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ORIGINAL

ENHANCING RECOVERY IN ATHLETES WITH DIABETIC FOOT ULCERS THROUGH VITAMIN D SUPPLEMENTATION: A META-ANALYSIS OF RANDOMIZED CONTROLLED TRIALS

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ABSTRACT

To systematically evaluate the potential impact of vitamin D supplementation on clinical parameters related to diabetic foot ulcers (DFU) in athletes, focusing on its implications for sports recovery and performance. Methods: The medical literature databases Embase, PubMed, Cochrane Library, Scopus, Wan fang, CNKI, and VIP were utilized. Searches were conducted using computer technology from the inception of each database until January 2024. Randomized controlled trials (RCTs) evaluating vitamin D supplementation for treating DFU in athletes were identified. Essential clinical indicators were extracted pre- and post-supplementation, including wound area (cm^2), depth (cm), and score; metabolic indicators such as fasting blood sugar (FBS), 2h postprandial blood sugar (2h PG), glycosylated hemoglobin (HbA1c), fasting insulin (FINS), and insulin resistance index (HOMA-IR); lipid profile markers including cholesterol (TC), triglycerides (TG), low-density (LDL) and high-density lipoprotein (HDL); and markers of inflammation and oxidative stress such as C-reactive protein (CRP), high-sensitivity CRP (hs-CRP), erythrocyte sedimentation rate (ESR), malondialdehyde (MDA), total antioxidant capacity (TAC), nitric oxide (NO), and glutathione (GSH). Results are presented as mean ± standard deviation (Mean ± SD). Meta-analysis, sensitivity grading, and publication bias assessment were performed using R software version 4.3.2. Results: This study included a total of 10 RCTs involving 781 athlete cases. Compared to the control group, vitamin D as a supplementary treatment significantly improved the wound area, depth, and score in DFU patients. The differences in means were [weighted mean difference (WMD) = -2.22cm^2, 95%

CI -3.21~-1.24 cm², I2=84%, P<0.01], [WMD = -0.26cm, 95% CI -0.49~-0.03 cm, I2=76%, P=0.02], and [WMD = -1.45 points, 95% CI -2.37~-0.53 points, I2=98%, P<0.01]; Significant reductions were also noted in glycemic parameters FBS, 2h PG, HbA1c, FINS, HOMA-IR, with [WMD = -0.56 mmol/L, 95% CI -0.91~- -0.22 mmol/L, I2=78%, P<0.01], [WMD = -0.86 mmol/L, 95% CI -0.64~- -0.22 mmol/L, I2=0%, P<0.01], [WMD = -0.76%, 95% CI -1.09~- -0.43%, I2=89%, P<0.01], [WMD = -3.31 μU/ml, 95% CI -4.35~- -2.26 μU/ml, I2=0%, P<0.01], and [WMD = -1.46, 95% CI -2.63~- -0.29%, I2=95%, P=0.01]. Lipid metabolism-related indicators such as TC and TG levels were reduced [WMD = -0.32 mmol/L, 95% CI -0.46~- -0.17 mmol/L, I2=46%, P<0.01], [WMD =-0.36 mmol/L, 95% CI -0.55~- -0.16 mmol/L, I2=68%, P<0.01]. Levels of inflammation-related markers CRP, hs-CRP, and ESR were significantly lowered [SMD = -0.82, 95% CI -1.14~-0.49, I2=0%, P<0.01], [SMD = -0.83, 95% CI -1.06~-0.59, I2=0%, P<0.01], [SMD = -0.62, 95% CI -0.86~-0.39, I2=0%, P<0.01]. Decreases in MDA levels [WMD = -0.45 μmol/L, 95% CI -0.64 to -0.26 μmol/L, I2=0%, P<0.01] and increases in NO levels [WMD = 1.78 μmol/L, 95% CI 0.01 to 3.55 μmol/L, I2=0%, P=0.05] were observed, supporting a role in reducing oxidative stress. No significant differences were found between the two groups in LDL-C, HDL-C, GSH, and TAC levels. Conclusion: Vitamin D supplementation holds potential as a therapeutic adjunct in the treatment of DFU in athletes, effectively promoting wound healing, improving metabolic health, suppressing inflammation, and reducing oxidative stress, thus potentially enhancing recovery and athletic performance.

KEYWORDS: Diabetic foot ulcer; Vitamin D; Randomized controlled trial; Meta-analysis

1. INTRODUCTION

Diabetic foot ulcers (DFUs) represent a severe complication of diabetes, characterized by chronic, non-healing wounds on the feet. These ulcers are particularly challenging in athletes, where they impair mobility, performance, and overall health outcomes. Despite conventional treatments, the recurrence and complication rates remain high, prompting the exploration of adjunct therapies such as vitamin D supplementation. Vitamin D has been noted for its role in modulating inflammation, enhancing immune function, and improving skin and bone health, which are critical in wound healing processes (Forlee, 2010).

The primary aim of this meta-analysis is to systematically assess the impact of vitamin D supplementation on the recovery of athletes with diabetic foot ulcers. This analysis focuses on several clinical outcomes, including wound healing rates, metabolic health indicators, and markers of inflammation and oxidative stress, to determine whether vitamin D can serve as an effective adjunct treatment in enhancing athletic recovery and performance (Zhang et al.,

2017). Athletes with diabetes face unique challenges, as rigorous training schedules and physical performance demands can exacerbate complications like foot ulcers. Improved healing and management of DFUs are crucial in this population to prevent severe outcomes such as amputations and to minimize downtime caused by injury.

Moreover, vitamin D's potential effects on muscle strength, pain reduction, and physical function are of particular interest in sports medicine, suggesting that its benefits may extend beyond enhancing wound healing to potentially improving overall athletic performance (Tardaguila-Garcia et al., 2020). This meta-analysis will review randomized controlled trials (RCTs) that have investigated the effects of vitamin D supplementation in athletes with DFU. Databases including Embase, PubMed, Cochrane Library, Scopus, Wan fang, CNKI, and VIP were searched from their inception through January 2024, focusing on trials that provided clear data on wound dimensions, glycemic control, lipid profiles, and inflammatory and oxidative markers pre- and post-supplementation (Tian et al., 1995).

Understanding the role of vitamin D in the treatment of diabetic foot ulcers within the athletic population could lead to more targeted and effective management strategies. It may also provide insights into broader applications of vitamin D in sports medicine, particularly in the context of chronic conditions and recovery optimization (Baines et al., 2014; Pittas et al., 2007).

2. Materials and Methods

2.1 Search Strategy

Search in seven databases including Embase, Cochrane Library, PubMed, Scopus, Wanfang, CNKI, and VIP from database inception to January 2024. Through the MeSH database word index, the citation retrieval vocabulary includes: 'Diabetic foot ulcers', 'Diabetic Feet', 'Vitamin D', '25-Hydroxyvitamin D2', '25-Hydroxyergocalciferol', etc. The Chinese search formula includes: 'diabetic foot ulcer', 'diabetic foot', 'Vitamin D', 'Vitamin D 2', 'calcitriol', 'Vitamin D 3', 'calcitriol'. Combining manual retrieval, a traceable retrieval of important reviews and references in the included literature. At the same time, revisit the clinical trial registration platform (https://clinicaltrials.gov/) to search for completed but unpublished clinical trials.

