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CLINICAL TRIAL REPORT

Effects of Oral Cholecalciferol on Chronic Wound Healing in Patients with Vitamin D Insufficiency or Deficiency

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Background: Chronic wounds significantly impact patients' physical and mental health. Several individuals with chronic wounds have low vitamin D levels. Most previous studies have concentrated primarily on diabetic foot ulcers. Few investigations have explored the effects of vitamin D supplementation on different types of chronic wounds.

Purpose: This study aimed to evaluate the impact of increasing serum 25-hydroxyvitamin D (25(OH)D) concentration on participants with chronic wounds and vitamin D insufficiency or deficiency following cholecalciferol (vitamin D3) supplementation. Additionally, it explored the combined effects of wound care and vitamin D supplementation on wound healing outcomes.

Patients and Methods: A total of 46 participants with chronic wounds who were admitted to a wound ostomy care clinic between February and December 2023 were enrolled and randomly assigned to intervention (n=23) and control (n=23) groups. Both groups received local wound treatment based on the tissue, infection, moisture, and edge (TIME) principles and were advised on dietary changes and sunlight exposure. The intervention group received 6000 international units (IUs) of oral cholecalciferol daily until week 5, after which doses were adjusted based on serum concentration.

Results: Of the 46 participants, 40 completed the study with 57 chronic wounds. Per-protocol analysis revealed a statistically significant difference in serum 25(OH)D concentration between the two groups at week 5 (mean ± standard deviation (SD): 36.75 ±7.23 vs 29.58±5.29 ng/mL, $P<0.01$). The intervention group had a shorter average wound healing time than the control group (mean ± SD: 15.59±6.27 vs 26.16±12.70 days, $P<0.01$). Additionally, wound area reduction rate, wound depth reduction rate, and pressure ulcer scale for healing (PUSH) scores were significantly higher in the intervention group ($P<0.05$).

Conclusion: These findings suggest that oral cholecalciferol supplementation increases 25(OH)D concentrations and promotes chronic wound healing.

Trial Registration: This trial was registered at the Chinese Clinical Trial Registry (https://www.chictr.org.cn/, Registration No. ChiCTR2200065482) on November 6, 2022.

Keywords: chronic wound, wound healing, vitamin D, serum 25-hydroxyvitamin D, cholecalciferol

Introduction

In clinical settings, chronic wounds are characterized by a lack of healing or any signs of improvement beyond four weeks.[1] A recent systematic review and meta-analysis reported that, worldwide, two to three individuals per 1000 population are affected by chronic wounds,[2] with approximately 15% of cases remaining unresolved even one year post-discharge.[3] However, in China, the prevalence of chronic wounds surpasses the global average, with about 1.7 chronic wounds per thousand hospitalized patients.[4] The higher prevalence is remarkably attributed to the country's rapidly aging population and the rising incidence of diabetes. Chronic wounds in China predominantly affect middle-aged and elderly individuals, with the majority of patients aging 60–80 years.[4] Older adults account for 55.1% of cases.[5] Furthermore, the national need for wound care reaches up to 100 million people annually, with over 30 million people requiring treatment

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for various complex and challenging wounds.[6] Chronic wounds pose a significant threat to patients' physical and mental health, worsening the economic and psychological burden on primary caregivers.[7] In China, venous leg ulcers, pressure injuries, and diabetic foot ulcers (DFUs) are the common chronic wounds in clinical practice, among which diabetic wounds are the most common, accounting for up to 52.5%,[5] involving 40 million cases.[8] Wound healing is affected by several factors, which can be divided into systemic factors and local factors. Systemic factors influencing wound healing include age, nutritional status, chronic diseases, medications, obesity, smoking, and alcohol abuse. Local factors include wound infection, as well as local compression or traction on the wound.[9] Chronic wounds are characterized by a high bacterial load, and infection is a primary factor that disrupts normal wound healing.[10]

Vitamin D is a crucial nutritional component essential for sustaining normal metabolism and bodily functions. It belongs to a group of biologically active fat-soluble steroid derivatives,[11] and its primary sources include skin synthesis (90%) and intestinal absorption (10%).[12] Vitamin D plays a role in enhancing the antimicrobial capabilities of the body, facilitating the elimination of free bacteria and disrupting biofilm by upregulating the expression level of the antimicrobial peptide leucine-leucine (LL)-37.[13] Furthermore, vitamin D metabolites can suppress the expression of tissue metalloproteinases in keratinocytes, reduce the production of matrix metalloproteinase (MMP)-1 and MMP-10,[14] enhance glial cell migration on fibrillar collagen, and support the degradation of nonviable tissue structures in wounds. Cholecalciferol, commonly known as vitamin D, is biologically inactive. Whether ingested or synthesized in the epidermis after sunlight exposure, it undergoes two hydroxylation metabolic steps: first in the liver to form 25-hydroxyvitamin D (25(OH)D), the main circulating form and marker of vitamin D status, and then in the kidney to produce 1,25-dihydroxyvitamin D, the active form of the hormone.[15]

Participants with chronic wounds mainly have vitamin D level below the recommended threshold (>30 ng/mL).[16] A study comparing 25 participants with chronic venous leg ulcers with 25 participants with acute surgical wounds found that although vitamin D deficiency level was comparable between the two groups (83.3% in the ulcer group and 80% in the control group), more participants in the ulcer group (32%) had severe vitamin D deficiency.[17] A study by Xiao Y et al[18] involving 4284 type 2 diabetic participants in Hunan, China, found a higher prevalence of vitamin D insufficiency in those with DFU compared with non-ulcerative diabetics (79.59% vs 71.21%, P=0.005). Additionally, vitamin D insufficiency was associated with an elevated risk of DFU (OR: 1.623; 95% CI: 1.174–2.243).

Although some studies have explored the role of vitamin D in chronic wound healing, verification studies are limited and have notable limitations. Firstly, most studies concentrated on DFUs and provided vitamin D supplementation.[19–21] Secondly, the doses of vitamin D supplementation vary significantly. For instance, Halschou-Jensen et al[20] used 6800 IU per day, exceeding the standard recommendation (for adults with vitamin D deficiency, the suggested dose is 6000 IU/d or 50,000 IU/week, followed by a maintenance dose of 1500–2000 IU/d).[16] In contrast, Wang et al[22] administered 4000 IU per day, below the recommended dose. The optimal dosing outlined in the *Consensus on the Clinical Application of Vitamin D and Its Analogues* has not been adequately evaluated in patients with chronic wounds. Additionally, supplementation durations are often unnecessarily long. Cholecalciferol has a half-life of approximately one day, and daily dosing stabilizes serum 25(OH)D levels,[23] which typically plateau after a certain period. A 28-week study in hemodialysis patients indicated that serum 25(OH)D level was stabilized after 30 days of supplementation.[24] Existing studies do not specify the point at which serum 25(OH)D reaches its peak, which may lead to unnecessary or excessive supplementation.

