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Original Article

Correlation between serum 25(OH)D levels and diabetic foot ulcers in elderly patients with type 2 diabetes mellitus

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Abstract: Objective: To explore the correlation between serum 25-hydroxyvitamin D (25(OH)D) levels and diabetic foot ulcers (DFU) in elderly type 2 diabetes mellitus (T2DM) patients. Methods: Data of 198 T2DM patients treated at Shanghai Traditional Chinese Medicine-Integrated Hospital from June 2021 to June 2023 were retrospectively analysed. Totally 80 patients with DFU were classified into the study group, while the other 118 were the control group. Outcome measures included serum 25(OH)D levels and nutritional status, the relationship between the severity of DFU and serum 25(OH)D levels, lipid-related and glucose-related indicators, and independent influencing factors for the severity of DFU in elderly T2DM patients. Results: The control group demonstrated significantly higher serum 25(OH)D levels compared to the study group (P<0.001), and a lower prevalence of 25(OH)D deficiency (65.25% vs. 86.25%, P=0.001). A strong inverse correlation was observed between Wagner grade and 25(OH)D levels (r=-0.746, P<0.001). The control group presented notably lower total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and triglycerides (TG) levels than the study group (P<0.001), but a notably higher high-density lipoprotein cholesterol (HDL-C) (P<0.001). Multivariate logistic regression analysis identified diabetes duration (OR: 1.15-9.23, P=0.026) and serum 25(OH)D levels (OR: 0.40-0.85, P=0.005) as independent predictors of DFU severity. Conclusion: 25(OH)D deficiency is strongly associated with the risk of DFU. Diabetes duration and serum 25(OH)D levels are independent risk factors for DFU severity in elderly patients with T2DM.

Keywords: Serum 25(OH)D, type 2 diabetes mellitus, diabetic foot ulcers, correlation, risk factors

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder characterized by persistent hyperglycemia, predominantly affecting the middle-aged and elderly population [1]. As a disease with heterogeneous pathogenesis, DM is broadly classified into type 1 (T1DM) and type 2 (T2DM), with (T2DM) typically associated with either insulin resistance, impaired insulin secretion, or a combination of both [2]. In China, the predominant type of DM is type 2 [3]. T2DM is prone to complications such as diabetic foot ulcers (DFU), renal function impairment and retinopathy [4]. Among these, DFU is one of the most severe complications of DM, with a high incidence rate, elevated risk of lower limb amputation, high associated mortality rates, complex etiology [5], and is currently lacking effective treatment options.

DFU is a type of diabetes complication caused by abnormal glucose metabolism leading to microvascular lesions, which subsequently result in peripheral neuropathy and microvascular dysfunction, ultimately leading to foot infections and ulcers [4]. Early clinical manifestations such as paresthesia, cold extremities, and sensory loss often go unrecognized by patients, allowing minor foot injuries to progress to severe ulcers [6]. Emerging evidence suggests that vitamin D status may play a crucial role in DFU pathogenesis. Clinical observations indicate that a substantial proportion of DFU patients requiring podiatric surgery present with vitamin D deficiency or insufficiency [6].

Vitamin D, a secosteroid hormone, undergoes hepatic 25-hydroxylation to form 25-hydroxyvitamin D [25(OH)D], which is the most reliable biomarker of vitamin D status [7]. Beyond its