2.2 Inclusion and exclusion criteria

Inclusion criteria for the study are as follows: (1) Randomized controlled trial (RCT); (2) Age ≥18 years and clear diagnosis of DFU patients; (3) Intervention measures: Vitamin D preparations as a single treatment or in combination with placebo or other conventional treatment regimens, with a

treatment duration of ≥2 weeks; (4) Study outcomes include at least one of the following changes in vitamin D preparations assessed before and after medication in diabetic ulcer patients: wound area (cm2), wound depth (cm), wound score, blood glucose index (FBS, 2h PG, HOMA-IR, FINS, HbA1c), lipid profile (TG, TC, LDL, HDL), inflammatory factors (CRP, hs-CRP, ESR), total antioxidant capacity (TAC), MDA, NO, GSH, etc.

Exclusion criteria: (1) Lack of relevant research data; (2) Non-RCT studies; (3) Basic or animal experiments; case reports; systematic reviews; retrospective studies; literature that has been published repeatedly; (4) Studies involving patients with malignant tumors, pregnant women, and lactating patients.

2.3 Extraction of relevant data and assessment of literature quality

Two researchers independently extracted the data and assessed the quality of each RCT study. The quality assessment included the titles, summaries, and figures of the studies listed, using a pre-designed datasheet to extract relevant information: first author's surname, year of publication, type of study design, intervention measures in the trial and control group, sample size, medication category and dose, participants' age, duration of intervention, and relevant study outcomes. The quality of RCTs was evaluated using the Cochrane bias risk tool.

2.4 Statistical Analysis

All variables analyzed in this study are continuous variables, presented as mean ± standard deviation (Mean ± SD). When the trend of discreteness is represented by standard error in the study, we use the standard formula to convert it to SD. We use the R4.3.2 version software to analyze continuous outcome variables, using weighted mean difference (WMD) and 95% confidence interval (CI) for outcomes with the same measurement unit, and standardized mean difference (SMD) for outcomes with different units or measurement methods.

Using the I2 statistic to study heterogeneity, this is a quantitative measure of inconsistency among different studies. When the I^2 range of studies is between 0% and 50%, it is considered to have low statistical heterogeneity, and we use the R software with a fixed-effect model to combine continuous variables. When the I^2 statistic of studies is greater than 50%, it is considered to have higher heterogeneity; therefore, it may be necessary to use random-effect models and heterogeneity tests in the R software. Additionally, R software version 4.3.2 is used for heterogeneity analysis and sensitivity analysis of included studies, with Egger's test assessing publication bias. All results and the significance of heterogeneity analysis are set at (α= 0.05).

3. Research findings

3.1 Literature search results and basic characteristics

A total of 1639 studies were retrieved for the research, and after screening, 10 articles were finally included (CHENG et al., 2018; HOU et al., 2021; Kamble et al., 2020; Li, 2023; LIN, 2023; Mozaffari-Khosravi et al., 2016; Razzaghi et al., 2017; WANG et al., 2020; Xin-Hsu et al., 2023; Yang, 2023). For a detailed flowchart of the literature search process, refer to Figure 1, and for the basic characteristics of the included literature, refer to Table 1. All 10 articles were at low risk of bias, as shown in Figure 2; all 10 articles used a random control method, and all mentioned the use of random methods; 2 articles were double-blinded, while the rest were open-label. All 10 articles had complete data and provided detailed descriptions of dropouts or lost follow-ups.

