Association Between Serum 25(OH)D3 Levels and Diabetic Foot Wound Healing: A Nested Case-Control Study (Postprint)

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Date: 2024-01-31T00:00:00+00:00

Abstract

Background: Diabetic foot (DF) is one of the severe chronic complications in diabetic patients. The incidence of DF among diabetic patients in China is as high as 15%, with poor prognosis, an annual amputation rate of up to 22%, an annual mortality rate of up to 11%, and high medical costs, which greatly reduce patients'quality of life and life expectancy. Vitamin D may play a positive role in DF wound healing, but there is currently insufficient clinical research to confirm this effect.

Objective: To explore the correlation between serum 25-hydroxyvitamin (OH)D3 [25(OH)D3] and DF wound healing.

Methods: A nested case-control study design was employed. DF patients with Wagner grade 2–4 who were hospitalized at the Affiliated Hospital of Zunyi Medical University from 2020 to 2021 were selected as study subjects. Patients were followed up for 3 months after discharge; 55 patients whose DF wounds remained unhealed were designated as the case group. Based on age, sex, and Wagner grade of the case group patients, a 1:2 matching was performed to obtain 110 patients whose DF wounds healed within 3 months after discharge as the control group. After admission and before vitamin D supplementation therapy, 2 mL of venous blood was drawn from patients to measure serum 25(OH)D3 levels. Detailed baseline data, biochemical and imaging indicators were collected: basic information included general demographic characteristics (age, sex, residence, education level), BMI, diabetes duration and family history, length of hospital stay, lifestyle habits (alcohol consumption, smoking status), history of hypertension, and Wagner grade; biochemical indicators included 25(OH)D3, glycated hemoglobin (HbA1c), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP); magnetic resonance imaging was performed to determine whether patients had concurrent osteomyelitis. Logistic regression analysis was used

to explore the relationship between different 25(OH)D3 levels and DF wound healing.

Results: The diabetes duration was longer in the case group than in the control group (P<0.001), the proportion with a family history of diabetes was lower than that in the control group (P=0.046), and serum 25(OH)D3 levels were lower than those in the control group (P<0.001); the difference in smoking status between the case and control groups was statistically significant (P<0.001). There were no statistically significant differences between the two groups in age, sex, residence, BMI, length of hospital stay, education level, alcohol consumption, proportion with a history of hypertension, Wagner grade, osteomyelitis incidence, HbA1c, ESR, or CRP (P>0.05). After adjusting for age, sex, residence, education level, BMI, alcohol consumption, smoking status, history of hypertension, family history of diabetes, diabetes duration, length of hospital stay, Wagner grade, osteomyelitis, HbA1c, ESR, and CRP, patients with serum 25(OH)D3 levels of 20-<30 ng/mL, 10-<20 ng/mL, and <10 ng/mL had risks of unhealed DF wounds that were 1.30 times (95%CI=1.12-1.63), 2.01 times (95%CI=1.55-2.80), and 2.29 times (95%CI=1.66-3.92) those of patients with serum 25(OH)D3 levels $ $30 ng/mL, respectively.

Conclusion: Serum 25(OH)D3 levels <30 ng/mL are an independent risk factor for unhealed DF wounds.

Full Text

The Correlation between Serum 25(OH)D3 Levels and Diabetic Foot Wound Healing: A Nested Case-control Study

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Abstract

Background: Diabetic foot (DF) is one of the most serious chronic complications in patients with diabetes. The incidence of DF among diabetic patients in China is as high as 15%, with a poor prognosis, an annual amputation rate