Thus, this study aimed to assess cholecalciferol (vitamin D3) supplementation in patients with chronic wounds who have not achieved the recommended vitamin D levels. The study explored the effects of cholecalciferol supplementation across different types of chronic wounds, assessed changes in serum 25(OH)D concentrations following supplementation, and examined its impact on wound healing by measuring wound area, wound depth, and the pressure ulcer scale for healing (PUSH). The findings may strengthen clinical evidence supporting vitamin D as an adjuvant therapy for chronic wounds.

Methods

This randomized controlled clinical trial was conducted between February 2023 and December 2023. Convenience sampling was used to recruit participants with chronic wounds from the Wound and Ostomy Care Clinic of a Class iii

Grade A hospital located in Guangzhou (China). Signed informed consent forms were provided by participants or their legal representatives. The Ethics Committee of Guangzhou Red Cross Hospital reviewed and approved the study protocol (Approval No. 2022–219-01), which was also registered in the Chinese Clinical Trial Registry on 6 November 2022 (Link: https://www.chictr.org.cn/, Registration No. ChiCTR2200065482).

Inclusion and Exclusion Criteria

The inclusion criteria involved individuals over 18 years of age with wounds persisting for at least four weeks, regardless of etiology. Eligible participants presented with chronic wounds, including but not limited to DFUs, pressure injuries, vascular ulcers, and postoperative wounds, and serum 25(OH)D concentration was below 30 ng/mL. Additional eligibility requirements included normal hepatic and renal function, the absence of gastrointestinal conditions, such as gastric resection, small intestine malabsorption, or chronic pancreatitis, as well as the exclusion of other significant organic pathologies. Furthermore, participants were required to have no documented history of hypersensitivity to vitamin D.

The exclusion criteria consisted of chronic wounds of malignant origin, those complicated by osteomyelitis, or wounds necessitating inpatient treatment due to an inability to achieve resolution through standard outpatient wound management. Pregnant or lactating individuals were also excluded. Furthermore, participants with a smoking index of ≥400, calculated as the product of the number of cigarettes smoked daily and the number of years of smoking, were ineligible. Excessive alcohol consumption, defined as more than 4 drinks per day or 14 drinks per week for men and more than 3 drinks per day or 7 drinks per week for women (where one standard drink contains 14 g of alcohol, equivalent to 360 mL of beer, 45 mL of 40% spirits, or 150 mL of wine), constituted an additional exclusion criterion. Individuals who had consistently taken oral supplements, particularly vitamin D, within the preceding three months, or those who had participated in other clinical trials within the three months prior to enrollment, were excluded from the study.

Participants were withdrawn from the study if they were lost to follow-up for less than one week due to various factors, including voluntary withdrawal by the participant or their legal representative, transfer to another hospital preventing continued follow-up, or other unforeseen reasons leading to loss of follow-up.

Study Design and Randomization

Given the significant influence of wound infection on the healing process and the predominant prevalence of DFUs among chronic wounds, this study adopted the presence or absence of diabetes and the clinical status of wound infection as stratification factors. The clinical diagnosis of infection was made by the attending physician, who evaluated a combination of clinical signs including persistent or escalating pain, erythema, fever, purulent discharge, excessive granulation tissue formation, enhanced tissue fragility, increased susceptibility to bleeding, the presence of epithelial bridges or cysts in the granulation tissue, wound ulceration or expansion, delayed wound closure, new or intensified pain, and the presence of an offensive odor.[25] Participants were stratified into four distinct groups based on the presence of diabetes and the infection status of the wound: (1) those with diabetes mellitus and clinically infected wounds, (2) those with diabetes mellitus and non-infected wounds, (3) those without diabetes mellitus, while with infected wounds, and (4) those without diabetes mellitus and non-infected wounds. In each stratified category, block randomization was employed to ensure participants' equal and unbiased distribution. For participants with chronic wounds and vitamin D insufficiency or deficiency, random assignment to either the intervention or control group was conducted in a 1:1 ratio. A random sequence of identifiers (A and B) was generated through the R programming language to create permuted blocks, where group A corresponded to the intervention group and group B to the control group.

Prior to participant enrollment, those not involved in the study printed the pre-generated randomization sequence, corresponding to the permuted blocks, onto individual slips of paper. These slips were then sequentially placed into sealed, numbered envelopes, with the group assignment concealed. Upon participant enrollment, these envelopes were opened sequentially to assign participants to the appropriate intervention group.

Conventional Wound Care

All the participants received wound treatment following an evaluation by a professionally trained international enterostomal therapist. To ensure the reliability and consistency of the findings, each wound was treated as an independent research unit, allowing for precise assessment of wound healing trajectories. Throughout the study, wound management followed the TIME principle, comprising tissue, infection, moisture, and edge of the wound, designed to optimize healing and address the primary factors influencing wound recovery.[26] Specialist nurses assessed the wound type, wound bed (including wound size, location, tissue type, exudate and presence of infection), wound edges (color, thickness, rolling, and undermining), and surrounding skin (color and integrity). The cleansing procedure adhered to a standardized approach, beginning with the cleaning of less contaminated areas to minimize the risk of cross-contamination. Dressing selection was customized to meet the unique requirements of each wound, based on its healing stage and exudate level. For infected wounds, topical treatments, such as silver-containing dressings, hypertonic saline dressings, or silver sulfadiazine cream were applied, followed by non-occlusive dressings to promote a moist environment conducive to healing. In the case of wounds with moderate-to-heavy exudate, highly absorbent materials, including alginate or foam dressings, were utilized to manage excess fluid, while wounds with minimal exudate were dressed with sterile gauze, and covered with a double layer for optimal absorption and protection.

The study incorporated well-established and reliable measurement techniques to assess wound healing. Wound's length and width were systematically measured using a standardized wound ruler, and these dimensions were used to calculate the wound area.[27] The depth of each wound was assessed using a probe, with the extent to which the probe penetrated the wound recorded as the wound depth.[28] Some wounds were irregular in shape, while most of them were round- or oval-shaped. The wound area was calculated by a professionally trained international enterostomal therapist based on the measurement of the shortest and longest radii of the wound.

Participants were instructed to avoid utilizng any vitamin D supplements other than the cholecalciferol provided within the scope of the study. They were further educated on the management of vitamin D insufficiency through dietary intake and increased sunlight exposure. The recommended dietary sources of vitamin D included fatty marine fish, such as salmon, sardines, and tuna, as well as fresh mushrooms and eggs.[29] Regarding sunlight exposure, participants were guided to expose their bare upper limbs and face (while ensuring their eyes were shielded) for approximately 20 min. In the summer months, they were advised to select time intervals between 8:00 am and 10:00 am or between 4:00 pm and 6:00 pm to minimize the risk of skin damage, while in the winter, midday or sunny periods were preferred for optimal sunlight exposure.[30] Participants were required to attend outpatient clinic visits for dressing changes 2 to 3 times a week until wound closure was achieved or until hospitalization was necessary for more intensive wound care. Successful wound healing was defined as the resolution of the wound without the need for further medical intervention, while the need for hospitalization for advanced wound repair or treatment was regarded as treatment failure.