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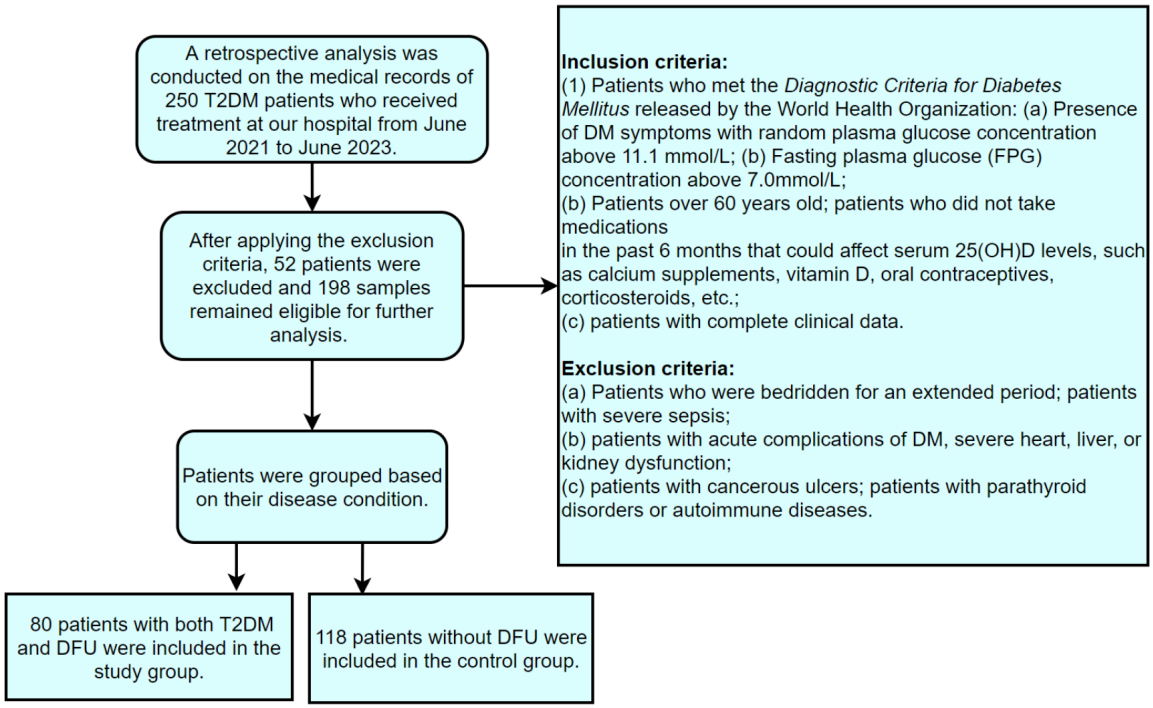

Figure 1. Screening flow of patients. 25(OH)D: 25-hydroxyvitamin D; T2DM: type 2 diabetes mellitus; DFU: Diabetic foot ulcers; DM: Diabetes mellitus; FPG: Fasting plasma glucose.

classical role in calcium homeostasis and bone metabolism [8], 25(OH)D exhibits pleiotropic effects including immunomodulation, anti-inflammatory actions, and cellular proliferation regulation [9, 10]. These properties may underlie the observed associations between vitamin D deficiency and various chronic diseases, including DM and its complications. Research shows that vitamin D supplementation can strongly alleviate the progression of DFU, including ulcer dimensions (length, width, depth) and erythema rate [11]. Tang et al. [12] found that vitamin D deficiency is strongly linked to increased all-cause mortality in Chinese DFU patients, suggesting potential therapeutic benefits of vitamin D repletion. However, the specific relationship between vitamin D status and DFU risk in the elderly Chinese T2DM populations remains underexplored.

Accordingly, this study analysed the serum 25(OH)D levels in elderly T2DM patients with DFU and investigated the mutual relationship between serum 25(OH)D levels and the occurrence of DFU, with the purpose of providing insights for the prevention and clinical treatment of DFU in elderly DM individuals.

Materials and methods

Case selection

A retrospective analysis was conducted on the medical records of 250 T2DM patients who received treatment at Shanghai Traditional Chinese Medicine-Integrated Hospital from June 2021 to June 2023. Totally 198 cases were screened out based on the inclusion and exclusion criteria. Among them, 80 patients with both T2DM and DFU were included in the study group, while 118 T2DM patients without DFU were included in the control group (**Figure 1**). The study was approved by the Ethics Committee of the Shanghai Traditional Chinese Medicine-Integrated Hospital (Approval number: TZ4092801).

Inclusion criteria: Patients who met the *Diagnostic Criteria for Diabetes Mellitus* released by the World Health Organization: (1) Presence of DM symptoms with random plasma glucose concentration above 11.1 mmol/L; (2) Fasting plasma glucose (FPG) concentration above 7.0 mmol/L [13]; patients over 60 years old; patients who did not take medications within the past 6 months that could affect serum

25(OH)D levels, such as calcium supplements, vitamin D, oral contraceptives, corticosteroids, etc.; patients with complete clinical data.

Exclusion criteria: Patients who were bedridden for an extended period; patients with severe sepsis; patients with acute complications of DM as well as severe heart, liver, or kidney dysfunction; patients with cancerous ulcers; patients with parathyroid disorders or autoimmune diseases.

