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Nutrition and Lower Extremity Ulcers: Causality and/or Treatment

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Abstract

The association between malnutrition, impaired wound healing, and the presence of chronic wounds has been recognized for a long time. It is widely believed that the lack of adequate nutrition increases the risk of developing wounds which have a great likelihood of progressing to chronicity due to lack of appropriate healing responses. This risk is particularly high in the aging population. For the individual patient, as well as patient populations, the diagnosis of malnutrition has been in dispute; further, there is lack of agreement of when and how to intervene nutritionally in those with wounds or healing deficits. This article examines the relationship of nutritional status with the presence and clinical evolution of leg ulcers in humans, focusing on diabetic and venous leg ulcers; we will further review the effect of nutritional therapy on the outcome of these ulcers.

Keywords

nutritional, healing deficits, malnutrition

Definition of Malnutrition

The World Health Organization defines malnutrition as "deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients"[1]; Merriam Webster's defines it "as faulty nutrition due to inadequate or imbalanced intake, impaired assimilation or utilization."[2] In the United States, deficiency of adequate, nutritionally appropriate caloric intake has been the generally accepted definition, regardless of etiology (poor intake, defective absorption, lack of interest, obesity, etc). Energy or protein deficiency, Kwashiorkor or Marasmus, respectively, are seldom seen in pure forms in the Western world, with most malnourished patients or elderly displaying characteristics of both. A more recent study characterized malnutrition as the presence of low body mass index, unintentional weight loss, low serum albumin and food intake less than 60% of the daily estimated requirement.[3] 40% to 60% of hospitalized older adults, up to 85% of nursing home residents and upward of 60% of home care patients are either in a state of malnutrition or at risk.[4] Level of independence in the elderly both cognitively and physically are inversely associated with staggeringly high rates of malnutrition.[5] Loss of appetite, financial distress and depression are further associated with the presence of malnutrition.[5-7] Obesity as a phenomena of impaired nutritional status is a relatively new problem in the world, seemingly ever increasing primarily in the Western world. It is of note that the most recent statistics from the World Health Organization indicate approximately 462 million individuals are underweight versus the nearly 1.9 billion adults classified as overweight or obese.[1]

Assessment of Malnutrition

Comprehensive evaluation of nutritional status should include patient history, complete physical exam, anthropometric measurements, and laboratory analyses. Anthropometric measures used include height, weight, body mass index (BMI), and estimates of body fat and muscle mass. Recommended laboratory measurements include albumin, retinal-binding prealbumin, transferrin, complete blood count, serum folate, vitamin B_{12}, and cholesterol.[8] Neither the physical nor biochemical assessments have not been found to correlate well with malnutrition and are time consuming, expensive, and often prone lack of reproducibility.

The nutritional assessment of the elderly is rendered more difficult because many of the clinical signs of malnutrition are also associated with normal aging. Various tools have been promulgated for the nutritional assessment of

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geriatric populations, aiming for simplicity, accuracy of prediction and reproducibility. These include (1) Nutritional Screening Initiative, levels I and II, which is well suited to community screening; it incorporates a simple nomogram to determine BMI and a questionnaire of clinical characteristics, eating habits, living environment, and mental and cognitive states plus laboratory data (albumin and serum cholesterol); (2) Mini Nutritional Assessment: created for the elderly, it can be applied in the ambulatory or hospital setting; it defines the condition of the malnourished patient, the risk of malnutrition, and the general nutritional status; it can be performed in approximately 10 minutes and is highly reproducible[5]; (3) Mini Nutritional Assessment–Short Form: created to reduce the time of administration to 10 minutes without losing diagnostic power, it correlates well the mini nutritional assessment, it has adequate sensitivity and specificity, and good internal consistence[9]; (4) Malnutrition Universal Screening Tool: initially, developed for non-institutionalized individuals, its use has been validated in various environments including hospital, clinics, and home residences[10]; drawbacks include the lack of any measure of functionality and a focus on acute disease; and (5) Subjective Global Assessment, designed to estimate nutritional status through clinical history and physical exploration, it has greater sensitivity and specificity; can be used to determine which patients require nutritional intervention and which would benefit from intensive nutritional support.[11]

In patients with malnutrition, evaluation of the potential risk for wound development and/or healing becomes the next challenge. Tools that factor malnutrition/nutritional status and the development of wounds such as the Norton, Waterlow, and Braden scales are used routinely in the hospital/institutional settings.[12,13] All the aforementioned tools address nutrition in addition to other key factors such as mobility/activity status, skin status, and moisture exposure. Clearly, development of wounds is multifactorial and nutritional deficits are a major contributor to risk for wound development. BMI alone is not a good predictor of protein deficiency. The National Pressure Ulcer Advisory Panel (NPUAP) evolved their own risk assessment that ranks mobility status along with baseline skin status at the base of the pyramid while perfusion, oxygenation, and nutritional status are on the second tier and age, health status, sensory perception and hematological measures are at the apex of the pyramid. Inadequate protein intake leading to edema in peripheral vasculature,[14] and acute and chronic inflammation[15] have all been implicated mechanistically in the evolution of wounds in the background of malnutrition.

