Original Article

Micronutrient status of patients with diabetic foot: A systematic review

Sholpan Batarbekova MSc[1], Dinara Zhunussova PhD[1], Gulmira Derbissalina PhD[1], Zhanagul Bekbergenova MSc[1], Nadezhda Maksimova PhD[2], Ayagoz Umbetzhanova PhD[1], Elmira Kelimberdiyeva PhD[1], Raushan Kassymova PhD[3], Gaukhar Kuanyshbayeva PhD[4], Altynay Imangaliyeva MSc[5]

[1]*Department of General Medical Practice, Astana Medical University, Astana, Kazakhstan*
[2]*Department of Physical and Rehabilitation Medicine, Central State Medical Academy, Moscow, Russia*
[3]*Department of General Medical Practice, Kazakh National Medical University, Almaty, Kazakhstan*
[4]*Department of Basics of medicine, Astana Medical University, Astana, Kazakhstan*
[5]*Department of Internal medicine, Astana Medical University, Astana, Kazakhstan*

Background and Objectives: Micronutrient status encompasses a range of indicators that reflect the levels and balance of macro- and microelements, as well as vitamins within the body. These essential substances, required in minimal amounts, are crucial for supporting normal physiological processes, immune system functioning, and tissue repair. The aim of this systematic review is to summarize data on the deficiency or excess of microelements, macroelements, and vitamins in patients with diabetic foot ulcers. **Methods and Study Design:** Databases were searched for studies on vitamin, macronutrient, micronutrient levels and their impact on the course, treatment and healing of diabetic foot ulcers. The Cochrane Risk of Bias tool was employed for assessing randomized trials, while the Newcastle-Ottawa Scale was utilized for evaluating observational studies in terms of quality and bias risk. **Results:** The findings revealed a notable correlation between deficiencies in vitamins D, C, A and the severity of clinical symptoms. Low vitamin D levels were linked to elevated proinflammatory cytokines. Higher concentrations of folate and vitamin B-12 were associated with improved ulcer healing, supplementation with zinc and magnesium contributed to a reduction in ulcer size. Inadequate intake of zinc, vitamins E, C was found to compromise antioxidant defences. Elevated ferritin levels may serve as an indicator of inflammation. **Conclusions:** The most important task is to adjust the intake of micronutrients to maintain balance and prevent deficiency and excess, which is important in the complex therapy of patients.

Key Words: diabetes mellitus type 2, diabetic foot ulcers, micronutrient status, vitamins, micronutrients

INTRODUCTION

Diabetes mellitus (DM), an endocrine disorder characterized by elevated blood glucose levels, is among the most prevalent and swiftly expanding diseases globally. By 2045, it is expected to impact 693 million adults, representing a more than 50% rise from the number of cases recorded in 2017.[1] Patients with DM can develop a variety of complications, including chronic non-healing diabetic foot (DFU). A diabetic foot refers to an infection, ulceration, or tissue damage affecting the foot, often associated with neuropathy and/or peripheral arterial disease (PAD) in the lower limbs.[2] DFUs are marked by a prolonged inflammatory phase, characterized by elevated levels of neutrophils and macrophages within the wound bed. This condition is accompanied by the continuous release of proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor (TNF)-α, and plasma C-reactive protein, while bacterial growth hampers the healing process.[3] The consequences include considerable pain and financial burdens for the patient, along with significant repercussions for the patient's family, healthcare providers, institutions, and society at large. Strategies including preventive measures, patient and healthcare education, combination therapy and close monitoring can reduce the negative impact of DFU.[4,5]

At the present time, there has been an increasing focus on the significance of micronutrients in the prevention and management of DFU. These micronutrients are crucial for numerous physiological functions, such as immune response, wound healing, and antioxidant protection. Deficiencies or imbalances of these substances can disrupt these processes, which in turn can increase the severity of DFU. Nutritional deficiencies can cause abnormal metabolic changes that slow down the wound

Corresponding Author: Dr Dinara Zhunussova, Department of General Medical Practice, Astana Medical University, Beibitshilik St 49/A, Astana, Kazakhstan
Tel: 877017324247
Email: zhunussova.d@amu.kz
Manuscript received 09 February 2025. Initial review completed 10 February 2025. Revision accepted 12 March 2025.
doi: 10.6133/apjcn.202508_34(4).0001

healing process. Gaining a more profound insight into the significance of micronutrients and products, along with the appropriate application of medications in the wound healing process, could result in the formulation of effective therapeutic strategies to promote the healing of diabetic wounds.[6]

METHODS

This systematic review was carried out following the PRISMA guidelines, and the study protocol has been registered with PROSPERO (CRD42024593953).[7]

Search strategy and data sources

The systematic review concentrated on English-language publications and studies released in the past decade (2014–2024) to ensure the evidence remains pertinent. We conducted a thorough search across three academic databases: PubMed, Web of Science, and Scopus. The primary terms and keywords utilized encompassed "micronutrient status," "vitamin deficiency," "mineral deficiency," "microelements," "nutrient deficiency," "diabetic foot," "diabetic foot syndrome," "diabetic foot ulcers," "clinical features," and "complications." A combination of keywords was employed, such as "vitamins," "minerals," "microelements," "macroelements," "nutrients," and "nutrient status." Using Boolean operators, the following search phrases were formulated: "micronutrient status" AND "diabetic foot," "vitamin deficiency" OR "mineral deficiency" AND "diabetic foot syndrome," and "micronutrients" AND "diabetic foot patients". The search was conducted on two occasions: once during the initial systematic review and again prior to final publication. Mendeley software was used to manage and record the search process, allowing us to organize the results and exclude duplicates. In addition to the automated database search, we manually reviewed the bibliographies of the selected articles to identify additional studies and examined the references of relevant articles to identify other relevant studies.

Inclusion criteria: Individuals aged 18 years and older who have been diagnosed with DFU due to type 2 diabetes mellitus, irrespective of the stage or severity of the condition. Studies must provide quantifiable outcomes, including blood concentrations of micronutrients, indicators of deficiency or insufficiency, the influence of micronutrient levels on the advancement and healing of DFU, and the impact of deficiencies on the occurrence of complications. Eligible study designs include randomized controlled trials, cohort studies, or case-control studies.

Exclusion criteria: Studies focusing exclusively on children and adolescents, animal or in vitro investigations, research that does not involve patients with DFU, studies addressing different diabetic complications, investigations not pertaining to micronutrient status, studies that do not provide quantitative data on micronutrients, publications in languages other than English, as well as reviews, commentaries, dissertations, reports, letters to the editor, and conference abstracts lacking original data. Additionally, clinical guidelines and methodological resources are also excluded.

Studies sections and data extraction

At the initial stage, three independent reviewers performed a preliminary assessment based on titles and abstracts. Only studies that met the established criteria were considered for analysis. All duplicates were removed before the selection process. Following this initial assessment, full texts of eligible articles were further assessed for inclusion and exclusion criteria. All reasons for exclusion were documented. If reviewers disagreed with the inclusion of certain studies, a discussion was held to reach a consensus. Once the compilation of included studies was completed, relevant data were collected from publications using a standardized data extraction form specifically designed for systematic review. Extracted information included authors, year, study type, inclusion and exclusion criteria, study duration, sample size, number of groups, gender distribution of participants, and number of males and females. We used the Kappa statistic to assess the consistency with which reviewers applied the inclusion and exclusion criteria and to check the quality of studies. This approach is intended to promote objectivity and impartiality in the selection and evaluation of studies. The assessment of quality and risk of bias was conducted using the Cochrane risk of bias scale for randomized trials and the Newcastle-Ottawa scale for observational studies.[8]

RESULTS

Search results

The initial search yielded 538 records from the databases. Following the removal of duplicates and a review of titles and abstracts, 149 full-text studies were evaluated for eligibility. Out of these, 78 studies were excluded: 43 were descriptive reviews, 38 – animal studies, 19 – case reports, 9 –series of cases, no full text available – 11. The review encompassed 29 primary studies, with a total of 5,839 participants (Figure 1).

Study selection and characteristics

The systematic review encompassed seven randomized double-blind placebo-controlled trials, seven cross-sectional studies, one analytical observational study with a cross-sectional design, three prospective cohort studies, three case-control studies and two retrospective cohort studies. Five studies were conducted in China, four each in Australia and Iran, three each in the United States and India, two studies in Greece, and one each in Bulgaria, Indonesia, Denmark, Egypt, Saudi Arabia, Italy, Germany, and Nigeria. The number of participants ranged from 16 to 1721, of which 23 to 847 were men and 7 to 874 were women (Table 1).

