



ROLE OF SOME MICRONUTRIENTS IN THE HEALING PROCESS OF DIABETIC ULCERS

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ABSTRACT:

Background: Diabetic foot ulcer (DFU) is among the most serious and traumatic complications of diabetes mellitus. Nutrition is essential in chronic wound healing as extra nutrients, including micronutrients, are often needed for proper tissue repair. We aim to examine and analyze the relationship between oral intake of some micronutrients and wound healing in patients with DFU.

Methods: A search was conducted in the Medline/Pubmed and Google Scholar databases, using comprehensive keywords, and articles published in the last 10 years were analyzed.

Review Results: Minerals represent an essential factor in the multifaceted wound healing process. Micronutrient deficiency affects all phases of wound healing, including collagen synthesis, fibroblast proliferation, and epithelization. Magnesium, zinc, selenium, and copper have been postulated as beneficial for DFU as they function as antioxidants modulate immunity, cell replication and differentiation, and tissue repair.

Conclusion: More research is needed to clarify and warrant the use of mineral supplementation for the prevention and healing of diabetic foot ulcers.

Keywords: micronutrients, diabetic foot ulcer, supplementation,

BACKGROUND

Diabetes mellitus (DM) is a chronic metabolic disease that manifests with numerous complications. It is a leading cause of non-traumatic lower limb amputations [1]. Currently, it is estimated that approximately 537 million people are affected by DM, with a worrying increase in the disease predicted in the coming years [2].

Diabetic foot ulcer (DFU) is one of the most significant and severe complications of diabetes, defined as a foot affected by ulceration associated with neuropathy and/or peripheral arterial disease of the lower limb in a patient with DM [1]. Diabetic foot is a common, serious, limb-threatening complication and is considered a major cause of morbidity and hospitalization in diabetic patients. Approximately 15-25% of DM patients develop DFU during their lifetime [1]. The global prevalence of diabetic foot ulcers (DFU) is 6.3%, higher in men and in type 2 DM compared to women and type 1 DM [3].

DFUs have a high recurrence rate – 40% within one year and 65% within five years. Moreover, about 85% of all amputations in diabetic patients are preceded by foot ulceration, which can further deteriorate into foot infection or gangrene. In addition, DFU is often a life-threatening complication [1].

Despite the severity of the problem, there are currently no reliable methods for predicting the occurrence of these ulcers [1]. The treatment of DFU remains one of the current challenges in medical science and practice. It requires a thorough understanding of the pathogenesis and a multifactorial approach to provide the best possible means of healing for the affected patients [1, 4].

Pathogenesis of DFU

Four main factors contribute to the pathogenesis of DFU: peripheral arterial disease, peripheral neuropathy, bacterial infection, and cellular dysfunction [5].

Peripheral arterial disease is one of the most important factors in the development of diabetic foot. In diabetic patients, vascular disease predominantly affects the arteries in the lower limbs. Atherosclerosis is a significant risk factor for the onset of peripheral vascular disease [6]. Insufficient blood supply induces severe ischemia of the skin of the lower limbs, leading to necrosis of the ulcerated tissues [5]. A thickening of the capillary basement membrane and endothelial dysfunction are among the most common structural changes in diabetic microcirculation [6].

Diabetic peripheral neuropathy is a central factor in the development of DFU. In this condition, nerves in the lower limbs are damaged by inflammation, oxidative stress, advanced glycation end-products, and reduced nitric oxide production. Peripheral neuropathy results in sensory, motor, and secretory dysfunctions in the skin of the lower limbs. There is a decrease in nerve innervation of the small muscles in the foot, along with a decline in peripheral sensation and vasomotor control of the foot's circulation [6]. These pathological changes alter the physical mechanics of the feet and lead to the loss of protective sensation (direct factors for ulcer formation). They also cause the skin to dry out, an unfavorable factor for the healing process of diabetic wounds [5]. Moreover, the production of neuropeptides that help in wound healing decreases, and this accelerates the progression of wounds and ulcers to gangrene [6].

