Journal of Health and Nutrition Research
Vol. 5, No. 2, 2026, pg. 879-890, https://doi.org/10.56303/jhnresearch.v5i2.1301
Journal homepage: https://journalmpci.com/index.php/jhnr/index

e-ISSN: **2829-9760**

Nutritional Interventions and Wound Healing Outcomes in Patients With Diabetic Foot Ulcers: A Systematic Review

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ARTICLES

Submitted: 23 February 2026

Accepted: 13 May 2026

Published: 01 August 2026

Keywords:
Diabetic foot ulcer, Nutritional interventions, Oral nutritional supplementation, Multidisciplinary care, Wound healing

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ABSTRACT

Diabetic foot ulcers (DFU) are a severe complication of diabetes mellitus that contribute to delayed wound healing, increased amputation risk, and substantial healthcare burden. Beyond vascular and metabolic abnormalities, malnutrition plays a critical role in prolonging inflammation, impairing collagen synthesis, and delaying tissue regeneration. Although nutritional support is increasingly incorporated into DFU management, its clinical effectiveness remains variably reported. Therefore, this study aimed to evaluate the effects of nutritional interventions and the association between nutritional status and wound healing outcomes in patients with DFU. This systematic review was conducted in accordance with PRISMA 2020 guidelines. The methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools. The review protocol was not registered in PROSPERO. Articles were retrieved from PubMed, Scopus, and ProQuest using the keywords “diabetic foot ulcer”, “nutritional intervention”, and “wound healing”. Inclusion criteria comprised original quantitative studies published in English between 2022 and 2026 involving adult DFU patients. Data were extracted using structured tables and synthesized narratively. Nine eligible studies demonstrated that nutritional interventions, including oral nutritional supplementation, micronutrient supplementation, dietary modification, and nutrition-related multidisciplinary approaches, were associated with greater wound size reduction, improved inflammatory biomarkers, and enhanced re-epithelialization. Observational evidence consistently showed that poor nutritional status was linked to higher ulcer severity and increased amputation risk. Nutritional optimization appears to be a clinically meaningful component of DFU management and may be beneficial when integrated into comprehensive care strategies.

Key Messages:

- Optimizing nutritional status and integrating targeted nutritional interventions into comprehensive care strategies are consistently associated with improved wound healing outcomes and reduced ulcer severity in patients with diabetic foot ulcers

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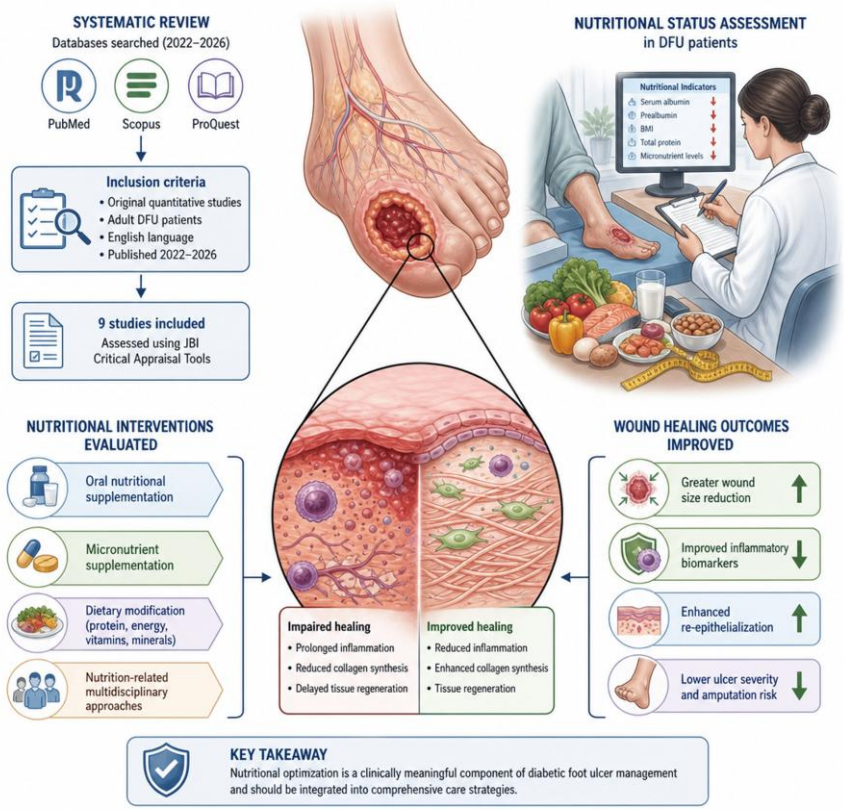
GRAPHICAL ABSTRACT



