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Association between vitamin D status and diabetic foot in patients with type 2 diabetes mellitus

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ABSTRACT

Aims/Introduction: To assess the association between vitamin D and diabetic foot (DF) in patients with type 2 diabetes mellitus (T2DM), in order to summarize clinical evidence in the prevention and treatment of DF.

Materials and methods: Between January 2012 and December 2019, a total of 1,721 hospitalized patients with type 2 diabetes mellitus were continuously enrolled in West China Hospital, Sichuan University, and divided into DF and non-DF groups according to whether they had DF, and divided into four subgroups according to the admission season. The 25-OH-vitamin D levels were compared between groups and subgroups, and independent risk factors discussed for the occurrence of DF.

Results: The vitamin D insufficiency and deficiency rate were higher in the DF group (77.51%) than in the non-DF group (59.2%). The 25-OH-vitamin D levels were lower in the DF group (35.80 nmol/L) than in the non-DF group (45.48 nmol/L) ($P < 0.001$). Patients with poor glycemic control had lower 25-OH-vitamin D levels ($P = 0.01$). The levels of 25-OH-vitamin D were lower in winter and spring. In the same season, the levels of 25-OH-vitamin D in patients with DF were still lower ($P < 0.001$). The 25-OH-vitamin D levels of patients with Wagner grades 0 to 5 showed a downward trend ($P = 0.114$). The 25-OH-vitamin D level was independently associated with diabetic foot ($P < 0.001$, OR = 0.986).

Conclusions: The low serum vitamin D level was significantly associated with a higher prevalence of DF among Chinese patients with type 2 diabetes mellitus. Although vitamin D levels vary seasonally, patients with DF were always at higher risk of having vitamin D insufficiency and deficiency.

INTRODUCTION

Diabetic foot (DF) is one of the most severe and painful chronic complications of diabetes mellitus. Poor wound healing leads to high hospitalization, high rates of lower extremity amputation, and also increases the risk of disability and mortality in patients with diabetes[1,2]. It has been estimated that the annual incidence of DF is about 2.4–2.6%[3]. There is a high prevalence of 3-year recurrence in patients with healed foot ulcers, which exceeds 50%[4]. Thus, diabetic foot has become a great burden on public health.

Vitamin D, a pleiotropic steroid hormone, is essential to the metabolism of calcium and phosphorus and the regulation of bone turnover. Moreover, it is known to participate in inflammatory response, immune function, the regulation of cell cycle, as well as multiple chronic diseases, including diabetes and its complications[5,6] In addition, vitamin D is correlated with HbA1c levels in diabetic patients[7] and low vitamin D levels also have been reported to be associated with low muscle strength[8]. About one billion people are facing vitamin D deficiency all over the world, mainly in the Middle East, China, Mongolia, and India[9]. It is worthy of note that the proportion is even higher in winter[10].

In the past few years, an inverse association between vitamin D levels and the occurrence and development of type 2 diabetes mellitus has been demonstrated[11–13]. Pena *et al.* studied the micronutrient status in diabetic patients with foot

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ulcers, which have revealed that vitamin D deficiency was the most common situation in patients with diabetic foot[14]. A number of preclinical evidence, as well as observational studies have reported a positive contribution of vitamin D to wound healing. However, whether vitamin D is associated with the occurrence and development of diabetic foot (DF) remains controversial.

More importantly, large-scale epidemiological studies on the association of vitamin D levels and diabetic foot among the Chinese population are scarce[11,15]. Thus, it is necessary to evaluate the association of vitamin D levels and diabetic foot among the large Chinese population. The primary aim of this study was to explore the prevalence of vitamin D deficiency, and to address the association between serum 25-OH-vitamin D levels and DF in a Chinese hospitalized type 2 diabetes mellitus population, in order to summarize clinical evidence in the prevention and treatment of DF.