Malnutrition and Lower Leg Ulcers

In examining the nexus between nutrition and lower leg chronic wounds, we will refer mainly to human studies. Aditionally, where information exists in some types of wounds (acute, pressure, etc), we would assume that biological principles apply generally to all wounds, particularly where specific data is not available on lower extremity wounds.

Lack of adequate nutrition impairs the wound collagen accumulation, impairs wound healing and promotes chronicity.[16] Intracellular collagen synthesis has an absolute requirement for energy, amino acids, oxygen, trace minerals, and vitamins.[17] The malnourished organism, which is in energy conserving mode and carries out minimal synthetic processes during acute injury phase, has to overcome this metabolic impediment for wound healing, which is above all a synthetic process

Chronic wounds are closely associated with malnutrition. This association is strongest with pressure ulcers, but not all studies agree.[18,19] Pressure ulcers of the lower extremities are typically seen in the heels as well as the lateral malleoli; with lack of mobility in the aged population, wounds of the lower legs can be in numerous places. Pressure ulcers developed as the individual is unable to shift pressure off of boney prominence or devices (catheter tubing, etc). Although poor nutrition alone is not a strong risk factor for developing venous leg ulcers (VLUs), patients with VLU often have poor nutritional indices. For example, older patients (>70 years of age) with VLU have a higher incidence of malnutrition, as assessed by anthropometric indices (BMI, arm/calf circumference, history of weight loss) and dietary history/assessment.[20] A thorough study of a small population of obese patients with VLU noted similar findings.[21] Total serum protein and albumin levels were below normal in 27% of patients with VLU.[22] Dietary profiling of VLU patients reveals increased consumption of fat, sodium and sugar along with a decreased vitamin C intake, when compared with recommended daily allowance (RDA) recommendations.[23] Significant deficits in vitamins A and E, carotenes, and zinc have also been described in the setting of chronic VLU.[24]

Patients with diabetic foot ulcers (DFUs) have similar or even higher degrees of malnutrition and nutritional deficits.[25] One-third of subjects older than 60 years with Wagner grade I to II ulcers of at least 4 weeks duration were found to have protein-calorie malnutrition.[26] Poor scores on Mini Nutritional Assessment are an independent predictor of amputation outcomes.[27] Furthermore, a BMI less than 25 kg/m^2 places diabetic patients at a higher risk for amputation. Nutritional status of diabetic patients correlates with the severity of the ulcer, risk of infection and with outcome; the severity of the DFU increases as the nutritional state deteriorates.[26]

Nutritional Therapy and Lower Leg Ulcers

Given the close correlation between nutritional status and the occurrence of lower extremity ulcers, it is an easy for clinicians to advice that nutritional therapy should be part and parcel of any treatment plan for such patients. Although

advice for nutritional intervention is almost universal, there is paucity of data or agreement in multiple areas: how to administer nutrition (enteral, parenteral, topical), what to administer, role of special nutrients, length of therapy, end points of therapy, and so on. The matter gets even more confusing as there is some data regarding efficacy of nutritional intervention in pressure ulcers, but precious little strong evidence in lower limb ulcerations.

As mentioned before, successful wound healing requires metabolically the presence of calories, protein, trace minerals, vitamins, and oxygen. Goodson and Hunt[28] have pointed out that successful wound nutrition is host nutrition, meaning correction of host nutritional deficits is key to successful wound healing.[28] Thus, provision of adequate calories and protein is key to reversing nutritional deficits, which, as mentioned, are often present in patient with chronic ulcers. Depending on the level of stress and preexisting degree of malnutrition, intake of 30 to 35 kcal/kg body weight and 1.2 to 1.5 g protein/kg is recommended in order to correct and maintain nutritional health in most individuals with wounds.[29] Although this indication has been put forth for pressure ulcers, there is no reason not to believe that it would apply to patients with other chronic wounds and with nutritional deficits. The recommendation is to continue this level of caloric and protein intake until wounds are resolved.[29] Nutritional supplementation was found to be beneficial for venous stasis wounds but not for diabetic and sickle cell ulcers.[30]

The nutropharmaceutical role of single nutrients on collagen synthesis and/or wound healing is still being studied. We will review some of these below; most of the available data are not derived from study of lower extremity ulcers, but whatever biologic value to wound healing is demonstrated may also apply to all manners of wounds.