Intervention Group

The oral dose used in this study was formulated according to the Consensus on the Clinical Application of Vitamin D and its Analogues published by the Chinese Society of Osteoporosis and Bone Mineral Diseases in 2018.[16] For all adults with vitamin D deficiency, a cholecalciferol level of 6000 IU/day or 500,000 IU/week was recommended, followed by a maintenance dose of 1500 to 2000 IU/day. The vitamin D supplementation was performed until week 8. In this study, participants in the intervention group received oral cholecalciferol (vitamin D3) at a daily dose of 6000 IU. After 5-week intervention, 25(OH)D concentration was re-evaluated. If the cholecalciferol concentrations were adequate, participants continued to take 1600 IU/day cholecalciferol until the eighth week. If the cholecalciferol concentrations were insufficient, participants were instructed to maintain a daily oral dosage of 6000 IU until the eighth week. Participants in the control group received standard wound care.

Observational Indices

The observational indices in this study mainly refer to the research on wounds performed by Jiang Qixia and other Chinese scholars,[31,32] including:

- Serum 25(OH)D: Fasting blood samples were collected from each participant at two time points (weeks 0 and 5) to measure serum 25(OH)D level. Serum 25(OH)D level was quantified using liquid chromatography-tandem mass spectrometry (I-CLASS Xevo, Waters Corporation, Milford, MA, USA) in accordance with national standards.[33] In brief, serum 25(OH)D_2 and 25(OH)D_3 levels were processed by protein precipitation with methanol/acetonitrile, followed by hexane extraction, nitrogen drying, and reconstitution in the initial mobile phase. Chromatographic separation was performed using liquid chromatography, and detection was carried out in multiple reaction monitoring modes with tandem mass spectrometry. Quantification was undertaken using the isotope internal standard method.

- Mean healing days: The number of days required for wound healing was recorded for both groups, from enrollment to the final assessment. Healing was defined as complete or partial wound closure with a residual wound area of less than one-fourth of the original size.[34]
- Reduction rate of wound area: The wound area was assessed and recorded at the beginning of the study and at the final weekly dressing change appointment at the wound care clinic. It was calculated as wound length (cm) × width (cm), and the reduction rate was determined using the formula: (pre-study wound area − the latest wound area after the study commenced)/pre-study wound area × 100%.
- Reduction rate of wound depth: Wound depth was measured at baseline and the final weekly dressing change appointment. The depth reduction rate was calculated using the following formula: depth reduction rate = (depth before study − the latest depth after study)/depth before study × 100%.
- The PUSH: This scale comprised three components: wound area (length × width), tissue type (epithelial, granulation, cartilaginous, or necrotic tissue), and exudate quantity (small, medium, or large).[35] Exudate levels were categorized as follows: small (penetration of up to one-third of a 7.5×7.5 cm gauze pad, with an exudate volume of less than 5 mL), medium (penetration of up to two-thirds of a 7.5×7.5 cm gauze pad, with an exudate volume of approximately 5–10 mL), and large (complete penetration of one or more 7.5×7.5 cm gauze pads, with an exudate volume exceeding 10 mL). Before the study and after each dressing change at the wound ostomy care clinic, participants were assessed using the PUSH scale, a validated tool widely utilized by international enterostomal therapists. The total PUSH score, calculated as the sum of all three components, ranged from 0 to 17, in which 0 indicated complete healing and higher scores reflected more severe wounds.

Determination of Sample Size

In this study, the primary outcome measure was the number of days of wound healing. Preliminary experiments indicated that the healing time in the intervention group was 17.57±6.18 days, while it was 33.5±15.97 days in the control group. The sample size for the two groups in a parallel 1:1 design was estimated using PASS 15 software, including a two-sided alpha level of 0.05 and a power of 0.90.[36] The initial calculation indicated that 18 participants were required for the intervention group and 18 for the control group. Accounting for a 20% follow-up loss, a minimum of 23 participants were needed in each group, resulting in a total of at least 46 participants being included in the study.

Safety and Adverse Effects

In this study, the incidence of adverse reactions in the intervention group was used as the safety assessment index. Once a week, the research participants were interviewed at the wound colostomy care clinic to determine whether they had experienced any symptoms of vitamin D intoxication in the preceding week, including polydipsia, polyuria, and vomiting.[16] The investigators promptly documented the timing, characteristics, and test results of the adverse events.

Statistical Analysis

The Full Analysis Set (FAS) was established based on the principle of Intention-to-Treat, which included data from all participants enrolled in the study. The Per-Protocol Set (PPS) was determined based on the principle of per-protocol analysis, which included the data from all participants who completed the study as originally planned. Two researchers used Epidata 3.0 software to review and enter the data. Any missing measurement data were completed using the sequence average approach. All analyses were performed using a two-sided test, with a confidence level of α=0.05, and P <0.05 was considered statistically significant.

SPSS 26.0 software was used to perform statistical analysis. Data on variables, including gender, wound type, and wound site were presented as frequency (constituent ratio) and analyzed using Chi-square test. The data related to age, body mass index (BMI), serum 25(OH)D level, wound area reduction rate, depth reduction rate, and PUSH score were analyzed using the Shapiro–Wilk test to determine their normal distribution status. Variables with a normal distribution were presented as the mean ± standard deviation (SD), and comparisons between two groups were made using a two-independent-sample *t*-test. If the data distribution deviated significantly from normality, the Square Root Transformation (SQRT) function was applied to adjust slightly skewed data to approximate a normal distribution. Data that could not be normalized through transformation were presented as median values with interquartile ranges, and the Mann–Whitney *U*-test was utilized for group comparisons.

Results

Participants

In the intervention group, 2 participants dropped out, and 21 participants completed the study as planned. In the control group, 4 participants dropped out, and 19 participants completed the study as planned, resulting in an overall drop-out rate of 13.0%. The dropouts in both groups were due to participants transferring to other hospitals for treatment. Both the FAS and PPS were used to analyze the general data of the study participants. The findings from both analytical approaches consistently demonstrated that the baseline general data from the intervention and control groups were stable and comparable. Table 1 shows the baseline demographic and clinical characteristics in the two groups (See Supplementary Figure 1).

Chronic Wounds

This study included a total of 57 wounds from 40 participants. FAS and PPS were used to analyze the wounds. The results from these two analytical approaches consistently indicated that the baseline wound data in the intervention and control groups were stable and comparable. Table 2 shows the chronic wounds in both groups.