METHODS

Patients recruitment, grouping situation and ethical consideration

We recruited 1,721 consecutive inpatients, including 547 patients with DF (DF group) and 1,174 patients without DF (non-DF group), from January 2012 to December 2019 at the Department of Endocrinology and Metabolism, West China Hospital, Sichuan University. The Biomedical Research Ethics Committee of West China Hospital of Sichuan University approved the study protocol, and the application for exemption of informed consent was passed. The diagnostic criteria of type 2 diabetes mellitus and diabetic foot were based on the American Diabetes Association classification[16] and the World Health Organization[17]. Only patients aged ≥18 years were included in this study. The exclusion criteria were as follows: (1) with other types of diabetes; (2) pregnant or lactating females; (3) with acute complications of diabetes or other stress states, such as surgery and trauma; (4) with rheumatologic, serious hepatic, cardiac, renal failure, malignancy, and endocrine diseases that affect the metabolism of vitamin D. Admission from December to May of each year was regarded as admission in winter and spring, and admission from June to November each year was regarded as admission in summer and autumn. Based on the above, the subjects were divided into two groups and four subgroups. The group assignment of population is presented in Figure 1.

Clinical and biochemical characteristics and vitamin D assessments

Demographics, comorbidities, and laboratory data were extracted from the electronic medical record system. The demographics included age, sex, body mass index (BMI), duration of diabetes, and smoking. The severity of diabetic foot was assessed by Wagner classification. The laboratory measurements collected included 25-OH-vitamin D, glycated hemoglobin (HbA1c), triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), albumin (ALB), creatinine (Cr), estimated glomerular filtration rate (eGFR), and serum uric acid (UA).

It was worth noting that the electrochemiluminescence immunoassay (Roche Cobas e601 analyzer) was used to determine the total serum 25-OH-vitamin D concentration and the functional sensitivity was 10.03 nmol/L. Combining the recommendations of the Institute of Medicine (IOM)[18], the US Endocrine Society[19] and the latest evaluation results of vitamin D levels worldwide in 2020[20,21], in this study, a serum level of 25-OH-vitamin D ≥ 50 nmol/L was defined as normal, 30 nmol/L ≤ 25-OH-vitamin D < 50 nmol/L as vitamin D insufficiency (VDI), and serum 25-OH-vitamin D < 30 nmol/L as vitamin D deficiency (VDD).

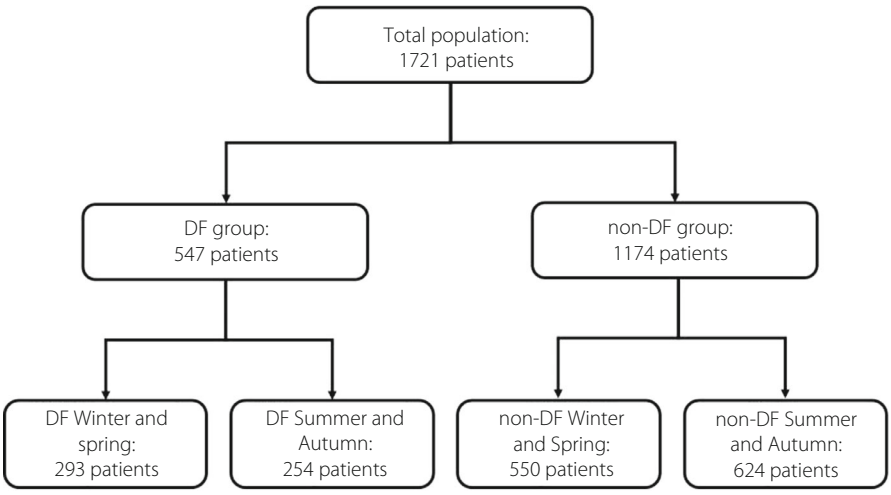

Figure 1 | Flow chart showing the grouping situation for study subjects. In the diabetic foot group, 293 patients were admitted in winter and spring, and 254 patients were admitted in summer and autumn. In the non-DF group, 550 patients were admitted in winter and spring, and 624 patients were admitted in summer and autumn.