Data collection and outcome measures

The basic information and physical condition data of patients were collected from the electronic medical record system of our hospital, including age, sex, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), DM duration, alcohol history, smoking history, place of residence, Wagner classification, total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), hemoglobin A1c (HbA1c), fasting plasma glucose (FPG), and serum 25(OH)D levels. Serum TC, HDL-C, LDL-C, and TG were determined using a fully automatic biochemical analyzer (model C10006, Abbott). HbA1c was quantified by high-performance liquid chromatography (Bio-Rad Variant II Turbo System, USA); FPG was analyzed using the glucose oxidase method (Roche Cobas c501 analyzer). Serum 25(OH)D levels were determined using an enzyme-linked immunosorbent assay, with the reagent kit from Roche Diagnostics Products (Shanghai) Co., Ltd.

Primary outcome measures: Serum 25(OH)D levels: Nutritional criteria for 25(OH)D [14]: 25(OH)D levels <20 ng/mL are defined as vitamin D deficiency; Levels between 20-30 ng/mL are defined as vitamin D insufficiency; Levels >30 ng/mL are defined as vitamin D sufficiency.

The relationship between the severity of DFU in patients in the study group and serum 25(OH)D levels: Patients were classified into five groups based on Wagner classification and compared regarding serum 25(OH)D levels. Wagner classification criteria for the severity of DFU [15]: Class 0: There is a risk of foot ulcers but no ulcers currently; Class 1: There are superficial ulcers on the foot without signs of infection, typically manifesting as neuropathic ulcers; Class 2: There are relatively deeper ulcers often accompanied by soft tissue infections but no osteomyelitis or deep abscesses; Class 3: There are deep ulcers with abscesses or osteomyelitis; Class 4: There are localized gangrene (toes, heel, or forefoot), characterized by ischemic gangrene, which is typically accompanied by neuropathy; Class 5: There is complete foot gangrene. Example images can be found in **Figure 2**. Pearson correlation analysis was performed to assess the association between serum 25(OH)D levels and the severity of DFU.

Independent risk factors analysis: Multivariate logistic regression analysis was performed to identify independent influential factors influencing the severity of DFU in patients.

Secondary outcome measures: The clinical baseline data (age, sex, BMI, SBP, DBP, duration of DM, alcohol history, smoking history, and place of residence), Lipid-related indicators (TC, LDL-C, HDL-C, and TG), glucose-related indicators were analyzed and compared between the two groups, and Receiver operating characteristic (ROC) curves were generated to evaluate the predictive power of independent influencing factors for DFU severity in elderly patients with T2DM. Additionally, the DeLong test was conducted to compare the ROC curves.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (IBM Corp, Armonk, NY, USA), and graph plotting was done using GraphPad Prism 7 (GraphPad Software, San Diego, USA). Counting data were presented as [n (%)], and comparisons were conducted using the chi-square test. Measurement data were normally distributed and expressed as mean ± standard deviation (SD), and the comparisons were performed using independent sample t-tests, paired t-tests or one way ANOVA analysis followed by Bonferroni test. Univariate and multivariate logistic regression analysis was performed to identify independent influencing factors influencing the severity of DFU in patients, and ROC curves were generated to evaluate the predictive power of independent influencing factors for DFU severity in elderly patients with T2DM. Pearson correlation analysis was performed to assess the association between serum 25(OH)