Amino Acids and Wound Healing

Amino acids are important for wound healing to occur. In the past three decades there has been increased recognition that several amino acids have specific effect of increasing collagen synthesis, in doses above and beyond those required for nutritional needs.

Arginine is considered an essential amino acid under periods of severe stress. In the growing animal much of the dietary arginine is used for the synthesis of connective tissue proteins and in the injured animal an increase in arginine intake would be expected to result in more reparative connective tissue synthesis.[31]

Using a micro-model where collagen accumulation occurs in a subcutaneously placed segments of polytetrafluoroethylene (PTFE) tubing, young healthy human volunteers (25-35 years) were found to have a significant increase in wound collagen deposition following oral supplementation with either 30 g of arginine aspartate (17 g of free arginine) or 30 g of arginine HCl (24.8 g of free arginine) daily for 14 days.[32] In a subsequent study of healthy elderly humans (67-82 years) daily supplements of 30 g of arginine aspartate for fourteen days resulted in significantly enhanced collagen and total protein deposition at the wound site when compared with placebo controls.[33] It should be noted that the effect of arginine is on collagen synthesis, as neither oral nor parenteral arginine affects epithelial healing.[32-34]

A small diverse group of patients with pressure ulcer treated with supplemental arginine, vitamin C, and zinc showed improved wound healing.[35] Similarly diets high in protein and arginine content led to better healing than standard hospital diet.[36] Markedly improved collagen synthesis was noted in healthy elderly humans given dietary supplementation of arginine, glutamine, and β-hydroxy β methylbutyrate (HMB).[37] A metabolite of leucine, HMB increases muscle mass and is most effective when coupled with exercise. In diabetic foot ulcer patients, supplemental arginine, glutamine, and HMB had a significant healing effect only in subjects with plasma albumin levels less than 40 g/L and in those with decreased limb perfusion, as measured by ankle-brachial indices.[38]

Ornithine, a metabolite of arginine in the urea cycle, as well as ornithine keto-glutarate also enhance wound collagen deposition in animals, although no studies in humans have yet been carried out.[39,40]

Wound Healing and Fatty Acids

Lipids, the primary structure of all cell membranes, play an integral though poorly understood role in the wound healing process. As a source of calories, other than glucose and protein, a diet replete in lipids may theoretically limit protein catabolism in the stressed or wounded state. Impaired wound healing has been documented in humans with essential fatty acid deficiencies.[41]

The role of fats in wound healing has not been widely studied. More recently interest in defining possible benefits of specific lipid types has emerged. The omega-3 fatty acids have anti-inflammatory properties by inhibiting eicosanoid production and other mediators such as platelet-activating factor (PAF), interleukin-1 (IL-1), and tumor necrosis factor–α (TNF-α).[42-44] Animals consuming diets enriched with omega-3 fatty acids had weaker wounds 30 days after injury. The weaker wounds did not contain less collagen; rather the omega-3 supplementation was thought to impair the quality, cross-linking, or spatial orientation of collagen fibrils.[45] In a human suction blister model, the daily consumption of omega 3-fatty acids (given as supplemental fish oil that contained 26 times and 12 times the daily recommended dosage, respectively, for eicosapentaenoic acid [EPA] and docosahexaenoic acid [DHA]) raised blister fluid IL-1 levels and lengthened healing time.[46] It does appear that fish oil supplements, especially in large doses,

adversely affect the healing response; it should be borne in mind that omega fatty acids are stored in fatty tissue and can reach supranormal levels quickly.

Vitamins and Wound Healing

Vitamin C deficiency has historical significance to wound healing because of its relation to scurvy, which has as its central element a failure in collagen synthesis and cross-linking. Ascorbic acid is a specific co-substrate for the enzymes 4-prolyl hydroxylase and lysil hydroxylase; biochemically, it is a reducing agent required for the conversion of proline and lysine to hydroxyproline and hydroxylysine, which are critical to collagen cross-linking and mechanical strength.[47]

Although the recommended dietary allowance for vitamin C is 70-90 mg/d, the clinical spectrum of its administration varies widely, with doses as high as 5g/day being safely administered.[48] There is no evidence to suggest that massive doses of ascorbic acid are of any substantial benefit to wound healing in nondeficient states; conversely, there is no evidence that excess vitamin C is toxic.[48,49]

