 (3.25)	5.57 (7.41)	0.025*
Lymphocytes (×10^9/L) (median, IQR)	1.42 (0.94)	1.48 (0.84)	0.722
MPV (mean ± SE)	9.48 ± 0.26	9.69 ± 0.24	0.555
PCT (mean ± SE)	0.26 ± 0.02	0.27 ± 0.02	0.578
PDW (mean ± SE)	15 ± 0.37	14.94 ± 0.38	0.905
NLR (median, IQR)	3.55 (2.90)	4.45 (5.86)	0.159
PLR (median, IQR)	162.96 (164.98)	179.96 (152.50)	0.0309*
Cholesterol (mean ± SE)	4.05 ± 0.19	4.13 ± 0.20	0.781
TG (mean ± SE)	1.06 ± 0.08	1.45 ± 0.13	0.023*
LDL (mean ± SE)	2.35 ± 0.17	2.37 ± 0.15	0.934
HDL (mean ± SE)	1.18 ± 0.08	0.99 ± 0.06	0.046*

WBC: White Blood Cell; **MPV:** Mean Platelet Volume; **PCT:** Plateletcrit; **PDW:** Platelet Distribution Width; **NLR:** Neutrophil To Lymphocyte Ratio; **PLR:** Platelet To Lymphocyte Ratio; **TG:** Triglyceride; **LDL:** Low-Density Lipoprotein; **HDL:** High-Density Lipoprotein.
*P < 0.05

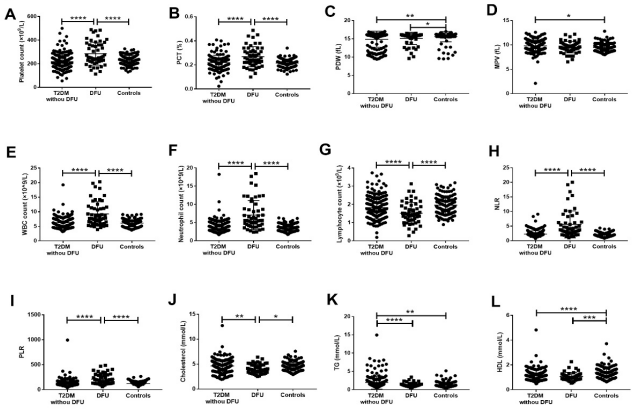

Figure 1: Blood and lipid indices in patients with type 2 diabetes (T2DM) and normal controls. **(A, B)** Platelet count and PCT levels were higher in patients with DFU, compared to those in patients without DFU and normal controls. **(C)** PDW levels were lower in patients with type 2 diabetes compared to those in normal controls. **(D)** Patients without DFU had higher MPV levels than normal controls. **(E-G)** WBC and neutrophil count were higher, and lymphocyte count was lower in patients with DFU, compared to those in patients without DFU, and normal controls. **(H, I)** Patients with DFU possessed higher NLR and PLR levels compared to patients without DFU, and normal controls. **(J)** Cholesterol levels were significantly lower in patients with DFU compared to those in patients without DFU, and normal controls. **(K)** Higher TG levels were observed in patients without DFU compared to those in patients with DFU, and normal controls. **(L)** Normal controls had higher HDL levels compared to patients with type 2 diabetes.

Table 4: Characteristics of patients between low- or high-risk DFU assessed by Wagner scores.

Variables	Wagner < 3 (n = 22)	Wagner ≥ 3 (n =31)	*P* values
Age (Years) (mean ± SE)	64.68 ± 1.94	64.23 ± 1.81	0.867
Gender (male, %)	10 (45.5)	23 (74.2)	0.033*
Smoking	17	6	0.219
Platelet count (×10^9/L) (mean ± SE)	256.6 ± 17.21	307.3 ± 18.74	0.065
WBC (×10^9/L) (median, IQR)	6.65 (2.21)	10.99 (6.44)	0.0001***
Neutrophils (×10^9/L) (median, IQR)	4.87 (1.35)	7.03 (6.66)	0.0001***
Lymphocytes (×10^9/L) (median, IQR)	1.39 (0.90)	1.48 (0.81)	0.488
MPV (mean ± SE)	9.80 ± 0.26	9.35 ± 0.19	0.161
PCT (mean ± SE)	0.25 ± 0.02	0.29 ± 0.016	0.121
PDW (mean ± SE)	15.57 ± 0.23	14.76 ± 0.36	0.087
NLR (median, IQR)	3.16 (2.99)	4.69 (5.90)	0.059
PLR (median, IQR)	163.95 (98.35)	198.48 (189.12)	0.505
Cholesterol (mean ± SE)	4.12 ± 0.23	4.04 ± 0.15	0.775
TG (mean ± SE)	1.43 ± 0.15	1.23 ± 0.09	0.233
LDL (mean ± SE)	2.32 ± 0.14	2.38 ± 0.14	0.776
HDL (mean ± SE)	1.09 ± 0.06	1.05 ± 0.06	0.0634

WBC: White Blood Cell; **MPV:** Mean Platelet Volume; **PCT:** Plateletcrit; **PDW:** Platelet Distribution Width; **NLR:** Neutrophil To Lymphocyte Ratio; **PLR:** Platelet To Lymphocyte Ratio; **TG:** Triglyceride; **LDL:** Low-Density Lipoprotein; **HDL:** High-Density Lipoprotein.
*P < 0.05, ***P < 0.001

Discussion

It was estimated that up to 25% of patients with type 2 diabetes develop foot ulcers during their lifetime. Nonhealing ulcers are responsible for 85% of nontraumatic lower extremity amputation [2,17]. Treatment for DFU costs excess burden and lowers the life quality in patients with type 2 diabetes. Identifying the early risk factors in the development of DFU is of great importance in promoting better prognosis in patients with type 2 diabetes.