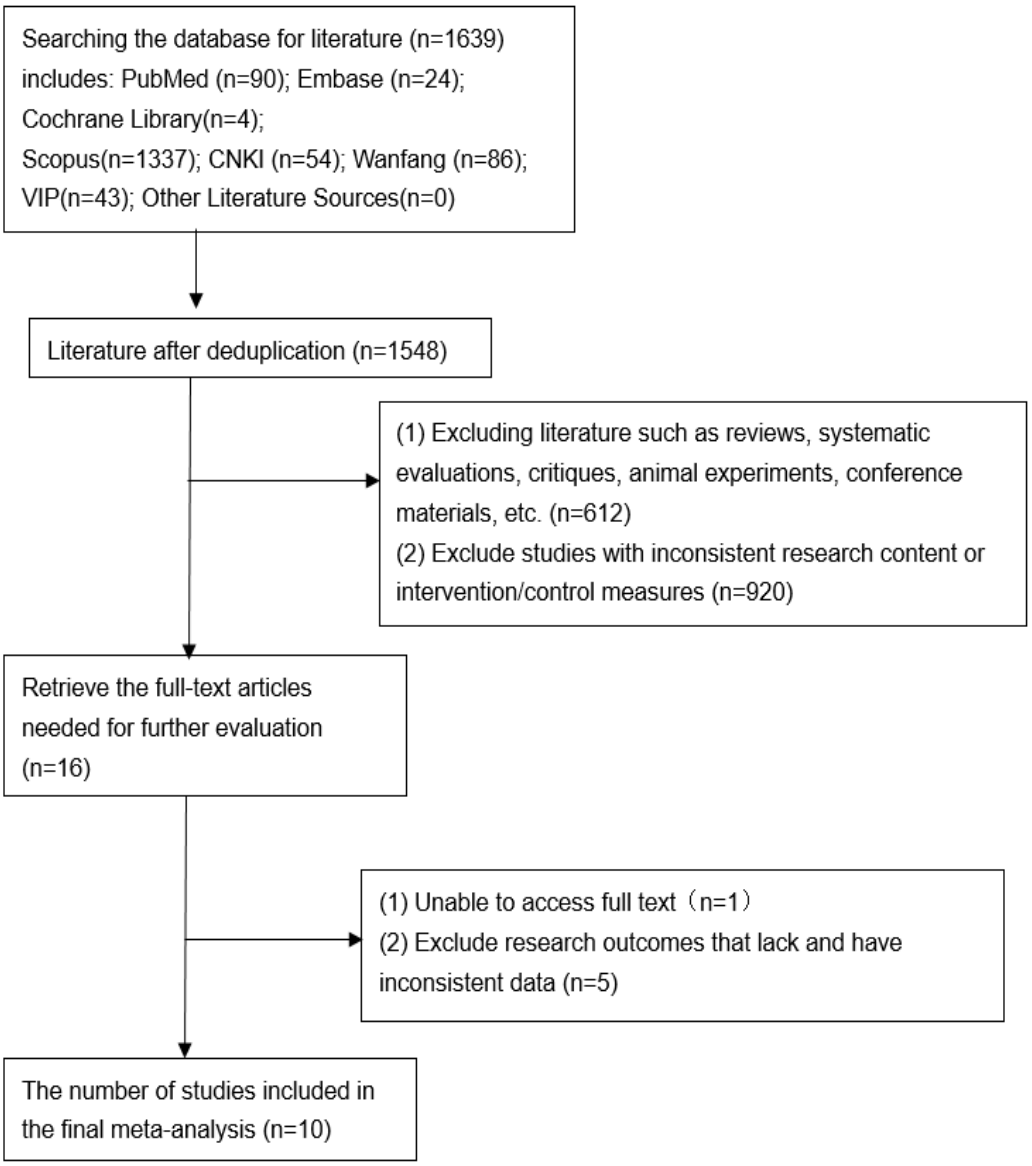

Figure 1: Flow diagram of literature selection process

Table 1(a): Inclusion of basic information for research

AUTHOR	YEAR	TYPE	COUNTRY	SAMPLE SIZE		GENDER (MALE/FEMALE)					OUTCOME INDICATOR
				Experimental	Control	Experimental	Control		Intervene Time（W）	Intervention Measures	
MOZAFFARI-KHOSRAVI ET AL.	2016	RCT	Iran	24	23	13/11	14/9	4	Vitamin D supplement 300,000 units/d	Vitamin D supplement 150,000 units/d	①②⑤⑮⑯
RAZZAGHI ET AL.	2017	RCT	Iran	30	30	22/8	22/8	12	Vitamin D supplement 50,000 units/2w	Placebo	①③⑤⑦⑧⑨⑩⑪⑫⑬⑭⑯⑰⑱⑲⑳
KAMBLE ET AL.	2020	RCT	India	30	30	25/5	23/7	12	Vitamin D supplement 60,000 units/w	Placebo	①②⑦⑩⑫⑬
WANG ET AL.	2020	RCT	China	93	93	62/31	68/25	12	Vitamin D supplement 400 units/d	Placebo	①②③④⑤⑦⑧⑨⑩⑪⑫⑬⑭⑯⑰⑱⑲⑳
YANG	2023	RCT	China	24	24	11/13	12/12	4	Vitamin D supplement 400 units/d + Conventional treatment + Alprostadil Injection 10ug/d	Conventional treatment + Alprostadil Injection 10ug/d	②④⑮

Table 1(b): Inclusion of basic information for research

AUTHOR	YEAR	TYPE	COUNTRY	SAMPLE SIZE		GENDER (MALE/FEMALE)				
				Experimental	Control	Experimental	Control		Intervene Time（W）	Intervention Measures	OUTCOME INDICATOR
LIN	2023	RCT	China	34	34	19/15	20/14	4	Vitamin D supplement 400 units/d + Conventional treatment + Alprostadil Injection 10ug/d	Conventional treatment + Alprostadil Injection 10ug/d	③④⑮
HOU	2021	RCT	China	38	38	20/18	21/17	8	Vitamin D2 supplement 10mg/d + Conventional treatment	Conventional treatment	①⑤⑥⑩⑪
LI	2023	RCT	China	41	41	26/15	25/16	4	Vitamin D supplement 400 units/d + Conventional treatment	Conventional treatment	①⑤⑥⑫⑬
CHENG ET AL.	2018	RCT	China	27	27	11/16	15/12	2	Vitamin D2 Injection 600,000 units + Conventional treatment	Conventional treatment	②⑭
XIN-HSU ET AL.	2023	RCT	China	50	50	28/22	30/20	12	Vitamin D2 Injection 600,000 units/w + Conventional treatment	Conventional treatment	①②③④⑤⑦⑧⑨⑩⑪⑫⑬

①Vitamin D ②Wound area ③Wound depth ④Wound assessment ⑤Fasting blood glucose (FBG) ⑥ Postprandial Blood Glucose (PBG) ⑦ Glycated Hemoglobin (HbA1C) ⑧ fasting insulin (FINS) ⑨ Insulin resistance index (HOMA-IR) ⑩ High-density lipoprotein cholesterol (HDL-C) ⑪Low-density lipoprotein cholesterol (LDL-C) ⑫cholesterol (TC) ⑬Triglycerides (TG)⑭ High-sensitivity C-reactive protein（hs-CRP）⑮C-reactive protein (CRP）⑯Erythrocyte sedimentation rate（ESR）⑰Nitric oxide (NO) ⑱Total Antioxidant Capacity (TAC) ⑲Malondialdehyde (MDA) ⑳glutathione (GSH)

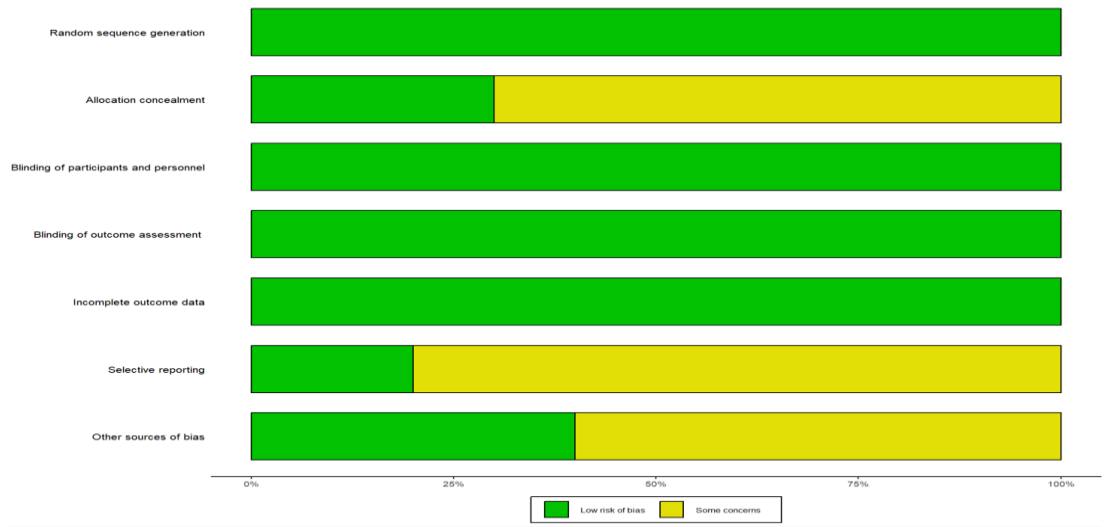

Figure 2: Risk map for literature bias

4. Meta-analysis results

4.1 The impact of supplementing with vitamin D on diabetic foot ulcer wounds

Wound area: This study included a total of 10 studies with 781 cases (CHENG et al., 2018; HOU et al., 2021; Kamble et al., 2020; Li, 2023; LIN, 2023; Mozaffari-Khosravi et al., 2016; Razzaghi et al., 2017; WANG et al., 2020; Xin-Hsu et al., 2023; Yang, 2023). Seven studies reported the impact of supplementing vitamin D on the wound area of DFU patients (CHENG et al., 2018; HOU et al., 2021; Kamble et al., 2020; Li, 2023; Mozaffari-Khosravi et al., 2016; Razzaghi et al., 2017; WANG et al., 2020; Xin-Hsu et al., 2023; Yang, 2023). As shown in Figure 3A, the heterogeneity test result was (I^2 = 84%, P < 0.01), indicating high heterogeneity among randomized controlled trials (RCTs); therefore, a random-effects model was used for analysis. The results showed that compared to the control group, the wound area of the foot in DFU patients significantly decreased after supplementing vitamin D (WMD= -2.22cm2, 95%CI -3.21~-1.24 cm2, P<0.01). Subgroup analysis results did not significantly alter our findings. Sensitivity analysis suggests that the overall combined effect was not influenced by any study, and no significant publication bias was found in the study (P = 0.3241).

