MEDICAL NUTRITION

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Nutritional management to support optimal wound healing in patients with diabetic foot ulcers

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1 | Executive Summary

In 2021, 537 million adults were living with diabetes and this number and consequently, healthcare cost, are expected to increase dramatically.[1] Unfortunately, the condition is often poorly controlled, which results in serious complications such as diabetic foot ulcers (DFU). These non- or poorly healing wounds below the ankle[2] develop in up to 34% of diabetic patients.[3] They are the main reason for lower extremity amputations and hospital admission in people with diabetes[4] and have a significant negative effect on healthcare costs[5] and quality of life.[6]

Malnutrition and specific micronutrient deficiencies are factors that may further impair wound healing in patients with diabetes.[7] Wound healing is a complex process that requires an adequate balance of energy, carbohydrate, protein, fat, vitamins, and minerals.[8] Oral nutrition supplements (ONS) containing proteins, omega-3 fatty acids, vitamins, and minerals are a convenient format to help patients meet their nutritional requirements. A systematic review and meta-analysis concluded that high-calorie, high-protein ONS or tube feeds enriched with arginine, zinc, and antioxidants were associated with improved healing in patients with pressure ulcers (PU) when compared with a standard formula.[9] Given the similarities in the pathogenesis of DFU and PU,[10] it is expected that many of the benefits seen in patients with PU also apply to those with DFU.

In this white paper, we explore the latest recommendations for nutritional therapy in patients with or at risk of DFU, and how this is creating new opportunities for tailored medical nutrition innovation. The paper does not discuss the use of nutrients in pharmaceutical medications for treatment purposes nor provide professional guidance regarding nutritional therapy in patients with DFU.

Diabetes and its complications

Diabetes mellitus, often simply referred to as diabetes, is a serious, chronic condition that occurs when the body cannot produce enough insulin or cannot effectively use insulin.[1] It affects an increasing number of adults, and this trend continues:[1] 537 million adults were living with diabetes in 2021 and this is expected to increase to 634 million by 2030, and to 783 million by 2045. Accordingly, the global health expenditures for adults with diabetes have been growing from USD 232 billion in 2007 to USD 966 billion in 2021, and are expected to continue to grow.[1]

When diabetes is not or only poorly controlled over an extended period, the elevated blood glucose levels (**hyperglycemia**) can induce serious damage, especially in the nerves (**neuropathy**) and blood vessels (**vascular disease**)[11] (See **Box 1**). As almost 1 in 2 adults with diabetes are unaware of the condition,[1] proper and timely management cannot always be implemented and hence, the damage develops unnoticed. Diabetic foot ulcers (DFU) are among the most common complications in patients with poorly controlled diabetes and one of the most frequent reasons for hospital admission in these patients.[4]

Box 1 | **Important terms to understand diabetes**

Hyperglycemia (high blood sugar) is the term for elevated glucose levels in the blood due to impaired action of insulin or when the body produces too little insulin.

Diabetic **neuropathy** is a type of damage of the nerves, often in legs or feet, frequently seen in patients with diabetes.

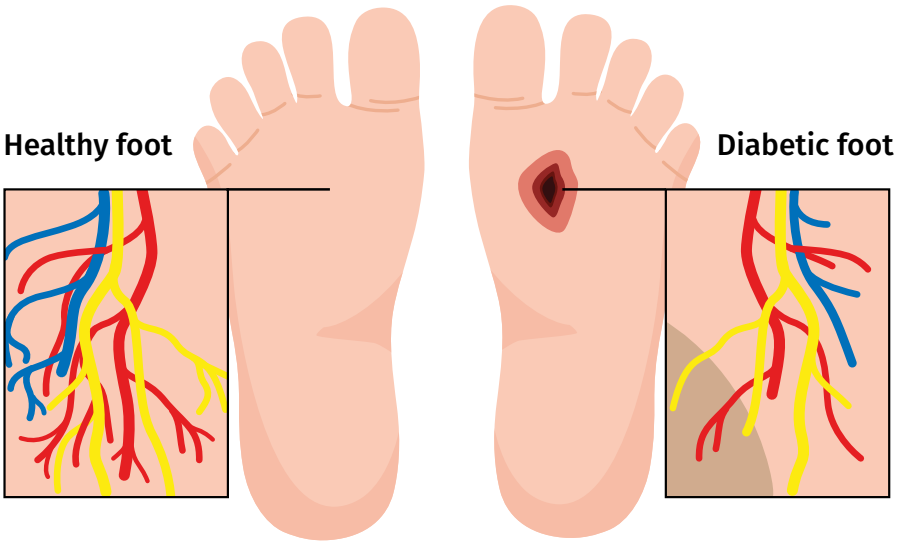
Diabetic **vascular disease** manifests as hardening of arteries if the blood glucose levels are poorly controlled over an extended period in patients with diabetes.