INTRODUCTION

Diabetes mellitus is a chronic disease with a global prevalence that has increased significantly over the past three decades (1). The number of people living with diabetes has increased from around 200 million in 1990 to 830 million in 2022, with adult prevalence rising from 7% to 14% (2). One of the most serious chronic complications is diabetic foot ulcer (DFU), which is associated with high rates of amputation and mortality (3). Approximately 31% of patients with DFU undergo lower limb amputation, underscoring the significant clinical burden of this complication (4). In addition to the clinical impact, DFU also imposes a substantial economic burden on healthcare systems and societal productivity (5).

DFU develops due to a combination of peripheral neuropathy, peripheral vascular disorders, and infections that synergistically worsen tissue damage (6). Wounds in DFU patients are often chronic and difficult to heal, especially in individuals with metabolic disorders and poor nutritional status (7). Diabetic foot infections worsen wound conditions through the involvement of various pathogens and increased antibiotic resistance (6). DFU has also been shown to significantly reduce patients' quality of life, particularly among those with larger or initial ulcers (8). The recurrence rate of DFU remains high, with more than one-third of patients experiencing recurrence during follow-up (9). The recurrence rate within two years can reach nearly 40%, indicating that DFU is a long-term clinical problem (10).

The wound healing process occurs through the dynamically coordinated phases of inflammation, proliferation, and remodeling (11). In diabetic patients, chronic hyperglycemia triggers the accumulation of AGEs, which increase oxidative stress and inflammation (12). AGEs can induce macrophage apoptosis and prolong the inflammatory phase in diabetic foot wounds (13). Increased matrix metalloproteinase-9 (MMP-9) contributes to extracellular matrix degradation and inhibits the proliferation phase (14). Persistent oxidative stress is also mediated by molecular regulation such as long noncoding RNAs that inhibit tissue regeneration (15).

Wound healing is highly dependent on adequate macronutrients and micronutrients that support collagen synthesis and angiogenesis (16). Protein requirements in wound conditions can increase to an

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average of 1.84±0.62 g/kg/day to support nitrogen balance (17). Omega-3 fatty acids have immunomodulatory and anti-inflammatory effects that are relevant to the wound healing process (18). Malnutrition is found in approximately 38% of DFU patients and is associated with poorer clinical outcomes (19). Deficiencies in albumin, hemoglobin, iron, and zinc are also associated with impaired wound healing (20).

Various nutritional interventions, such as oral supplementation, dietary modification, and nutrition education, have been reported to potentially improve wound healing in DFU patients (21). Micronutrient supplementation, such as vitamin C, vitamin D, and zinc, has shown inconsistent results regarding wound healing time (22). A multidisciplinary approach that includes nutritional aspects has been shown to improve survival and amputation-free survival in long-term follow-up (23).

The heterogeneity of outcome reporting in DFU studies limits comparisons of the effectiveness of available interventions (24). The existing evidence remains fragmented and shows high variation in study design (25). Variations in clinical trial methodologies also limit the integration of research results and highlight the need for more standardized evidence synthesis (26).