Vitamin D

In the research conducted by Maggi et al. (2014), 14 participants received an administration of 300,000 IU of vitamin D3, while 16 were assigned to a placebo group. The initial prevalence of 25(OH)D deficiency was notably high, with 38% in the placebo group and 29% in the treatment group, compared to 63% and 71% at baseline, respectively. Following the administration of a single dose of vitamin D3, a statistically significant increase in blood levels of 25(OH)D was observed at the 12-week

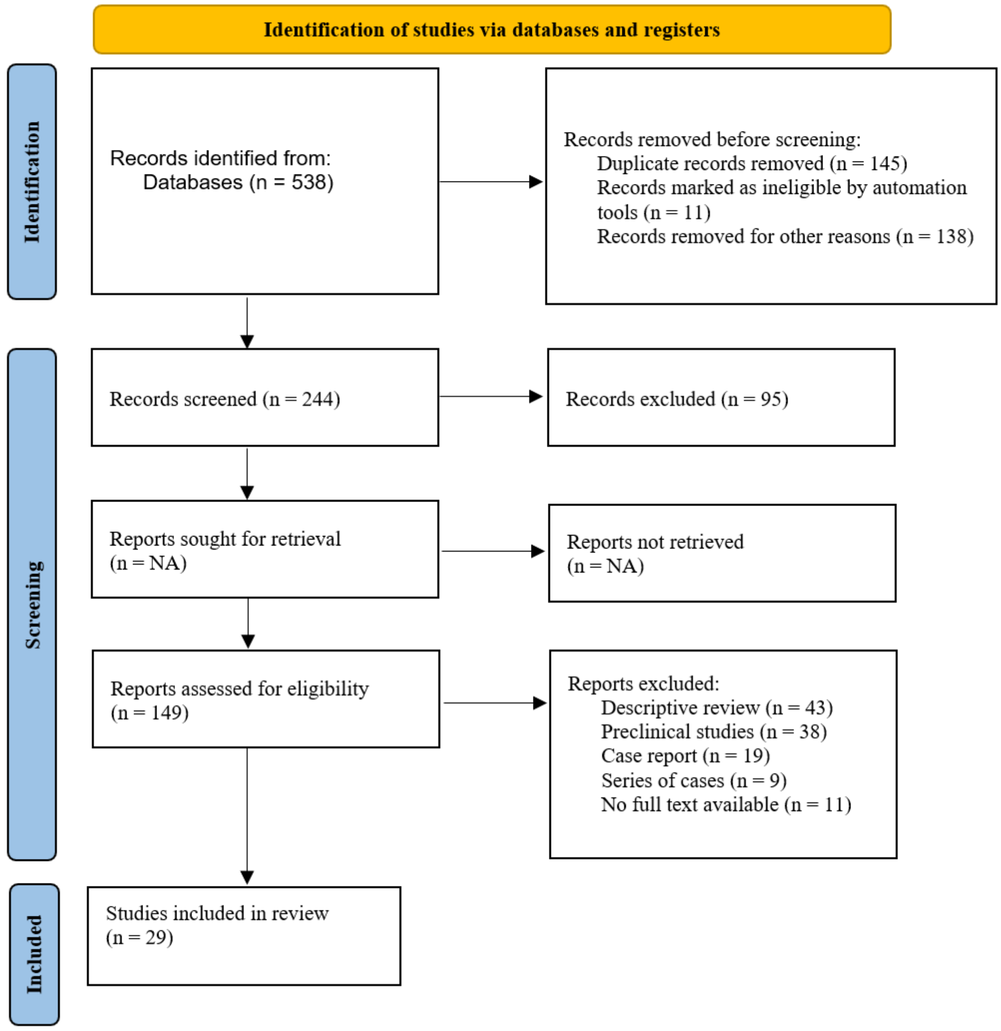

Figure 1. PRISMA flowchart of study selection for the systematic review of micronutrient status in patients with diabetic foot.

mark (p=0.0015) compared to baseline. However, in the past 24 weeks, the significance of the results had decreased (p=0.0046), although the levels of 25(OH)D remained within the normal range: 50 nmol/L at 12 weeks and 40 nmol/L at 24 weeks.[9]

In the study by Tiwari et al. (2014) 112 patients diagnosed with DM and foot infections, as well as 107 patients without infections. Vitamin D deficiency was identified in 71.4% of those with DFU and in 61.6% of the control group. Severe vitamin D deficiency was more prevalent among the infected patients compared to those in the control group, with rates of 48.2% and 20.5%, respectively. Patients exhibiting 25-hydroxyvitamin D levels of 25 nmol/L demonstrated significantly elevated levels of IL-1b and IL-6 when compared to patients with vitamin D levels at 50 nmol/L.[10]

In the study by Afarideh et al. (2016), the level of 25(OH)D was the only factor independent of DFU (OR 2.194; 95% CI 1.003, 4.415). The authors suggest that a sharp increase in the content of 25(OH)D in the blood in chronic active DFU may be associated with changes in the inflammatory status. It is believed that 25(OH)D and IL-8 have common mechanisms in the pathogenesis of diabetic foot.[11]

The research by Razzaghi et al. (2017) demonstrated that a 12-week regimen of vitamin D supplementation led to a substantial decrease in ulcer dimensions: the length reduced from -2.1 ±1.1 to -1.1±1.1 cm (p< 0.001), the width from -2.0±1.2 to -1.1±1.0 cm (p< 0.02), and the depth from -1.0±0.5 to -0.5±0.5 cm (p< 0.05). In comparison to the placebo group, those receiving vitamin D supplementation exhibited a notable increase in blood levels of 25-hydroxyvitamin D (12.9±10.0 vs. -1.8±15.7 ng/mL, p< 0.05).[12]

He et al. (2017) discovered that patients suffering from diabetic peripheral neuropathy (DPN) exhibited notably lower serum 25(OH)D levels (15.59±7.68 ng/mL) and a considerably higher rate of vitamin D deficiency (80%) in comparison to those showing signs of DPN (17.66±7.50 ng/mL; 64.5%) and individuals without this condition (18.35±6.60 ng/mL; 61.7%) (all p<0.01).[13]

In the research by Feldkamp et al. (2018), the levels of 25-hydroxyvitamin D3 were found to be significantly higher (p<0.01) in patients with DM compared to those with DFU, but lower (p<0.01) than those in healthy controls. Among the 88 patients with DFU, a substantial 84.6% exhibited 25-hydroxyvitamin D3 levels below 20 ng/mL. Additionally, 55.8% of these patients demonstrated a notable deficiency in 25-hydroxyvitamin D3. Only 12% of the patients (n=16) managed to attain levels exceeding 20 ng/mL.[14]

Table 1. Characteristics of studies included in the systematic review

Row	Authors	Year	Country	Study design (Defined by authors)	Inclusion criteria
1	Stefania Maggi et al.[9]	2014	Italy	Randomized, double-blind, placebo-controlled trial	Outpatients from the Diabetic Foot Unit of the Policlinico Abano Terme (PD) who were 60 or older with type 2 diabetes mellitus and diabetic foot complications
2	Shalbha Tiwari et al.[10]	2014	India		
3	Mohsen Afarideh et al.[11]	2016	Iran	Cross-sectional study	Willing to participate and were diagnosed with type 2 diabetes as per the American Diabetes Association criteria
4	Reza Razzaghi et al.[12]	2017	Iran	Randomized, double-blind, placebo-controlled trial	Grade 3 DFU aged 40–85 years who referred to the Shahid Beheshti Clinic in Kashan, Iran
5	Shalbha Tiwari et al.[10]	2014	India		
6	Mohsen Afarideh et al.[11]	2016	Iran	Cross-sectional study	Willing to participate and were diagnosed with type 2 diabetes as per the American Diabetes Association criteria

Row	Authors	Exclusion criteria	Duration of the study	Sample size	Number of groups	Male	Female	Vitamins, micronutrients, macronutrients
1	Stefania Maggi et al.[9]	Patients with previous or current tumoral disease with less than 1-year quoad vitam prognosis, with severe chronic or auto-immune inflammatory diseases, vitamind3 contra-indications (chronic renal failure, renal lithiasis, hypercalcemia, hypercalciuria, allergy to calciferol or excipients), gastrointestinal disorders which impair drug absorption or receiving bone-active agents or antithrombotic therapy		30	2	23	7	Vitamin D3
2	Shalbha Tiwari et al.[10]	Patients exhibiting clinical evidence of vascular insufficiency or taking immune-suppressants, multivitamins and Ca supplements	2	219	148		71	Vitamin D
3	Mohsen Afarideh et al.[11]	Type 1 diabetes, class III/IV heart failure according to the New York Heart Association, inflammatory or infectious diseases, autoimmune and rheumatic diseases, malignancy, hematological diseases, pregnancy, severe renal or liver failure/cirrhosis, history of surgical and angioplasty interventions and treatment with anti-inflammatory drugs, immunosuppressants and vitamin D supplements	January 2014 - September 2014	90	3			Vitamin D
4	Reza Razzaghi et al.[12]	Pregnant and breast-feeding patients, participants who consumed vitamin D supplements during the past 3 months, anticipated changes in medications throughout the study and patients with history of diseases which influence the development of DFU including chronic trauma	November 2015 - January 2016	60	2	44	16	Vitamin D
5	Shalbha Tiwari et al.[10]			306	3			Vitamin D3
6	Mohsen Afarideh et al.[11]	Type 2 diabetic patients with the Hansen disease or varicose veins or peripheral arterial diseases, patients on vitamin D or calcium supplementation or on drugs that interfere with vitamin D metabolism, patients with infections in sites other than the foot	September 2012 - June 2014	176	2	88	88	Vitamin D

Table 1. Characteristics of studies included in the systematic review (cont.)