It is estimated that about 50% of patients with DFU show clinical signs of infection (either locally or systemically) [6]. Bacterial infection of the wound delays the healing process. This is due to decreased beneficial and increased harmful inflammatory factors [5]. Chronic hyperglycemia, a characteristic of diabetes mellitus, creates an environment suitable for bacterial growth, mainly aerobic Gram-positive cocci, Gram-negative aerobes and drug-resistant bacteria, which were the common microorganisms isolated from the diabetic foot. In extreme situations, the bacterial infection of soft tissue may spread to the bones and other surrounding tissues and organs. The growth of pathogenic bacteria further worsens the development and progression of DFU [6].

The functional state of the cells in the wound directly determines the quality of healing. The microenvironment of diabetic wounds is unsuitable for normal cellular functions in the different wound healing stages [5]. During the inflammatory phase, there is an imbalance between the pro-inflammatory and anti-inflammatory effects of macrophages and neutrophils and a prolongation in the inflammatory cascade. In the proliferative phase, the proliferation and migration of endothelial cells are impaired. In the remodeling phase, fibroblasts differentiate and secrete abnormal amounts of collagen. Additionally, there is dysfunction in the proliferation and differentiation of keratinocytes [5].

Oxidative stress is a key player in the pathogenesis of DFU [7]. Numerous studies have demonstrated a direct connection between oxidative stress and diabetes by measuring oxidative stress biomarkers. A hyperglycemic state can elevate levels of markers for oxidative stress-induced DNA damage, lipid peroxidation products, and protein oxidation products while also reducing the activity of antioxidant enzymes [8]. Oxidative stress promotes the formation of inflammatory mediators, and inflammation, in turn, increases the production of reactive oxygen species. Therefore, controlling the reactions initiated by reactive oxygen species can be beneficial in preventing prolonged inflammation and pathological changes in DM [8, 9].

Nutrition and DFU

Nutrition is one of the numerous factors that can affect the wound healing process. The relationship between nutrition and wound healing has been known for centuries [1]. There is evidence that patients with DFU are at high risk of malnutrition [10]. The incidence of developing moderate or severe infection is approximately 70% in malnourished patients with DFU, compared to only 5% in well-nourished patients [10]. Malnutrition is associated with an increased frequency of lower limb amputation as well as the severity of the amputation. The rate of major amputations (above the ankle) is nearly 11 times higher in the malnourished group compared to patients who were well-nourished [10].

In patients with DM, in addition to inadequate protein intake, there is a significantly lower intake of micronutrients such as vitamin E, B1, B2, B3, B6, magnesium, calcium, zinc, iron, and potassium, which are necessary for wound healing [1, 10].

Micronutrients are trace elements and minerals that the body needs in small quantities. They are essential for cellular metabolism, especially during tissue regeneration. They can act as co-factors or activators of enzymes necessary for wound repair [11]. Micronutrients influence the healing process through antioxidant and anti-inflammatory activity and participate in the collagen stabilization process, regulation of cell growth, and differentiation [12]. Previous studies have shown that DM affects the homeostasis of many micronutrients [11]. Additionally, serum levels of some of them are significantly reduced in cases of DFU compared to diabetics without ulcers [13].

On the other hand, the administration of nutritional supplements, combined with nutrition education, significantly accelerates wound healing in patients with DFU compared to those who received standard care regimens [10].

This study aims to examine and analyze the relationship between oral intake of magnesium, zinc, selenium, and copper and wound healing in patients with diabetic foot ulcers.

MATERIALS AND METHODS:

A search was conducted in the Medline/PubMed and Google Scholar databases, and articles published in the last 10 years were analyzed. The following keywords were used: "trace elements," "micronutrients," "diabetes," "wound healing," "diabetic foot ulcer," and "supplementation," combined with "magnesium," "zinc," "selenium" and "copper". Studies were considered eligible based on the following criteria: original articles, clinical and experimental studies, review articles; articles that assess the micronutrients (magnesium, zinc, selenium, copper) and their effects on DFU. The exclusion criterion was the lack of a connection between the micronutrients and DFU.

REVIEW RESULTS:

Magnesium

Magnesium (Mg) is an essential co-factor for enzymes involved in carbohydrate and lipid metabolism and acts as an anti-inflammatory agent [14]. Mg is an important micronutrient for protein and collagen synthesis and tissue growth during wound healing [11].