Serum 25 (OH) D

After treatment, serum 25(OH)D concentration reached 30 ng/mL in 31 participants. The highest concentration was 58.00 ng/mL in the intervention group (n=19) and 34.42 ng/mL in the control group (n=12). The PPS analysis indicated

Table 1 Baseline Characteristics of Adults (>18 Years) with Chronic Wounds (≥4 weeks Duration) and Vitamin D Insufficiency/Deficiency (Serum 25(OH)D <30 ng/mL): Analysis by FAS and PPS Methods

Variable	**FAS**			**PPS**		
	Intervention Group (*N*=23)	**Control Group (*N*=23)**	***P*-value**	**Intervention Group (*N*=21)**	**Control Group (*N*=19)**	***P*-value**
Gender (n, %)			0.55[a]			0.54[a]
Male	14 (60.9%)	12 (52.2%)		12 (57.1%)	9 (47.4%)	
Female	9 (39.1%)	11 (47.8%)		9 (42.9%)	10 (52.6%)	
Diabetes (n, %)			0.24[a]			0.52[a]
Yes	13 (56.5%)	9 (39.1%)		11 (52.4%)	8 (42.1%)	
No	10 (43.5%)	14 (60.9%)		10 (47.6%)	11 (57.9%)	
Age (years)	64.09±13.58	57.96±15.03	0.15[b]	63.71±14.10	59.26±16.25	0.36[b]
BMI (kg/m^2)	23.13±3.83	23.29±4.14	0.89[b]	23.16±3.98	23.64±4.39	0.72[b]
Serum 25 (OH) D (ng/mL)	20.57±4.90	21.28±5.25	0.64[b]	20.44±5.09	20.98±5.68	0.75[b]

Notes: *P*-value is considered significant if less than 5%. [a]Chi-square test. Values are expressed as frequency (n) and percentage (%). [b]Independent Samples *t*-test. Values are presented as mean ± SD.

Abbreviations: BMI, body mass index; FAS, Full Analysis Set; PPS, Per-protocol Set; Serum 25(OH)D, Serum 25-hydroxyvitamin D.

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Table 2 Wound Data From Adults (>18 Years) with Chronic Wounds (≥4 weeks Duration) and Vitamin D Insufficiency/Deficiency (Serum 25(OH)D <30 ng/mL): Analysis by FAS and PPS Methods

Variable	FAS			PPS		
	Intervention Group (*N*=34)	Control Group (*N*=29)	*P*-value	Intervention Group (*N*=32)	Control Group (*N*=25)	*P*-value
Types of wounds (n, %)			0.52 [a]			0.59 [a]
Diabetic foot ulcers	15 (44.1%)	8 (27.6%)		14 (43.8%)	8 (32.0%)	
Pressure injuries	1 (2.9%)	1 (3.4%)		1 (3.1%)	1 (4.0%)	
Venous leg ulcer	3 (8.8%)	2 (6.9%)		3 (9.4%)	2 (8.0%)	
Arterial leg ulcer	1 (2.9%)	1 (3.4%)		1 (3.1%)	1 (4.0%)	
Post-operative wounds	9 (26.5%)	8 (27.6%)		9 (28.1%)	6 (24.0%)	
Wound with poor suture healing	0 (0.0%)	1 (3.4%)		0 (0.0%)	0 (0.0%)	
Burns	0 (0.0%)	3 (10.3%)		0 (0.0%)	3 (12.0%)	
Trauma	4 (11.8%)	5 (17.2%)		4 (12.5%)	4 (16.0%)	
Others	1 (2.9%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Duration of wounds (n, %)			0.08[a]			0.09[a]
1-3 months	18 (52.9%)	25 (75.8%)		16 (50.0%)	22 (75.9%)	
3-6 months	8 (23.5%)	2 (6.1%)		8 (25.0%)	2 (6.9%)	
6-12 months	2 (5.9%)	0 (0.0%)		2 (6.2%)	0 (0.0%)	
≥12 months	6 (17.6%)	6 (18.2%)		6 (18.8%)	5 (17.2%)	
Wound site (n, %)			0.57[a]			0.51[a]
Head and neck	1 (2.9%)	1 (3.4%)		0 (0.0%)	1 (4.0%)	
Shoulder and back	2 (5.9%)	1 (3.4%)		2 (6.2%)	1 (4.0%)	
Abdomen	2 (5.9%)	4 (13.8%)		2 (6.2%)	1 (4.0%)	
Waist	0 (0.0%)	1 (3.4%)		0 (0.0%)	1 (4.0%)	
Upper limbs	0 (0.0%)	0 (0.0%)		0 (0.0%)	0 (0.0%)	
Sacrococcygeal region	1 (2.9%)	1 (3.4%)		1 (3.1%)	1 (4.0%)	
Lower limbs	10 (29.4%)	12 (41.4%)		10 (31.2%)	12 (48.0%)	
Foot	18 (52.9%)	9 (31.0%)		17 (53.1%)	8 (32.0%)	
Wound infection (n, %)	12 (35.3%)	10 (34.5%)	0.95[a]	10 (31.1%)	7 (28.0%)	0.79[a]
Wound length (cm)	1.21±0.41	1.22±0.47	0.98[b]	1.21±0.42	1.22±0.43	0.88[b]
Wound width (cm)	1.06±0.27	1.07±0.32	0.90[b]	1.06±0.28	1.09±0.31	0.77[b]
Wound area (cm)	1.33±0.63	1.39±0.84	0.73[b]	1.32±0.65	1.40±0.79	0.69[b]
***Wound depth (cm)**	0.79±0.29	0.77±0.34	0.854[b]	0.77±0.30	0.70±0.32	0.506[b]
PUSH (scores)	8.18±1.87	8.52±2.57	0.56[b]	8.19±1.91	8.56±2.40	0.52[b]

Notes: *Wound depth: The depth of each wound was assessed using a probe, with the extent to which the probe penetrated the wound recorded as the wound depth. In the FAS, there were 20 wounds in the intervention group and 17 in the control group. In the PPS, there were 19 wounds in the intervention group and 14 in the control group. *P*-value is considered significant if less than 5%. [a] Chi-square test. Values are expressed as frequency (n) and percentage (%). [b] Independent Samples *t*-test. Values are presented as mean ± SD.

Abbreviations: FAS, Full Analysis Set; PPS, Per-protocol Set; PUSH, Pressure Ulcer Scale for Healing.

a significant difference in serum 25(OH)D concentration between the two groups at week 5 ($P<0.01$). After 5 weeks of treatment, an independent samples *t*-test was employed to assess the difference in serum 25(OH)D concentration between the two groups. The findings indicated that the serum 25(OH)D concentration increased by 16.31±7.82 ng/mL in the intervention group and by 8.60±7.57 ng/mL in the control group ($P<0.01$) (Table 3).

Mean Healing Days

In the intervention group, healing days ranged up to 29 days, with the shortest being 7 days and an average of 15.59±6.27 days. Conversely, the longest healing time was 52 days and the shortest was 7 days in the control group, with an average of 26.16±12.70 days. PPS analysis indicated that the intervention group had significantly shorter mean wound healing days compared with the control group ($P<0.01$) (Table 4).