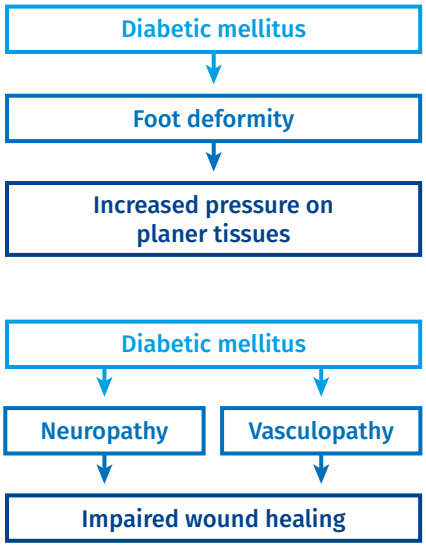
Diabetic foot ulcers (DFU) are open sores or wounds and are frequently located at the bottom of the feet in patients with diabetes.

Causes of diabetic foot ulcers (DFU)

DFU are non- or poorly healing wounds below the ankle[2] and their pathophysiology is complex:[12] inadequately controlled blood glucose levels, nerve damage and reduced blood flow in the limbs, as well as poor foot care contribute to their development.[13] They are usually found in the areas of the foot that encounter repetitive trauma and pressure sensations.[13] Neuropathy reduces the sensation of pain that would normally prevent the repetitive injuries to develop. In combination with other changes such as dry skin, this can result in increased callus or blister formation, and hence increase risk of infection, inflammation, tissue death (necrosis) and the development of ulcers.[14]

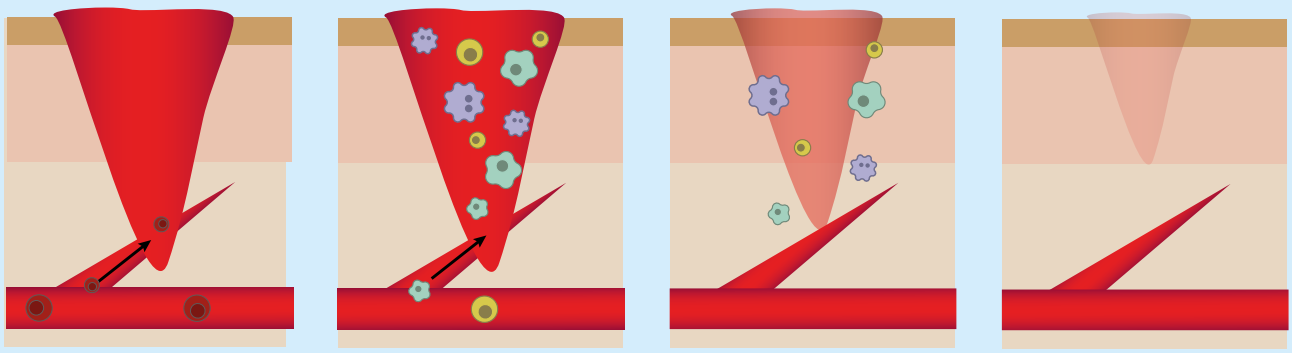
DFU are often characterized by chronic inflammation, impaired immune response, increased susceptibility to infection, and suboptimal healing.[15] Diabetes disrupts almost all phases of the healing process (See **Box 2**) and diabetic wounds have a prolonged inflammatory phase, which increases the risk for the development of chronic wounds.[16] Reestablishing blood supply, another crucial part of proper wound healing, is frequently impaired in diabetic wounds.[16] Moreover, scar tissue is characterized by lower collagen synthesis as well as a reduced ability to contract, making them more vulnerable to outside stresses.[16] These wounds are highly susceptible to infections, and hence, sepsis, and are at an increased risk of progression to DFU.[17]





Recreated from Zwanenburg, P. R., Backer, S. F. M., Obdeijn, M. C., Lapid, O., Gans, S. L., & Boermeester, M. A. (2019). A Systematic Review and Meta-Analysis of the Pressure-Induced Vasodilation Phenomenon and Its Role in the Pathophysiology of Ulcers. Plastic and reconstructive surgery, 144(4), 669e-681e. https://doi.org/10.1097/PRS.0000000000006090