Table 1 | Demographic and clinical characteristics in the two groups

	Total (n = 1721)	DF group (n = 547)	non-DF group (n = 1174)	P
Age	66 (57, 74)	67 (59, 75)	66 (56, 74)	0.001
BMI	24.16 (21.97, 26.67)	23.31 (21.48, 25.39)	24.52 (22.27, 27.10)	<0.001
Gender				
Male	847 (49.2%)	346 (63.3%)	501 (42.7%)	<0.001
Female	874 (50.8%)	201 (36.7%)	673 (57.3%)	
Duration of type 2 diabetes mellitus				
<5 years	444 (25.8%)	100 (18.3%)	344 (29.3%)	
5–10 years	442 (25.7%)	145 (26.5%)	297 (25.3%)	<0.001
>10 years	835 (48.5%)	302 (55.2%)	533 (45.4%)	
Smoking history				
Smoking	584 (33.9%)	260 (47.5%)	324 (27.6%)	<0.001
Non-smoking	1137 (66.1%)	287 (52.5%)	850 (72.4%)	

The two groups, DF group and non-DF group; DF, diabetic foot; BMI, body mass index.

Table 2 | Laboratory characteristics in the two groups

Variable	Total (n = 1721)	DF group (n = 547)	non-DF group (n = 1174)	P
25-(OH)-VD (nmol/L)	42.03 (30.79, 55.60)	35.8 (26.19, 48.09)	45.48 (33.44, 59.25)	**<0.001**
HbA1c (%)	7.8 (6.7, 9.6)	7.8 (6.8, 9.5)	7.8 (6.6, 9.6)	0.560
TG (mmol/L)	1.37 (1.01, 1.98)	1.3 (0.98, 1.83)	1.39 (1.02, 2.06)	0.010
TC (mmol/L)	4.13 (3.40, 4.94)	3.89 (3.19, 4.72)	4.25 (3.55, 5.01)	<0.001
HDL-C (mmol/L)	1.15 (0.92, 1.42)	1.03 (0.85, 1.3)	1.19 (0.97, 1.46)	<0.001
LDL-C (mmol/L)	2.26 (1.69, 2.91)	2.12 (1.58, 2.74)	2.32 (1.75, 3)	<0.001
ALB (g/L)	41.4 (37.7, 44.4)	38.4 (34.1, 41.6)	42.6 (39.2, 45.3)	<0.001
Cr (μmol/L)	71 (58, 90.5)	83 (65, 110.7)	66 (56, 82)	<0.001
eGFR (mL/min/1.73 m^2)	85.05 (63.79, 97.45)	76.21 (54.41, 93.68)	87.57 (69.03, 99.41)	<0.001
UA (μmol/L)	328 (269, 394)	324 (252, 398)	331 (275, 391)	0.083
Ca^{2+} (mmol/L)	2.25 (2.16, 2.35)	2.21 (2.09, 2.3)	2.27 (2.18, 2.37)	<0.001

The two groups, DF group and non-DF group; DF, diabetic foot; HbA1c, glycated hemoglobin; TG, triglycerides; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; ALB, albumin; Cr, creatinine; eGFR, estimated glomerular filtration rate; UA, serum uric acid.

Statistical analysis

SPSS 18.0 software was used for statistical analyses. All continuous variables involved in this study did not conform to a normal distribution. Non-normally distributed continuous variables were reported as median and interquartile range (IQR, 25–75%) and compared by the Mann-Whitney test. The chi-square test was used for categorical variables, which were summarized by frequency counts with percentages (n/%). The multivariate regression analysis was used to identify the association between the variables. A P value below 0.05 was considered statistically significant. Graphs were drawn using GraphPad Prism 7 software.

RESULTS

Characteristics of participants and vitamin D status

The demographic, clinical, and laboratory characteristics are shown in Tables 1 and 2. The median age was 66 (IQR 57, 74) years, and 49.2% of patients were men. In the total population, 48.5% of patients had a diabetes duration of more than 10 years, and 33.9% of patients had a history of smoking. The median BMI was 24.16 (IQR 21.97, 26.67) kg/m^2, with a median glycated hemoglobin (HbA1c) level of 7.8 (IQR 6.7, 9.6) %. The vitamin D insufficiency and deficiency rate in the study population was 64.96%. The vitamin D insufficiency and deficiency rates in the DF group were higher than that in the non-DF group (77.51% vs 59.2%, P < 0.001). The vitamin D status of patients is displayed in detail in Figure 2. The median level of 25-OH-vitamin D in the total population was 42.03 (IQR 30.79, 55.60) nmol/L. The level of 25-OH-vitamin D was lower in the DF group than that in the non-DF group [35.80(IQR 26.19, 48.09) vs. 45.48(IQR 33.44, 59.25) nmol/L, P < 0.001].