of 22%, and an annual mortality rate of 11%. The high medical costs significantly reduce patients' quality of life and life expectancy. Vitamin D may play a positive role in DF wound healing, but sufficient clinical studies are lacking to confirm this effect. **Objective:** To explore the correlation between serum 25-hydroxyvitamin D3 [25(OH)D3] and DF wound healing. **Methods:** A nested case-control study design was used to select DF patients with Wagner grades 2–4 who were hospitalized at the Affiliated Hospital of Zunyi Medical University from 2020 to 2021. Patients were followed up for 3 months after discharge. Fifty-five patients whose DF wounds remained unhealed were selected as the case group. The control group consisted of 110 patients whose DF wounds healed within 3 months after discharge, matched 1:2 according to age, sex, and Wagner grade. After admission and before vitamin D supplementation, 2 mL of venous blood was drawn to measure serum 25(OH)D3 levels. Detailed baseline data, biochemical, and imaging indices were collected, including general demographic characteristics (age, sex, residence, education level), BMI, diabetes duration and family history, length of hospital stay, lifestyle habits (alcohol consumption, smoking status), history of hypertension, and Wagner grade. Biochemical parameters included 25(OH)D3, glycated hemoglobin (HbA1c), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Magnetic resonance imaging was performed to determine whether patients had osteomyelitis. Logistic regression analysis was used to explore the relationship between different 25(OH)D3 levels and DF wound healing. **Results:** The case group had a longer diabetes duration (P<0.001), a lower proportion of family history of diabetes (P=0.046), and lower serum 25(OH)D3 levels (P<0.001) compared with the control group. There was a statistically significant difference in smoking status between the two groups (P<0.001). No statistically significant differences were observed between the two groups in age, sex, residence, BMI, length of hospital stay, education level, alcohol consumption, proportion with hypertension history, Wagner grade, incidence of osteomyelitis, HbA1c, ESR, or CRP (P>0.05). After adjusting for age, sex, residence, education level, BMI, alcohol consumption, smoking status, hypertension history, family history of diabetes, diabetes duration, length of hospitalization, Wagner grade, osteomyelitis, HbA1c, ESR, and CRP, patients with serum 25(OH)D3 levels of 20–<30 ng/mL, 10–<20 ng/mL, and <10 ng/mL had 1.30 times (95%CI=1.12–1.63), 2.01 times (95%CI=1.55–2.80), and 2.29 times (95%CI=1.66–3.92) higher risk of DF wound non-healing, respectively, compared with patients with serum 25(OH)D3 levels $ $30 ng/mL. **Conclusion:** Serum 25(OH)D3 levels <30 ng/mL are an independent risk factor for DF wound non-healing.

Keywords: 25-dihydroxyvitamin D3; Diabetic foot; Wound healing; Paired case-control study

Introduction

Diabetic foot (DF) is one of the most serious chronic complications of diabetes mellitus. Over 15% of diabetic patients develop DF as their disease progresses, with an annual amputation rate as high as 22% and an annual mortality rate of 11%. The high medical costs impose a tremendous burden on patients, families, and the nation [1]. Armstrong et al. [2] reported that DF significantly reduces patients' quality of life and increases hospitalization duration. In the United States, more than 70,000 patients undergo amputation due to DF annually, and over 50% die within 2 years after amputation, with DF-related mortality exceeding that of most cancers. Rastogi et al. [3] conducted a 14-year multicenter prospective study of 2,880 patients, evaluating amputation and mortality rates in patients with neuropathic DF, finding that 1 in 3 patients required amputation and 1 in 6 died. The latest 2021 data from the International Diabetes Federation show that the global diabetic population has reached 537 million, projected to increase to 643 million by 2030 [4]. As the number of diabetic patients continues to rise, DF will place an even greater burden on global healthcare systems and may become one of the most costly diabetes complications [5]. Therefore, actively identifying factors affecting DF wound healing and providing timely treatment are crucial for reducing DF-related amputation and mortality rates and alleviating the economic burden.

Vitamin D is a steroid hormone essential for calcium-phosphorus metabolism and bone turnover, and it also participates in regulating inflammatory responses, immune function, and cell cycle [6]. Previous studies have shown that serum 25-hydroxyvitamin D3 [25(OH)D3] levels are lower in diabetic patients compared with healthy controls, and even lower in DF patients than in diabetic patients without DF [7]. Clinical studies indicate that vitamin D plays an important role in all stages of wound healing by affecting cell proliferation and remodeling. Additionally, vitamin D enhances antimicrobial peptide expression, helps eliminate microorganisms, inhibits pro-inflammatory responses, and enhances anti-inflammatory reactions [8]. However, research on the correlation between serum 25(OH)D3 levels and DF wound healing is currently insufficient. Therefore, this study enrolled 165 DF patients to explore the relationship between serum 25(OH)D3 and DF wound healing.

Methods

1.1 Study Subjects A nested case-control study design was employed. DF patients with Wagner grades 2–4 who were hospitalized at the Affiliated Hospital of Zunyi Medical University from 2020 to 2021 were selected. Inclusion criteria: (1) DF diagnosis confirmed based on clinical manifestations and laboratory findings; (2) patients in good physical condition able to tolerate the entire debridement process; (3) informed consent obtained from patients and/or their families; (4) age $ $18 years. Exclusion criteria: (1) combined immune system disease; (2) combined malignant tumor; (3) poor physical condition with severe cardiopulmonary insufficiency unable to tolerate debridement; (4) immunosup-

pressant use within 3 months before admission; (5) history of amputation; (6) non-cooperative patients and/or families. After discharge, patients were followed up for 3 months. Fifty-five patients whose wounds remained unhealed constituted the case group. Based on age, sex, and Wagner grade matching, 110 patients whose wounds healed within 3 months after discharge were selected as the control group at a 1:2 ratio, totaling 165 study subjects. Informed consent was obtained from all patients and their families.