Box 2: Wound healing process



The acute wound healing process consists of several distinct phases that are frequently impaired in patients with diabetes, resulting in chronic wounds (recreated from Andrade *et al* 2022[17])

Living with diabetic foot ulcers (DFU)

It was estimated that up to 34% of patients with diabetes develop DFU[3] and they are one of the most frequent reasons for hospital admission in people with diabetes.[4] Without prompt intervention and proper treatment, DFU can result in soft tissue and/or bone infection, and may eventually require amputation of the affected limb or parts of it: Up to 85% of diabetes-related lower extremity amputations are preceded by DFU.[18] Prognosis is generally poorer as seen in a cohort in the UK, where mortality rates were 2.5-fold higher in patients with DFU compared to the diabetic controls without such wounds.[19]

Consequently, DFU have a significant negative effect on healthcare costs: An estimate for the U.S. published in 2014 concluded that USD[9] to USD[13] billion were spent on DFU in addition to the general costs of diabetes management.[5] They affect quality of life through a range of factors: DFU interfere with activities of daily living and increase dependence, cause pain, decrease mobility, disturb sleep, and last but not least, frequently evoke negative emotions such as anxiety, fear, hopelessness and depression.[6]

Diabetic foot ulcer, wound healing & malnutrition

According to the American Limb Preservation Society,[20] improvements in wound care, including nutritional interventions, can increase life expectancy and quality of life, while reducing cost of care. Wound healing is a complex process that requires an adequate balance of various nutrients to support repair and remodeling of tissue[21] (See **Box 3** overleaf). Malnutrition and / or specific micronutrient deficiencies are factors that may impair wound healing in patients with diabetes.[7] It is widespread in patients with DFU, particularly if they are elderly:[21] available studies report that significant proportions of patients were found to be at risk of malnutrition (49-70%) or malnourished (15-62%). [22-27] Moreover, a recent review concluded that patients with DFU have increased risk of being deficient in vitamin A, B12, C, D and E as well as in iron, selenium, and zinc.[28]

Due to the complexity of wound healing combined with the multifactorial nature of malnutrition, outcomes of studies on the association of malnutrition and wound healing varied: In some, nutritional status was an independent predictor of patient outcome such as amputation rates or mortality. [4,26,27] Other studies failed to show a significant beneficial effect of nutritional status on wound healing.[23,25] Still, a review of the topic concluded that this inconsistency is more likely due to differences in e.g., patient population, and that the complied data indicated a negative impact of malnutrition in patients with DFU.[22] In patients in general, malnutrition is associated with increased risk for complications, length of hospital stay and mortality.[29]

Oral nutritional supplements (ONS) containing proteins, DHA and EPA, vitamins, and minerals are a convenient format to support patients to meet their nutritional requirements. However, only very few studies assessed their effect in patients with DFU: One study compared an ONS containing protein and micronutrients with a placebo ONS and found no significant effect on wound healing.[23] However, the authors attribute this to methodological problems in this study rather than a lack of effect.[23] Another study tested the effect of an ONS with the amino acids arginine, glutamine, and β-hydroxy β-methylbutyrate (HMB) (See **Box 4**) compared to a standard ONS and only found an effect in the subgroup of patients with specific vascular complications.[30] Consequently, a recent Cochrane review concluded that there was insufficient evidence to support or refute the use of ONS for management of DFU.[31]

Box 4: Amino acids

Amino acids are the building blocks for protein and can also be used as a source of energy.

***Essential* amino acids** cannot be made in the body and need to be provided by the diet.

***Conditionally essential* amino acids** can generally be built from other nutrients, but become essential in specific conditions, i.e., when requirements are increased due to illness and stress.

In the absence of data on DFU, studies in patients with PU may be considered as DFU and PU are chronic wounds that share similar pathogenesis.[10] In line with this, Wound Care Canada[32] recommends the use of guidelines for the nutritional management of PU[33] (See **Box 5**) to be used for patients with DFU until specific guidelines become available.