Increasing studies have revealed that dyslipidemia is an important contributing factor for not only macrovascular, but also microvascular complications of diabetes, including neuropathy and retinopathy [18]. Limited studies have investigated the correlation between dyslipidemia and DFU. DFU arises from poor microvascular circulation and neuropathy, and is associated with cardiovascular disease (CVD) and excess mortality. It has been reported that lipid-lowering therapy, such as statins, could reduce CVD morbidity and mortality in patients with DFU [19]. In addition, statins could also benefit the microvascular complications and peripheral neuropathy of diabetes, lowering the extremity amputation risk of patients with DFU [17,18,20]. Therefore, lipid metabolism has a great influence on the development, severity, and healing of DFU. In our study, we compared the lipid levels of patients with DFU, patients without DFU, and healthy candidates. Patients without DFU had higher levels of cholesterol and TG compared to those in patients with DFU. HDL levels were decreased in patients with type 2 diabetes compared to those in normal controls. We further analyzed the correlation of lipid levels with severity, infection, and prognosis of DFU. Our study revealed that dyslipidemia, especially low

HDL levels were correlated with increased infection risk and retardation of healing in DFU.

Infection is one of the most common complications of DFU, resulting in lower extremity amputations and early mortality. Surgical intervention and amputation are sometimes inevitable for the infection control [21]. Thus, wound infection is a critical predictor for poor wound healing and amputation [22]. Early recognition and appropriate treatment with antibiotics is imperative to improve outcomes[23]. The platelet interaction with neutrophils is central in initiating the immune response [6]. Our study revealed that patients with DFU had higher platelet counts, PCT levels, WBC count, neutrophil count, NLR and PLR levels, and lower lymphocyte count compared to patients without DFU and normal controls, indicating that patients with DFU were in an inflammatory state. Patients with nonhealing DFU and Wagner scores over 3 had higher WBC and neutrophil counts. It was reported that PLR was a prognostic marker for inflammation, and could be a predicative factor for high-risk DFU [3,24]. In our study, increased PLR and TG levels, and decreased HDL levels were observed in patients with Wagner scores higher than 3, indicating inflammation and dyslipidemia had great influence on the severity and poor prognosis of DFU. According to the bacteria culture results, we divided the patients with DFU into bacteria positive and bacteria negative groups. Patients with bacterial infection on foot ulcers had higher platelet, WBC, and neutrophil counts, higher PCT and PLR levels, and lower HDL levels compared to patients negative in bacteria culturing. These observations further validated the intercorrelation of infection and dyslipidemia in DFU.

The platelet-lipid interplay regulates both intra- and extra-platelet lipid metabolism and platelet activation, influencing inflammatory responses. We observed that patients with DFU had dysregulated lipid and blood indices. Here we analyzed the correlation between blood indices and lipid levels in patients with DFU. Platelet count was positively correlated with PCT and TG levels. Furthermore, PCT was negatively correlated with HDL levels. Thus, the platelet-lipid interaction may play an important role in the development of DFU.

Cigarette smoking is a risk factor for macrovascular disease, and causes an early death due to the development of macrovascular complication in type 2 diabetes [25]. Furthermore, smoking also contributes to microvascular complications in type 2 diabetes [26]. In the present study, patients with bacterial infection or nonhealing DFU after 1-year follow-up had higher smoking prevalence. Although we didn't observe a significant correlation between smoking and Wagner scores, we found that male patients had higher Wagner scores compared to female patients. The smoking rate in men patients is 69.7%, which is much higher than that in women patients (5%). Therefore, smoking cessation can not only lower the macrovascular complications in type 2 diabetes, but also be favorable in the prevention and healing of DFU.

It was found that insulin use, hyperlipidemia were risk factors for DFU [27,28]. Our study demonstrated that insulin use was associated with higher Wagner scores, but it did not affect the healing or amputation rate in DFU. Antithrombotic and lipid-lowering drugs were regularly used in treatment for peripheral artery diseases [29]. It was reported that patients with DFU who used cilostazol had better prognosis in the healing and remission of peripheral artery symptoms compared to aspirin. However, in our study, these medications were not yet found to have significant effects in lowering the severity or promoting the prognosis of DFU. Anti-thrombotic and lipid lowering therapies were not commonly used for treatment of the diabetic foot patients. Most of the patients received aspirin and statins had comorbidities with CVD. Few patients received cilostazol (n = 3) for treatment of DFU; therefore, larger cohort was needed for further investigations on these anti-thrombotic and lipid-lowering drugs in treatment of DFU. Still, medications targeting peripheral vascular diseases can be of great importance in treatments of DFU besides regular anti-diabetic therapies.

Our study demonstrated that bacterial infection on foot ulcers, dyslipidemia, and smoking were important risk factors for the development and progression of DFU. Medications on peripheral vascular diseases such as anti-thrombotic and lipid-lowering drugs, and lifestyle interventions were important methods for better prognosis of DFU.

Data availability

Data are available upon request.

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Conflict of interest

The authors declare that they have no conflicts of interest.

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