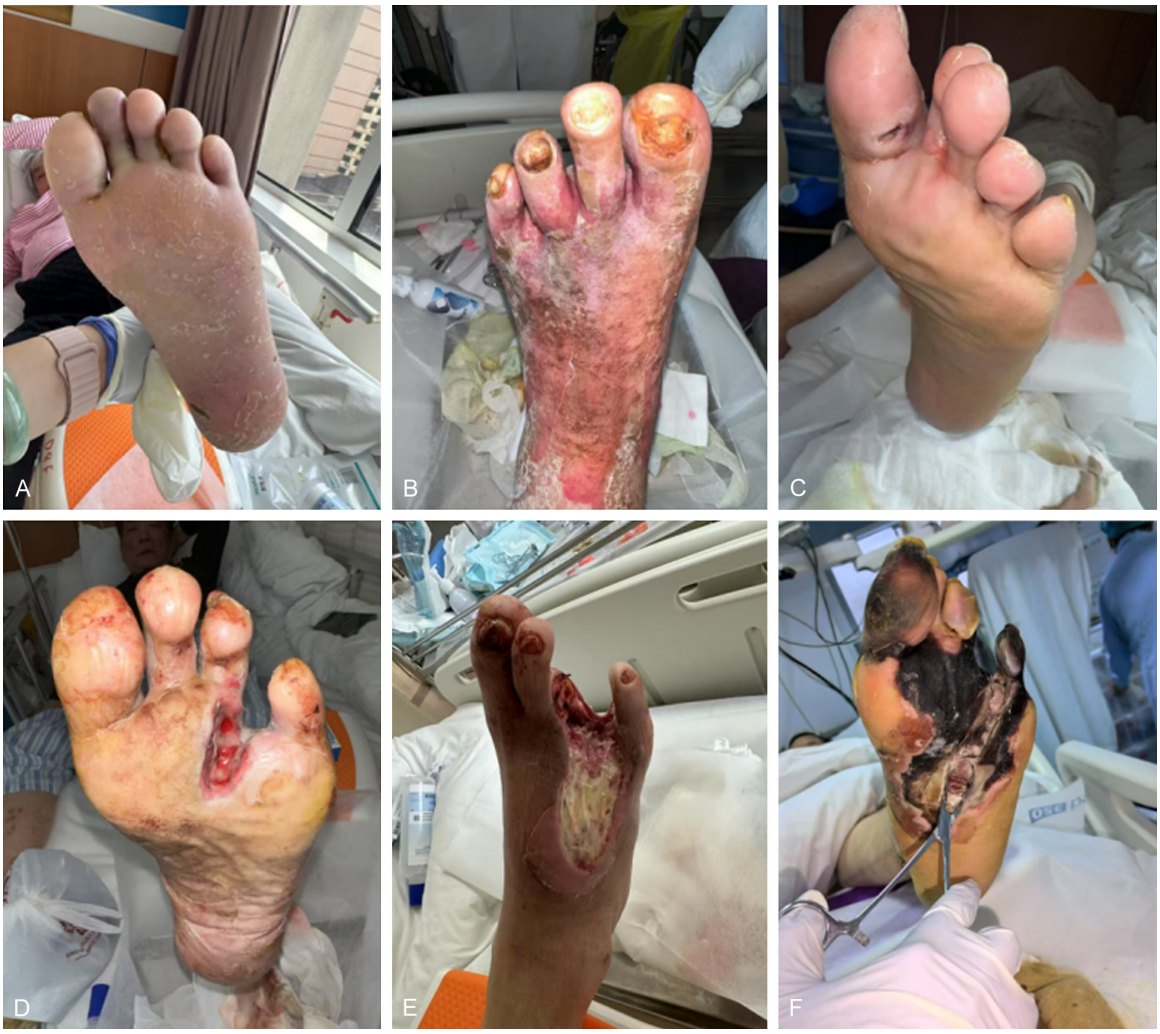

Figure 2. Typical DFU cases with different Wagner classes. Typical DFU cases of Wagner class 0 (A), Wagner class 1 (B), Wagner class 2 (C), Wagner class 3 (D), Wagner class 4 (E) and Wagner class 5 (F). Note: DFU: Diabetic foot ulcer.

D levels and the severity of DFU. P<0.05 indicates a significant difference.

Results

Baseline data comparison

There was no notable differences regarding age, sex, SBP, DBP, alcohol history, smoking history, and place of residence between the two groups (P>0.05). However, the study group exhibited significantly higher BMI and longer duration of DM than the control group (both P<0.05, **Table 1**).

25(OH)D status comparison

The control group had notably higher serum 25(OH)D levels than the study group (P<0.001). However, the study group had a higher portion of 25(OH)D deficient patients than the control group (P=0.001, **Table 2**).