The heterogeneity of nutritional interventions and inconsistency in outcomes indicate a gap in understanding the effectiveness of nutritional interventions in DFU. In recent years, there has been a growing number of studies published between 2022 and 2026 evaluating various nutritional interventions in DFU management, including advanced oral supplementation, micronutrient-based therapies, and multidisciplinary approaches. However, the increasing volume of heterogeneous evidence has made it difficult to draw consistent conclusions. Therefore, an updated systematic review focusing on recent evidence is needed to synthesize findings and clarify the role of nutritional interventions in DFU wound healing outcomes. Therefore, this study aims to systematically review various nutritional interventions and evaluate their effect on wound healing outcomes in patients with DFU.

METHODS

Study Design

This study was conducted as a systematic review to evaluate the effectiveness of nutritional interventions on wound healing outcomes in patients with diabetic foot ulcers (DFU). The review was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA 2020) guidelines. Due to the heterogeneity of study designs, intervention types, and outcome reporting, a narrative synthesis approach was applied.

Search Strategy

A comprehensive literature search was conducted across three electronic databases: PubMed, Scopus, and ProQuest. The search included articles published between January 2022 and March 2026.

The search strategy employed Boolean operators (AND, OR) using the following keyword combinations: (“diabetic foot ulcer” OR “diabetic foot” OR DFU) AND (“nutritional intervention” OR “nutrition therapy” OR “oral nutritional supplementation” OR ONS OR “micronutrient supplementation” OR “diet modification” OR “nutrition education”) AND (“wound healing” OR “wound closure” OR “time to healing” OR “wound size reduction” OR “healing rate” OR amputation OR “length of stay”). Filters were applied to limit results to: English language, Full-text availability, and Original research articles.

Eligibility Criteria

Studies were selected based on predefined inclusion and exclusion criteria. Inclusion criteria: (1) Adult patients diagnosed with diabetic foot ulcers (DFU), (2) studies evaluating nutritional interventions, including oral nutritional supplementation (ONS), micronutrient supplementation, diet modification, nutrition education, or nutrition-based multidisciplinary approaches, (3) studies reporting clinical wound-related outcomes such as wound healing rate, time to healing, wound size reduction, recurrence, infection, amputation, length of stay, or quality of life, (4) quantitative study design (Randomized controlled trials, quasi-experimental studies, cohort studies, case-control studies, cross-sectional studies), (5) original research articles published in English between 2022 and 2026 and available in full-text. Exclusion criteria:

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(1) studies not specifically involve DFU patients, (2) studies assessing nutritional status without examining wound-related clinical outcomes, (3) review articles, editorials, letters, conference abstracts, and study protocols, (4) studies lacking clear reporting of wound healing outcomes.

Study Selection

All identified records were imported into reference management software to remove duplicates. The selection process was conducted in two stages: (1) title and abstract screening, and (2) full-text review based on the predefined eligibility criteria. Two independent reviewers screened the titles and abstracts and assessed full-text eligibility. Any discrepancies were resolved through discussion and consensus. If disagreement persisted, a third reviewer was consulted. Screening and eligibility assessments were performed systematically to ensure consistency in study selection. The study selection process is presented in the PRISMA flow diagram (Figure 1).

Quality Assessment

The methodological quality of included studies was assessed using the Joanna Briggs Institute (JBI) Critical Appraisal Tools, adapted to each study design. Quality assessment was conducted independently by two reviewers. Any disagreements were resolved through discussion or consultation with a third reviewer. The appraisal evaluated: Appropriateness of study design, sampling adequacy, measurement validity and reliability, control of confounding factors, and outcome reporting transparency.

Studies were not excluded solely on quality scores. However, methodological rigor was considered during interpretation of findings, with greater interpretive weight given to studies with higher methodological quality.

Data Extraction

Data extraction was conducted independently by two reviewers using standardized data extraction forms. The following information was collected: (1) Author and year of publication, (2) country of study, (3) study design, (4) sample size and participant characteristics, (5) type and duration of nutritional intervention, (6) wound healing-related outcomes, (7) key findings. Where available, quantitative effect measures (e.g., mean difference, odds ratio, hazard ratio, confidence intervals) were recorded.