Vitamin D and glycemic control

Glycemic control was classified based on HbA1c levels as either good (<7%) or poor (≥7%)[22]. Compared with those with good glycemic control (n = 531), patients with poor glycemic control

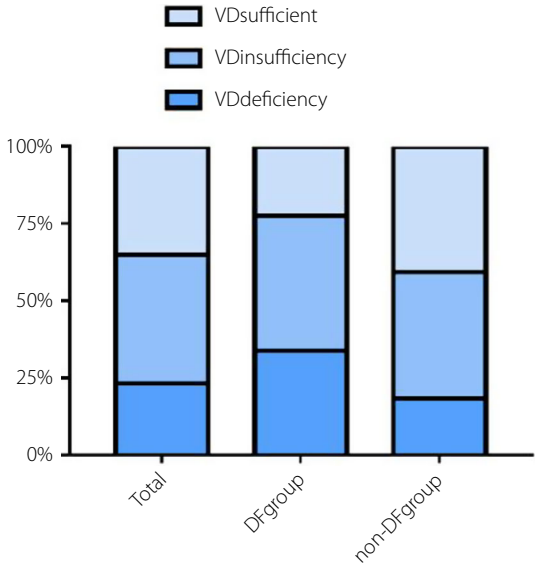

Figure 2 | Bar graphs show the prevalence rates of vitamin D sufficiency, insufficiency, and deficiency among groups. The rates of vitamin D sufficiency, insufficiency, and deficiency in the total population were respectively 35.04, 41.72, and 23.24%. The rates of vitamin D sufficiency, insufficiency, and deficiency in diabetic foot group were respectively 22.49, 43.69, and 33.82%. The rates of vitamin D sufficiency, insufficiency, and deficiency in non-DF group were respectively 40.80, 40.80, and 18.40%.

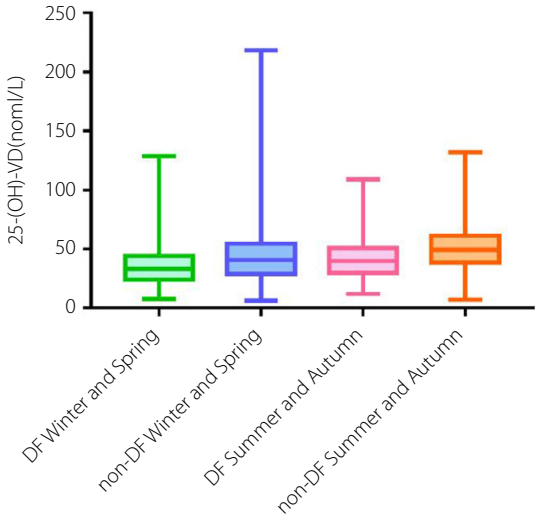

Figure 3 | Bar graphs show the serum vitamin D levels in hospitalized patients with diabetic foot and non-DF in different seasons.

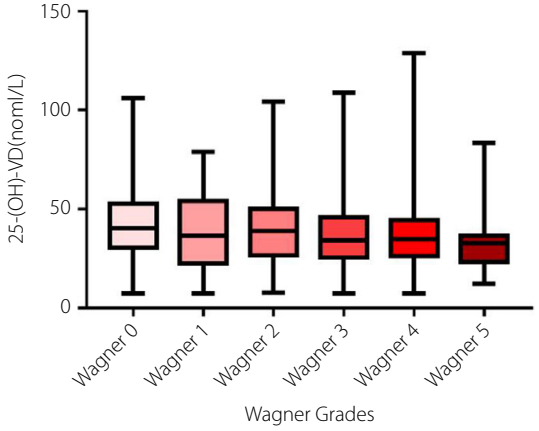

Figure 4 | Bar graphs show the serum vitamin D levels among patients with diabetic foot with different Wagner grades.