Row	Authors	Year	Country	Study design (Defined by authors)	Inclusion criteria
7	Robert M Greenhagen et al.[16]	2019	USA	A retrospective review of charts	Patients aged 18 years and older who underwent surgery on the foot and ankle joint with the same surgeon
8	Guilherme Pena et al.[17]	2020	Australia	Prospective cohort study	Age ≥18 years, able to have follow-ups and presence of foot ulcer
9	John Deakin Lees Brookes et al.[18]	2020	Australia	Retrospective cohort analysis	The presence of a diabetic foot, hospitalization during a set period, and testing of 3 or more nutrition markers of interest
10	Jiezhi Dai et al.[19]	2020	China	Prospective study	Patients who have been diagnosed with type 2 diabetes based on diagnostic criteria
11	Weiwei Tang et al.[20]	2022	China		Only patients aged ≥18 years
12	Fenglin Wang et al.[21]	2022	China	Case-control study	Age over 18 years, diagnosis of diabetes

Row	Authors	Exclusion criteria	Duration of the study	Sample size	Number of groups	Male	Female	Vitamins, micronutrients, macronutrients
7	Robert M Greenhagen et al.[16]			100	2	56	44	Vitamin D3
8	Guilherme Pena et al.[17]		February 2017 - September 2018	131		104	27	Vitamin A, vitamin C, vitamin D, vitamin E, copper, zinc, ferritin
9	John Deakin Lees Brookes et al.[18]		October 2017 - November 2017	48		41	7	Vitamin C, vitamin D, vitamin B12, zinc, selenium, iron
10	Jiezhi Dai et al.[19]	Type 1 diabetes mellitus, thyroid diseases, rheumatological, severe hepatic, cardiac, renal insufficiency and malignant neoplasms, pregnant women and patients who have taken vitamin D supplements in the last 6 months	January 2019 - October 2019	51	2	29	22	Vitamin D
11	Weiwei Tang et al.[20]	Other types of diabetes, pregnant or lactating women, with acute complications of diabetes or other stressful conditions such as surgery and trauma, with rheumatological, serious disorders of liver, heart, kidney function, malignant neoplasms and endocrine diseases affecting vitamin D metabolism	January 2012 - December 2019	1721	2 groups and 4 subgroups	847	874	Vitamin D
12	Fenglin Wang et al.[21]	Severe impairment of consciousness or poor general condition complicated by a malignant tumor, serious heart, liver and kidney failure, a history of diseases affecting the level of 25-OH-vitamin D in the blood serum, such as diseases of the thyroid gland and parathyroid glands, osteoporosis and bone fractures, and a history of medications affecting the level of 25-OH-vitamin D in the blood serum, such as calcium, vitamin D, oral contraceptives, glucocorticoids and so on	January 2019 - October 2021	429	2	276	153	Vitamin D

Table 1. Characteristics of studies included in the systematic review (cont.)

Row	Authors	Year	Country	Study design (Defined by authors)	Inclusion criteria
13	Ani S Todorova et al.[22]	2020	Bulgaria	Cross-sectional study	
14	Mufqi Handaru Priyanto et al.[23]	2023	Indonesia	Analytical observational study with a cross-sectional design	Patients who wished to participate in the study signed a consent form for the study, aged > 18 years, met the diagnostic criteria for type 2 diabetes
15	Ying Tang et al.[24]	2023	China		The duration of the ulcer is from four weeks or longer, the ulcer area is 2-20 cm2 and 2-4 degrees according to Wagner, the ankle-shoulder index was 0.4-0.9, and type 2 diabetes mellitus was diagnosed
16	Sofia Tsitsou et al.[25]	2023	Greece	Cross-sectional study	The presence of an active ulcer, regardless of its classification, localization, chronicity and the presence or absence of infection
17	Peter M Halschou-Jensen et al.[26]	2021	Denmark	Randomized, Parallel, Double-Blind and Controlled Trial	Patients with diabetes and with 1 or more ulcers of the foot or lower leg without complete healing for more than 6 weeks

Row	Authors	Exclusion criteria	Duration of the study	Sample size	Number of groups	Male	Female	Vitamins, micronutrients, macronutrients
13	Ani S Todorova et al.[22]	Vitamin D supplementation, estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m2, type 1 diabetes, pregnancy, and diabetic ketoacidosis	July 2018 - March 2020	242	2 groups and 2 subgroups	140	102	Vitamin D
14	Mufqi Handaru Priyanto et al.[23]	Patients who took vitamin D supplements during the last 1 month and had concomitant diseases: systemic infection, autoimmune diseases and rheumatism, malignant neoplasms, end-stage renal failure (hemodialysis) and severe liver disease	November 2020 - May 2021	81	2	32	49	Vitamin D
15	Ying Tang et al.[24]	Bedridden for a long time, acute complications associated with diabetes, severe dysfunction of the heart, liver and kidneys, wound ulcer, parathyroid disease, autoimmune diseases, taking any drugs that affect the level of 25 (OH) VD in serum, such as calcium, vitamin D, oral contraceptives and glucocorticoids etc., severe septicemia	January 2019 - January 2021	356	3 groups 2 subgroups	199	157	Vitamin D
16	Sofia Tsitsou et al.[25]	Pregnancy, lactation, liver and kidney failure, malabsorption and intake of vitamin D supplements	September 2019 - January 2020	96	3	72	24	Vitamin D
17	Peter M Halschou-Jensen et al.[26]	Pregnancy/breastfeeding, taking vitamin D at a dose of more than 20 mcg per day or having a history of diseases affecting vitamin D metabolism, granulomatous diseases such as tuberculosis, sarcoidosis or silicosis, hypercalcemia, impaired renal function (creatinine >150 mmol/l and/or eGFR <40 ml/min), liver failure (ALAT >70 u/l), bone diseases, for example osteogenic sarcoma, skin tumors, drug treatment of epilepsy, uncontrolled arterial hypertension (>150/100 mmHg), the need for surgical treatment or vascular surgery, patients with critical ischemia, sepsis or ulcers that required surgical treatment at the first visit, patients with irregularly shaped wounds between the toes	April 2016 - July 2018	48	2	40	8	Vitamin D

Table 1. Characteristics of studies included in the systematic review (cont.)

Row	Authors	Year	Country	Study design (Defined by authors)	Inclusion criteria
18	Reham Hammad et al.[27]	2023	Egypt		The presence of diabetes mellitus from medical records
19	Mutasem Ababneh et al.[28]	2024	Saudi Arabia	Cross-sectional study	18- to 75-year-old individuals having T2D with foot ulcers
20	Jenny E Gunton et al.[29]	2020	Australia	Randomized, Double-Blind, Placebo-Controlled Trial	Adults who went to the high-risk foot clinic at Westmead Hospital and who currently had a foot ulcer
21	Khanh Phuong S Tong et al.[30]	2022	USA	Cross-sectional study	Male or female patients aged 18 years and older
22	Hailey R Donnelly et al.[31]	2023	Australia	Prospective cohort study	

Row	Authors	Exclusion criteria	Duration of the study	Sample size	Number of groups	Male	Female	Vitamins, micronutrients, macronutrients
18	Reham Hammad et al.[27]	A history of cancer, liver, kidney or autoimmune diseases, type 1 diabetes mellitus, patients with diabetic foot associated with infection, from the second to the fifth degree according to the Meggitt–Wagner classification, patients with type 2 diabetes mellitus with morbid obesity (body mass index [BMI] > 35 kg / m22)		90	2	57	33	Vitamin D3
19	Mutasem Ababneh et al.[28]	Pregnant and breastfeeding patients, those unable to ambulate, illiterate, severely affected by mental illnesses or malignant disease, and other related issues, which could hinder the completion of a written questionnaire	February - May 2022	88		66	22	Vitamin D, vitamin B12, folic acid, ferritin
20	Jenny E Gunton et al.[29]	Inability to give informed consent due to cognitive or language problems, the decision to amputate at the first visit	January 2018 - March 2019	16	2			Vitamin C
21	Khanh Phuong S Tong et al.[30]	Active wound infection, untreated osteomyelitis, gangrene, immunodeficiency diseases, the presence of multiple diabetic foot ulcers, dementia or cognitive impairment, as well as a history of current cancer	July 2019 - December 2019	42	2	35	7	Vitamin C
22	Hailey R Donnelly et al.[31]		2017 - 2020	115		94	21	Vitamin C, vitamin A, vitamin E, vitamin B12, zinc, sodium

Table 1. Characteristics of studies included in the systematic review (cont.)