Box 5: Guidelines on the prevention and treatment of pressure ulcers (PU)[33]*

- **Energy** intake for adults with or at risk of PU and at risk of malnutrition should be in the range of 30 to 35 kcal/kg/d
- This should be adjusted e.g., if they are obese or have had significant unintended weight loss
- **Protein intake** of 1.25 to 1.5 g/kg/d is recommended for patients at risk of malnutrition or malnourished with or at risk of PU
- ONS with high protein, arginine and micronutrients should be used if patients have PU stage III or IV or multiple PU and nutrient requirements cannot be meet with high-protein, high-energy ONS
- **Vitamin and mineral supplements** are recommended when dietary intake is poor or deficiencies are confirmed or suspected

In patients with PU, a systematic review and meta-analysis concluded that high-calorie, high-protein ONS enriched with arginine, zinc, and antioxidants were associated with improved healing when compared with a standard ONS.[9] Moreover, a nutritional intervention with such an ONS was shown to be cost-effective as it reduced the spending for PU care.[34] Therefore, and considering the high prevalence of malnutrition in these patients,[22-27] an ONS containing adequate levels of energy, protein as well as essential nutrients is a promising component for the care of DFU. This is further supported by an observational study that found patients with DFU who were taking dietary supplements were significantly more likely to achieve healing.[35]

* In the absence of specific guidelines for DFU, it is recommended to follow those for PU[40]

Box 3: Nutrients for wound healing

Wound healing is a complex process that requires an adequate balance of various nutrients to support the cellular activities essential for repairing and remodeling of tissue.[21] Energy, carbohydrate, protein, fat, vitamin, and mineral metabolism may affect the healing process:[8]

- **Energy** intake for adults with PU who are at risk of malnutrition should be in the range of 30 to 35 kcal/kg/d.[33] This should be adjusted e.g., in adults who are obese or who have had significant unintended weight loss.[33]
- **Fats** and **carbohydrates** are primary sources of energy for the healing process. An adequate intake of carbohydrates can prevent the depletion of amino acids and proteins needed for specific functions e.g., in the immune system.[8]
- **DHA** and **EPA**, long-chain omega-3 fatty acids, play an important role in the immune system.[36] Importantly, they also support the resolution of inflammation and hence, support tissue healing.[37] Conversion from their precursors is generally low and further impaired in conditions such as insulin resistance.[38] This underscores the importance of adequate intake of preformed DHA and EPA in patients with diabetes. An intervention with an ONS containing DHA and EPA showed an association with decreased PU progression and a reduction in an indicator for systemic inflammation, when compared to a standard ONS.[39]
- **Protein** is critical for all stages of wound healing: it is required for the synthesis of enzymes involved in wound healing, immunological processes such as inflammatory response, production of collagen and connective tissue, and the formation of new blood vessels.[7,40] Achieving adequate protein intake is particularly important in older patients who are at increased risk of sarcopenia (loss of muscle) and decreased immune function.[41] For patients with DFU, protein intake of 1.25 to 1.5 g/kg/d is recommended,[32] in line with recommendations for those with PU[33] and similar to what is thought desirable for older adults with acute or chronic disease (1.2 to 1.5 g/kg/d).[42]
- **Arginine** is a conditionally essential amino acid that contributes to protein synthesis and collagen deposition, the immune response, vascular function as well as other aspects of wound healing.[8,43] Hence, supplementation is recommended for wound healing if depletion of body stores is likely due to the stress of illness.[44]
- **Glutamine** is also considered a conditionally essential amino acid as levels tend to decrease after major surgery, trauma, and sepsis.[44] It is an important source of fuel when e.g., immune and epithelial cells need to multiply rapidly[8] and there is some evidence for a beneficial effect of glutamine on wound healing.[45]
- **Leucine** is an essential amino acid, which helps to maintain muscle protein when combined with a high-protein diet and may improve glucose homeostasis.[46] Preclinical data shows a beneficial effect of leucine on the recovery of connective tissue after injury.[47] In combination with arginine and glutamine, supplementation with β-hydroxy β-methylbutyrate (HMB), a metabolite of leucine, increased collagen synthesis in healthy elderly volunteers, indicating a potential benefit for wound healing.[48] Moreover, mobility is often compromised in patients with chronic wounds and leucine supplementation may help reduce loss of muscle mass.[49]
- **Vitamin A** is required for the formation of new tissue, synthesis of collagen, and for the immune system,[40] and deficiency is linked to impaired wound healing.[8] Given its role in the release of insulin as well as in energy metabolism, it might also play a role in diabetes management.[50]
- **Vitamin C** also plays a role in collagen synthesis and protein metabolism, and it has important antioxidant and anti-inflammatory effects. Deficiencies result in impaired healing, and immune response and in increased susceptibility to wound infection.[8] Moreover, there is some evidence that supplementation with vitamin C improves glycemic control and blood pressure in diabetic patients.[51] In addition, people with obesity[52] and patients with diabetes[52] and hypertension[53] had lower vitamin C levels compared to healthy controls. The increased oxidative potential of such conditions results in higher requirements for this dietary antioxidant, which are difficult to meet with the diet alone.
- **Vitamin D** plays an important role in the immune system and muscle maintenance, it helps mitigate the negative effects of inflammation and is involved in wound healing as well as glucose management.[54] Low levels of vitamin D were associated with increased prevalence of microvascular complications in diabetic patients.[55] Supplementation had beneficial effects on wound healing in patients with DFU when compared to a placebo.[56] It also improved insulin sensitivity in insulin-resistant and vitamin D deficient women.[57]