Data Synthesis

Due to the heterogeneity in intervention types, study designs, follow-up duration, and outcome measurement methods, quantitative meta-analysis was not performed. Instead, findings were synthesized narratively. Quantitative studies were summarized based on direction and magnitude of effect, while observational studies were synthesized according to identified associations between nutritional status and wound-related outcomes. The synthesis aimed to provide an integrated overview of the role of nutritional interventions in relation to wound healing outcomes among DFU patients.

RESULTS

Study selection

The study selection process followed the PRISMA 2020 framework. A total of 524 records were identified through database searching (PubMed, Scopus, and ProQuest). After removing 22 duplicate records, 502 articles remained for title and abstract screening. During initial screening, 471 articles were excluded for the following reasons: Not involving diabetic foot ulcer (DFU) population (n = 162), not evaluating nutritional interventions (n = 148), not reporting wound healing-related outcomes (n = 97), and non-original studies (reviews, editorials, or protocols) (n = 64). Thirty-one full-text articles were assessed for eligibility. After full-text review and methodological appraisal using the Joanna Briggs Institute (JBI) tools, 22 studies were excluded due to failure to meet the predefined inclusion criteria or lack of relevant nutritional intervention components. Finally, nine studies published between 2022 and 2026 were included in the qualitative synthesis. The detailed study selection process is presented in Figure 1.

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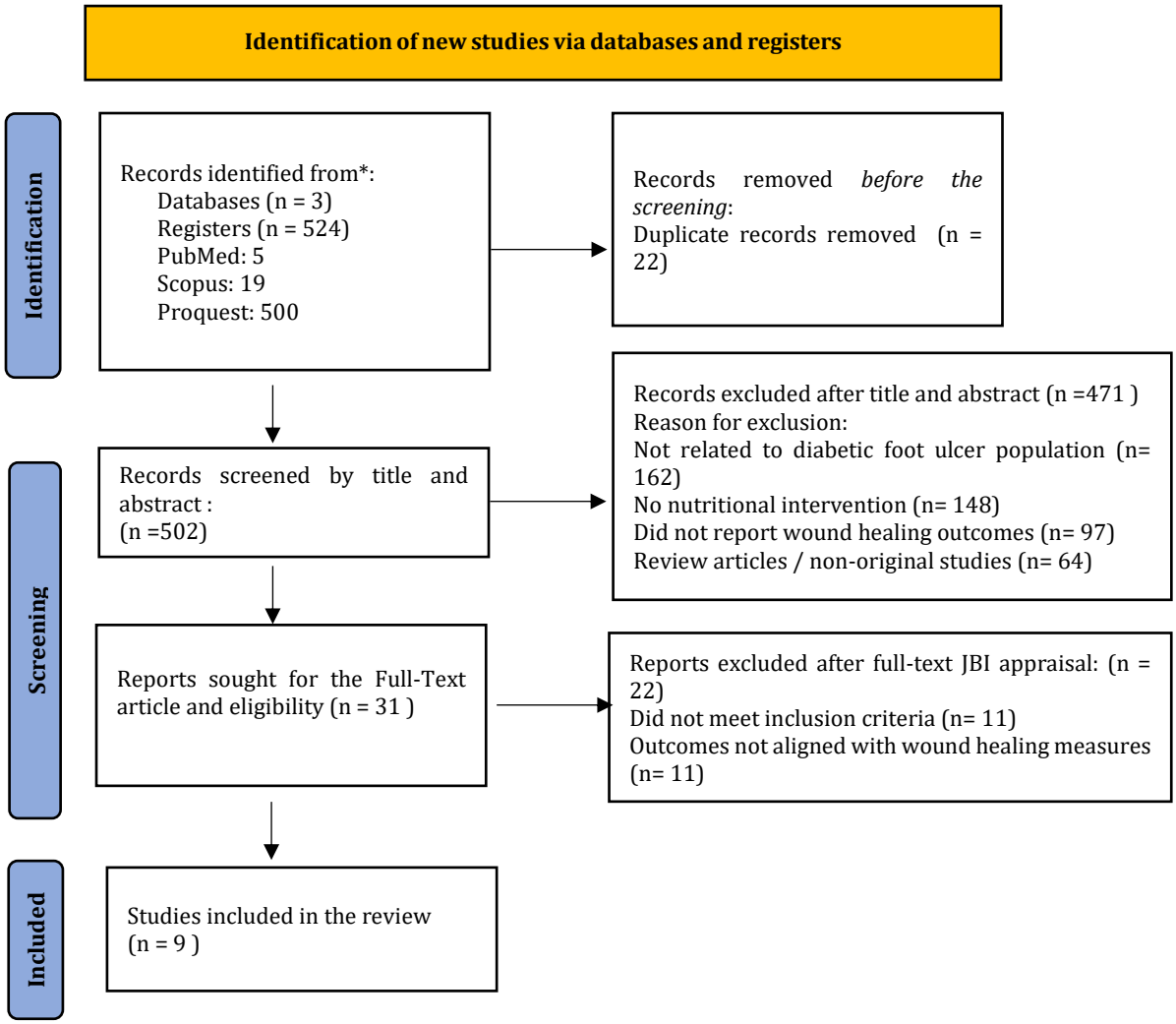