Row	Authors	Year	Country	Study design (Defined by authors)	Inclusion criteria
23	Joseph V Boykin Jr et al.[32]	2020	USA	Retrospective cohort study	The early stage of a diabetic foot ulcer should not have a surface depth (i.e. without open fascia, tendons or bones), in the examined wound in the anamnesis there should be no signs of concomitant cellulite of the lower extremities, osteomyelitis or gangrene in the wound area, documented compliance with recommended methods of treatment of wounds associated with diabetic foot and wound relief therapy, subsequent examination and drug treatment, the presence of non-invasive segmental Dopplerography for the examined ulcers on the lower limb, the presence of chronological records of measurements of the wound area (cm2) (length ×width), allowing to determine the approximate area of the wound based on clinical observations for 4-week periods before and after the start of treatment with high doses of folic acid
24	Charu Yadav et al.[34]	2020	India	Case-control study	Outpatients and inpatients attending the podiatric clinic and the diabetes clinic of the institutional constituent hospitals
25	Mansooreh Momen-Heravi et al.[35]	2017	Iran	Randomized, Double-Blind, Placebo-Controlled Trial	Patients with grade 3 DFU according to "Wagner-Meggitt's" criteria aged 40-85 years who referred to the Shahid Beheshti Clinic in Kashan, Iran

Row	Authors	Exclusion criteria	Duration of the study	Sample size	Number of groups	Male	Female	Vitamins, micronutrients, macronutrients
23	Joseph V Boykin Jr et al.[32]	Taking platelet growth factor before treatment with high doses of folic acid, bioengineered human skin substitutes or wound treatment with negative pressure; at the same time, the appointment of any changes in medications to control glycemia or replace medications for the treatment of cardiovascular diseases (for example, hypertension, CHF, COPD) within 1 month after the start of taking high doses of folic acid, chemotherapy, immunosuppressive treatment, biological or antimalarial therapy within 1 month after treatment with high doses folic acid, reduction of the wound area by more than 50% 4 weeks before the start of treatment	November 2018 - April 2019	52				Folic acid
24	Charu Yadav et al.[34]	Chronic kidney disease, liver ailments, malignancy and/or microvascular complications revealed by history taking, routine clinical and biochemical examinations were excluded from the study, pregnant and lactating women, chronic smokers and alcoholics		64				Zinc, copper, magnesium
25	Mansooreh Momen-Heravi et al.[35]	Pregnant and breastfed patients, participants who consumed zinc supplements during past 3 months, change in consuming medications throughout the study and patients with history of diseases which influence the development of DFU including chronic trauma	August 2015 - November 2015	60	2	42	18	Zinc

Table 1. Characteristics of studies included in the systematic review (cont.)

Row	Authors	Year	Country	Study design (Defined by authors)	Inclusion criteria
26	Hassan Afzali et al.[36]	2019	Iran	Randomized, Double-Blind, Placebo-Controlled Trial	Patients with grade 3 DFU according to “Wagner-Meggitt’s” criteria, aged 40–85 years who were referred to the Shahid Beheshti Clinic in Kashan, Iran
27	Elizabeth Bosede Bolajoko et al.[37]	2017	Nigeria	Case-control study	Males and nonpregnant and nonlactating females between the ages of 40 and 60 years, participants with Wagner’s Grade 2 ulcer classification (i.e. ulcer involving ligament, tendon, joint capsule, or fascia but no abscess or osteomyelitis)
28	Triantafyllos Didangelos et al.[33]	2021	Greece	Prospective, double-blind, placebo-controlled trial	Adults (>18 years old) with DM2 and established DN, both peripheral and autonomic (DPN and DAN, respectively), having a good glycemic control (glycated hemoglobin (HbA1c) between 6.5 and 7.5%) that was stable in the last year before participating in the study, having metformin treatment for at least 4 years, low vitamin B12 levels according to suggested normal values for DM2 patients over 60 years old (<400 pmol/L)
29	Rui He et al.[13]	2016	China	Cross-sectional study	

Row	Authors	Exclusion criteria	Duration of the study	Sample size	Number of groups	Male	Female	Vitamins, micronutrients, macronutrients
26	Hassan Afzali et al.[36]	Pregnant and breastfed patients, participants who consumed magnesium, vitamin E or other antioxidative supplements during past 3 months, taking anti-inflammatory agents, change in consuming medications throughout the study and patients with history of diseases which influence the development of DFU including chronic trauma	November 2017 - September 2018	57	2	45	12	Vitamin E, magnesium
27	Elizabeth Bosede Bolajoko et al.[37]	Gangrene or severely impaired arterial supply in their feet, bone infection in their ulcers, or immediate risk of major above ankle/knee amputations, participants with renal, liver, and cardiac problems or impairment such as hypertension and other complications of DM or comorbid diseases		120	2			Vitamin C, vitamin E, copper, manganese, zinc
28	Triantafyllos Didangelos et al.[33]	Pernicious anemia, alcoholism, gastrectomy, gastric bypass surgery, pancreatic insufficiency, malabsorption syndromes, chronic giardiasis, acute infection or cardiovascular event in the last 6 months, surgery involving the small intestine, or HIV infection.	January 2018 - February 2020	90	2	48	42	B12
29	Rui He et al.[13]	Patients with type 1 diabetes mellitus or specific types of diabetes mellitus, acute complications of diabetes, osteomalacia, history of cerebral infarction, degenerative changes in cervical vertebra and parathyroid conditions including hyperparathyroidism and hypoparathyroidism and patients receiving oral vitamin D supplement	January 2014 - November 2014	861	3	502	359	Vitamin D

In the study by Danny Darlington et al. (2019) involving patients with DFU who experienced adverse outcomes such as amputation or death, 97% were found to have low vitamin D levels, with an average concentration of 17.05 ng/mL. This finding was statistically significant (p<0.001) when compared to 59.18% of patients who underwent grafting or achieved wound healing. Among patients receiving treatment for foot infections lasting less than six months, 78.9% exhibited normal vitamin D levels (p=0.0006).[15]

In the research by Greenhagen et al. (2019), the average serum vitamin D3 concentration across the entire cohort was found to be 20.96 ng/mL, suggesting that the levels were insufficient. Specifically, 55% of the participants exhibited a deficiency in vitamin D, while 24% were classified as insufficient, and 21% maintained adequate vitamin D3 levels in their blood. There was a significant trend indicating lower vitamin D3 levels (p=0.05) among patients with neuropathy when compared to those without the condition (p=0.05).[16]

In a cohort study by Pena et al. (2020), 131 patients with DFU were examined. The findings revealed that vitamin D deficiency was the most prevalent nutritional deficiency, affecting 55.7% of the participants.[17]

A retrospective cohort study by Brookes et al. (2020) included 48 patients, among whom 57.9% (n=22) were found to have low levels of vitamin D, with an average concentration of 46.3 ± 8.3 nmol/L.[18]

In the research by Dai et al. (2020), it was found that the levels of 25-OH vitamin D were significantly lower in patients suffering from DFU compared to the control group (p=0.0001). All individuals with DFU exhibited a deficiency in 25-OH vitamin D, with 9 patients classified as having severe deficiency. Among the 30 patients diagnosed with DM, 23 (76.67%) demonstrated a deficiency in 25-OH vitamin D; none of these patients were identified as having severe deficiency.[19]

In the research by Tang et al. (2022), it was observed that the prevalence of vitamin D deficiency was significantly greater in the DFU group compared to the non-DFU group, with rates of 77.51% versus 59.2% (p< 0.05). The average level of 25-hydroxyvitamin D across the entire population was recorded at 42.03 nmol/L, with the DFU group exhibiting lower levels than their non-DFU counterparts: 35.80 nmol/L compared to 45.48 nmol/L (p< 0.05). Patients who maintained poor blood glucose control had diminished 25-OH-vitamin D levels at 40.98 nmol/L, as opposed to those who achieved good control, who had levels of 44.82 nmol/L (p=0.01).[20]

In the research by Wang et al. (2022), it was observed that among patients without DFU, 74.33% were vitamin D deficient, 21.93% had vitamin D insufficiency, and 3.74% maintained adequate vitamin D levels. Conversely, in the cohort of patients with DFU, 86.78% exhibited vitamin D deficiency, 9.91% were found to be insufficient in vitamin D, and 3.31% had sufficient vitamin D levels.[21]

