The Role of Nutrition in Chronic Wound Care Management

What patients eat affects how they heal.

BY LELAND JAFFE, DPM AND STEPHANIE WU, DPM, MSC

The multi-faceted approach to the management of chronic wounds can be a daunting challenge. Treatment strategies for chronic wounds of the lower extremity often entail a multidisciplinary approach focusing on therapies, including off-loading modalities, serial wound debridements, assessment of arterial vascular inflow, and managing bacterial bioburden. While these do represent the major pillars of chronic wound management, evaluation and optimization of nutritional status should be included as part of the comprehensive treatment of the chronic wound patient.

Hippocrates in 5th century B.C. recognized the value of nutrition and the potential of certain foods for good health and said "Let food be thy medicine and medicine be thy food." Wound healing requires the body to be in an anabolic state that necessitates specific macro- and micronutrients as well as proper hydration to fuel the physiologic process. Since dietary depletion may contribute to wound chronicity,[1] proper assessment of nutritional status is paramount to predict healing potential.

The complex wound healing cascade progresses from hemostasis, inflammation, proliferation, and ultimately tissue remodeling. Among other factors, this process relies on adequate levels of macro-and micro-nutrients to ensure a timely progression through these stages. Patients who are malnourished may lack the necessary fundamental building blocks to promote tissue regeneration, leading to wound chronicity.[1] Patients may be malnourished for a number of reasons, including limited financial resources, lack of family support, dietary constraints, anxiety, depression, and diminished appetite. Malnourishment ensues if a patient's nutritional intake does not meet the body's metabolic demands.

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Malnutrition

Malnutrition is defined as loss of body tissue and diminished body functions caused by inadequate nutritional intake.[2] Firstly, during a period of malnourishment the patient will deplete the liver's glycogen stores to ensure glucose is continually supplied to vital body cellular functions. However, glycogen stores are often depleted within the first 24 hours following starvation. The continued stress of starvation will increase the metabolic rate and result in the release of cortisol from the adrenal glands.[3] This will improve the body's ability to mobilize amino acids from protein sources to support hepatic gluconeogenesis and continually supplying the body with glucose. During this stress response with increased cortisol production, elevated levels of inflammatory cytokines, including interleukin 1 (IL-1), interleukin 6 (IL-6), and tumor necrosis factor alpha will be elevated, contributing to a delay in wound healing.[4]

This systemic inflammation will also cause a decrease in negative acute phase reactants including albumin and pre-albumin.[4] With continual lack of nutritional intake, the body will begin metabolizing fat for energy, sparing the sustained breakdown of muscle tissue for protein.[3] This transition from primarily protein to fat metabolism will minimize muscle and overall weight loss. A consequence of adipose tissue depletion, however, may contribute to increased pressure on osseous prominences leading to pressure ulcer formation.

Following the depletion of fat stores, the body will again rely primarily on skeletal muscle for energy demands, resulting in rapid weight loss and overall cachexia. Clinically, a malnourished status will contrib-

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ute to impaired immunity,[5] decreased muscle mass leading to weakness and immobility,[6] and an overall decrease in wound healing potential.[7]

Assessment of Nutritional Status

Nutritional status associated with an increased risk for the development of ulcers include reduced body mass index (BMI), low body weight, altered ability to dine independently, reduced food intake, low dietary protein intake, low serum albumin concentration (<3.5 mg/dL), and decreased total lymphocyte count (< 1.8 x 109/L). While no cause-effect relationship can be established between malnutrition and ulcer formation, a thorough nutritional screening mechanism is important to identify patients at risk of a potential nutritional deficit.

The Mini Nutritional Assessment (MNA)

The Mini Nutritional Assessment (MNA) is a frequently referenced tool to assist in identifying malnutrition, particularly in the elderly population.[8] The MNA screening tool evaluates multiple parameters, including food intake and decline, weight loss, mobility, neuropsychological problems, BMI, and calf circumference to define nutritional risk. Patients frequently recognized as high risk for nutritional deficit include the elderly, patients with food intolerance (chemotherapy), limited income, depression, lack of teeth/dentures, and inability to self-feed.

Patients with diabetes and ulcerations have also been recognized as a cohort at risk of malnutrition, resulting in a poor prognosis of healing.[9] Zhang and colleagues identified that as the severity of the Wagner diabetic foot ulceration classification increased, the patient's nutritional status declined.[9]

Assessment of nutritional status also includes anthropomorphic data and an overall clinical assessment of the patient. The physical examination includes findings such as coarse hair and reduced skin turgor.[10] Other clinical findings suggestive of nutritional depletion include muscle atrophy, reduced subcutaneous tissue, and localized/generalized edema.[11] The prevalence of obesity, defined as a body mass index (BMI) > 30, is on the rise in the United States and involves 36.5% of the adult population.[12] Obesity should not rule out the possibility of a malnourished status, as excess adipose tissue may conceal underlying skeletal muscle atrophy.[13]