Hypomagnesemia, due to low intake and increased loss of Mg, is common in poorly controlled diabetes. Previous studies have shown that low serum levels of Mg are associated with DFU. Hypomagnesemia is also linked to the development of neuropathy and abnormal platelet activity, which are risk factors for the development of DFU [15]. Clinical studies investigating the effects of Mg supplementation on wound recovery are limited. It has been found that daily use of Mg supplements for 12 weeks leads to a significant increase in serum Mg in diabetic patients and significantly reduces the length, width, and depth of ulcers. Additionally, Mg supplementation improves glucose metabolism parameters (fasting plasma glucose, serum insulin levels, and HbA1c), serum hs-CRP, and plasma levels of TAC [15].

Another clinical study evaluated the effects of combined supplementation of Mg (250 mg magnesium oxide) and vitamin E (400 IU) on wound healing, glycemic control, lipid profiles, and biomarkers of inflammation and oxidative stress among patients with DFU. The results were similar – reduced wound area parameters and a beneficial effect on glycemic control, lipid profile, hs-CRP, and oxidative markers (TAC and MDA levels) [16].

Zinc

Zinc (Zn) is the second most abundant trace element in the human body after iron. It is a fundamental micronutrient crucial for the function of over 300 enzymes and plays a pivotal role in cellular processes such as cell division and apoptosis [13]. Zn is involved in the synthesis and secretion of insulin, as well as in hormonal signaling pathways. Zinc deficiency is associated with impaired glucose tolerance and insulin resistance [17]. It also participates in protection against free radicals [13].

Zinc plays a key role in wound healing as it acts as a co-factor in various transcription factors and enzyme systems, e.g. zinc-dependent matrix metalloproteinases are responsible for degrading the extracellular matrix [1].

Diabetes disrupts zinc homeostasis. Additionally, zinc levels are significantly lower in patients with DFU compared to those without DFU [7]. Clinically, 12-week administration of zinc supplements (220 mg zinc sulfate containing 50 mg elemental zinc) has a beneficial effect on ulcer size parameters (length and width), metabolic profile, and oxidative status in patients with DFU [7]. Another study shows that a combination of Zn and vitamin E effectively improves the wound healing process in oral mucosal ulcers in diabetic rats [18].

Selenium

Selenium (Se) as an integral part of selenoproteins (glutathione peroxidase (GPX) and thioredoxin reductase (TxnRd) families), is involved in antioxidant defense, regulation of redox signaling and maintenance of cell vi-

talinity [19, 20]. Se can sustain normal cell growth and proliferation, protein folding, and mitochondrial function [20]. A study by Kreindl et al. demonstrated that treating fibroblasts cultured in high glucose with selenium compounds (selenocysteine and sodium selenite) modifies the extracellular matrices, creating a surface more conducive to the migration of microvascular endothelial cells [21]. In addition, selenium supplementation decreases the level of anti-elastin antibodies and slows down the degradation of elastin and the degeneration of the vascular walls [22].

Numerous studies have suggested that Se is an immunomodulator as it regulates innate and adaptive immunity to infections [20]. Its anti-inflammatory effects are linked to the reduction of 5-LOX and COX-2. Additionally, Se decreases the expression and phosphorylation of NF-κB and the secretion of pro-inflammatory cytokines induced by NF-κB [19].

Se is involved in glucose metabolism by exhibiting an insulin-mimetic effect through its stimulating effect on the tyrosine kinases involved in the insulin signaling cascade and regulates insulin secretion [20]. Data have been published that Se supplementation delays the production of antibodies against late glycation end products [23].

Studies indicate significantly reduced concentrations of Se in patients with DFU [24]. A combined antioxidant supplement administered over 16 weeks (1000 mg vitamin C + 400 mg vitamin E + 100 μg selenium) has demonstrated a positive effect on oxidative stress and wound healing in patients with T2DM and foot ulcers [9].