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Table 3 Comparison of Serum 25(OH)D Concentrations at Baseline and End-Intervention in Two Groups of Adults (>18 Years) with Chronic Wounds (≥4 weeks Duration) and Vitamin D Insufficiency/Deficiency (Serum 25(OH)D <30 ng/mL)

Item (ng/mL)	Intervention Group (*N*=21)	Control Group (*N*=19)	*P*-value[a]
Serum 25(OH)D concentration at baseline	20.44±5.09	20.98±5.68	0.751
Serum 25(OH)D concentration at week 5	36.75±7.23	29.58±5.29	**0.001**
Δ serum 25(OH)D concentration	16.31±7.82	8.60±7.57	**0.003**

Notes: *P*-value is considered significant if less than 5%. Statistically significant *P*-values (<0.05) are shown in bold. [a]Independent Samples *t*-test. Values are presented as mean ± SD.
Abbreviation: Serum 25(OH)D, Serum 25-hydroxyvitamin D.

Table 4 Comparison of Mean Healing days in Two Groups of Adults (>18 Years) with Chronic Wounds (≥4 weeks Duration) and Vitamin D Insufficiency/Deficiency (Serum 25(OH)D <30 ng/mL)

Groups	*N*	Mean healing days	*P*-value[a]
Intervention group	32	15.59±6.27	**0.001**
Control group	25	26.16±12.70	

Notes: *P*-value is considered significant if less than 5%. Statistically significant *P*-values (<0.05) are shown in bold. [a]Independent Samples *t*-test. Values are presented as mean ± SD.

Wound Area Reduction Rate

It was revealed that both treatment groups were effective in improving the area reduction rate of chronic wounds over time. In the intervention group, the median reduction rate of wound area reached 100.0% by week 3, whereas it did not reach 100.0% in the control group until week 5. Statistically significant differences in the wound area reduction rate were identified between the two groups from the first week to the sixth week ($P<0.05$) (Table 5).

Wound Depth Reduction Rate

The findings indicated that the two treatment groups were effective in enhancing the depth reduction rate of chronic wounds over time. In the intervention group, the median depth reduction rate reached 100.0% by week 3, whereas in the

Table 5 Comparison of Wound Area Reduction Rate, Wound Depth Reduction Rate, and PUSH Scale Scores From week 1 to week 7 in Two Groups of Adults (>18 Years) with Chronic Wounds (≥4 weeks Duration) and Vitamin D Insufficiency/Deficiency (Serum 25 (OH)D <30 ng/mL)[a]

Time	Wound area Reduction Rate (%)					Wound Depth Reduction Rate (%)					PUSH Scale Score (scores)				
	Intervention Group (*N*=32)		Control Group (*N*=25)		*P*-value	Intervention Group (*N*=19)		Control Group (*N*=14)		*P*-value	Intervention Group (*N*=32)		Control Group (*N*=25)		*P*-value
	Med	IQR	Med	IQR		Med	IQR	Med	IQR		Med	IQR	Med	IQR	
Week1	58.5	34.0–75.6	28.9	9.2–57.5	**0.012**	25.0	0.0–50.0	13.3	0.0–100.0	0.970	6.0	4.3–8.0	6.0	4.0–10.0	0.576
Week2	86.0	66.7–100.0	34.6	19.9–78.4	**0.001**	80.0	50.0–100.0	40.0	0.0–100.0	0.306	4.0	0.0–5.8	6.0	4.0–9.0	0.062
Week3	100.0	90.5–100.0	61.6	41.4–100.0	**0.002**	100.0	100.0–100.0	66.7	25.0–100.0	**0.007**	0.0	0.0–4.0	4.0	0.0–7.5	**0.007**
Week4	100.0	100.0–100.0	80.0	66.0–100.0	**<0.001**	100.0	100.0–100.0	73.3	25.0–100.0	**<0.001**	0.0	0.0–0.0	4.0	0.0–5.5	**<0.001**
Week5	100.0	100.0–100.0	100.0	82.3–100.0	**<0.001**	100.0	100.0–100.0	96.7	45.8–100.0	**0.001**	0.0	0.0–0.0	0.0	0.0–4.0	**<0.001**
Week6	100.0	100.0–100.0	100.0	100.0–100.0	**0.020**	100.0	100.0–100.0	100.0	100.0–100.0	0.244	0.0	0.0–0.0	0.0	0.0–0.0	**0.020**
Week7	100.0	100.0–100.0	100.0	100.0–100.0	0.258	/	/	/	/	/	0.0	0.0–0.0	0.0	0.0–0.0	0.258

Note: [a]P values were assessed by Mann–Whitney *U*-test. *P*-value is considered significant if it is less than 5%. Statistically significant *P*-values (<0.05) are shown in bold.
Abbreviation: PUSH, Pressure Ulcer Scale for Healing.

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control group, it reached 100.0% by week 6. Statistically significant differences in the wound depth reduction rate were noted between the two groups from the third week to the fifth week ($P<0.05$) (Table 5).

PUSH Scale Scores

The findings indicated that the two treatment groups contributed to a gradual reduction in PUSH scale scores for chronic wounds over time. In the intervention group, the median score decreased to 0.0 by week 3, whereas it was reduced to 0.0 by week 5 in the control group. Statistically significant differences in the PUSH scale scores between the two groups were found from the third week to the sixth week ($P<0.05$) (Table 5).

Adverse Effects

During the study period, none of the participants reported experiencing vitamin D toxicity reactions, such as polydipsia, polyuria, vomiting, or loss of appetite.

Discussion

The findings of this study demonstrated a statistically significant increase in serum 25(OH)D concentration by week 5 when compared with baseline in both the intervention and control groups. Notably, the serum 25(OH)D concentration in the intervention group was substantially higher than that in the control group at week 5, thereby emphasizing the superior efficacy of cholecalciferol supplementation over routine care in enhancing serum 25(OH)D concentration within a defined time frame. More importantly, the mean serum 25(OH)D concentration in the control group remained below the threshold of 30 ng/mL, the minimum level required for vitamin D sufficiency, at week 5. This suggests that the usual care regimen, which involved standard wound management practices along with dietary and sun exposure guidance, did not significantly ameliorate vitamin D insufficiency in the short-term. Although dietary intake and sun exposure represent important directions for addressing vitamin D deficiency, it is well established that dietary sources contribute only about 10% of the total vitamin D required by the human body. In addition, the majority of participants in this study were middle-aged or elderly individuals, a demographic group whose ability to acquire vitamin D from food sources is limited due to a decline in metabolic function and diminished gastrointestinal absorption efficiency as they age.[37] Moreover, the capacity for vitamin D synthesis in the skin under sunlight exposure in elderly individuals is only 30% that of younger individuals under comparable sunlight conditions.[38] Consequently, despite the provision of dietary recommendations and guidance on sun exposure in the control group, the short-term effect on increasing serum 25(OH)D concentration was minimal. However, chronic vitamin D insufficiency is particularly detrimental to the healing of chronic wounds. Bacterial biofilms (BBF) are a common feature in chronic wounds, mainly hindering the normal healing process by protecting pathogens from the immune response and antimicrobial treatments.[39] Vitamin D has shown to upregulate antimicrobial peptides, including cathelicidins and β-defensins, enhancing the body's defense against infections and bacterial biofilm formation,[40] thereby supporting more effective wound healing. Additionally, vitamin D facilitates the maturation of monocytes into macrophages with improved migration and pathogen-engulfing functions, promoting effective clearance while reducing excessive immune-related tissue damage.[41] In the context of delayed wound healing, participants with chronic wounds not only experience increased pain,[42] but also face limitations in daily activities, contributing to a significant psychological burden. More critically, prolonged delayed healing can lead to heightened infection risk, ultimately posing life-threatening consequences. Hence, it is imperative for participants with chronic wounds, particularly those who are middle-aged or elderly and whose vitamin D concentrations are insufficient, to receive high-dose cholecalciferol supplementation over a short-term period. Such an intervention not only improves vitamin D levels, but also accelerates wound healing, mitigates pain, reduces infection risks, and enhances such patients' overall quality of life.