Moreover, adipose tissue is considered poorly vascularized, causing a further delay in wound healing due to decreased oxygenated blood flow to a wound bed. Anthropometric measurements include patient's BMI, recent weight loss, and head circumference (in children). Unintentional weight loss of <5% in 6 months is defined as mild loss, 5-10% as moderate-severe loss, and >10% as severe loss of weight.[14]

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Macronutrients in Wound Healing

Wound healing is an anabolic event that requires adequate intake of macronutrients, including carbohydrates, fats, protein, and water. Fats provide about 9 kcal per gram, carbohydrates about 4 kcal per gram, and protein about 4 kcal per gram. Protein is a macronutrient that is critically important during the entire cascade of the wound healing process. Protein stores within the body may be diminished due to overall decreased intake, or excessive daily protein loss via wound exudate.[15] The daily recommended protein intake for a healthy individual is 0.8 grams of protein per 24 hours. This number may vary based upon activity level, total caloric intake, and gender.

Patients with open wounds, however, may require an additional 1.25 to 1.5 grams of protein per kilogram of body weight to support the anabolic process of wound healing.[16] The body increases protein demand about 250% and caloric demand 50% to support synthesis of new tissue and maintain lean body mass (LMB) stores.[17]

Numerous factors involved in the inflammatory phase of healing are primarily protein-driven and include macrophages, phagocytes, leukocytes, and lymphocytes.[18] With a blunted immune response and a diminished inflammatory phase of wound healing due to protein deficiency, clearing of cellular and bacterial debris will be compromised. This could prolong the inflammatory phase of wound healing and limit the ability to progress towards tissue proliferation. A decrease in protein availability will also decrease fibroblastic activity and collagen production during the proliferative stage of healing.[19]

Protein malnutrition can present in a patient with decreased protein intake, absorption, or metabolism, contributing to insufficiencies in LBM. Protein deficiency may also stem from a deficiency in certain amino acids such as arginine and glutamine. Arginine is a conditionally essential amino acid, especially during times of stress. It is acquired from diet and derived endogenously from citrulline in a reaction catalyzed by arginine synthetase. Arginine functions as a precursor to collagen formation and production of nitric oxide, thus promoting tissue formation and oxygenation of the wound.[20,21]

Glutamine is another amino acid that has been suggested to serve a function during the cascade of wound healing.[16] As with arginine, glutamine is conditionally essential during injury or disease as demand outstrips supply. It is involved in protein synthesis as a precursor for nucleotides and glutathione and is essential for immune system function. Glutamine serves as a fuel source for fibroblasts, epithelial cells, lymphocytes, and macrophages, and indirectly assists in the process of inflammation and phagocytosis. Therefore, supplementation of glutamine has

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often been suggested in cases of nutritional depletion.[16]

Carbohydrates and fats compose the other two macronutrients that are important during the stages of wound healing. Carbohydrates are metabolized to form glucose, providing 4 kcal of energy per gram of carbohydrate ingested. Glucose is the body's main energy source, providing the fuel needed for collagen production during the proliferative phase of healing.[22] However, hyperglycemia can have detrimental effects on tissue repair, including decreased fibroblastic activity,[23] reduced growth factor production and effectiveness,[23] and a compromise in cell-mediated immunity.[24,25]

Adequate fat intake is also important, providing 9 calories per gram of fat. Dietary fat is not only an essential source of calorie dense energy, but is needed for the absorption of fat-soluble micronutrients, including vitamins A, D, E, K, and the omega-3 (alpha-linolenic acid) and omega-6 fatty acids (linoleic acid).

A proper ratio of omega-3 to omega-6 essential fatty acids is important for optimal health, as too much omega-6 fat can lead to elevated arachidonic acid, prolonging systemic inflammation within the body. Moreover, adequate daily intake of carbohydrates and fats prevents the body from utilizing dietary or tissue proteins as a source of energy.

Fluid intake should also be considered in the nutritional assessment and recommendations for wound treatment.[26] Adequate hydration is necessary not only to maintain normal skin turgor but to also assist with vascular inflow and oxygenation of tissues. The recommended daily fluid intake for wound care patients is 1 mL of fluid per 1 kcal ingested,[19] or 30-35 mL per kg of body weight.[22] Special considerations should be given to patients with underlying medical conditions that result in either excessive fluid retention such as renal or cardiac disease, or fluid loss in cases of diarrhea, fever, diuresis, and copious wound exudate. Proper hydration also facilitates the transportation of macro-and micro-nutrients to the site of tissue injury to augment healing. Adequate hydration status can be assessed through the evaluation of serum sodium, blood urea nitrogen measurement (normal 7-23 mg/dl), or urine-specific gravity.

Micronutrients in Wound Healing

Micronutrient intake should be evaluated and optimized in patients with open wounds. This includes the consumption of essential vitamins, amino acids, and minerals that support wound healing through hemostasis, inflammation, proliferation and remodeling. Following an initial insult to the skin, the body responds by creating hemostasis. Vitamin K is the necessary nutrient that supports blood coagulation and this can be found in leafy green vegetables, kale, broccoli, cucumber, or asparagus. Following hemostasis, platelets involved with hemostasis degranulate and release growth factors into the wound that assist in the recruitment of macrophages and neutrophils.