Vitamin A deficiency impairs wound healing. Subsequently, vitamin A was shown to enhance wound healing even in nondeficient states. More important, vitamin A, administered either topically or systemically, reverses the anti-inflammatory effects of corticosteroids on wound healing.[50,51] Vitamin A has also been proposed as therapy for wound healing impaired by diabetes, tumor formation, chemotherapeutic agents, or radiation. Vitamin A increases the inflammatory response in wounds through enhanced lysosomal membrane lability, increased macrophage influx and activation and stimulation of collagen synthesis. In the severely injured (such as burn victims), doses of vitamin A as high as 25 000 IU/d (5 times the recommended daily dose) have been advocated and used without any significant side effects. Larger doses of vitamin A do not improve wound healing further and prolonged excessive intake can be toxic; therefore, it is typically supplemented for 10 to 14 days to avoid any negative consequences.

Micronutrients

Of the numerous trace elements present in the body, copper, zinc, and iron have the closest relationship to wound healing. Copper is a required cofactor for cytochrome oxidase and the cytosolic antioxidant superoxide dismutase. Lysyl oxidase is a key copper enzyme utilized in the synthesis of connective tissue, where it catalyzes the crosslinking of collagen and strengthens the collagen framework.

Zinc, the most well-known element for wound healing, has been used empirically in dermatological conditions for centuries. Zinc is essential to wound healing in both animals and humans. It is a cofactor for RNA and DNA polymerase and consequently involved in DNA synthesis, protein synthesis, and cellular proliferation. Zinc deficiency impairs the critical roles each of these processes play in wound healing. Zinc levels less than 100 μg/100 mL have been associated with decreased fibroblast proliferation and collagen synthesis.[52] These defects are readily reversed with repletion of zinc to normal levels. Zinc levels can be depleted in settings of severe stress as well as in patients receiving long-term steroids. In these settings, it is recommended that patients receive both vitamin A and zinc supplements to improve wound healing. The current RDA for zinc is 15 mg. A randomized double-blind placebo controlled study in diabetic foot wounds (Wagner grades II, III, and IV) noted decreased measurements of length and width as well as significant changes in metabolic profiles with use of 220 mg zinc sulfate (50 mg elemental zinc) over a 12-week period.[53] It should be stressed that no studies have demonstrated improvement in wound healing after the administration of zinc to patients who are not zinc deficient.[54] Topical application of zinc in VLU can be of benefit when used in conjunction with appropriate wound bed preparation.[55]

Iron is required for the hydroxylation of proline and lysine and as a result, severe iron deficiency can result in impaired collagen production. As a part of the oxygen transport system, iron can affect wound healing, but again, this only occurs in settings of severe iron-deficiency anemia. In the clinical setting, iron deficiency is quite common and can result from blood loss, infectious etiologies, malnutrition, or an underlying hematopoietic disorder. Unlike other deficiencies of trace elements, iron deficiency can be easily detected and treated. Hypovolemia rather than specific levels of hemoglobin have been shown to adversely affect wound healing most likely by decreasing oxygen and nutrient delivery to the healing wound site.

Other Nutrients and Wound Healing

Honey, ancient in use for wound care from ancient Egypt and Rome to warfare care through the centuries, has been "rediscovered" within the past 2 decades. In burns, ulcers, and mixed wounds, honey appears to have favorable wound healing properties, particularly in mild to moderate superficial burns.[56,57] The high content in sugar, water, proteins, as well as the presence of some B complex vitamins, minerals antioxidants (flavonoids, ascorbic acid, catalase, selenium) and enzymes in honey (invertase, amylase, glucose oxidase) may explain the purported benefits as topical treatment, rather than as a nutrient. Honey exposed to gamma radiation is considered medical grade and can dilute wound exudate and activate neutrophils. Second, flavonoids have antibacterial activity. Third, honey has low free water activity preventing bacterial growth and drawing fluid away from the wound via osmosis. Last, the pH of honey inhibits growth of microorganisms. Application of honey or honey

dressings to VLU has not improved outcomes at 12 weeks.[58] Comparison of honey application on DFUs with povidone iodine did not find a significant effect in healing rates with the use of honey.[59] All in all, the support for wide topical usage of honey on wounds remains unproven.[60]

The nexus of nutrition to wounds and wound healing is very strong. There is a paucity of high-quality data regarding the use of nutrition in reversing wound risk or improving wound healing. Recommendations to add 500 mg vitamin C, 17 mg zinc, and 17 g arginine daily have been made and soft data provided for such use; additionally, it appears totally safe. Prevention of wounds is multifaceted, reversing malnutrition is a monumental task and treatment of wounds as they relate to one's state of nutrition continues to be a major clinical challenge.

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