Copper

Copper (Cu) is a fundamental element for the homeostasis of the body and the third most abundant essential transition metal in humans [25]. Cu is crucial for the regulation of various enzymes and the synthesis of structural components, and in many physiological pathways and biological processes such as angiogenesis, response to hypoxia, and neuromodulation [25]. As a component of copper/zinc superoxide dismutase, copper is essential in managing oxidative stress [25]. It significantly contributes to the immune system by mitigating tissue damage from oxidative stress and modulating the inflammatory response [26]. Additionally, copper is a necessary co-factor for protein synthesis and vital for collagen formation, and its deficiency can lead to impaired wound healing [27]. On the other hand, excessive exposure to copper can cause toxicity in many human organs, leading to various systemic alterations [25, 28].

The clinical studies comparing plasma or serum Cu levels in patients with T1DM, T2DM and healthy individuals show conflicting findings [28]. Some authors report that there isn't any statistically significant difference in Cu levels in T2DM patients and healthy controls [29]. Other studies have shown a close relationship between copper serum levels and altered glycemic control [25, 30]. Total Cu and ceruloplasmin levels were higher in T1DM patients compared to healthy controls [31]. In another study of 97 patients with T2DM, 85.5% had Cu deficiency

[32]. Given the essential role of Cu, the imbalance of copper can lead to the progression of diabetes-related complications, including DFU [25].

Information about a close relation between DFU and Cu serum level is scarce and the existing results are again contradictory. Bozkurt et al. reported that the mean values of Cu and Zn were higher in patients with diabetic foot infection (DFI) and DM, and the elevation of Cu in DFI and DM groups was positively correlated with Cu/Zn ratios [33]. A recent study revealed that decreased serum Cu levels in diabetics with DFU are positively correlated with the duration of the disease [13]. We didn't find data about supplementation with Cu alone and its effect on DFU.

Micronutrients (minerals) are essential for a plethora of body functions. Ensuring they are present in adequate amounts is vital for everyone's health. Therefore, if necessary, they should be provided with dietary supplements to meet the individual daily requirements. On the other hand, it is known that there are interactions between trace elements that affect their absorption and bioavailability in the body. These interactions have been demonstrated in experimental absorption studies and, to some extent, have been confirmed in supplementation studies. Negative effects of zinc supplementation on iron and copper status have been reported [34]. Magnesium and selenium supplementation resulted in increased losses of copper [35].

CONCLUSION:

The nutritional status of patients with diabetes is a pivotal factor that influences the development and progression of diabetic foot ulcers. Although limited, clinical studies suggest the potential inclusion of micronutrient supplements or supplements that contain micronutrients in the comprehensive treatment of DFU. Magnesium, zinc, and selenium supplementation has a beneficial effect on patients with DFU by reducing the size of ulcers. The role of copper depends on its levels in the

body. Clinical studies on the application of copper as a dietary supplement are limited, but there is evidence of improved glycemic control in patients with diabetes mellitus. Based on this, we may hypothesize that copper supplementation could have a beneficial effect on the chronic complication of DFU. Alongside the strong reasons for incorporating micronutrients into the comprehensive treatment of DFU, there are also challenges. Additional systematic studies are needed to track the effects of micronutrients on each of the stages of wound healing, as well as their influence on the molecular mechanisms involved in the pathogenesis of DFU. In clinical practice, achieving a good therapeutic outcome also requires considering individual differences in nutrient intake and determining the optimal doses of micronutrients. Consequently, incorporating dietary supplements with trace elements into the treatment plan for diabetes can be an important step in preventing serious health consequences and improving the overall quality of life for these patients.

Abbreviations:

5-LOX - 5-lipoxygenase

COX-2 - cyclooxygenase-2

Cu - copper

DFI - diabetic foot infection

DFU - diabetic foot ulcer

DM - diabetes mellitus

GPx - glutathione peroxidase

HbA1c - hemoglobin A1c; glycated hemoglobin

hsCRP - high-sensitivity C-reactive protein

MDA - malondialdehyde

Mg - magnesium

NFκB - nuclear factor kappa B

Se - selenium

T1DM - type 1 diabetes mellitus

T2DM - type 2 diabetes mellitus

TAC - total antioxidant capacity

Zn - zinc

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