(n = 1,190) had lower 25-OH-vitamin D levels [40.98(IQR 30.17, 53.98) vs. 44.82 (IQR 32.30, 59.56) nmol/L, P = 0.01].

Seasonal fluctuation of vitamin D

As Figure 3 shows, there was a seasonal fluctuation with lower 25-OH-vitamin D levels in winter and spring than in summer and autumn. In the DF group, the vitamin D levels of those admitted in winter and spring were lower than those admitted in summer and autumn [33.05(IQR 23.86, 43.97) vs. 39.77(IQR 29.47, 50.70) nmol/L, P < 0.001]. The same was true in the non-DF group [40.47(IQR 28.48, 54.10) vs. 49.15(IQR 38.37, 61.15) nmol/L, P < 0.001]. Among those admitted in winter and spring, the vitamin D levels of the DF group were lower than that of the non-DF group [33.05(IQR 23.86, 43.97) vs. 40.47(IQR 28.48, 54.10) nmol/L, P < 0.001]. The same was true in those admitted in summer and autumn [39.77(IQR 29.47, 50.70) vs. 49.15(IQR 38.37, 61.15) nmol/L, P < 0.001].

Wagner classification and independent risk factor

As shown in Figure 4, in the DF group, the patients' vitamin D levels of Wagner grades 0–5 showed a downward trend, but the difference was not statistically significant(P = 0.114). In consideration of the effects of diabetic complications on diabetic foot and vitamin D levels, we evaluated diabetic complications in the study population, as shown in Table 3. These factors were taken into account in multivariate logistic regression analysis. Multivariate logistic regression analysis showed that 25-OH-vitamin D was independently related to diabetic foot, and it was a protective factor for DF (P < 0.001, OR = 0.986, 95% CI: 0.979–0.993), as shown in Table 4 and Figure 5. In addition, the multivariate logistic regression analysis was performed after grouping by vitamin D status (vitamin D deficiency vs. insufficiency vs. normal, and vitamin D deficiency was regarded as the control group). The results showed that patients with normal vitamin D were less likely to develop diabetic foot than those with vitamin D deficiency (P = 0.016, OR = 0.621, 95% CI: 0.421–0.915), as shown in Table 5.

DISCUSSION

This study found that the 25-OH-vitamin D levels in the DF group were significantly lower than that in the non-DF group.

Table 3 | The diabetic complications in the two groups

Variable	Total (n = 1721)	DF group (n = 547)	non-DF group (n = 1174)	P
DN, N (%)	722 (42.0%)	392 (71.7%)	330 (28.1%)	<0.001
DR, N (%)	529 (30.7%)	292 (53.4%)	237 (20.2%)	<0.001
DPN, N (%)	1139 (66.2%)	531 (97.1%)	608 (51.8%)	<0.001
PAD, N (%)	459 (26.7%)	283 (51.7%)	176 (15.0%)	<0.001
DAN, N (%)	839 (48.8%)	448 (81.9%)	391 (33.3%)	<0.001

The two groups, DF group and non-DF group; DF, diabetic foot; DN, diabetic nephropathy; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; PAD, peripheral arterial disease; DAN, diabetic autonomic neuropathy.

Table 4 | Multivariate logistic regression analysis of risk factors for diabetic foot in patients with type 2 diabetes mellitus

	OR	95% (CI)		P
		Lower limit	Upper limit	
25-(OH)-VD	0.986	0.979	0.993	**<0.001**
TG	0.745	0.652	0.852	<0.001
HDL-C	0.288	0.188	0.443	<0.001
DN	2.297	1.706	3.093	<0.001
DR	1.913	1.423	2.571	<0.001
DPN	13.49	7.729	23.546	<0.001
PAD	4.354	3.211	5.904	<0.001
DAN	4.727	3.481	6.42	<0.001
Smoking history	1.581	1.176	2.127	0.002

Did not enter the equation: age, sex, season of admission, BMI, LDL, CHOL; DF, diabetic foot; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; DN, diabetic nephropathy; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; PAD, peripheral arterial disease; DAN, diabetic autonomic neuropathy.