In this study, the mean wound healing time in the intervention group was approximately 2 weeks shorter than that in the control group, and the wound area and depth reduction rate of the intervention group were better than those of the control group. This may be associated with the downregulation of the expression of certain MMP gene family members in keratinocytes,[14] the facilitation of keratinocyte migration on fibrillar collagen, the interaction with low levels of transforming growth factor β1, and the stimulation of dermal fibroblast proliferation[43] after cholecalciferol supplementation. Vitamin D can improve the anti-bacterial biofilm (anti-BBF) effect by promoting the expression of antimicrobial peptides,[44] enhancing the antibacterial properties of monocytes/macrophages,[45] and facilitating chronic wound healing by downregulating MMPs and fostering collagen synthesis.[14]

The findings of this study align with those of previous research conducted by Halschou-Jensen et al, Liu et al, and Wang et al. Halschou-Jensen et al[20] who investigated the efficacy of high-dose versus low-dose cholecalciferol supplementation in the treatment of chronic DFUs. Participants whose ulcers had not healed after more than six weeks were divided into two groups: high-dose group receiving 6800 IU/day of oral cholecalciferol for 48 weeks (or until wound healing) and low-dose group receiving 800 IU/day for the same duration. The study found that the high-dose group had a significantly higher wound healing rate than that in the low-dose group (70.0% vs 35.0%, P=0.01). Additionally, the wound area decreased from 1.25 (0.4–3.2) cm² to 0 (0.0–0.8) cm² in the high-dose group, compared to a decrease from 2.1 (0.8–5.0) cm² to 1.0 (0.0–3.1) cm² in the low-dose group (P<0.05). This study confirmed the effectiveness of high-dose cholecalciferol in promoting the healing of chronic DFUs. However, it also showed that serum 25(OH)D concentration in the high-dose group peaked at week 24 and then declined by week 48, indicating unnecessary supplementation after the peak level was reached. Similarly, Liu et al[46] conducted a study where they orally administered 3125 IU/day of vitamin D until wound healing was achieved in participants with grade 2 DFUs. They found a higher wound healing rate in the intervention group compared to the control group (90% vs 60%, P=0.02). However, because serum 25(OH)D concentration was not measured before and after the supplementation period, the precise relationship between vitamin D concentration and wound healing was not established. Wang et al[22] randomized 186 DFU participants into two groups: one receiving 4000 IU/day of cholecalciferol for 12 weeks, and the other receiving a placebo. After 12 weeks, the serum 25(OH)D concentration in the intervention group was significantly higher than in the control group (28.11±12.59 vs 18.47±8.55 ng/mL). The wound area in the intervention group decreased from 14.71±6.38 cm² to 4.33 ±1.85 cm², while the wound depth decreased from 1.13±0.57 cm to 0.44±0.19 cm. In contrast, the control group experienced a reduction in wound area from 14.80±6.47 cm² to 7.57±2.11 cm², and a decrease in wound depth from 1.26±0.50 cm to 0.65±0.23 cm. This study further confirmed that vitamin D supplementation could significantly improve the wound condition in DFUs. However, the oral cholecalciferol dose of 4000 IU/day was lower than the recommended therapeutic dose for vitamin D deficiency treatment in China, which might limit the ability to maximize the increase in serum 25(OH)D concentration and, consequently, the wound healing response. In contrast to the studies mentioned above, this study included participants with various types of chronic wounds, indicating that cholecalciferol supplementation is effective across different wound types. However, the healing mechanisms of different chronic wounds may vary, necessitating further clinical studies to explore and validate the effects of cholecalciferol supplementation in diverse chronic wound types.

In this study, chronic wounds were evaluated using the PUSH scale, which included area (length × width), tissue type (epithelial tissue, granulation tissue, cartilaginous tissue, necrotic tissue), and exudate quantity (small, medium, large). As time progressed, both the intervention and control groups exhibited a reduction in PUSH scale scores. Although the difference in the rate of area reduction between the two groups was statistically significant during the first 2 weeks, there was no significant difference in PUSH scores between the two groups during this period. This lack of difference may be attributed to the time required for wound tissue transformation and a reduction in exudate volume, which takes time to manifest. In wounds with necrotic tissue, frequent debridement is necessary to remove all undesirable materials, including necrotic tissue, foreign bodies, and hyperkeratotic tissue.[47] Wang Shaoting et al[22] evaluated wounds using the Bates-Jensen wound assessment tool, which includes 8 items, such as granulation tissue, exudate volume, necrotic tissue volume, and wound opacity. They found a decrease in the intervention group's score from 22.37±5.72 to 0.44±0.19, compared with a reduction in the control group's score from 21.99±6.18 to 17.39±7.35. The Bates-Jensen Wound Assessment Tool comprises 15 items, excluding wound name and shape, with the remaining 13 assessing factors, such as size, depth, and margin.[48] While the Bates-Jensen tool provides a more detailed assessment of wound changes compared with the PUSH scale used in this study, it requires more time to administer. Given that participants in this study were outpatients, the PUSH scale was employed for dynamic assessment of chronic wounds, considering the time constraints.

Limitations

This study had numerous limitations. Firstly, this study recruited only participants with chronic wounds from a grade A hospital in Guangzhou, Guangdong Province, for a randomized controlled trial, relying on a single sample source and a limited number of cases. Secondly, due to cost and study constraints, no blinding was implemented, which might introduce bias. Thirdly, the dropout rate reached 13%, as six participants were referred to other hospitals for treatment and could not be followed up, leading to sample loss. Fourthly, dietary supplementation and UV exposure were not systematically recorded, which might influence the assessment of vitamin D level. Finally, data on concurrent drug treatments were not collected, which could confound the interpretation of results.

Strengths

In this study, participants with chronic wounds who did not achieve the recommended vitamin D concentration received conventional wound care combined with cholecalciferol supplementation, while those who received only conventional wound care served as the comparison group. It was found that short-term high-dose cholecalciferol supplementation could significantly improve vitamin D concentration and promote wound healing. In addition, participants in this study covered diverse types of chronic wounds, indicating that cholecalciferol supplementation could be effective for different types of chronic wounds, making the results of the study more general and clinically applicable. Moreover, this study followed the recommended dosage and method in the Consensus on the Clinical Application of Vitamin D and its Analogues, and avoided the problems, such as uneven supplementation dose and extremely long supplementation time in existing studies. This study evaluated the effects of cholecalciferol supplementation on increasing serum 25(OH) concentration and wound healing, providing a safe and effective vitamin D supplementation scheme for clinical practice, as well as adding evidence to the current clinical research on vitamin D supplementation in the treatment of chronic wounds.