Figure 1. PRISMA flow diagram

Study characteristics

The nine included studies were conducted across multiple countries, including the United States, Australia, China, Egypt, Romania, and Poland, reflecting diverse healthcare settings. The study designs included: Randomized Controlled Trials (RCTs) (n = 3), Cohort studies (prospective and retrospective) (n = 2), Case-control study (n = 1), Cross-sectional study (n = 1), Prospective controlled study / quasi-experimental (n = 1), and Secondary data analysis (n = 1). Sample sizes ranged from 28 to 55,409 participants. All studies involved adult patients with DFU, including varying degrees of severity.

Oral Nutritional Supplementation

Three studies evaluated oral nutritional supplementation (ONS) as an intervention to improve wound healing outcomes. A retrospective cohort study demonstrated that wound-specific oral nutritional supplementation significantly improved wound size reduction compared to standard care (27). Overall, ONS interventions were associated with improved wound healing parameters, particularly in wound size reduction and inflammatory control.

Micronutrient-Based and Integrative Interventions

Micronutrient-based and pharmacological nutritional interventions were evaluated in two studies. A randomized controlled trial found that combination therapy with cilostazol and selenium significantly reduced ulcer dimensions compared to standard treatment (28). Another study using integrative therapy (combining ozone, PEMF, probiotics, and dietary modification) demonstrated

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significantly higher re-epithelialization rates and improved glycemic and inflammatory markers compared to control (29). These findings suggest that micronutrient-based and integrative approaches may enhance wound-healing outcomes, although heterogeneity in interventions limits direct comparison.