In the research by Todorova et al. (2022), a mere 2.9% of participants demonstrated adequate levels of 25(OH)D, while 14.5% exhibited insufficient levels and a substantial 82.6% were found to be deficient. 37.2% of the participants recorded 25(OH)D levels below 10 ng/mL. The overall mean level of 25(OH)D across the entire study group was 12.6 ng/mL. Among patients with DFU, the 25(OH)D levels were significantly lower compared to those without DFU, measuring 11.6 ng/mL versus 13.5 ng/mL (p=0.001). Furthermore, within the DFU cohort, the 25(OH)D levels were markedly lower when compared to the subgroup without complications (p=0.001), as well as between the subgroup with diabetic polyneuropathy and those without complications (p=0.031).[22]

The analytical study by Priyanto et al. (2023) revealed that vitamin D levels in patients with DM and DFU were significantly lower (8.90 ng/mL) compared to those without DFU (16.25 ng/mL), with a p-value of 0.001.[23]

Similarly, Tang et al. (2023) found that the blood levels of 25 (OH) vitamin D in patients with DFU were markedly lower than in those with DM, measuring 10.3 ng/mL versus 15.7 ng/mL, respectively, with a p-value of 0.002. These findings indicate a notable rise in the prevalence of vitamin D deficiency and insufficiency among DFU patients as the Wagner score increases (χ^2=40.31, p<0.001). Additionally, it was observed that the severity of infection correlates with a higher likelihood of encountering vitamin D deficiency and insufficiency in this condition (χ^2=23.86, p<0.001).[24]

In the research by Tsitsou et al. (2023), the assessment of vitamin D levels among healthy participants revealed that 82.1% exhibited sufficient levels, while 17.9% were classified as insufficient, and none were identified with abnormal levels. For patients without DFU, the distribution was 48.6% sufficient, 42.9% insufficient, and 8.6% abnormal. Among patients with DFU, 42.4% sufficient, 45.5% insufficient, and 12.1% abnormal (p=0.019).[25]

In the study by Halschou-Jensen et al. (2023), participants were assigned to receive either a high daily dose (170 μg) or a low daily dose (20 μg) of cholecalciferol. The initial serum 25(OH)D levels were recorded as 54.8±23.8 for the high-dose group and 55.2±28.4 for the low-dose group (p=0.947). Throughout the study, patients underwent surgical interventions. The average concentration of 25(OH)D for patients with healed DFU was 54.75±24.27, compared to 56.96 ± 35.85 for those without DFU (p=0.738). The authors concluded that high doses of vitamin D significantly enhanced the likelihood of recovery (adjusted OR 4.11, 95% CI 1.11–17.29).[26]

Hammad et al. (2023) reported that individuals with DFU and PAD exhibited significantly lower counts of non-classical monocytes and reduced levels of vitamin D3 compared to those without PAD. A positive correlation was noted between the percentage of non-classical monocyte counts and vitamin D3 levels (r=0.4, p<0.05).[27]

In a study conducted by Ababneh et al. (2024), which included 66 men and 22 women, vitamin D deficiency emerged as the most prevalent nutritional deficiency, affecting 43.2% of the participants.[28]

Vitamin C

Brookes et al. (2020) found that 58.7% (n=27) of patients exhibited low vitamin C levels, with an average concentration of 22.6±5.8 μmol/L. Notably, there were statistically significant differences in albumin, hemoglobin, and vitamin C levels when comparing the amputation and non-amputation groups. The mean vitamin C level among patients who underwent amputation was 15.7 (14.5) μmol/L, whereas it was 28.4 (14.1) μmol/L for those who did not undergo amputation ($p < 0.01$). Furthermore, 33.3% of patients in the amputation group had low vitamin C levels, in contrast to 76% of patients receiving conservative management, who had critically low vitamin C levels.[18]

In the research by Gunton et al. (2021), participants were divided into two groups: one received a daily dose of 500 mg of vitamin C in sustained-release capsules, while the other group was administered an inactive control (glucosamine sulfate capsules at a dose of 1000 mg). Notably, half of the participants were found to be vitamin C deficient at the start of the study. After an 8-week period, the reduction in ulcer size was markedly more pronounced in the vitamin C group compared to the glucosamine group, which showed a reduction of only 14% (p=0.041). The average time required for a 50% healing of ulcers was significantly less for those receiving vitamin C, with a median of 20 days, versus 48 days for the glucosamine group (p=0.028). All ulcers in the vitamin C group healed without necessitating amputation.[29]

In the research conducted by Tong et al. (2022), the prevalence of vitamin C deficiency was found to be 41.8% among patients suffering from DFU, whereas the control group, which did not have diabetes or ulcers, exhibited no deficiency. Furthermore, vitamin C levels were significantly lower in the poorly controlled HbA1c patients compared to the non-diabetic control group (p=0.002). The average vitamin C level in the control group was recorded at 0.8 mg/dL (0.4), while patients with controlled HbA1c showed a mean value of 0.7 mg/dL (0.7), and those with uncontrolled HbA1c had a mean of 0.4 mg/dL (0.3). The group with poorly controlled HbA1c exhibited larger wound sizes than those with well-controlled HbA1c (p=0.46).[30]

As per widely recognized guidelines, the recommended daily intake of vitamin C is 90 mg for men and 75 mg for women. However, a prospective cohort study by Donnelly et al. (2023) involving 115 participants with active forms of DFU revealed that only 26% of the participants adhered to these dietary recommendations.[31]

Vitamin A

A study by Pena et al. (2020) revealed that plasma vitamin A levels in 131 patients suffering from DFU were found to be the second most deficient, following vitamin D. Approximately 27% of the patients maintained normal levels of vitamin C, while the remainder exhibited suboptimal or low concentrations of this vitamin in their blood.[17]

In a separate study by Donnelly et al. (2023), it was observed that participants surpassed the recommended daily intake levels for both vitamin A and sodium. Specifically, the recommended intake for vitamin A is set at 700 mcg/day for women and 900 mcg/day for men. Actual consumption was significantly higher, with women averaging 996.7 mcg/day (SD=564.2) and men averaging 1124.0 mcg/day (SD=1128.5).[31]

Vitamin B-9

In a study conducted by Boykin et al. (2020), 29 patients diagnosed with early DFU administered high doses of folic acid. The results indicated that 90% of the participants experienced complete healing of their ulcers within the study duration. The average serum folate level in this cohort was reported at 192 ng/mL, with individual levels ranging from 87 to 301 ng/mL. The mean concentration of vitamin B-12 was found to be 2810 pg/mL, with values spanning from 1375 to 4779 pg/mL.[32]

In another investigation by Ababneh et al., which examined micronutrient status in 88 DFU patients, a statistically significant difference was observed between those with cardiovascular diseases and folic acid levels (p=0.041). The prevalence of folic acid deficiency in this group was recorded at 12.5%, with normal levels ranging from 10.4 to 42.4 nmol/L. Normal ferritin values are typically between 30 and 400 mg/L, low ferritin levels were noted in 29.5% of patients.[28]

Vitamin B-12

In a prospective, double-blind, placebo-controlled trial conducted by Didangelos et al. (2021), 90 patients diagnosed with type 2 diabetes, who had been using metformin for a minimum of four years and were experiencing peripheral and autonomic neuropathy, were randomly divided into two groups: an experimental group (n=44) that received vitamin B-12 and a control group (n=46) that received a placebo. At the start of the study, all participants had baseline vitamin B-12 levels below 400 pmol/L. In the experimental group, vitamin B-12 levels rose significantly from 232.0±71.8 pmol/L at baseline to 776.7±242.3 pmol/L during the control phase (p<0.0001), whereas no significant changes were noted in the control group.33

Minerals

In the research by Yadav et al. (2020), an assessment of mineral levels revealed a statistically significant decrease in serum zinc (p=0.000), copper (p=0.000), and magnesium (p=0.032) in patients with DFU when compared to those without DFU (p<0.05). The reference ranges for these minerals in a healthy non-diabetic population are as follows: serum zinc at 60–120 μg/dL, copper at 80–155 μg/dL, and magnesium at 1.8–2.6 mg/dL. Correlation analyses indicated an inverse relationship between these minerals and glycemic indices, with zinc exhibiting the strongest association in both groups.[34]

In the research by Momen-Heravi et al. (2017), the first group received zinc sulfate supplements at a dosage of 220 mg, which included 50 mg of elemental zinc, while the second group was given a placebo. The results indicated that zinc supplementation led to a notable increase in serum zinc levels (+12.7±4.7 vs. -3.5±4.0 mg/dL, p<0.001) compared to the placebo group. After 12 weeks of treatment, those receiving zinc demonstrated a significant decrease in both ulcer length (-1.5±0.7 vs. -0.9±1.2 cm, p=0.02) and width (-1.4±0.8 vs. -0.8±1.0 cm, p=0.02).[35]