The macrophages and neutrophils, in turn, secrete inflammatory cytokines including interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-alpha, and matrix metalloproteinases (MMPs) that assist in the removal of bacteria and cellular debris. This process results in the formation of free radicals and reactive oxidative species (ROS) that can damage healthy tissue.[22]

Nutrients rich in antioxidants, including vitamins E, C, A and selenium, can neutralize the free radicals and augment wound healing (Table 1). Following the removal of cellular damaged matrix and bacterial contents, the quantity of inflammatory cytokines and MMPs decrease, and the wound progresses to the proliferative and inflammatory phases of healing.[27] This anabolic process relies on a multitude of vitamins and minerals, including but not limited to vitamin A, vitamin C, copper, iron, and zinc. Vitamin A has been beneficial to support collagen deposition in the wound and can also antagonize the negative effects of corticosteroids on wound healing.[28]

TABLE 1

Nutrient	Food Sources
Vitamin E	Almond, Spinach, Avocado, Olive oil
Vitamin C	Red pepper, Orange, Grapefruit , Strawberry
Vitamin A	Carrot, Sweet Potato, Spinach, Kale, Broccoli
Selenium	Chia seeds, Salmon, Tuna, Eggs

Vitamin C

Vitamin C is a water-soluble vitamin that is critical in the proliferative phase of healing, as fibroblasts rely on this vitamin for the production of collagen.

Copper and Iron

Finally, the minerals copper and iron support the formation of collagen. Copper further assists with the cross-linking of collagen, strengthening the repair process. Supplementation of these vital minerals should be based on each patient's serum depletion.

There are 50 known essential nutrients for sustaining human life. Numerous published clinical trials have attempted to determine the macro-or micro-nutrient supplementation that will positively impact wound healing. An article recently published in the *Journal of Diabetes and Its Complications* attempted to determine the effect of vitamin D supplementation on wound healing in patients with diabetic foot ulcers. In this prospective, randomized double-blinded, placebo-controlled trial, 50,000IU vitamin D supplements every two weeks for 12 weeks appeared to play a role in improved glycemic index, which indirectly improved wound healing.[29]

Zinc

Zinc is an essential trace mineral for over 300 enzymes. It plays an important role in the metabolism of proteins, carbohydrates, and nucleic acids. Zinc also maintains struc-

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ture and integrity of cell membranes, and deficiency of zinc can result in an increased susceptibility to oxidative damage. Deficiency of zinc is more common in vegetarians as the bio-availability of zinc from a vegetarian diet is lower than from a non-vegetarian diet.

Vegetarians consume high levels of legumes and whole grains that contain phytates which bind zinc and inhibit its absorption.[30] Long-term alcohol consumption impairs zinc absorption and increases its urinary excretion.[31] Digestive disorders such as ulcerative colitis and Crohn's disease, as well as certain medications, can also impair zinc absorption. Quinolone antibiotics, including ciprofloxacian and tetracycline, can interact with zinc in the gastrointestinal tract, inhibiting the absorption of both zinc and the antibiotic.[32]

A study published in *Wound Repair and Regeneration* in 2017 determined that the supplementation of 220 mg zinc sulfate, containing 50 mg elemental zinc, for 12 weeks in diabetic patients with foot ulcerations resulted in a reduction in ulceration length and width, and improvement in metabolic profiles as compared to the placebo group.[33] Razzaghi and colleagues published another randomized control trial in 2017 evaluating the efficacy of magnesium supplementation and the effects on wound healing and metabolic status. The outcome of this study determined that a daily supplement of 250 mg magnesium oxide for 12 weeks resulted in significant reductions in ulcer length, width, and depth, with an overall improvement in metabolic control.[34]

Several other studies have been performed to help practitioners provide evidence-based recommendations to the patient to augment wound healing.

Proper nutritional assessment is critical to evaluate and screen for patients with chronic wounds who may be nutritionally depleted, thus potentially compromising the process of wound healing. The nutritional goal is for the patient to consume nutrient dense foods and have proper hydration that supports the anabolic process of wound healing. While some studies are inconclusive regarding the recommendations of specific vitamin and mineral supplementation, it does appear evident that meeting the balanced macro- and micro-nutrient needs of the patient will help to support the wound healing process. **PM**

The nutritional goal is for the patient to consume nutrient dense foods and have proper hydration that supports the anabolic process of wound healing.

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Dr. Leland Jaffe is an Assistant Professor in the Department of Medicine and Radiology at Scholl College of Podiatric Medicine. In addition to teaching, Dr. Jaffe serves on two wound care panels and is involved in research with the Center for Lower Extremity Ambulatory Research (CLEAR) at Scholl College.

Dr. Wu is Associate Dean of Research and Professor of Surgery; Professor, Stem Cell and Regenerative Medicine. She is Director at the Center for Lower Extremity Ambulatory Research (CLEAR) of the Dr. William M. Scholl College of Podiatric Medicine at Rosalind Franklin University of Medicine and Science.