Wound depth: Three studies reported the impact of supplementing vitamin D on the wound depth of DFU patients (Razzaghi et al., 2017; WANG et al., 2020; Xin-Hsu et al., 2023). As shown in Figure 3B, the heterogeneity test results (I^2=72%, P=0.02) indicated heterogeneity among the experiments, and a random effects model analysis was conducted. The results indicated a significant improvement in the wound depth of foot ulcers in DFU patients after supplementing vitamin D compared to the control group (WMD= -0.26cm, 95% CI -0.49~-0.03cm, P=0.02). Further sensitivity analysis revealed that the

robustness of the results was affected by excluding the study by Wang et al., and no significant publication bias was found (P=0.1537).

Wound assessment: Four studies reported the impact of vitamin D supplementation on wound scores in DFU patients (Li, 2023; WANG et al., 2020; Xin-Hsu et al., 2023; Yang, 2023). Heterogeneity test results as shown in figure 3C (I^2=93%, P<0.01) indicated heterogeneity among studies. Random effects model analysis revealed that, compared to the control group, diabetic foot ulcer patients showed significantly decreased diabetes scores (SMD= -1.55, 95%CI -2.39~-0.72, P<0.01). Subgroup analysis indicated a significant decrease in wound scores when the intervention period was ≤4 weeks (SMD=-1.28, 95%CI -1.64~-0.92, P<0.01). Sensitivity analysis suggested that the combined effect was not significantly influenced by any study and no significant publication bias was found (P=0.6488).

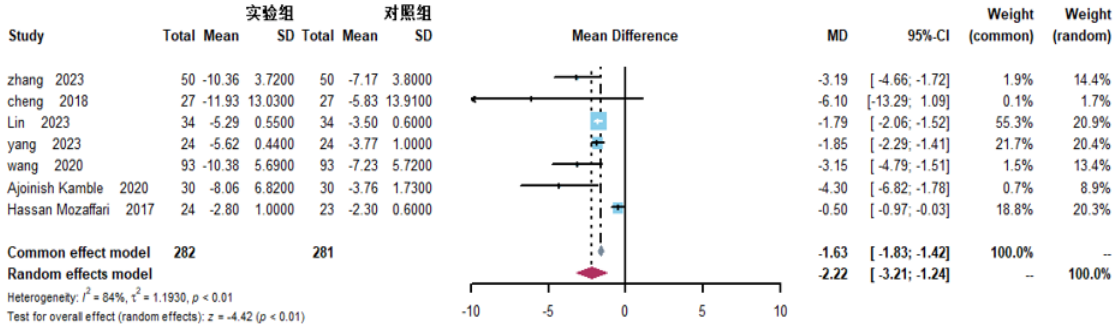

Figure 3 A: Meta forest plot of wound area in two patient groups

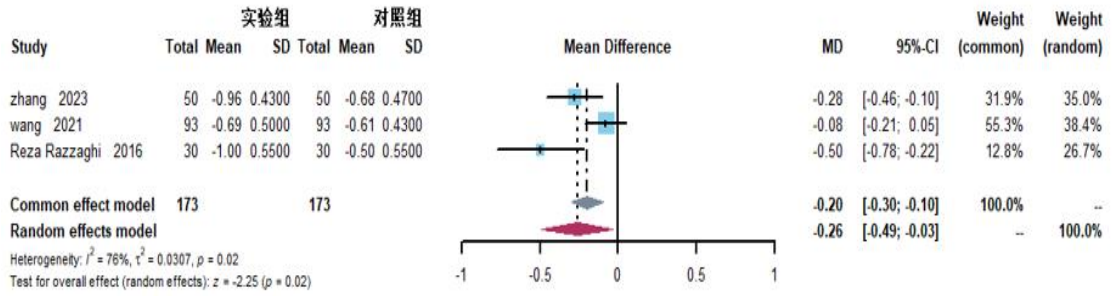

Figure 3B: Meta forest plot of wound area in two patient groups

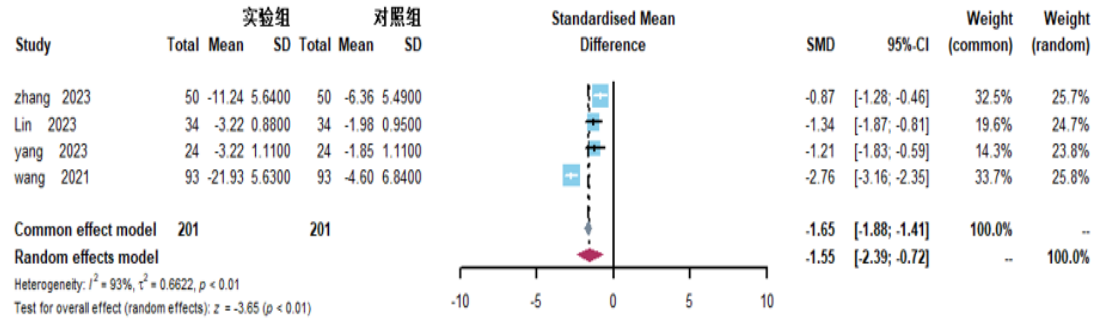

Figure 3C: Meta forest plot of wound area in two patient groups

4.2 The impact of supplementing with vitamin D on sugar and lipid metabolism

4.2.1 Sugar metabolism level

Six studies reported the impact of vitamin D supplementation on FBG levels (HOU et al., 2021; LIN, 2023; Mozaffari-Khosravi et al., 2016; Razzaghi et al., 2017; WANG et al., 2020; Xin-Hsu et al., 2023). As shown in Figure 4A, the heterogeneity result was (I^2 = 78%, P < 0.01), indicating heterogeneity among the studies. Using a random-effects model, the results indicated (see Appendix) that compared to the control group, FBG levels in DFU patients supplemented with vitamin D significantly decreased (MD= -0.87mmol/L, 95%CI -0.91~-0.22mmol/L, P<0.01). Subgroup analysis revealed a significant decrease in heterogeneity when grouped by intervention time, with FBG levels showing a more significant decrease when intervention time was ≥4 weeks (MD= -0.98mmol/L, 95%CI -1.10~-0.87mmol/L, P<0.01). Sensitivity analysis suggested that removing the study by HOU 2021 eliminated heterogeneity (HOU et al., 2021), but the overall effect was not significantly influenced by any study, with potential reasons for heterogeneity changes linked to the type, dosage, and intervention time of medication used in that study. No significant publication bias was found in this study (P=0.099).