Moreover, the proportion of vitamin D insufficiency and deficiency in the DF group were significantly higher than in the non-DF group. In fact, Tiwari *et al.* firstly assessed the vitamin D status in patients with diabetic foot infection in India and concluded that vitamin D deficiency was more prevalent and severe in patients with diabetic foot infection than those without infection[23]. This conclusion was confirmed in their subsequent research[24]. Meanwhile, they reported that severe vitamin D deficiency was associated with elevated inflammatory cytokine concentrations and suggested a vitamin D concentration value of <25 nmol/L as the 'cut-off' for unfavorable immunological alterations in diabetic patients. Since then, several observational studies have been reported in succession. However, the results of these studies have been inconsistent. Also in India, the difference in the serum level of vitamin D between diabetic patients with and without foot infections was not found to be statistically significant in a cross-sectional study reported in 2019[25]. A similar conclusion has also been drawn by a recent study conducted in a Mediterranean country[26]. Nevertheless, Afarideh *et al.*[27] came to contrary conclusions in Iranian patients. Similar observational studies have been done in Europe[28,29] and the results show that patients with diabetic foot syndrome are at high risk of low vitamin D levels. At present, there have been only two research studies conducted in China[11,15], and only one had a relatively large sample capacity[11]. It is worth mentioning that both of their findings are in accordance with ours. Moreover, our multivariate logistic regression analysis likewise revealed that vitamin D was an independent risk factor for diabetic foot and might have some level of protective effect on the occurrence of diabetic foot. However, the amplitude (OR = 0.986) was very small and false-positive results cannot be ruled out, when we regarded vitamin D as a continuous variable. But when we grouped vitamin D status into vitamin D normal/insufficiency/deficiency groups, the results still showed that a normal vitamin D level was a protective factor for diabetic foot compared with vitamin D deficiency (P = 0.016, OR = 0.621, 95% CI: 0.421–0.915).

However, aside from the study conducted in Hunan and our study, the sample sizes of most existing studies are relatively small. Thus, the persuasiveness of these conclusions is open to question and the exact relationship between vitamin D and diabetic foot is still confusing. In spite of this contradiction, the abundance of preclinical data also tend to the favorable effects of vitamin D on diabetic foot until now, especially on wound healing[30–39]. Vitamin D may be involved in the wound healing by the following means: (1) regulates inflammation during wound healing through interacting with the TGF-β signaling pathway to promote the normal inflammatory response[30] and suppresses NF-κB-mediated inflammatory gene expression to reduce the persistent inflammation[31], just as observed in the study of Tiwari[24]; (2) has an effect on vascular regeneration through promoting SDF1 expression by increasing hypoxia-inducible factor signaling[32] and augmenting proangiogenic factors, such as VEGFA, HIF-1α and angiogenin gene expression[33]; (3) may be involved in the self-renewal, migration, and differentiation of epidermal stem cells and progeny to promote wound re-epithelialization[34,35]; (4) induce the antimicrobial peptide gene expression[36,37] and suppress endoplasmic reticulum stress[38] and oxidative stress[39]; (5) may play an indirect role during wound healing due to its effect on improving glycemic control[40]. We reported a lower level of 25-OH-vitamin D in patients with poor glycemic control when compared with good glycemic control patients, which was consistent with the results