Table 1. Characteristics included studies

Reference & Country	Study Design	Sample Size & Participant Characteristics	Intervention & Duration	Outcomes Measures	Key Findings
(7) (Poland)	Prospective observational study	N = 106 patients with chronic wounds	Nutritional assessment (no experimental intervention), 12 months	Albumin, Hb, CRP, NRI, wound area, exudate, tissue destruction	Lower albumin, Hb & NRI are associated with larger wound area and severity, and malnutrition is strongly linked to poor wound characteristics.
(30) (USA)	Retrospective cohort study	N = 55,409 Medicare patients with DFU	Specialty care (endocrinology, ID, vascular, podiatry, etc) vs no specialty care	Ulcer progression, major amputation, death	Specialty care is associated with significantly longer event-free survival (aHR 0.22-0.34).
(27) USA	Retrospective cohort study	N=341 inpatients with chronic wounds	Wound-specific oral nutritional supplement (≥ 14 days) + standard care vs standard care	Weekly wound size reduction, discharge wound size	61.1% vs 34.5% wound reduction, significantly greater improvement with supplementation
(29) China	Case control study	N=389 DFU patients	Observational (CONUT score & NLR analysis)	Amputation, amputation-free survival	Nutritional status (CONUT) & NLR independently predicted amputation risk
(31) China	Cross-sectional study	N=577 DF patients (Wagner grade 1-5)	Nutritional assessment (mini nutritional assessment)	Nutritional score, HbA1c, Hb, albumin, WBC	A worse Wagner grade is associated with poorer nutritional status
(28) Egypt	Randomized controlled trial	N=69 non-ischemic DFU patients	Cilostazol vs Cilostazol + Selenium vs standard care, 3 months	Ulcer length, width, depth, HMMP-9	Combination therapy significantly reduced ulcer dimensions, with the greatest improvement in the cilostazol group
(32) Romania	Prospective controlled study	N=28 DFU patients	Integrative therapy (ozone + PEMF + probiotics + diet) vs ozone alone, 8 weeks	Re-epithelialization, HbA1c, CRP	86.2% vs 58.2% re-epithelization, improved glycemic & inflammatory markers
(33) USA	Randomized controlled trial	N=29 DFU patients	Nutrition supplementation + education vs standard care, 12 weeks	CRP, IL-6, IL-10, TTP	Significant reduction in IL-6 (p=0.001), improved inflammatory profile
(34) Australia	Secondary data analysis	Adult with active DFU (sample size not specified in snippet)	Observational dietary intake assessment	Macronutrient & micronutrient intake vs guidelines	The majority did not meet protein, zinc, vitamin A & E recommendations

Footnote:
Hb: Hemoglobin; CRP: C-reactive protein; NRI: Nutritional Risk Index; NLR: Neutrophil-to-Lymphocyte Ratio; CONUT: Controlling Nutritional Status score

Dietary Modification and Nutritional Counseling

One randomized controlled trial assessed the role of dietary optimization and nutritional education in patients with DFU. The study demonstrated significant improvement in inflammatory profiles,

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including reductions in CRP and IL-6 levels (33). Additionally, a secondary data analysis reported that most DFU patients did not meet recommended intake levels for protein and essential micronutrients such as zinc and vitamins A and E (31), indicating a gap in dietary adequacy among this population.

Nutritional Status as a Prognostic Indicator

Four observational studies evaluated nutritional status as a predictor of wound-related outcomes. A prospective observational study reported that lower albumin, hemoglobin (Hb), and Nutritional Risk Index (NRI) were associated with larger wound area and increased tissue damage (7). Similarly, a case-control study found that higher Controlling Nutritional Status (CONUT) scores and neutrophil-to-lymphocyte ratio (NLR) independently predicted amputation risk (28). A cross-sectional study further showed that higher Wagner grades were significantly associated with poorer nutritional status (32). Collectively, these findings indicate that malnutrition is strongly associated with increased wound severity and poorer clinical outcomes in DFU patients.

Multidisciplinary and Specialty Care Approaches

One large retrospective cohort study involving Medicare patients demonstrated that specialty multidisciplinary care was associated with significantly longer amputation-free survival compared to non-specialty care (30). These findings highlight the importance of integrating nutritional assessment into multidisciplinary DFU management strategies to improve clinical outcomes.

Summary of Findings

Across the nine included studies, nutritional interventions demonstrated a generally favorable effect on wound healing outcomes in patients with DFU. Wound-specific oral nutritional supplementation (WS-ONS) was reported to have greater wound size reduction compared with standard care. Micronutrient-based and integrative interventions showed potential benefits in enhancing re-epithelialization and reducing ulcer dimensions. Observational evidence consistently indicated that poor nutritional status, reflected by low albumin levels, higher CONUT scores, and lower NRI values, was associated with greater wound severity and increased risk of amputation. Overall, the findings suggest that nutritional optimization plays a supportive and potentially clinically meaningful role in improving wound healing outcomes among patients with diabetic foot ulcers.