Wagner classes and 25(OH)D levels correlation

DFU patients were divided into 5 subgroups based on the Wagner classification. There were 8 cases in Wagner class 1, 13 cases in Wagner class 2, 22 cases in Wagner class 3, 32 cases in Wagner class 4, and 5 cases in Wagner class 5. As the Wagner class increased, there was a decreasing trend in 25(OH)D levels (P<0.001). Multiple-group analysis revealed that, except for no significant difference in 25(OH)D levels between the Wagner class 1 and class 2 groups

Table 1. Baseline data

Factors	Control group (n=118)	Study group (n=80)	χ^2/t	P
Age (years)	68.8±9.3	68.0±5.5	0.677	0.499
Sex (kg/m^2)			1.329	0.249
Male	61	48		
Female	57	32		
BMI	22.67±1.13	23.21±1.54	2.833	0.005
Systolic blood pressure (mmHg)	130.16±13.69	133.12±17.21	1.345	0.180
Diastolic blood pressure (mmHg)	81.68±9.76	84.30±14.76	1.503	0.135
DM duration mellitus (Years)	3.45±0.16	10.07±2.50	28.64	<0.001
History of drinking			2.265	0.132
Yes	18	19		
No	100	61		
History of smoking			0.114	0.736
Yes	29	18		
No	89	62		
Place of incidence			0.137	0.713
Rural areas	79	52		
Urban areas	38	28		

Notes: BMI: Body mass index; DM: Diabetes mellitus.

Table 2. The nutritional status of 25(OH)D in the two groups

	25(OH)D deficiency [n (%)]	25(OH)D insufficiency [n (%)]	25(OH)D sufficiency [n (%)]	Serum 25(OH)D levels (ng/mL)
Control group (n=118)	77 (65.25%)	35 (29.66%)	6 (5.08%)	16.56±4.01
Study group (n=80)	69 (86.25%)	11 (13.75%)	0 (0.00%)	10.21±2.77
χ^2	10.851	6.768	4.195	
P	0.001	0.009	0.041	
χ^2		12.112		5.366
P		0.002		<0.001

Note: 25(OH)D: 25-hydroxyvitamin D.

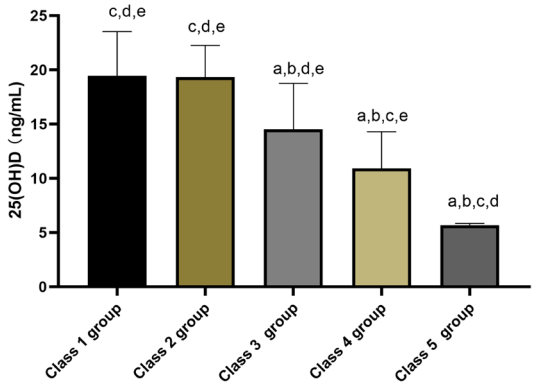

Figure 3. Variations in 25(OH)D levels with different Wagner classes. [a]P<0.001 vs. the class 1 group; [b]P<0.001 vs. the class 2 group; [c]P<0.001 vs. the class 3 group; [d]P<0.001 vs. the class 4 group; [e]P<0.001 vs. the class 5 group. 25(OH)D: 25-hydroxyvitamin D.

(P>0.05), there were significant differences in pairwise comparisons between all other groups (P<0.001, **Figure 3**). Using Pearson correlation analysis, serum 25(OH)D levels were significantly negatively correlated with the severity of DFU (r=-0.746, P<0.001, **Figure 4**).

Metabolic parameters analysis

For the analysis of lipid-related indicators, the control group had notably lower levels of TC, LDL-C, and TG than the study group (all P<0.001), but had a notably higher HDL-C (P<0.001, **Figure 5**). For the analysis of blood glucose-related indicators, the control group had notably lower HbA1c and FBG than the study group (all P<0.001, **Figure 6**).

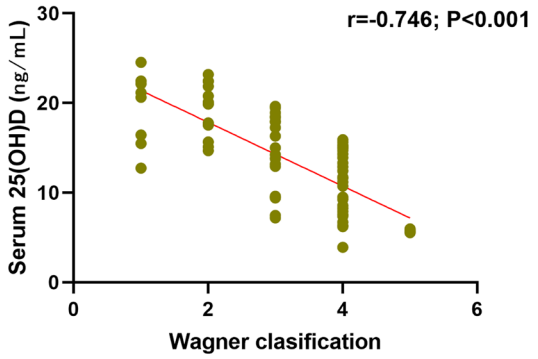

Figure 4. Pearson correlation analysis between Wagner classification and 25(OH)D levels. Note: 25(OH)D: 25-hydroxyvitamin D.