Two studies reported the effect of vitamin D supplementation on PBG, as shown in Figure 4B (HOU et al., 2021; LIN, 2023). There was no heterogeneity between the studies (I^2^=0%, P=0.41). Using a fixed-effect model, the results suggested (MD= -0.86mmol/L, 95%CI -1.38~-0.33mmol/L, P<0.01), indicating that vitamin D supplementation can significantly reduce PBG in DFU patients. Four studies (Razzaghi et al., 2017; WANG et al., 2020; Xin-Hsu et al., 2023) reported the impact on HbA1c, as shown in Figure 4C. The heterogeneity result was significant (I^2^=89%, P<0.01). The research exhibits heterogeneity, utilizing a random-effects model. The results indicate (MD= -0.76%, 95%CI -1.09~-0.43%, P<0.01). Further sensitivity analysis reveals that the overall effect is not significantly influenced by any single study, and no apparent publication bias is detected (P=0.4136). Three studies simultaneously reported the impacts on FINS and HOMA-IR, as shown in Figure 4D, 4E (Razzaghi et al., 2017; WANG et al., 2020; Xin-Hsu et al., 2023). Among them, the FINS studies show no heterogeneity (I2=0%, P=0.46), using a fixed-effects model, indicating (MD= -3.31uU/ml, 95%CI -4.35~-2.26uU/ml, P<0.01), suggesting that vitamin D supplementation significantly reduces fasting insulin levels in patients. For HOMA-IR, there is heterogeneity among the studies (I2=82%, P<0.01), employing a random-effects model. The results show (SMD= -1.20, 95%CI -1.83~-0.57, P<0.01). Sensitivity analysis indicates that the overall effect is not significantly influenced by any individual study, and no significant publication bias is found (P = 0.9409).