1.2 Research Methods After enrollment, trained researchers conducted face-to-face interviews using a standardized questionnaire to collect data on residence, education level, and lifestyle habits (alcohol consumption, smoking status). Baseline data, biochemical indices, and imaging indices were collected from medical records. Baseline data included general demographic characteristics (age, sex), BMI, diabetes duration and family history, hypertension history, and Wagner grade. Biochemical parameters included 25(OH)D3, glycated hemoglobin (HbA1c), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Imaging indices included magnetic resonance imaging to determine osteomyelitis.

1.3 Definitions and Diagnostic Criteria Regular alcohol consumption was defined as drinking at least once weekly for more than 6 months; regular smoking was defined as smoking at least one cigarette daily for more than 6 months. According to the Chinese Guidelines for the Prevention and Treatment of Diabetic Foot (2019 Edition) (I) [9], DF was defined as skin and deep tissue destruction distal to the ankle joint in diabetic patients, often combined with infection and/or varying degrees of lower extremity arterial occlusion, severely involving muscles and bone tissue. Wagner grading criteria: Grade 0, intact skin but with risk factors for foot ulcer; Grade 1, superficial ulcer without deep tissue involvement or infection; Grade 2, deep ulcer often combined with soft tissue infection or multiple purulent foci but without tendon or bone damage; Grade 3, deep ulcer involving muscle and bone tissue with deep abscess and osteomyelitis; Grade 4, localized foot gangrene usually combined with neuropathy; Grade 5, complete foot gangrene.

1.4 Serum 25(OH)D3 Level Detection After admission and before vitamin D supplementation, 2 mL of venous blood was drawn. Serum 25(OH)D3 levels were measured using electrochemiluminescence immunoassay. Based on the results, patients were divided into four groups: 25(OH)D3 $ $30 ng/mL, 20-<30 ng/mL, 10-<20 ng/mL, and <10 ng/mL.

1.5 Statistical Analysis All data were double-blindly entered by two individuals. SPSS 25.0 software was used for statistical analysis. Normally distributed continuous variables were expressed as mean ± standard deviation, and independent samples t-test was used for intergroup comparison. Non-normally

distributed continuous variables were expressed as median (P25, P75), and rank-sum test was used for comparison. Categorical variables were expressed as percentages, and chi-square test was used for intergroup comparison. Logistic regression analysis was used to explore the relationship between serum 25(OH)D3 and DF wound healing. P<0.05 was considered statistically significant.

Results

2.1 Baseline Data Comparison The case group had a longer diabetes duration than the control group (P<0.001), a lower proportion of family history of diabetes (P=0.046), and lower 25(OH)D3 levels (P<0.001). There was a statistically significant difference in smoking status between the case and control groups (P<0.001). No statistically significant differences were found between the two groups in age, sex, residence, BMI, length of hospital stay, education level, alcohol consumption, proportion with hypertension history, Wagner grade, osteomyelitis incidence, HbA1c, ESR, or CRP (P>0.05) .

2.2 Effect of Serum 25(OH)D3 on Diabetic Foot Wound Healing After adjusting for age, sex, residence, education level, BMI, alcohol consumption, smoking status, hypertension history, family history of diabetes, diabetes duration, length of hospitalization, Wagner grade, osteomyelitis, HbA1c, ESR, and CRP, patients with serum 25(OH)D3 levels of 20-<30 ng/mL, 10-<20 ng/mL, and <10 ng/mL had 1.30 times (95%CI=1.12-1.63), 2.01 times (95%CI=1.55-2.80), and 2.29 times (95%CI=1.66-3.92) higher risk of DF wound non-healing, respectively, compared with patients with serum 25(OH)D3 levels $ $30 ng/mL .