Univariate and multivariate logistic analysis of the severity of DFU in elderly patients with type 2 diabetes

To analyze the independent risk factors affecting the severity of DFU in elderly patients with type 2 diabetes, we grouped the patients based on the Wagner classification of DFU. Patients with Wagner grade 0-2 were assigned to the mild group (n=21), while those with grade 3-5 were assigned to the severe group (n=59). We included the patients' BMI, DM duration, serum 25(OH)D, glycated hemoglobin (HbA1c), and fasting blood glucose in the univariate logistic analysis. The results showed significant differences between the two groups in DM duration and serum 25(OH)D levels (P<0.05, **Table 3**).

Subsequently, we used the severity of DFU as the dependent variable (mild group =1, severe group =0) and DM duration and serum 25(OH)D as independent variables (input as original values). Logistic regression analysis was performed using the backward LR method. The results revealed that DM duration (CI: 1.15-9.23; P=0.026) and serum 25(OH)D (CI: 0.40-0.85; P=0.005) were independent risk factors influencing the severity of DFU in elderly T2DM patients (**Table 3**).

Predictive efficacy of independent risk factors for DFU in elderly patients with type 2 diabetes

ROC curves were plotted to evaluate the predictive efficacy of these two screened out independent risk factors (DM duration and serum 25(OH)D) for DFU in elderly patients with type 2 diabetes. The results showed that the area under the curve (AUC) for DM duration and serum 25(OH)D in predicting DFU severity was 0.870 and 0.920, respectively (**Figure 7**). Using the DeLong test to compare the ROC curves, we found no significant difference in the predictive efficacy between DM duration and serum 25(OH)D (**Table 4**), suggesting that while both DM duration and 25(OH)D levels are strong predictors of DFU severity, neither is statistically superior to the other.

Discussion

DFU is a serious complication in T2DM patients, typically characterized by severe infections, significant incidence, and mortality rates [17]. Beyond its clinical implications, DFU imposes a profound psychological burden on affected individuals and contributes to substantial socioeconomic costs [18]. Notably, it is the leading cause of non-traumatic lower limb amputations worldwide [19]. Therefore, early identification of risk factors for DFU can help prevent severe complications in DM patients. Emerging evidence suggests a potential link between vitamin D status and DFU development in this population [20].

In this study, 25(OH)D levels were significantly lower in the patients with DFU compared to the those without DFU, with a higher prevalence of vitamin D deficiency observed in the former. This finding indicates a significant association between 25(OH)D levels and DFU occurrence. This result is consistent with prior research by of Tang et al. [21], which demonstrated that vitamin D deficiency/insufficiency elevates DFU risk. Furthermore, tour study revealed an inverse correlation between 25(OH)D levels and DFU severity based on the Wagner classification, with progressively lower vitamin D levels observed in advanced ulcer stages. This may be due to factors such as prolonged bed rest, reduced limb mobility, decreased physical activity, and deteriorating nutritional status in DFU patients, leading to an increased risk of worsening 25(OH)D deficiency. Therefore, preventing vitamin D deficiency and maintaining appropriate 25(OH)D levels may help in the prevention and adjunctive treatment of DFU.

In this study, we used multivariate logistic regression analysis to identify independent factors influencing the severity of DFU in elderly patients with T2DM. The results showed that