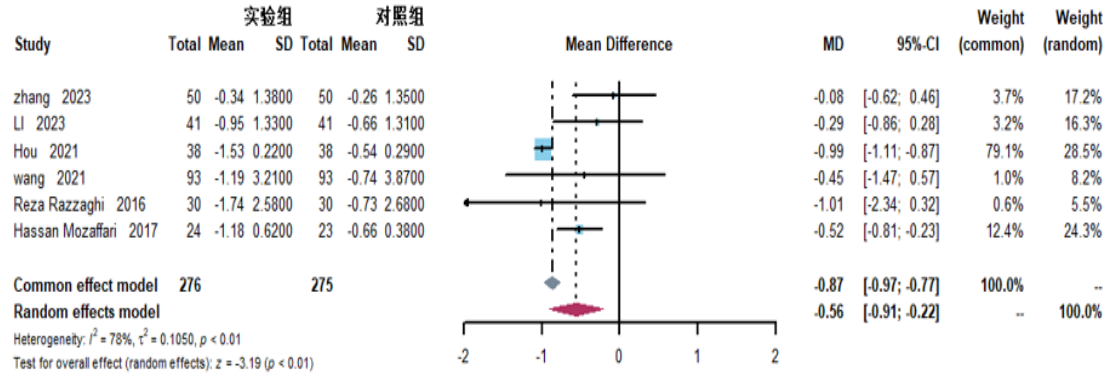

Figure 4A.: Meta forest plot of FBS in two patient groups

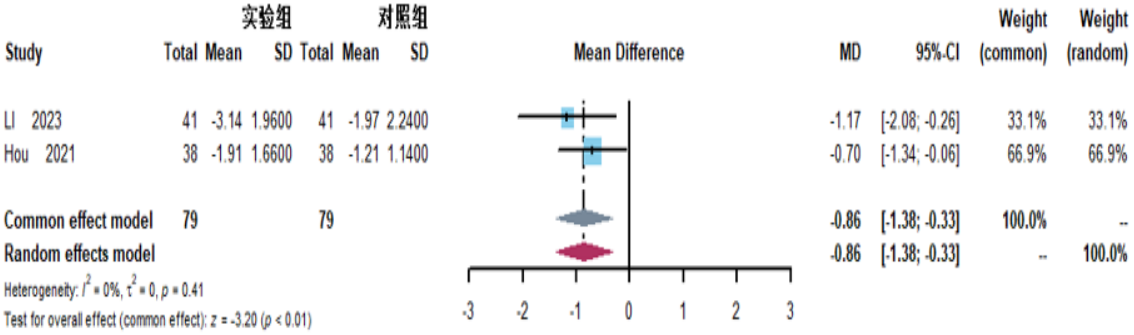

Figure 4B: Meta forest plot of PBG in two patient groups

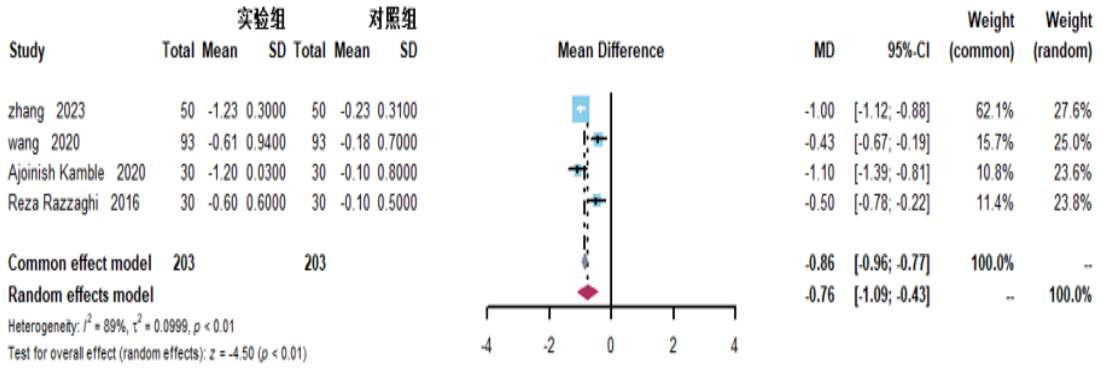

Figure 4C: Meta forest plot of HbA1c in two patient groups

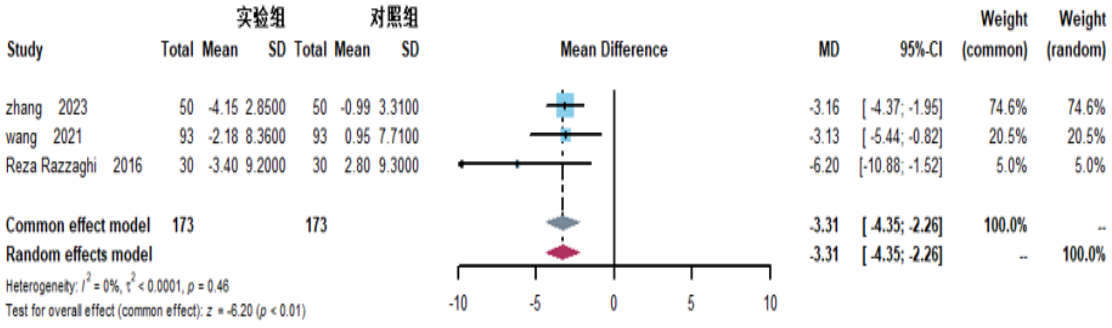

Figure 4D: Meta forest plot of FINS in two patient groups

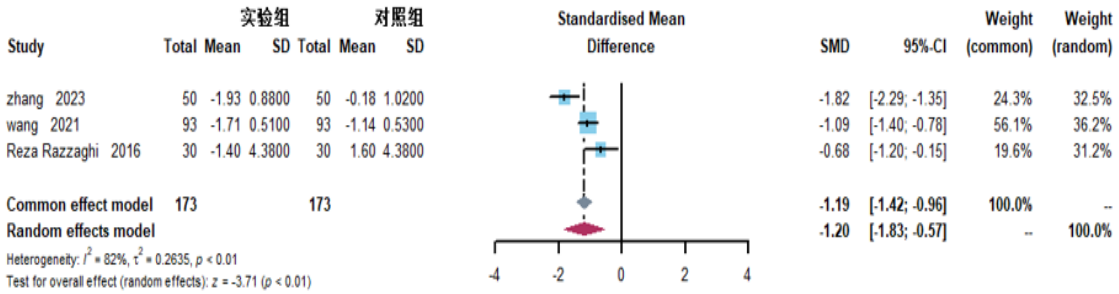

Figure 4E: Meta forest plot of HOMA-IR in two patient groups

4.2.2 lipid metabolism level

Five studies reported changes in TC and TG levels in DFU patients after vitamin D supplementation (LIN, 2023; Razzaghi et al., 2017; WANG et al., 2020; Xin-Hsu et al., 2023). Among the studies on TC, there was low heterogeneity (I2=46%, P=0.12) using a fixed-effect model, as shown in 5A (MD= -0.32mmol/L, 95%CI -0.46~-0.17mmol/L, P<0.01), suggesting a significant reduction in TC levels after vitamin D supplementation. For TG, there was heterogeneity among the related studies (I2=68%, P=0.01), using a fixed-effect model, as shown in 5B (MD= -0.36mmol/L, 95%CI -0.55~-0.16mmol/L, P<0.01), indicating a significant decrease in TG levels. Further subgroup analysis did not reveal significant changes in heterogeneity. Sensitivity analysis suggests that the overall effect was not significantly influenced by any study, and no significant publication bias was observed (P = 0.1038). Three studies reported the impact on LDL-C levels, with no heterogeneity between studies (I2=0%, P=0.77) (HOU et al., 2021; WANG et al., 2020; Xin-Hsu et al., 2023). The results of the fixed-effects model analysis (MD= -0.06mmol/L, 95%CI -0.24~0.12mmol/L, P=0.52) indicated no significant difference in LDL-C levels between the two groups. No publication bias was found in the studies (P = 0.1856). Five studies reported the impact of vitamin D supplementation on HDL-C levels, with heterogeneity between studies (I^2 = 0%, P = 0.77). The results of the random-effects model analysis (MD= 0.08mmol/L, 95%CI -0.01~0.17mmol/L, P=0.08) suggested no significant difference in HDL-C levels between the two groups. Sensitivity analysis showed that the overall effect was not significantly influenced by any study and no publication bias was present (P = 0.8499).

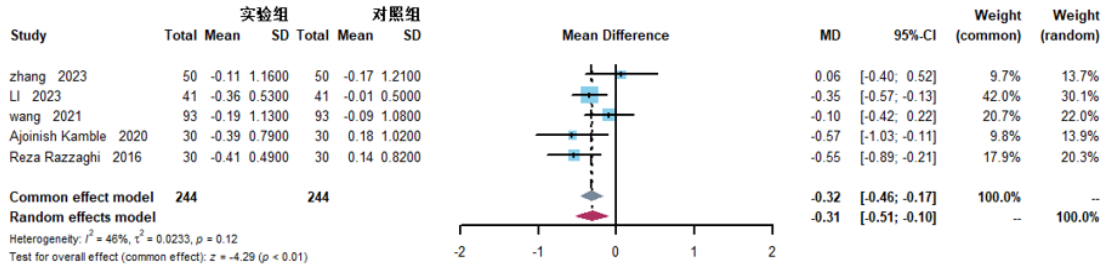

Figure 5A: Meta forest plot of TC in two patient groups

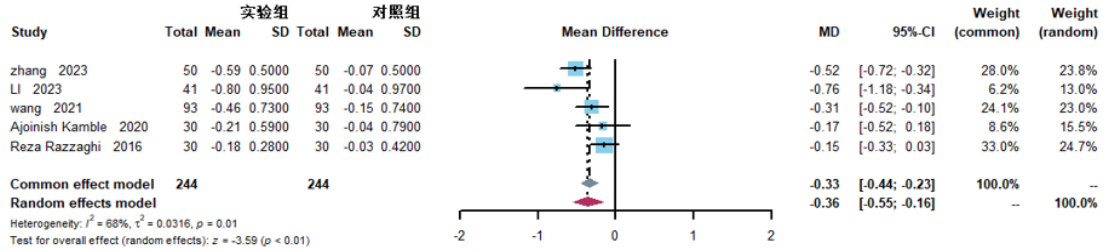

Figure 5B: Meta forest plot of TG in two patient groups

4.3 The impact of vitamin D supplementation on inflammation and oxidative stress markers

4.3.1 Impact on inflammatory markers

Three studies reported the effect of vitamin D supplementation on CRP in DFU patients (LIN, 2023; Mozaffari-Khosravi et al., 2016; Yuan et al., 2018). There were no heterogeneities among the studies, so a fixed-effect model was used. The results are shown in Figure 6A (SMD= -0.82, 95% CI -1.14~ -0.49, P<0.01), indicating a significant decrease in CRP levels compared to the control group. Three studies reported the impact on hs-CRP levels (CHENG et al., 2018; Razzaghi et al., 2017; WANG et al., 2020). There was no heterogeneity in the studies, and a fixed-effect model was applied. The results are shown in Figure 6B (SMD= -0.83, 95% CI -1.06~ -0.59, P<0.01), suggesting a significant decrease in hs-CRP levels in patients supplemented with vitamin D compared to the control group. Another three studies reported changes in ESR levels (Mozaffari-Khosravi et al., 2016; Razzaghi et al., 2017; WANG et al., 2020). Using a fixed-effect model, the results are shown in Figure 6C (SMD= -0.62, 95% CI -0.86~ -0.39, P<0.01), indicating a significant decrease in ESR levels compared to the control group. Sensitivity analysis of each study showed that the overall effect was not significantly influenced by any particular study, and there was no publication bias (P=0.2758, P=0.4166, P=0.0502).