Recommendations for Future Research

1. Efforts should be made to increase the sample size, including and classifying wounds with diverse conditions, and further analyzing the effects of oral cholecalciferol on chronic wound healing.
2. In future research, a professional team could conduct a double-blind study to enhance the reliability of the research findings.
3. It is recommended that future research should systematically document each participant's dietary supplementation and UV exposure. Collecting these data will enable researchers to control for additional variables and interpret the results more accurately.

Conclusion

This study indicated that short-term, high-dose oral cholecalciferol effectively increased serum 25(OH)D concentration in participants with chronic wounds and vitamin D insufficiency or deficiency. Importantly, supplementation significantly shortened the time to healing and accelerated the reduction in wound area and depth. The findings highlighted the potential of incorporating oral vitamin D supplementation into existing wound care protocols, such as the TIME principle, thereby providing preliminary evidence to support the development of screening strategies and expert consensus for vitamin D management in Chinese patients with chronic wounds. In terms of clinical perspective, routine assessment of serum 25(OH)D level in patients with chronic, hard-to-heal wounds should be considered. Oral vitamin D supplementation may serve as an adjunctive therapy to enhance wound healing, potentially leading to faster recovery and improved outcomes. These measures may also help mitigate both the clinical and economic burden associated with chronic wounds.

Abbreviations

FAS, Full Analysis Set; PPS, Per-protocol Set; SQRT, Square Root Calculations; MMP, Matrix Metalloproteinase; MMPS, Matrix Metalloproteinases; DFU, Diabetic Foot Ulcer; BMI, Body Mass Index; TIME, Tissue, Infection, Moisture and Edge of wound; PUSH, Pressure Ulcer Scale for Healing; UV, Ultra Violet; IUs, International Units;

Serum 25(OH)D, Serum 25-hydroxyvitamin D; LL, Leucine-Leucine; Anti-BBF, Anti-Bacterial Biofilm; BBF, Bacterial biofilms.

Data Sharing Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Informed Consent

Signed informed consent forms were provided by participants or their legal representatives. The Ethics Committee of Guangzhou Red Cross Hospital reviewed and approved the study protocol (Approval No. 2022-219-01), which was also registered in the Chinese Clinical Trial Registry on 6 November 2022 (Link: https://www.chictr.org.cn/, Registration No. ChiCTR2200065482).

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

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References

1. Tan Q, Xu Y. Theories and strategies of chronic wound treatment. *Zhonghua Shao Shang Za Zhi*. 2020;36(9):798–802. doi:10.3760/cma.j.cn501120-20200728-00361
2. Martinengo L, Olsson M, Bajpai R, et al. Prevalence of chronic wounds in the general population: systematic review and meta-analysis of observational studies. *Ann Epidemiol*. 2019;29:8–15. doi:10.1016/j.annepidem.2018.10.005
3. Lindholm C, Searle R. Wound management for the 21st century: combining effectiveness and efficiency. *Int Wound J*. 2016;13 Suppl 2(Suppl 2):5–15. doi:10.1111/iwj.12623
4. Jiang YF. Epidemiology of chronic cutaneous wounds in China. *Wound Repair Regen*. 2011; 19(2):181–8.
5. Meng H, Su JL, Wang R, Shen Q, Li Y. 889 cases of hospitalised patients with chronic difficult wound surfaces Clinical epidemiological studies. *Acad J Chin PLA Med School*. 2022;43:253–258.
6. Fu XB. To guide the discipline construction of wound treatment and the training of wound treatment specialists with the general idea of establishing a research hospital. *Chin Res Hosp*. 2016;3:2–5.
7. Chen Y, Zeng Y. Correlation of depression and anxiety with social support and quality of life in patients with chronic wounds. *Zhong Nan Da Xue Xue Bao Yi Xue Ban*. 2018;43(9):1032–1036. doi:10.11817/j.issn.1672-7347.2018.09.016
8. Wang GQ, Tang PF. Progress in the treatment of chronic wounds. *Acad J Chin PLA Med School*. 2018;39:444–446+450.
9. Thomas Hess C. Checklist for factors affecting wound healing. *Adv Skin Wound Care*. 2011;24(4):192. doi:10.1097/01.ASW.0000396300.04173.ec
10. Ren SQ, Yang J, Yan P, et al. Retrospective analysis of 177 cases of chronic refractory wounds pathogen infection status and drug resistance. 2019;29:2348-2352. *Chin J Nosocomiol*. 2019;29:2348–2352.
11. Li HX, Gong ML, Deng XL. Multi-centre survey and analysis of vitamin D levels in Chinese older people. *Chin J Lab Med*. 2021;44:39–44.
12. Piantanida E, Gallo D, Veronesi G, et al. Cardiometabolic healthy and unhealthy obesity: does vitamin D play a role? *Endocr Connect*. 2017;6(8):943–951. doi:10.1530/EC-17-0304
13. Li J, Dong RJ, Li JS, Zhang Y, Li YY. Antimicrobial and immunomodulatory mechanisms of the antimicrobial peptide LL-37. *Chin J Infect Control*. 2022;21:104–110.
14. López-López N, González-Curiel I, Treviño-Santa Cruz MB, et al. Expression and vitamin D-mediated regulation of matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs) in healthy skin and in diabetic foot ulcers. *Arch Dermatol Res*. 2014;306(9):809–821. doi:10.1007/s00403-014-1494-2
15. Holick MF. Vitamin D deficiency. *N Engl J Med*. 2007;357(3):266–281. doi:10.1056/NEJMra070553
16. Xia WB, Zhang ZL, Lin H, Jin XL, Yu W. Consensus on the clinical use of vitamin D and its analogues. *Chin J Osteoporosis Bone Min Res*. 2018;11:19.
17. Renner R, Garibaldi MDS, Benson S, Ronicke M, Erfurt-Berge C. Nutrition status in patients with wounds: a cross-sectional analysis of 50 patients with chronic leg ulcers or acute wounds. *Eur J Dermatol*. 2019;29(6):619–626. doi:10.1684/ejd.2019.3678