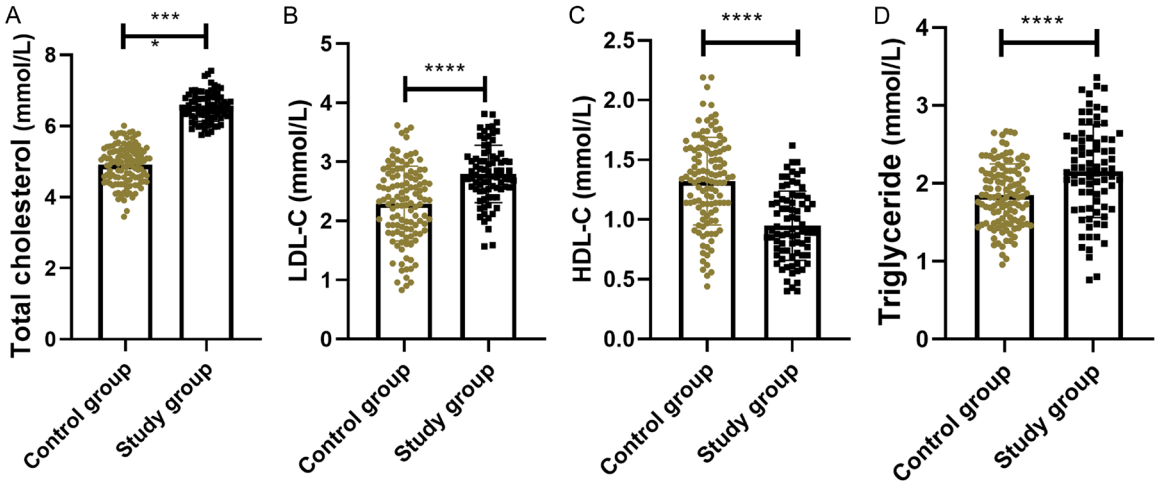

Figure 5. Comparison of lipid-related indicators between the two groups. A: Comparison of total cholesterol between the two groups; B: Comparison of LDL-C between the two groups; C: Comparison of HDL-C levels between the two groups; D: Comparison of triglyceride levels between the two groups of patients. ****P<0.001; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol.

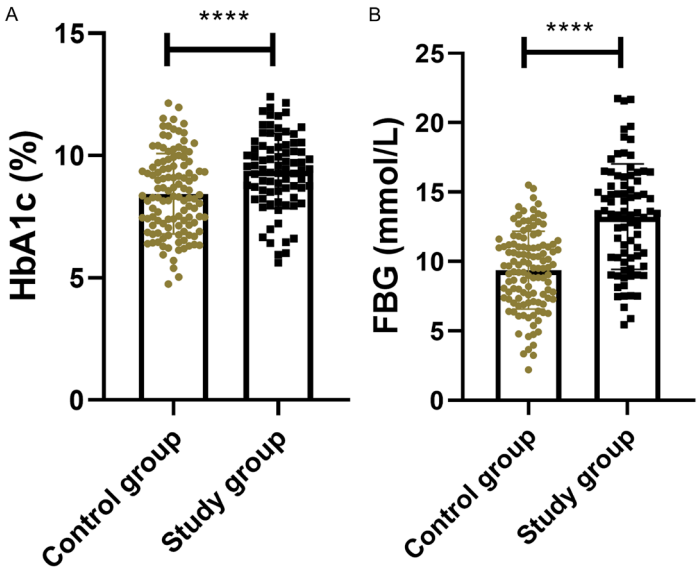

Figure 6. Comparison of blood glucose-related indices between two groups. A: Comparison of HbA1c between the two groups; B: Comparison of FBG levels between the two groups. ****P<0.001; HbA1c: Glycated hemoglobin; FBG: Fast blood glucose.

DM duration emerged as a crucial predictor of DFU progression, with prolonged disease duration being significantly associated with increased ulcer severity through multiple pathological mechanisms: (1) Cumulative damage from chronic hyperglycemia: Sustained hyperglycemia promotes the accumulation of advanced glycation end products (AGEs), triggering oxidative stress and inflammatory responses that impair vascular endothelial function and accelerate atherosclerosis. At the microvascular level, hyperglycemia induces basement membrane thickening and reduces blood perfusion, resulting in chronic ischemic conditions in foot tissues that not only elevate ulcer risk but also delay wound healing [22]. (2) Progression of diabetic peripheral neuropathy (DPN): As a major contributing factor to DFU development, prolonged DM duration leads to sensory nerve damage and subsequent loss of protective sensation in the feet. This impairs patients' ability to perceive mechanical pressure, temperature changes, or minor trauma, making them susceptible to ulcer formation from repetitive friction or pressure. Concurrent motor neuropathy causes foot muscle atrophy and structural deformities (e.g., Charcot foot deformity), further exacerbating abnormal plantar pressure distribution and ulcer development [23]. (3) Immune dysfunction and increased infection risk: Chronic diabetes compromises immune function through impaired neutrophil chemotaxis and macrophage dysfunction, significantly increasing susceptibility to foot infections. When ulcers become complicated by infections such as

Table 3. Univariate and multivariate analysis of the severity of DFU in elderly patients with type 2 diabetes

	Univariate analysis					Multivariate analysis				
	β	S.E	Z	P	OR (95% CI)	β	S.E	Z	P	OR (95% CI)
BMI	0.28	0.23	1.22	0.223	1.32 (0.84-2.06)					
DM duration	1.67	0.49	3.43	<0.001	5.29 (2.04-13.71)	1.18	0.53	2.22	0.026	3.26 (1.15-9.23)
HbA1c	-0.01	0.20	-0.07	0.945	0.99 (0.67-1.45)					
25(OH)D	-0.58	0.16	-3.61	<0.001	0.56 (0.41-0.77)	-0.53	0.19	-2.82	0.005	0.59 (0.40-0.85)
FBG	0.03	0.09	0.37	0.714	1.03 (0.87-1.22)					

Notes: DFU: Diabetic foot ulcers; BMI: Body mass index; DM: Diabetes mellitus; 25(OH)D: 25-hydroxyvitamin D; HbA1c: Glycated hemoglobin; FBG: Fast blood glucose.