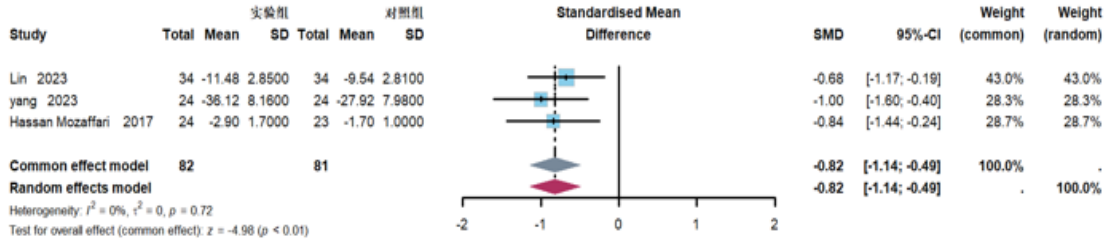

Figure 6A: Meta forest plot of CRP in two patient groups

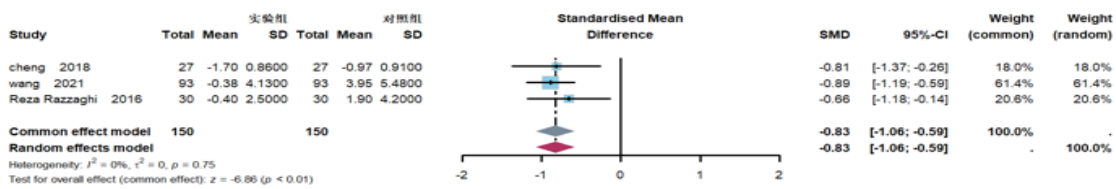

Figure 6B: Meta forest plot of hs-CRP in two patient groups

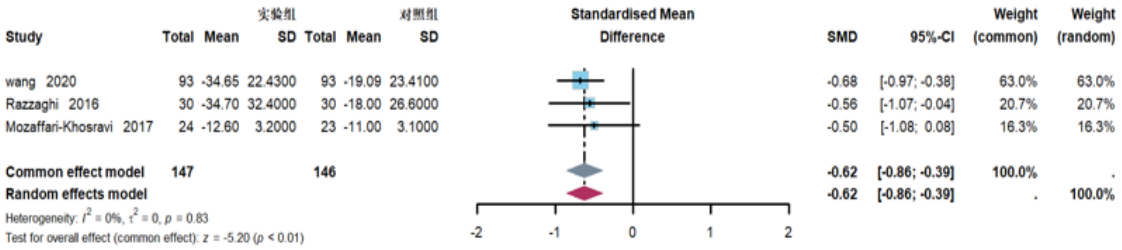

Figure 6C: Meta forest plot of ESR in two patient groups

4.3.2 Impact on oxidative stress markers

Two studies reported the impact of supplemental vitamin D on oxidative markers (Mozaffari-Khosravi et al., 2016; WANG et al., 2020). There were no heterogeneities among the studies for each marker, so a fixed-effects model was used. Compared to the control group, the experimental group showed a significant decrease in MDA levels (MD= -0.45μmol/L, 95%CI -0.64~ -0.26μmol/L, P＜0.01) and a significant increase in NO levels (MD= 1.78μmol/L, 95%CI 0.01~ 3.55μmol/L, P=0.05) as shown in Figures 7A and 7B. However, there were no significant differences in GSH and TAC levels between the experimental and control groups: GSH (MD= -1.32μmol/L, 95%CI -28.08~ 25.45μmol/L, P=0.91), TAC (MD= -0.59mmol/L, 95%CI -41.40~ 42.58μmol/L, P=0.99).

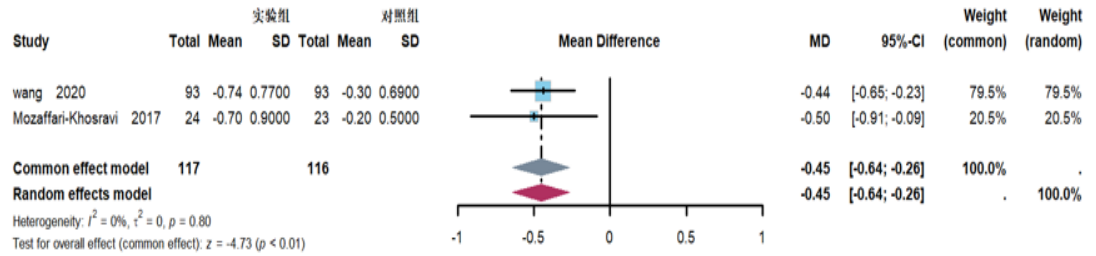

Figure 7A: Meta forest plot of MDA in two patient groups

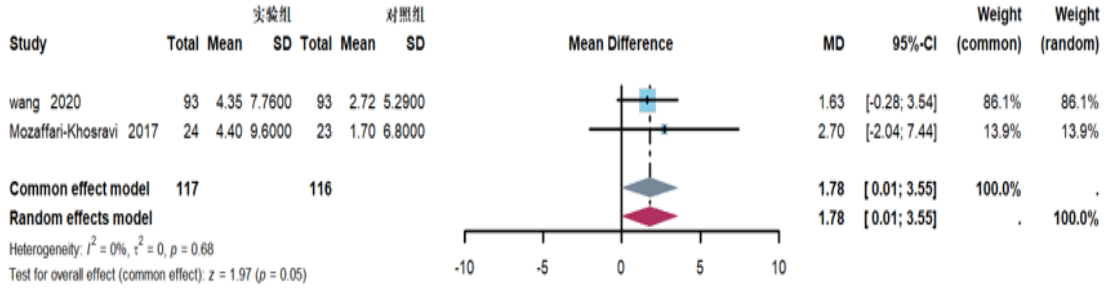

Figure 7B: Meta forest plot of NO in two patient groups

5. Discussion

This study conducted a systematic meta-analysis of 10 randomized

controlled trials. It evaluated the impact of external vitamin D supplementation on wound area, wound depth, wound score, glycemic parameters (FBS, 2h PG, HbA1c, FINS, HOMA-IR), lipid parameters (TG, TC, LDL-C, HDL-C), inflammatory markers (CRP, hsCRP, ESR), and oxidative stress markers (MDA, NO, GSH, TAC) in DFU patients. The shortest intervention time in these studies was 2 weeks, and the longest was 12 weeks. The results showed that under vitamin D supplementation, the experimental group of DFU patients, compared to the control group, exhibited significant improvements in wound area, wound depth, and wound score. Glycemic parameters, inflammatory markers, lipid parameters (TG, TC), and oxidative stress marker MDA levels were significantly reduced, while NO levels were significantly increased. However, no significant differences were found in LDL-C, HDL-C, GSH, or TAC between the two groups. Most of the results in the study did not show heterogeneity. For those that did, subgroup analysis was conducted as mentioned earlier. A few results could not determine the source of heterogeneity due to the small number of studies included. In this study, the wound area, depth, and wound score of DFU patients in the experimental group all significantly improved, indicating that supplementing vitamin D may promote wound healing in DFU patients. Related in vitro studies suggest that vitamin D improves wound healing in diabetic mice induced by streptozotocin (STZ) by inhibiting endoplasmic reticulum stress and nuclear factor κB-mediated inflammation gene expression (Yuan et al., 2018). Another study found that human skin fibroblasts treated with vitamin D enhanced the wound healing capacity mediated by skin fibroblasts, suggesting that supplementing vitamin D may be an important factor in improving wound healing for patients lacking vitamin D (Ding et al., 2016). Furthermore, the study found that supplementation of vitamin D significantly reduced the glucose metabolism indicators in DFU patients, including FBS, 2h PG, HbA1c, HOMA-IR, and FINS levels. Uncontrolled blood sugar levels in diabetic patients are one of the risk factors for the development of diabetic foot complications. The positive impact of vitamin D supplementation on diabetes outcomes may be due to its ability to improve blood sugar control and other metabolic parameters. Vitamin D likely affects insulin sensitivity and secretion by influencing intracellular calcium, thereby helping in the treatment of diabetes. Vitamin D deficiency leads to an increase in parathyroid hormone levels, resulting in an increased intracellular calcium concentration (Holick, 2007). The sustained increase in intracellular calcium may inhibit insulin secretion and the active intracellular calcium flow required for insulin target cell perception of insulin action, leading to the inhibition of GLUT-1 and GLUT-2 in pancreatic cells and weakening the post-receptor binding action of insulin and deactivation of GLUT-4 (Worrall & Olefsky, 2002). Therefore, the role of vitamin D is to remove a large amount of glucose from the bloodstream and maintain its stable supply to the tissues, thereby combating complications such as DFU, which are mainly caused by prolonged exposure to high blood sugar levels, damaging the peripheral nerves, leading to diabetic peripheral neuropathy, ultimately evolving