Discussion

DF patients have low immunity, high wound infection rates, and slow healing. The goal of DF treatment is to achieve rapid wound healing, prevent infection, avoid amputation and death, improve quality of life, and reduce amputation and mortality rates [10]. Vitamin D plays an important regulatory role in diabetes progression. Low serum vitamin D levels are associated with insulin resistance and impaired β-cell function, and populations with low vitamin D levels are more susceptible to diabetes [11-12]. Studies have found that low serum vitamin D is associated with increased risk of DF, and DF patients have significantly lower serum vitamin D levels than non-DF diabetic patients [13-14]. Research shows that serum 25(OH)D3 levels in DF patients with healed wounds are three times those in patients with unhealed wounds, and high serum 25(OH)D3 is a protective factor for DF wound healing [15]. Priyanto et al. [16] found that DF patients with serum 25(OH)D3 <10 ng/mL had significantly higher risk of wound non-healing than those with levels $ $10 ng/mL. The researchers suggested that serum 25(OH)D3 <10 ng/mL should be considered a critical value for adverse immunological changes in DF patients [13]. This study suggests that after adjusting for risk factors including age, sex, residence,

education level, BMI, alcohol consumption, smoking status, hypertension history, family history of diabetes, diabetes duration, length of hospitalization, Wagner grade, osteomyelitis, and diabetic neuropathy, low serum 25(OH)D3 remains an independent risk factor for DF wound non-healing. DF patients with serum 25(OH)D3 levels of 20-<30 ng/mL, 10-<20 ng/mL, and <10 ng/mL had 1.30 times (95%CI=1.12-1.63), 2.01 times (95%CI=1.55-2.80), and 2.29 times (95%CI=1.66-3.92) higher risk of non-healing, respectively, compared with those with levels $ $30 ng/mL. Wang et al. [17] found that vitamin D is an independent protective factor for DF, and vitamin D supplementation may help prevent DF and improve prognosis. Compared with subjects with normal vitamin D levels, those with vitamin D <15 ng/mL had a 3-6 times higher risk of hypertension events during 4-year follow-up, suggesting that vitamin D has important regulatory effects on vascular function [18]. Additionally, vitamin D has been recommended as an immune agonist; supplementation can counteract cytokine-induced apoptosis, inhibit inflammatory responses, and reduce oxidative stress in DF patients, thereby exerting anti-inflammatory effects [19]. Therefore, appropriate vitamin D supplementation for DF patients with insufficient or deficient levels may promote wound healing and shorten healing time.

DF often affects diabetic patients for life, and age is an important determinant of complication susceptibility. Multiple studies have shown that the incidence of DF and related complications (DF, DF with infection, and amputation) increases with diabetes duration and age [20-21]. In this study, the mean age of DF patients was 65.6 years, and the mean diabetes duration was 11.6 years, consistent with previous findings. Smoking is one of the important modifiable risk factors for diabetes. Research shows that compared with non-smokers, diabetic patients have gradually decreasing glycemic control rates with increased smoking amount and duration (P<0.01) [22]. This study found significant differences in smoking status between the case and control groups (P<0.001), suggesting that smoking is detrimental to DF wound healing. Previous studies have found that men have higher diabetes prevalence and risk of related complications (gangrene, amputation) [23]. This study showed that men accounted for a large proportion of DF patients (63.0%), consistent with previous research.

Priyanto et al. [16] reported that lower serum 25(OH)D3 levels are associated with higher risk of DF wound non-healing. In Chinese populations, 31.6% of DF patients have vitamin D deficiency and 42.2% have vitamin D insufficiency. After multivariate adjustment, vitamin D remains independently associated with increased all-cause mortality and amputation rates in DF patients [24]. Halschou-Jensen et al. [25] found that in DF patients, high-dose vitamin D supplementation (170 g/d) effectively promoted chronic DF wound healing compared with low-dose supplementation (20 g/d). The mechanism may involve vitamin D inhibiting secretion of T helper 1 cytokines interferon-γ and interleukin-2 while stimulating Th2 cytokine production, thereby promoting wound healing [26]. It may also be related to increased vitamin D receptor expression in wounds [27]. The specific mechanisms require further investigation.

In summary, this study analyzed the relationship between serum 25(OH)D3 levels and DF wound healing. After adjusting for potential confounders (including age, sex, residence, education level, and BMI), low serum 25(OH)D3 is an independent risk factor for wound non-healing in DF patients. Therefore, measuring serum vitamin D levels in DF patients and providing timely supplementation may facilitate early wound healing. However, this study had a small sample size, and larger, rigorously designed prospective cohort studies are needed for validation.

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Author Contributions: WU Yunfeng, LUO Yanhong, JIANG Pingnan, and CHEN Xia were responsible for case data collection; JIANG Pingnan, WU Min, and YANG Jia were responsible for data organization and statistical analysis; WU Yunfeng and LUO Yanhong drafted the manuscript; YANG Yan was responsible for quality control; CAI Yulan planned and supervised the study execution. All authors approved the final manuscript.

Conflict of Interest: None declared.

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(Received: September 25, 2023; Revised: January 8, 2024)

Note: Figure translations are in progress. See original paper for figures.