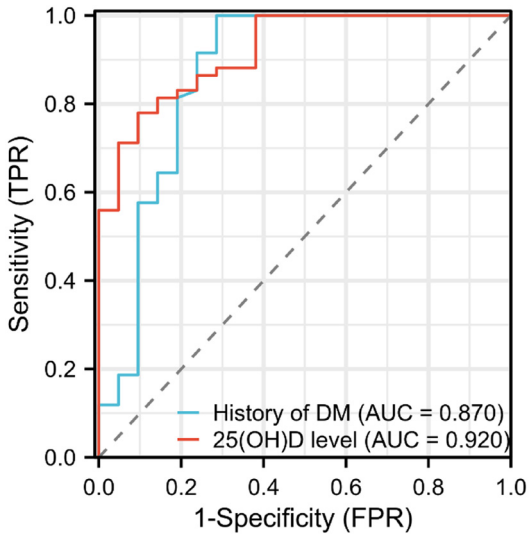

Figure 7. Predictive efficacy of independent risk factors for DFU in elderly patients with type 2 diabetes. DFU: Diabetic foot ulcers; DM: Diabetes mellitus; 25(OH)D: 25-hydroxyvitamin D.

Table 4. Pairwise comparison of ROC curves

25_OH_D_level - History of DM	
Difference between areas	0.0504
Standard Error[a]	0.0613
95% Confidence Interval	-0.0697 to 0.171
Z statistic	0.823
Significance level	P=0.4106

Notes: [a]DeLong et al., 1988 [16]; ROC: Receiver operating characteristic; DM: Diabetes mellitus; 25(OH)D: 25-hydroxyvitamin D.

osteomyelitis or necrotizing fasciitis, both disease severity and amputation risk rise substantially [24]. These findings are corroborated by Gong et al. [25], who reported significantly longer DM duration in patients requiring major amputations compared to those with minor or no amputations, providing robust support for our conclusions.

Furthermore, our study also identified serum 25(OH)D as an independent risk factor for DFU in elderly T2DM patients. 25(OH)D is an essential substance in the body, with skin synthesis and intestinal absorption being the two main sources of 25(OH)D [8]. 25(OH)D can inhibit T cell proliferation, suppress the secretion of pro-inflammatory Th1 cytokines (such as IFN-γ and IL-2), while promoting anti-inflammatory Th2 responses, facilitating wound healing [26]. Research by Kuria et al. [27] suggests that 25(OH)D influences multiple stages of wound healing, accelerating the healing process and regulating various cells involved in proliferation and remodeling stages. 25(OH)D also enhances the expression of antimicrobial peptides for microbial clearance, simultaneously boosting anti-inflammatory responses and inhibiting pro-inflammatory reactions [28]. Moreover, 25(OH)D can inhibit the expression of inflammatory cells and factors through cellular immunity, elevate anti-inflammatory factor levels, and exert immunomodulatory effects [10]. 25(OH)D can also upregulate the gene expression of β-defensin 2 and antimicrobial peptides, enhancing the ability of monocyte macrophages to eliminate pathogenic microorganisms [29]. Thus, 25(OH)D deficiency may exacerbate DFU risk by impairing these critical pathways.

This study does have certain limitations. This is a retrospective study, and the conclusions are based on existing data and statistical analysis. Therefore, further research is needed to validate these results and explore the underlying mechanisms in more depth. Additionally, the grouping based on Wagner classification is

decided with some subjectivity, which may compromise the objective assessment of DFU severity. Therefore, additional studies remain necessary to validate these findings and further elucidate the underlying pathological mechanisms.

Conclusion

25(OH)D deficiency is strongly associated with the risk of DFU. DM duration and serum 25(OH)D levels are independent risk factors for DFU severity in elderly patients with T2DM.

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Disclosure of conflict of interest

None.

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