In the study by Brookes et al. (2020), the average zinc level among a cohort of 48 patients with DFU was recorded at 10.6 ± 1.8 μmol/L, which is below the recommended range of 12 to 20 μmol/L.16 Additionally, Pena et al. (2020) found that patients experiencing more severe foot conditions were likely to have lower zinc levels (p=0.05).[18]

In the research by Afzali et al. (2019), the administration of magnesium and vitamin E supplements resulted in a significant decrease in ulcer dimensions: length (β -0.56 cm; 95% CI, -0.92, -0.20; *p*=0.003), width (β -0.35 cm; 95% CI, -0.64, -0.05; *p*=0.02), and depth (β -0.18 cm; 95% CI, -0.33, -0.02; *p*=0.02) when compared to a placebo group.[36]

Meanwhile, the study by Donnelly et al. (2023) identified that 37% of the 115 participants had inadequate zinc intake, based on the recommended daily allowances of 8 mg for women and 11 mg for men, which fall short of the Australian nutrient reference values. The average intake of vitamin E was found to be below the recommended guidelines in 86% of cases.[31]

The research by Bolajoko et al. (2017) revealed notable differences in lipid peroxide levels, 8-hydroxyl-2'-deoxyguanosine, glutathione peroxidase, total antioxidant status, vitamin C (*p*=0.003), vitamin E, selenium between the DFU group and the control group (*p*=0.001). A significant negative correlation was observed between selenium and 8-hydroxyl-2'-deoxyguanosine (*p*=0.029), while a significant positive relationship was identified between vitamin C and glutathione peroxidase (*p*=0.001) within the DFU group.[37]

In the investigation by Pena et al. (2020), it was reported that 5.9% of patients exhibited low ferritin levels (below 30 μg/L), whereas those with more severe foot disease presented with increased ferritin levels (*p*=0.004).[17] Brookes et al. (2020) found that the average selenium level was 10.7±0.26 μmol/L, with normal values established between 0.8 and 1.4 μmol/L. Additionally, the mean iron level was recorded at 8.4 (5.9), while the recommended range is between 11 and 32 μmol/L.[18] (Figure 2).

DISCUSSION

Nutritional deficiencies in individuals with DM result in reduced fat deposits in areas susceptible to pressure, thereby heightening the risk of pressure ulcers. Additionally, these deficiencies hinder collagen synthesis necessary for healing, diminish energy reserves, and impact the patient's mobility. The adverse effects of nutritional shortcomings on the immune response further contribute to the deterioration of skin health. The challenges associated with the healing process in diabetic feet are multifaceted, and inadequate nutrition only serves to worsen the situation.[38,39]

Our analysis aligns with previous research that emphasizes the crucial role of micronutrients in the development of DFU. A systematic review by Kurian et al. identified vitamin D as a key indicator, revealing significantly lower levels (MD: -10.82 ng/mL, 95% CI: -20.47 to -1.16).[40] A meta-analysis demonstrated that patients with DFU exhibited markedly reduced vitamin D levels, and a notably higher prevalence of vitamin D deficiency compared to those without DFU.[41] This finding is further supported by the meta-analysis conducted by Dai et al., which established a significant correlation between severe vitamin D deficiency and an elevated risk of developing diabetic foot syndrome (OR 3.22, 95% CI 2.42–4.28; *p*=0.64, I^2=0%).[42] Lin et al. reported that individuals with DFU had considerably lower vitamin D levels (MD: -6.48; 95% CI: -10.84 to -2.11, *p*<0.004) and a greater frequency of vitamin D deficiency.[43]

Another systematic review showed that vitamin D levels were lower in patients with DFU compared with those without DFU [OR: -5.77; 95% CI: -7.87 to -3.66; χ^2 = 84.62; mean difference: 9; I^2: 89%; *p*<0.001 and *p* for overall effect < 0.001]. Low vitamin D levels were observed among hospitalized patients (OR: -6.32; 95% CI: -11.66 to -0.97; χ^2 = 19.39; mean difference: 2; I^2 for

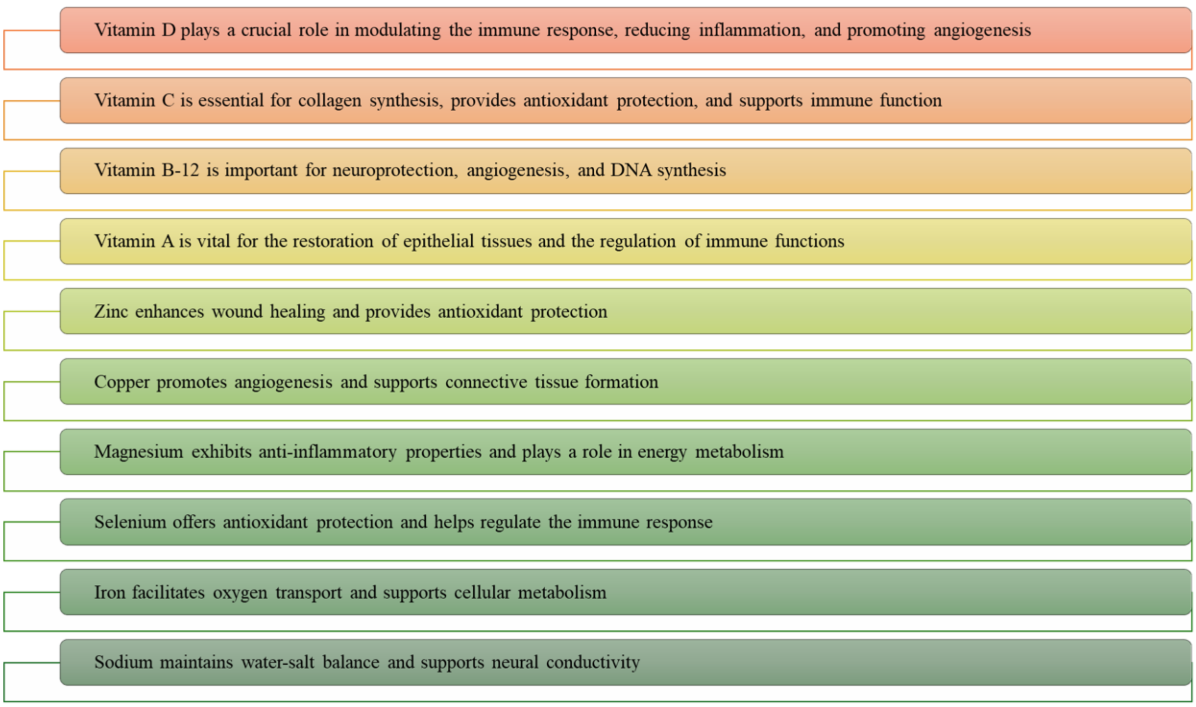

Figure 2. The relationship between nutrients and diabetic foot

heterogeneity: 90%; *p*=0.02).[44] Among all the effects of vitamin C on skin health, its effect on wound healing stands out as the most significant and reproducible. Available data also supports the importance of vitamin C, as it is a key element for collagen synthesis and effective functioning of the immune system, which helps reduce the likelihood of infections and facilitate their fight.[45] Impaired wound healing may indicate an early sign of vitamin C deficiency. The localization of vitamin C at the injury site, resulting from both local inflammation and heightened collagen production, underscores the potential benefits of supplementation.[46]

Vitamin A is crucial for the regeneration of the epidermis following tissue damage, facilitating healing and restoring skin integrity. It also mitigates the adverse effects of anti-inflammatory steroids on the regeneration process. Beyond its role during the inflammatory phase, retinoic acid enhances the production of extracellular matrix components, such as type I collagen and fibronectin, encourages the proliferation of keratinocytes and fibroblasts, and diminishes the activity of destructive matrix metalloproteinases.[47,48] Zinc plays a key role in insulin secretion, receptor transport and sensitivity, free radical protection, and acts as a necessary cofactor for enzymes involved in the healing process.[49,50]

In the research conducted by Lee et al., the micronutrient status of patients with DFU was analyzed in comparison to standard values to identify factors affecting the healing of chronic wounds. The findings revealed that 97.8% exhibited low iron levels, while 93.2% had decreased zinc levels.[51] Copper plays a crucial role in skin repair and the development of new blood vessels, facilitating the healing process by enhancing the production of vascular endothelial growth factor and promoting angiogenesis, which is triggered by hypoxia-inducible factor 1-alpha.[52]