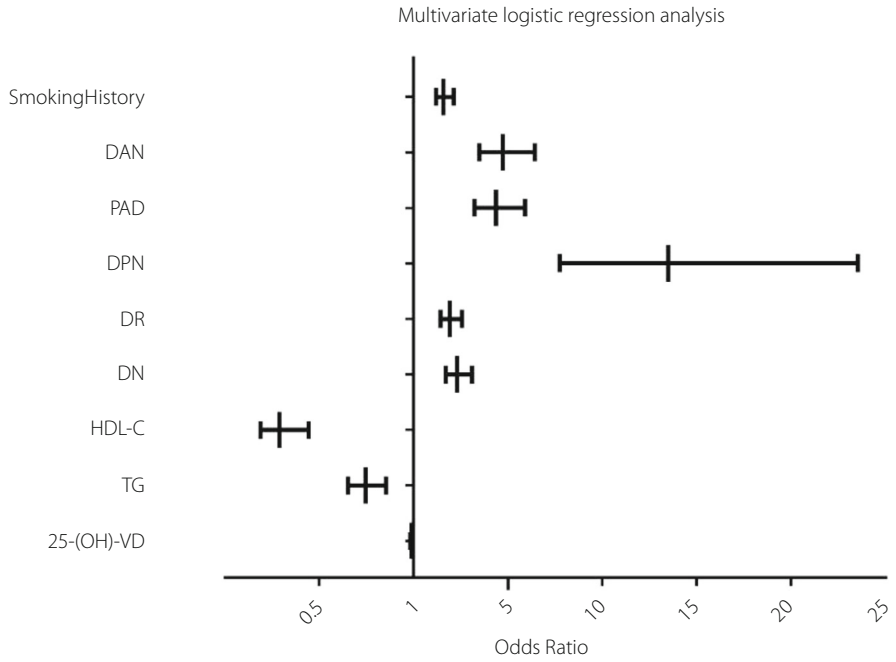

Figure 5 | Forest map shows the results of the multivariate logistic regression analysis. The 25-OH-vitamin D was independently related to diabetic foot, and it was a protective factor for diabetic foot ($P < 0.001$, OR = 0.986, 95% CI: 0.979–0.993).

Table 5 | Multivariate logistic regression analysis of risk factors for diabetic foot in patients with type 2 diabetes mellitus

	OR	95% (CI)		*P*
		Lower limit	Upper limit	
VD grade				**0.019**
VD grade 2	0.961	0.676	1.366	0.823
VD grade 3	0.621	0.421	0.915	**0.016**
Admission time	0.745	0.558	0.995	0.046
TG	0.751	0.657	0.858	<0.001
HDL-C	0.282	0.184	0.433	<0.001
DN	2.376	1.762	3.204	<0.001
DR	1.959	1.457	2.636	<0.001
DPN	13.334	7.643	23.262	<0.001
PAD	4.354	3.208	5.909	<0.001
DAN	4.676	3.442	6.351	<0.001
Smoking history	1.575	1.169	2.121	0.003

Did not enter the equation: age, sex, BMI, LDL, CHOL; DF, diabetic foot; VD grade: vitamin D deficiency and it was regarded as the control group; VD grade 2: vitamin D insufficiency; VD grade 3: vitamin D normal; admission time: season of admission; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; DN, diabetic nephropathy; DR, diabetic retinopathy; DPN, diabetic peripheral neuropathy; PAD, peripheral arterial disease; DAN, diabetic autonomic neuropathy.

of Darraj *et al*[41]. That is to say, the positive contribution of vitamin D on glycemic control is also supported in our study. Therefore, from the pathophysiological mechanism, patients with type 2 diabetes with vitamin D deficiency are more likely to suffer from diabetic foot ulcer. In other words, we could regard vitamin D deficiency as the causative factor of the development of diabetic foot ulcer. On the other hand, patients who already have diabetic foot are associated with an increased risk of aggravating vitamin D deficiency due to long periods of being bedridden, immobilization of the affected limb, less physical exercise, decreased nutritional status, and other reasons. However, the causal relationship between vitamin D and diabetic foot is unclear. From current studies, we hold the opinion that diabetic foot and vitamin D level have an effect on each other.

As is well known, the vitamin D concentrations vary strongly by season[42]. To our knowledge, this is the first study to assess the seasonal fluctuation of vitamin D among patients with diabetic foot. We found a seasonal fluctuation of vitamin D with lower levels in winter and spring, particularly in patients with diabetic foot. Moreover, the vitamin D levels were also lower in the DF group during the same season when compared with patients without diabetic foot. Vitamin D is mainly derived from the synthesis in the skin under ultraviolet B exposure. Because of this, numerous factors could cause significant effects on vitamin D levels, such as season, time of day, latitude, altitude, air pollution, skin pigmentation, sunscreen use, and the rays passing through glass and plastic[43]. This may be part of the reason for the inconsistent results of current studies. Therefore, it is necessary to screen the vitamin D status of type 2 diabetes mellitus patients in winter and spring, especially those

with diabetic foot. Besides, it could be of significance to advise timely vitamin D supplementation.