Table 2. Quality appraisal of included studies using the Joanna Briggs Institute (JBI) tools

Reference	Study design	JBI Tool Used	Yes	No	Unclear	Overall Quality
(7)	Prospective observational	JBI Cohort Checklist	9	2	0	High
(30)	Retrospective cohort	JBI Cohort Checklist	10	1	0	High
(27)	Retrospective cohort	JBI Cohort Checklist	8	3	0	Moderate
(29)	Case-control study	JBI Case-Control Checklist	8	2	0	High
(31)	Cross-sectional study	JBI Cross-Sectional Checklist	7	1	0	High
(28)	RCT	JBI RCT Checklist	10	2	1	High
(32)	Prospective controlled study	JBI Quasi-Experimental Checklist	7	2	0	Moderate-High
(33)	RCT	JBI RCT Checklist	10	2	1	High
(34)	Secondary analysis (cross-sectional)	JBI Analytical Cross-Sectional	6	2	0	Moderate

DISCUSSION

This systematic review synthesizes evidence from nine studies published between 2022 and 2026 examining the role of nutritional interventions and nutritional status in wound healing outcomes among patients with DFU. The findings are interpreted alongside supporting literature to provide a biological and clinical context. Overall, the evidence suggests that nutritional optimization is associated with improved wound healing parameters, including reduced wound size, improved inflammatory control, and lower amputation risk. This is consistent with broader evidence indicating that nutritional status is closely linked

https://doi.org/10.56303/jhnresearch.v5i2.1301

to disease outcomes through its effects on metabolic demand, vascular function, and tissue perfusion (35). However, heterogeneity in study design, intervention types, and outcome measures limits direct comparability and generalizability.

Oral Nutritional Supplementation (ONS)

Several interventional studies demonstrated that wound-specific oral nutritional supplementation (WS-ONS) contributes to improved wound healing parameters. Patients receiving wound-specific oral nutritional supplementation showed significantly greater wound size reduction compared with standard care alone (27). Nutritional supplementation combined with education significantly reduced IL-6 levels, indicating improved inflammatory modulation (33). Adequate protein intake is essential during the inflammatory and proliferative phases of wound healing (36). Micronutrients such as vitamins A, C, E, zinc, selenium, arginine, and glutamine play immunomodulatory roles in chronic wound repair (37). Essential amino acids and omega-3 fatty acids contribute to immune regulation and collagen synthesis in diabetic wound environments (16). Supplementation with beta-hydroxy-beta-methylbutyrate (HMB), arginine, and glutamine has been reported to accelerate wound healing time through enhanced collagen synthesis (38). High-calorie, high-protein supplementation enriched with arginine and antioxidant vitamins significantly reduced wound extent in patients with chronic ulcers (39). Together, these findings suggest that ONS may serve as an important adjunctive therapeutic strategy rather than merely supportive dietary supplementation.

Micronutrient and Pharmaco-Nutritional Approaches

Micronutrient-based interventions also demonstrated potential benefits in selected trials. The combination of cilostazol and selenium significantly reduced ulcer dimensions compared to standard care (28). Integrative therapy that included dietary optimization and probiotic supplementation resulted in higher re-epithelialization rates compared with control groups (32). Supporting literature indicates that selenium nanoparticles have been shown to accelerate diabetic wound healing through enhanced antioxidant activity (40). Selenium-based hydrogel formulations improved tissue regeneration in diabetic wound models (41). Probiotics exhibit immunomodulatory and antibiofilm properties that may enhance re-epithelialization (42). Modulation of the gut-skin axis through probiotics may reduce systemic inflammation relevant to chronic wounds (43). Although these adjunctive strategies appear promising, differences in formulation, dosage, and delivery routes limit definitive conclusions regarding optimal micronutrient protocols. However, most supporting evidence originates from preclinical or heterogeneous clinical settings, which may limit direct clinical applicability in DFU populations.