A systematic review by Amini et al. indicated that various nutrients, including magnesium, vitamin D, vitamin E, and vitamin C, not only positively influence DFU but also aid in improving glycemic control, lipid profiles, and decreasing inflammatory and oxidative stress.[53]

Therapeutic and preventive nutrition plays a critical role in the prevention and treatment of diabetes at every stage. It includes an individual nutrition plan tailored to an individual's health status, lifestyle, and unique characteristics. And it is a vital component of diabetes care, encompassing nutritional assessment, diagnosis, intervention, and ongoing monitoring, all aimed at promoting sustainable lifestyle changes and adjusting interventions as needed. Adequate caloric intake is fundamental to preventing the onset of diabetes and to dietary therapy. Regular monitoring of micronutrient status and appropriate care are essential to identify deficiencies, take corrective action, improve wound healing, strengthen the immune system, and enhance the patient's overall health. Adopting this strategy will result in significant improvements, more effective rehabilitation, and a reduced risk of complications. Consistent assessment of micronutrient levels and proper management are critical to identify deficiencies, take corrective action, promote wound healing, strengthen the immune system, and enhance the patient's overall health. Adopting this approach will result in significant improvements, more effective rehabilitation, and a reduced risk of complications.[54]

Conclusion

A review indicates that deficiencies in micronutrients, especially vitamins D and C, are prevalent among patients with DFU. Notably, vitamin D deficiency is particularly severe in individuals with chronic active ulcers and significant infections, as demonstrated by markedly lower serum 25-hydroxyvitamin D levels in these patients compared to those without DFU. Following vitamin D, vitamin A ranks as the second most frequently observed deficiency. A limited number of patients exhibited normal vitamin C levels, while the majority presented with suboptimal or deficient levels, potentially hindering the ulcer healing process. Conversely, elevated blood folate levels correlate with enhanced healing outcomes, and treatment involving high-dose folic acid has shown significant improvements in patient conditions. Furthermore, the average levels of folate and vitamin B-12 among those receiving high-dose treatments were considerably above normal, underscoring their crucial role in the therapeutic regimen. Research indicates that patients with DFU exhibit lower levels of zinc, copper, magnesium, and selenium when compared to those without ulcers. Individuals supplementing zinc and magnesium have reported a decrease in ulcer size. A significant portion of these patients exhibited deficiencies in zinc, as well as vitamins E and C, which negatively impact the body's antioxidant defenses and may hinder the healing process of ulcers. Many patients surpass the recommended intake levels for vitamin A and sodium, potentially leading to adverse health effects. Elevated ferritin levels have been observed in patients suffering from more advanced stages of ulcers. These findings highlight the crucial need for monitoring and addressing micronutrient levels to enhance treatment outcomes for individuals with DFU.

We are confident that the findings from our systematic review will greatly enhance our comprehension of the impact of micronutrients on the progression and management of diabetic foot disease. Our objective was to uncover critical relationships between micronutrient deficiencies, and both delayed wound healing and the heightened risk of infection and amputation. By utilizing the gathered data, we can formulate clinical guidelines aimed at refining clinical practices, which will encompass the early identification of micronutrient deficiencies and their timely correction to improve treatment results.

CONFLICT OF INTEREST AND FUNDING DISCLOSURES

The authors affirm that there are no conflicts of interest to disclose.

REFERENCES

1. Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol. 2020;16:377-90. doi: 10.1038/s41581-020-0278-5.
2. van Netten J, Bus SA, Apelqvist J, Lipsky BA, Hinchliffe RJ, Game F, et al. Definitions and criteria for diabetic foot disease. Diabetes Metab Res Rev. 2020;36: e3268. doi: 10.1002/dmrr.3268.

3. Burgess JL, Wyant AW, Abdo BA, Kirsner RS, Jozic I. Diabetic wound-healing science. Medicina (Kaunas). 2021;57:1072. doi: 10.3390/medicina57101072.
4. Schaper NC, van Netten J, Apelqvist J, Bus SA, Hinchliffe RJ, Lipsky BA. Practical guidelines on the prevention and management of diabetic foot disease (IWGDF 2019 update). Diabetes Metab Res Rev. 2020;36:e3266. doi: 10.1002/dmrr.3266.
5. International Diabetes Federation. Clinical practice recommendation on diabetic foot: A guide for health care professionals. Brussels: International Diabetes Federation; 2017.
6. Kulprachakarn K, Ounjaijean S, Wungrath J, Mani R, Rerkasem K. Micronutrients and natural compounds status and their effects on wound healing in the diabetic foot ulcer. Int J Low Extrem Wounds. 2017;16:244-50. doi: 10.1177/1534734617737659.
7. Haddaway NR, Page MJ, Pritchard CC, McGuinness LA. PRISMA2020: An R package and Shiny app for producing PRISMA 2020-compliant flow diagrams, with interactivity for optimised digital transparency and open synthesis. Campbell Syst Rev. 2022;18:e1230. doi: 10.1002/cl2.1230.
8. Jørgensen L, Paludan-Müller AS, Laursen RT, Savović J, Boutron I, Sterne AC, et al. Evaluation of the Cochrane tool for assessing risk of bias in randomized clinical trials: overview of published comments and analysis of user practice in Cochrane and non-Cochrane reviews. Syst Rev. 2016;5:e25. doi: 10.1186/s13643-016-0259-8.
9. Maggi S, Siviero P, Brocco E, Albertin M, Romanato G, Crepaldi G. Vitamin D deficiency, serum leptin and osteoprotegerin levels in older diabetic patients: an input to new research avenues. Acta Diabetol. 2013;51:461-9. doi: 10.1007/s00592-013-0540-4.
10. Tiwari S, Pratyush DD, Gupta SK, Singh SK. Vitamin D deficiency is associated with inflammatory cytokine concentrations in patients with diabetic foot infection. Br J Nutr. 2014;112:1938-43. doi: 10.1017/S0007114514003018.
11. Afarideh M, Ghanbari P, Noshad S, Ghajar A, Nakhjavani M, Esteghamati A. Raised serum 25-hydroxyvitamin D levels in patients with active diabetic foot ulcers. Br J Nutr. 2016;115:1938-46. doi: 10.1017/S0007114516001094.
12. Razzaghi R, Pourbagheri H, Momen-Heravi M, Bahmani F, Shadi J, Soleimani Z, 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;31:766-72. doi: 10.1016/j.jdiacomp.2016.06.017.
13. He R, Hu Y, Zeng H, Zhao J, Chai Y, Lu F, et al. Vitamin D deficiency increases the risk of peripheral neuropathy in Chinese patients with type 2 diabetes. Diabetes Metab Res Rev. 2017;33:e2820. doi: 10.1002/dmrr.2820.
14. Feldkamp J, Jungheim K, Schott M, Jacobs B, Roden M. Severe vitamin D3 deficiency in the majority of patients with diabetic foot ulcers. Horm Metab Res. 2018;50:615-9. doi: 10.1055/a-0648-8178.
15. Darlington CJD, Kumar SS, Jagdish S, Sridhar MG. Evaluation of serum vitamin D levels in diabetic foot infections: A cross-sectional study in a tertiary care center in South India. Iran J Med Sci. 2019;44:474-82. doi: 10.30476/ijms.2018.44951.
16. Greenhagen RM, Frykberg RG, Wukich DK. Serum vitamin D and diabetic foot complications. Diabet Foot Ankle. 2019;10:1579631. doi: 10.1080/2000625X.2019.1579631.
17. Pena G, Kuang B, Cowled P, Howell S, Dawson J, Philpot R, et al. Micronutrient status in diabetic patients with foot ulcers. Adv Wound Care (New Rochelle). 2020;9:9-15. doi: 10.1089/wound.2019.0973.
18. Brookes JD, Jaya JS, Tran H, Vaska A, Werner-Gibbings K, D'Mello AC, et al. Broad-ranging nutritional deficiencies predict amputation in diabetic foot ulcers. Int J Low Extrem Wounds. 2019;19:27-33. doi: 10.1177/1534734619876779.
19. Dai J, Yu M, Chen H, Chai Y. Association between serum 25-OH-vitamin D and diabetic foot ulcer in patients with type 2 diabetes. Front Nutr. 2020;7:109. doi: 10.3389/fnut.2020.00109.
20. Tang W, Chen L, Ma W, Chen D, Wang C, Gao Y, et al. Association between vitamin D status and diabetic foot in patients with type 2 diabetes mellitus. J Diabetes Investig. 2022;13:1213-21. doi: 10.1111/jdi.13776.
21. Wang F, Zhou L, Zhu D, Yang C. A retrospective analysis of the relationship between 25-OH-vitamin D and diabetic foot ulcer. Diabetes Metab Syndr Obes. 2022;15:1347-55. doi: 10.2147/DMSO.S358170.
22. Todorova AS, Jude EB, Dimova RB, Chakarova NY, Serdarova MS, Grozeva GG, et al. Vitamin D status in a Bulgarian population with type 2 diabetes and diabetic foot ulcers. Int J Low Extrem Wounds. 2020;21:506-12. doi: 10.1177/1534734620965820.
23. Priyanto MH, Legiawati L, Yunir E, Miranda E. Comparison of vitamin D levels in diabetes mellitus patients with and without diabetic foot ulcers: An analytical observational study in Jakarta, Indonesia. Int Wound J. 2023;20:2028-36. doi: 10.1111/iwj.14066.
24. Tang Y, Huang Y, Luo L, Xu M, Deng D, Fang Z, et al. Level of 25-hydroxyvitamin D and vitamin D receptor in diabetic foot ulcer and factor associated with diabetic foot ulcers. Diabetol Metab Syndr. 2023;15:10. doi: 10.1186/s13098-023-01002-3.
25. Tsitsou S, Dimosthenopoulos C, Eleftheriadou I, Andrianesis V, Tentolouris N. Evaluation of vitamin D levels in patients with diabetic foot ulcers. Int J Low Extrem Wounds. 2021;22:27-35. doi: 10.1177/1534734620984584.
26. 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. 2021;22:466-74. doi: 10.1177/15347346211020268.
27. Hammad R, Abdel MW, Farouk N, Zakaria MY, Eldosoky MA, Elmadbouly AA, et al. Non-classical monocytes frequency and serum vitamin D3 levels are linked to diabetic foot ulcer associated with peripheral artery disease. J Diabetes Investig. 2023;14:1192-201. doi: 10.1111/jdi.14048.
28. Ababneh M, Al MA, Robert AA, Amer M, Al RR, Al FM, et al. Micronutrient status in patients with diabetic foot ulcers: A cross-sectional study in Saudi Arabia. J Fam Med Prim Care. 2024;13:356-62. doi: 10.4103/jfmpc.jfmpc_1109_23.
29. Gunton JE, Girgis CM, Lau T, Vicaretti M, Begg L, Flood V. Vitamin C improves healing of foot ulcers: A randomised, double-blind, placebo-controlled trial. Br J Nutr. 2020;126:1451-8. doi: 10.1017/S0007114520003815.
30. Green SJ, Ortiz J, Wu SC. Association between hemoglobin A1c, vitamin C, and microbiome in diabetic foot ulcers and intact skin: A cross-sectional study. Health Sci Rep. 2022;5:e718. doi: 10.1002/hsr2.718.
31. Donnelly HR, Clarke ED, Collins CE, Collins RA, Armstrong DG, Mills JL, et al. Most individuals with diabetes-related foot ulceration do not meet dietary consensus guidelines for wound healing. Int Wound J. 2023;21:e14483. doi: 10.1111/iwj.14483.
32. Boykin JV, Hoke GD, Driscoll CR, Dharmaraj BS. High-dose folic acid and its effect on early-stage diabetic foot