On the other hand, it was found that as the Wagner grade increases, the 25-OH-vitamin D levels of patients with diabetic foot showed a gradual, yet not significant, downward trend. It may be due to factors such as wound size, location, depth, infection, secretions, and treatment not being taken into account in the assessment of the severity of diabetic foot[44].

Until now, only two randomized controlled trials have been done showing that supplementation of vitamin D could promote wound healing in DF patients[45,46]. Our study revealed that the vitamin D level in DF patients with type 2 diabetes mellitus was lower than those without diabetic foot. So, this gives us a hint that vitamin D supplementation may be a potential adjunctive therapeutic option for diabetic foot. In other words, preventing vitamin D deficiency and keeping appropriate levels of vitamin D could be helpful for the prevention and adjuvant treatment of diabetic foot. Based on the above, although there are contradictory results[25–27], a large number of studies and meta-analyses still show a clear connection between low vitamin D levels, vitamin D deficiency, and diabetic foot[11,15,23,24,28,29,47,48]. Although this connection does not mean necessarily correlation or causal connection, it also has great significance for the treatment and management of diabetic foot. Moreover, the screening of vitamin D levels in diabetic patients could assess the risk of diabetic foot to a certain extent.

There are a few limitations in this study. Firstly, we only included Chinese adults from West China Hospital, Sichuan University, who were Asian. This conclusion may not generalizable to other races or regions. Secondly, although the study population included were all inpatients, differences in outdoor activities and sun exposure between patients with and without diabetic foot were avoided to some extent. For all we know, patients with diabetic foot are bedridden for long periods as a result of the immobilization of the affected limb. Unfortunately, our results may not be applicable to the general household population. Thirdly, more than half of the diabetic patients were not included in the study because of the lack of data on vitamin D levels and incomplete data, which may lead to offset results. This means that more patients may have been facing vitamin D deficiency and the rate of vitamin D deficiency may be higher than reported in this article. Thus, the effects of vitamin D on diabetic foot might be underestimated. We believe that this condition could be avoided in the future with popularizing vitamin D screening. Moreover, this was a retrospective study and we did not check the level of vitamin D annually in the population, so that the temporality of the association between vitamin D and diabetic foot has not been assessed. Also this was a retrospective study and the assessment of lifestyles was very difficult, so lifestyle factors were not included. Last but not least, our study included the inherent limitations of a retrospective study. A RCT would be ideal, but a retrospective study with a relatively large sample size, well-defined study population, and strong quality control could be acceptable if a sufficient number of RCTs is not conducted yet. Further well-designed research should be done to verify whether there are associations between vitamin D and diabetic foot, and to assess the action of vitamin D in the prevention and treatment of diabetic foot.

Vitamin D deficiency is a common condition among Chinese patients with type 2 diabetes mellitus. The low serum vitamin D level was significantly associated with a higher prevalence of diabetic foot among Chinese patients with type 2 diabetes mellitus. We firstly assessed the seasonal fluctuation of vitamin D in patients with diabetic foot. Although vitamin D levels vary seasonally, patients with diabetic foot were still at higher risk of having vitamin D insufficiency and deficiency. Vitamin D screening or supplementation in Chinese patients with type 2 diabetes mellitus may prevent diabetic foot or improve the prognosis of diabetic foot, especially in winter and spring.

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DISCLOSURE

The authors declare no conflict of interest.

Approval of the research protocol: The study was approved by Biomedical Research Ethics Committee of West China Hospital of Sichuan University.

Informed consent: Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

Approval date of registry and the registration no. of the study/-trial: January 1, 2019 and No. ZYGD18025.

Animal studies: N/A.

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