Nutritional Status as a Prognostic Indicator

Observational studies generally identified malnutrition as a significant predictor of adverse wound outcomes. Lower albumin levels, hemoglobin, and Nutritional Risk Index (NRI) values were associated with larger wound areas and greater tissue destruction (7). Higher CONUT scores independently predicted amputation risk among DFU patients (29). Higher Wagner grades were significantly associated with poorer nutritional status (31). Beyond the included studies, supporting evidence from the broader literature further suggests that low serum albumin levels are associated with reduced microvascular density and impaired granulation tissue formation (44). Nutritional indices such as GNRI, PNI, and CONUT have been identified as independent predictors of mortality in DFU populations (45). Additionally, malnutrition based on GLIM criteria has been associated with prolonged length of hospital stay (19). Poor adherence to healthy dietary patterns has been linked to an increased risk of diabetic foot complications (46).

Collectively, these findings suggest that nutritional status may be an important determinant of wound severity and progression. In addition to biochemical markers such as albumin and hemoglobin, broader aspects of nutritional status, including body composition, also play an important role in wound healing outcomes. Evidence suggests that reduced muscle mass and increased fat mass are associated with delayed wound healing in patients with type 2 diabetes mellitus, as muscle supports tissue perfusion and immune function, while excess adiposity contributes to chronic inflammation and impaired microcirculation (47).

https://doi.org/10.56303/jhnresearch.v5i2.1301

Multidisciplinary and Integrated Care

The findings from the included studies indicate that specialty care incorporating nutritional assessment is associated with longer amputation-free survival among Medicare patients with DFU (30). In addition to these findings, supporting studies from the broader literature demonstrate that multidisciplinary team management combined with intensive metabolic control significantly improved wound healing rates and psychological outcomes (48). Integrated limb salvage programs have also been shown to improve long-term survival and reduced major amputation rates (49). Furthermore, coordinated immune and metabolic management plays an important role in chronic diabetic wound care (50). Complementing these approaches, structured educational interventions such as booklet-based education have been shown to improve patients' knowledge, self-efficacy, and self-care behaviors, thereby supporting adherence to dietary, metabolic, and treatment regimens within integrated care models (51). Collectively, these findings suggest that nutritional optimization and patient education should be considered as integral components of comprehensive DFU management rather than delivered in isolation. These findings suggest that nutritional optimization may be considered as part of comprehensive DFU management rather than delivered in isolation. Complementing these approaches, structured educational interventions such as booklet-based education have been shown to improve patients' knowledge, self-efficacy, and self-care behaviors, thereby supporting adherence to dietary, metabolic, and treatment regimens within integrated care models.

Limitations

This review has several limitations. First, a meta-analysis could not be performed due to significant heterogeneity in study design, intervention types, and outcome measurements. Second, only English-language articles were included, which may introduce language bias. Third, the reliance on narrative synthesis may limit the objectivity of the findings compared to quantitative pooling methods. Finally, variations in sample size and follow-up duration across studies may affect the generalizability of the conclusions. Additionally, potential publication bias and variation in reporting quality across studies may have influenced the overall interpretation of findings.

CONCLUSION

Nutritional status may be an important determinant of wound healing outcomes in patients with diabetic foot ulcers. While nutritional interventions demonstrate potential benefits in improving wound-related parameters, the heterogeneity of existing evidence precludes definitive conclusions. Future research should prioritize well-designed randomized controlled trials with standardized outcome measures to strengthen the evidence base and inform clinical guidelines.

DECLARATION OF THE USE OF AI

The authors declare that no artificial intelligence (AI), AI-assisted technologies, or large language models (LLMs) were used in the conception of the study, data analysis, or the drafting, writing, and editing of this manuscript. The only exception is the graphical abstract, which was created using the design platform Illustrae (https://illustrae.co/). The authors take full responsibility for the content and accuracy of the graphical abstract and the entire manuscript.

FUNDING

This research has not received funding.

ACKNOWLEDGMENTS

The author would like to thank all authors and affiliated institutions for their support during the manuscript preparation process.

https://doi.org/10.56303/jhnresearch.v5i2.1301

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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