ulcer wound healing. Wound Repair Regen. 2020;28:517-25. doi: 10.1111/wrr.12804.
33. Didangelos T, Karlafti E, Kotzakioulafi E, Margariti E, Giannoulaki P, Batanis G, et al. Vitamin B12 supplementation in diabetic neuropathy: A 1-year, randomized, double-blind, placebo-controlled trial. Nutrients. 2021;13:395. doi: 10.3390/nu13020395.
34. Yadav C, Srikantiah RM, Manjrekar P, Shenoy MT, Chaudhury D. Assessment of mineral pathophysiology in patients with diabetic foot ulcer. Biol Trace Elem Res. 2019;195:366-72. doi: 10.1007/s12011-019-01868-3.
35. Momen-Heravi M, Barahimi E, Razzaghi R, Bahmani F, Gilasi HR, Asemi Z. Expression of concern: The effects of zinc supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Wound Repair Regen. 2017;25:512-20. doi: 10.1111/wrr.12537.
36. Afzali H, Jafari AK, Momen-Heravi M, Razzaghi R, Amirani E, Bahmani F, et al. The effects of magnesium and vitamin E co-supplementation on wound healing and metabolic status in patients with diabetic foot ulcer: A randomized, double-blind, placebo-controlled trial. Wound Repair Regen. 2019;27:277-84. doi: 10.1111/wrr.12701.
37. Bolajoko EB, Akinosun OM, Anetor J, Mossanda KS. Relationship between selected micronutrient deficiencies and oxidative stress biomarkers in diabetes mellitus patients with foot ulcers in Ibadan, Nigeria. Turk J Med Sci. 2017;47:1117-23. doi: 10.3906/sag-1601-95.
38. Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. Diabetes Res Clin Pract. 2019;157:107843. doi: 10.1016/j.diabres.2019.107843.
39. Moore ZE, Corcoran MA, Patton D. Nutritional interventions for treating foot ulcers in people with diabetes. Cochrane Database Syst Rev. 2020;7:CD011378. doi: 10.1002/14651858.CD011378.
40. Kurian SJ, Baral T, Unnikrishnan MK, Benson R, Munisamy M, Saravu K, et al. The association between micronutrient levels and diabetic foot ulcer: A systematic review with meta-analysis. Front Endocrinol (Lausanne). 2023;14:1152854. doi: 10.3389/fendo.2023.1152854.
41. Li X, Kou S, Chen G, Zhao B, Xue J, Ding R, et al. RETRACTED: The relationship between vitamin D deficiency and diabetic foot ulcer: A meta-analysis. Int Wound J. 2023;20:3015-22. doi: 10.1111/iwj.14177.
42. Dai J, Jiang C, Chen H, Chai Y. Vitamin D and diabetic foot ulcer: A systematic review and meta-analysis. Nutr Diabetes. 2019;9:7. doi: 10.1038/s41387-019-0078-9.
43. Lin J, Mo X, Yang Y, Tang C, Chen J. Association between vitamin D deficiency and diabetic foot ulcer wound in diabetic subjects: A meta-analysis. Int Wound J. 2022;20:55-62. doi: 10.1111/iwj.13836.
44. Mirghani HO. Vitamin D deficiency among outpatients and hospitalized patients with diabetic foot ulcers: A systematic review and meta-analysis. World J Meta-Anal. 2023;11:218-27. doi: 10.13105/wjma.v11.i5.218.
45. Carr A, Maggini S. Vitamin C and immune function. Nutrients. 2017;9:1211. doi: 10.3390/nu9111211.
46. Bechara N, Flood VM, Gunton JE. A systematic review on the role of vitamin C in tissue healing. Antioxidants (Basel). 2022;11:1605. doi: 10.3390/antiox11081605.
47. Li Y, Wongsiriroj N, Blaner WS. The multifaceted nature of retinoid transport and metabolism. Hepatobiliary Surg Nutr. 2014;3:126-39. doi: 10.3978/j.issn.2304-3881.2014.05.04.
48. Polcz ME, Barbul A. The role of vitamin A in wound healing. Nutr Clin Pract. 2019;34:695-700. doi: 10.1002/ncp.10376.
49. Lin P, Sermersheim M, Li H, Lee HU, Steinberg SM, Ma J. Zinc in wound healing modulation. Nutrients. 2017;10:16. doi: 10.3390/nu10010016.
50. Poudel R, Bhusal Y, Tharu B, Kafle N. Role of zinc in insulin regulation and diabetes. J Soc Health Diabetes. 2017;5:83-7. doi: 10.1055/s-0038-1676241.
51. Lee SH, Kim SH, Kim KB, Kim HS, Lee YK. Factors influencing wound healing in diabetic foot patients. Medicina (Kaunas). 2024;60:723. doi: 10.3390/medicina60050723.
52. Salvo J, Sandoval C. Role of copper nanoparticles in wound healing for chronic wounds: literature review. Burns Trauma. 2022;10:tkab047. doi: 10.1093/burnst/tkab047.
53. Amini MR, Aalaa M, Nasli-Esfahani E, Atlasi R, Sanjari M, Namazi N. The effects of dietary/herbal supplements and the serum levels of micronutrients on the healing of diabetic foot ulcers in animal and human models: a systematic review. J Diabetes Metab Disord. 2021;20:973-88. doi: 10.1007/s40200-021-00793-4.
54. Nutrition and Metabolic Management Branch of China International Exchange and Promotive Association for Medical and Health Care, Clinical Nutrition Branch of Chinese Nutrition Society, Chinese Diabetes Society, Chinese Society for Parenteral and Enteral Nutrition, Chinese Clinical Nutritionist Center of Chinese Medical Doctor Association. Chinese Guidelines for Medical Nutrition Therapy for Patients with Diabetes (2022 Edition). Asia Pac J Clin Nutr. 2024;33:118–152. doi:10.6133/apjcn.202406_33(2).0001.