Box 3: **Nutrients for wound healing** *continued*

- **Vitamin E** is an antioxidant, it maintains and stabilizes cellular membranes, is involved in collagen synthesis, has anti-inflammatory properties, and is needed for vitamin C recycling.[7] Preclinical data have indicated that vitamin E supplementation may support wound healing and have a beneficial effect on glucose management.[58] In combination with magnesium, vitamin E had beneficial effects on wound healing and glucose management in patients with DFU.[59]
- **Vitamin K** has the haemostatic capacity that most influences wound healing. Vitamin K is a co-factor for the synthesis of prothrombin and clotting factors VII, IX, and X[8,60] and in conjunction with calcium[61] is important in initiating blood clotting at the site of the wound.[8,60,61] Deficiency may lead to continued haematoma formation within a wound, which can impair healing and predispose to infection.[8,60]
- **Copper** is needed for a range of essential enzymes and is involved in the development of collagen fibers.[7] Moreover, it plays an important role in the immune system by countering the tissue damage induced by oxidative stress and by modulating the inflammatory response.[62]
- **Selenium** plays a role in a range of immune functions, including antioxidant defense[63] and it helps regulate inflammation by preventing excessive and chronic inflammation.[64] Selenium deficiency was shown to result in an impaired immune defense and hence an increased susceptibility to infections.[65]
- **Zinc** is essential for cell replication and growth, it is crucial for protein and collagen synthesis as well as the immune system.[66] Importantly, deficiency manifests as an imbalanced inflammatory response and increased oxidative stress.[67] Moreover, it is associated with impaired wound healing[8] and supplementation showed beneficial effects on healing in patients with DFU.[68]

Your end-to-end partner for medical nutrition innovation

The care of patients with DFU is complex and nutrition is increasingly seen as an essential component of holistic care.[20] Moreover, it is important to offer tailored medical nutrition solutions that will address the special nutritional requirements presented by patients during the different stages of the patient journey. However, creating targeted medical nutrition solution takes more than ingredients. It takes a partner who is inspired by patients and guided by the scientific evidence in the development of innovative nutritional solutions for optimal care.

As a purpose-led company, DSM is passionate about supporting the health, recovery, and independence of patients of all ages and the elderly, as well as reducing the burden on global healthcare systems. We take an evidence-based and human-centric approach to innovation; to ensure the patient's needs and preferences are addressed in a way that will ultimately enhance their quality of life. When you partner with us, you get access to the broadest nutritional ingredient offering in the industry, as well as customized solutions and expert services to support at every stage of your product's development.

DSM offers medical nutrition solutions designed with the benefit of:

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- **Extensive industry expertise**
- **Unrivalled formulation and application knowledge**
- **Science-led innovation capabilities**
- **A global network and local support**

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We provide a complete portfolio of science-based and high-quality nutritional ingredients. From vitamin straights as individual ingredients, including vitamins as active pharmaceutical ingredients for parenteral nutrition, to nutrients such as EPA and DHA from marine and algae sources, our ingredients can be used in a range of medical nutrition formulations.

Customized solutions

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Expert services

We are committed to adding value at every stage of development – from concept to consumption – through the broad range of expert services available across our global network. These services support the development of medical nutrition solutions that successfully address the needs and format preferences of the elderly and patients under medical supervision.

For further insights and information on how DSM can be your end-to-end partner in developing innovative, appealing medical nutrition solutions that will meet the complex nutritional needs of patients with DFU, please visit ***www.dsm-medicalnutrition.com***.

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