into DFU. In addition, the research by Shashanka and Palachandra found an indirect correlation between HbA1c and ulcer grade. The study suggests that elevated levels of HbA1c may be associated with slower wound healing rates, serving as an independent biomarker for wound healing assessment in diabetic foot ulcer patients. The study also observed significant differences in certain lipid metabolism indicators (TG, TC levels) in DFU patients supplemented with vitamin D compared to the control group, with TG and TC levels significantly reduced. However, no significant differences were found in HDL-C and LDL-C levels between the two groups. Juan R. and others' research shows that high levels of LDL, TC, TG, and Lp(a), as well as low levels of HDL, are associated with an increased risk of developing diabetic foot ulcers (Ulloque-Badaracco et al., 2022). Dyslipidemia in diabetes is associated with a higher risk of peripheral vascular disease because it plays a central role in the occurrence and progression of atherosclerosis. Dyslipidemia in diabetes is also related to microvascular complications, such as peripheral neuropathy associated with the impact of fatty acids on mitochondrial transport (Savelieff et al., 2020). The deposition of these substances related to lipid metabolism leads to oxidative stress, subsequently triggering an increase in pro-inflammatory cytokines and neuronal apoptosis. Due to the association of neuropathy and peripheral vascular diseases with the development of DFU, related studies have also found that low levels of HDL-C and high levels of TG are associated with an increase in diabetic peripheral neuropathy, while HDL-C has not shown any correlation (Alavi et al., 2014). Therefore, supplementing with vitamin D may play a protective role in regulating lipid levels in the occurrence and development of DFU.

Finally, this study found that compared to the control group, inflammatory markers CRP, hs-CRP, ESR levels, and oxidative stress marker MDA showed a significant decrease in DFU patients supplemented with vitamin D, while NO levels showed a significant increase. GSH and TAC levels did not show significant changes. Some studies suggest that high-sensitivity C-reactive protein (hs-CRP) is associated with DFU, and a decrease in hs-CRP levels is a molecular marker for wound healing (Zubair et al., 2012). Elham and colleagues' meta-analysis showed that supplementing vitamin D significantly reduces CRP (ES = -0.42; 95% CI: -0.55, -0.29, P < 0.001), MDA concentration (ES = -0.37; 95% CI: -0.48, -0.25, P < 0.001), while TAC (ES = 0.68; 95% CI: -0.31, 1.66, P = 0.179) and GSH activity (ES = 0.08; 95% CI: -0.44, 0.60, P = 0.757) did not significantly change. This is consistent with the findings of the study. Other research has shown that different methods of administering vitamin D, such as oral administration, may be associated with significant improvements in inflammation and oxidative stress (Guo et al., 2021). In patients with metabolic diseases such as obesity and diabetes, oral and oral plus intramuscular injection of exogenous vitamin D supplements can significantly reduce CRP levels (Zou et al., 2021). The effect of vitamin D supplementation after varies depending on the individual's health condition. For

example, the supplementation of vitamin D has a greater impact on inflammation and oxidative stress indicators in diabetes patients. Studies suggest that vitamin D may inhibit the proliferation of monocytes and T cells in diabetes patients, while stimulating activity, leading to a decrease in pro-inflammatory cytokines such as CRP, TNF-α, IL-1, IL-6, and IL-8 levels, and an increase in anti-inflammatory cytokines such as IL-10.These improved cytokines can ameliorate insulin resistance, dyslipidemia, and atherosclerosis (Querfeld, 2013). The impact mechanism of vitamin supplementation on oxidative stress in patients is currently unclear, with some studies suggesting that vitamin D can reduce oxidative stress, while another study found no relevant effects (Zhao et al., 2021). Current research has found that vitamin D can enhance the gene expression of various antioxidants, including GSH and TAC, by binding to the vitamin D response element (VDRE). Additionally, vitamin D exhibits membrane antioxidant properties due to its structural similarity to cholesterol and phytosterols (Wiseman, 1993). Vitamin D intake can reduce oxidative stress by increasing antioxidant capacity and decreasing the production of reactive oxygen species. MDA levels are considered a marker of lipid peroxidation, and supplementing with vitamin D can lower lipid peroxidation. The increased expression of glucose-6-phosphate dehydrogenase (G6PD) enzyme, which has multiple antioxidant functions, appears to be the reason for vitamin D's antioxidant effects on most tissues (Bao et al., 2008). In the current meta-analysis, TAC and GSH levels were not affected by vitamin D, but this study did not show significant differences in results. This may be due to several reasons: differences in the type of vitamin D used, different dosing regimens, and characteristics of the study population. Conclusion: This meta-analysis has comprehensively examined the role of vitamin D supplementation in the treatment and recovery of athletes with diabetic foot ulcers (DFUs). Our findings suggest that vitamin D, as an adjunct therapy, significantly enhances wound healing and improves several clinical parameters crucial for athletic health and performance.

5.1 Key Findings

Wound Healing: Vitamin D supplementation was associated with a notable improvement in the wound area, depth, and overall wound score. These enhancements are critical for athletes, as they directly impact mobility and the ability to train and compete.

Metabolic Health: Supplementation resulted in significant improvements in glycemic control, including reductions in fasting blood sugar, postprandial glucose levels, and glycosylated hemoglobin. These effects contribute to better overall diabetes management, reducing the risk of complications and improving energy metabolism essential for athletic performance.

Lipid Profiles: Positive changes in lipid metabolism, evidenced by

reduced levels of total cholesterol and triglycerides, suggest an additional benefit of vitamin D in cardiovascular health, which is vital for endurance and overall physical fitness.

Inflammatory and Oxidative Stress Markers: The decrease in markers such as C-reactive protein and malondialdehyde and the increase in nitric oxide indicate that vitamin D can mitigate inflammation and oxidative stress, factors known to affect recovery and performance in athletes.

5.2 Implications for Sports Medicine and Athletic Training:

The ability of vitamin D to enhance wound healing can significantly reduce recovery times, helping athletes return to training and competition more quickly. The improvement in metabolic and cardiovascular health parameters can aid in the long-term health and fitness levels of athletes, potentially extending their professional careers. The anti-inflammatory and antioxidative effects of vitamin D are beneficial not just for managing DFUs but also for overall injury prevention and recovery.

5.3 Recommendations for Future Research:

Further studies are recommended to explore the optimal dosage and duration of vitamin D supplementation specific to different sports disciplines and athlete populations. Additionally, research should investigate the synergistic effects of vitamin D with other nutritional and therapeutic interventions aimed at managing diabetes and enhancing athletic performance.

6. Conclusion

Vitamin D supplementation presents a promising adjunct therapy for enhancing the recovery of athletes from diabetic foot ulcers. By improving wound healing, metabolic health, and reducing inflammation, vitamin D not only helps in managing a critical complication of diabetes but also supports broader aspects of health and performance critical to athletic success. This research supports the incorporation of vitamin D assessment and supplementation into sports health practices, particularly for athletes at risk of or dealing with DFUs.

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