18. Xiao Y, Wei L, Xiong X, Yang M, Sun L. Association between vitamin D status and diabetic complications in patients with type 2 diabetes mellitus: a cross-sectional study in Hunan China. *Front Endocrinol*. 2020;11:564738. doi:10.3389/fendo.2020.564738
19. Razzaghi R, Pourbagheri H, Momen-Heravi M, et al. The effects of vitamin D supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: a randomized, double-blind, placebo-controlled trial. *J Diabetes Complications*. 2017;31(4):766–772. doi:10.1016/j.jdiacomp.2016.06.017
20. Halschou-Jensen PM, Sauer J, Bouchelouche P, Fabrin J, Brorson S, Ohrt-Nissen S. Improved healing of diabetic foot ulcers after high-dose vitamin D: a randomized double-blinded clinical trial. *Int J Low Extrem Wounds*. 2023;22(3):466–474. doi:10.1177/15347346211020268
21. Caj A, Li YJ. Role of vitamin D in the treatment of type 2 diabetic foot ulcers. *China Rural Health*. 2019;11:62+61.
22. Wang ST, Wu PP, Wang ZJ, Li DJ, Deng WT, Wang SP. Effects of vitamin D supplementation on wound healing, glucose metabolism, inflammation and oxidative stress in diabetic foot ulcers. *Eval Anal Drug-Use Hosp China*. 2020;20:940–944.
23. Grant WB, Lordan R. Vitamin D for COVID-19 on trial: an update on prevention and therapeutic application. *Endocr Pract*. 2021;27(12):1266–1268. doi:10.1016/j.eprac.2021.10.001
24. Delanaye P, Lanot A, Bouquegneau A, et al. Monitoring 25-OH and 1,25-OH vitamin D levels in hemodialysis patients after starting therapy: does it make sense? *Clin Chim Acta*. 2023;539:50–54. doi:10.1016/j.cca.2022.11.032
25. Gardner SE, Frantz RA, Doebbeling BN. The validity of the clinical signs and symptoms used to identify localized chronic wound infection. *Wound Repair Regen*. 2001;9(3):178–186. doi:10.1046/j.1524-475x.2001.00178.x
26. Schultz GS, Barillo DJ, Mozingo DW, Chin GA. Wound bed preparation and a brief history of TIME. *Int Wound J*. 2004;1(1):19–32. doi:10.1111/j.1742-481x.2004.00008.x
27. Langemo D, Anderson J, Hanson D, Hunter S, Thompson P. Measuring wound length, width, and area: which technique? *Adv Skin Wound Care*. 2008;21(1):42–45; quiz45–47. doi:10.1097/01.ASW.0000284967.69863.2f
28. Goldman RJ, Salcido R. More than one way to measure a wound: an overview of tools and techniques. *Adv Skin Wound Care*. 2002;15(5):236–243. doi:10.1097/00129334-200209000-00011
29. Tolan NV. Development of a 25-Hydroxyvitamin D liquid chromatography-tandem mass spectrometry assay, cleared by the food and drug administration, via the de novo pathway. *Clin Lab Med*. 2018;38(3):553–564. doi:10.1016/j.cll.2018.05.006
30. Rodopaios NE, Petridou A, Mougios V, et al. Vitamin D status, vitamin D intake, and sunlight exposure in adults adhering or not to periodic religious fasting for decades. *Int J Food Sci Nutr*. 2021;72(7):989–996. doi:10.1080/09637486.2021.1887821
31. Jiang QX, Wang JD, Dong S, Peng Q, Huang XL. The use of two methods to protect the skin in the negative pressure therapy of chronic wounds. *Chin J Nurs*. 2020;55:39–44.
32. Jiang QX, Zhu YL, Fan LH, et al. Study of the efficacy and safety of topical oxygen therapy in the treatment of traumatic wounds. *J Traumatic Surg*. 2023;25:755–761.
33. National Health Commission of the People's Republic of China. Screening method for vitamin D deficiency in population: WS/T 677-2020 [EB/OL]. (2020-05-06) [2025-08-29].
34. W J. Comprehensive external treatment of traditional Chinese medicine for stage II-IV diabetic foot ulcer (draft). *Chin J Surg Integr Trad West Med*. 2012;18:318–320.
35. Song WQ, Qin YR, Liu MM, Cheng SL, Qin HZ. Practice of pressure ulcer management using PUSH score. *Chin Nurs Manage*. 2016;16:869–872.
36. Wang RP. Sample size estimation methods in the design of randomized controlled clinical trials. *Shanghai Med Pharmaceut J*. 2023;44:48–52.
37. Gao PP, Li PP, Cai XM. Evaluation of the effect of stratified vitamin D supplementation in the vitamin D-deficient elderly population. *Acta Nutrimenta Sinica*. 2019;41:332–337.
38. Vieth R, Ladak Y, Walfish PG. Age-related changes in the 25-hydroxyvitamin D versus parathyroid hormone relationship suggest a different reason why older adults require more vitamin D. *J Clin Endocrinol Metab*. 2003;88(1):185–191. doi:10.1210/jc.2002-021064
39. Liu J, Liu Y. Research advances on the formation mechanism and diagnosis of bacteria biofilms in chronic wounds. *Zhonghua Shao Shang Za Zhi*. 2021;37(7):692–696. doi:10.3760/cma.j.cn501120-20200327-00198
40. Luo Y, McLean DT, Linden GJ, McAuley DF, McMullan R, Lundy FT. The naturally occurring host defense peptide, LL-37, and its truncated mimetics KE-18 and KR-12 have selected biocidal and antibiofilm activities against Candida albicans, Staphylococcus aureus, and Escherichia coli in vitro. *Front Microbiol*. 2017;8:544. doi:10.3389/fmicb.2017.00544
41. Ortiz-Prado E, Vasconez-Gonzalez J, Izquierdo-Condoy JS, et al. Cholecalciferol (vitamin D3): efficacy, safety, and implications in public health. *Front Nutr*. 2025;12:1579957. doi:10.3389/fnut.2025.1579957
42. Price PE, Fagervik-Morton H, Mudge EJ, et al. Dressing-related pain in patients with chronic wounds: an international patient perspective. *Int Wound J*. 2008;5(2):159–171. doi:10.1111/j.1742-481X.2008.00471.x
43. Ding J, Kwan P, Ma Z, et al. Synergistic effect of vitamin D and low concentration of transforming growth factor beta 1, a potential role in dermal wound healing. *Burns*. 2016;42(6):1277–1286. doi:10.1016/j.burns.2016.03.009
44. Lowry MB, Guo C, Zhang Y, et al. A mouse model for vitamin D-induced human cathelicidin antimicrobial peptide gene expression. *J Steroid Biochem Mol Biol*. 2020;198:105552. doi:10.1016/j.jsbmb.2019.105552
45. Trochoutsou AI, Kloukina V, Samitas K, Xanthou G. Vitamin-D in the immune system: genomic and non-genomic actions. *Mini Rev Med Chem*. 2015;15(11):953–963. doi:10.2174/1389557515666150519110830
46. Liu FP, Zou YQ, Wang H, Zou T. Oral vitamin D combination tanning aid for the treatment of diabetic foot. *Mod Preventive Med*. 2010;37:4029–4030.
47. Li M, Wu JQ, Huang SQ. Interpretation of international expert consensus on "Early biofilm treatment strategy for refractory wounds: wound hygiene". *Chin Nurs Res*. 2021;35:5.
48. Harris C, Bates-Jensen B, Parslow N, Raizman R, Singh M, Ketchen R. Bates-Jensen wound assessment tool: pictorial guide validation project. *J Wound Ostomy Continence Nurs*. 2010;37(3):253–259. doi:10.1097/WON.0b013e3181d73aab