A Clinical Approach to Nutrition and Wound Healing

A patient's diet matters.

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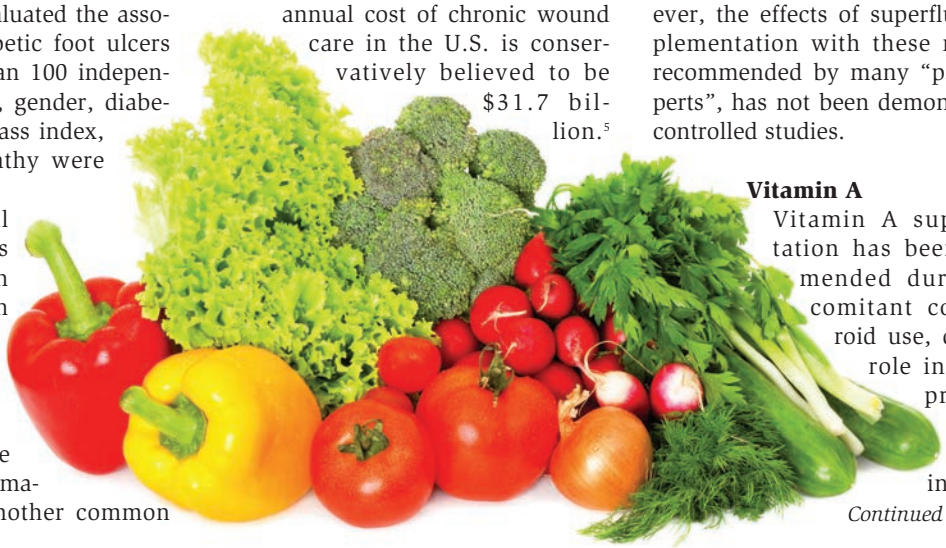
Nutrition plays a vital role in living a healthy lifestyle; however, it is often overlooked in the management of chronic wounds and diabetic wounds in particular. Unaddressed malnutrition is a significant risk factor for delayed wound closure and post-operative complications. How many of us really take the time to include nutrition in our patient assessment and pre-operative protocols? Because of the prevalence of diabetes, complications of glycosylation—such as delayed wound healing, impaired growth factor production, altered cell migration, and impaired collagen synthesis—are well known.[1] HbA1c levels have been shown to be an important biomarker in predicting wound-healing rate in diabetic patients. In an examination of 71 studies that evaluated the association between diabetic foot ulcers (DFUs) and more than 100 independent variables… age, gender, diabetes duration, body mass index, HbA1C and neuropathy were most predictive.[2]

Other nutritional deficiencies are less common and often overlooked. Vitamin D plays an important role in wound healing, and supplementation has been shown to decrease ulcer size and inflammatory biomarkers.[3] Another common supplement, arginine, has been hypothesized to enhance wound healing through its formation of collagen and increased nitric oxide production.[4] Numerous other nutrients have been shown to be essential for healing of acute and chronic wounds.

To simply ignore the role of nutrition in wound healing would be to neglect a powerful tool that can be used to our advantage.

Dietary management is an integral aspect of inpatient hospital care. However, nutritional status is not routinely evaluated during the clinical assessment of outpatient chronic wounds or surgical candidates. The annual cost of chronic wound care in the U.S. is conservatively believed to be $31.7 billion.[5]



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Definitive data on the effects of nutritional supplementation on wound closure has been scarce, but the burden of chronic ulceration management has prompted a need for new studies. It is generally accepted that vitamin and mineral supplementation is helpful in patients with known vitamin deficiency; however, the effects of superfluous supplementation with these nutrients, recommended by many "pseudo experts", has not been demonstrated in controlled studies.

Vitamin A

Vitamin A supplementation has been recommended during concomitant corticosteroid use, due to its role in collagen production and enhancing growth

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factors such as transforming growth factor-beta (TGF-beta) and insulin-like growth factor-1 (IGF-1), all suppressed during steroid use.[6] Despite the pro-collagen effect of vitamin A supplementation with concurrent corticosteroid use, there is little information about universal applicability of vitamin A supplementation on wound healing.

Vitamin B Complex

While vitamin B complex has not traditionally been associated with wound healing, a 2015 paper showed that vitamin B supplementation has anti-diabetic effects and improves wound closure in diabetic rat models.[7] This is likely explained by the fact that diabetes depletes folate, vitamin B6, and vitamin B12 levels, and supplementation can enhance healing, and in some cases improve symptoms of diabetic neuropathy.[8]

Vitamin C

Possibly the most well-studied and understood nutrient in the context of wound healing is vitamin C. Numerous studies have provided convincing evidence that vitamin C enhances wound healing regardless of deficiency. A recent 2018 study demonstrated that high-dose vitamin C supplementation in addition to mesenchymal stem cells drastically improves wound closure in diabetic mice compared to either component in isolation.[9] Another study showed that vitamin C had a pleiotropic effect on genes that promoted fibroblast proliferation and histologically showed enhanced wound matrix deposition and organization through its favorable genetic impact.[10] Vitamin C is a co-factor for collagen synthesis, has anti-inflammatory characteristics, and stimulates fibroblast proliferation. This profile of effects causes vitamin C to be an enticing supplement for any clinician who treats wounds.

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Vitamin D

Similarly, vitamin D has an extensive array of effects on glucose homeostasis, inflammatory cell migration, and angiogenesis. Tiwari, et al. found that vitamin D deficiency was prevalent and more severe in diabetics with foot ulcers, likely explained by its association with elevated inflammatory cytokine markers.[11]

A recent 2017 paper showed a significant reduction of ulcer length, width, depth, and erythema in patients with diabetic foot ulcers following high dose vitamin D supplementation.[12] Countless physicians have encountered the challenges presented by non-healing wounds, and their association with vitamin D deficiency is undeniable. Dr. Caroline Fife, a wound care specialist, notes that many patients that she tests are severely vitamin D-deficient, including those already on supplements. She recently presented a patient with a stubborn non-healing wound dehiscence following surgery. The wound almost completely closed after three weeks of high dose vitamin D supplementation.[12] This scenario is not unique and vitamin D levels must be considered for patients with chronic wounds or ulcerations.

Zinc

Certain metals are essential co-factors for enzymes that play critical roles in cellular and immune function. Zinc, for example, is required for cell growth, membrane repair, and immune cell migration. Zinc supplementation has been shown to reduce ulcer length and width in patients with diabetic foot ulcers.[13] Individuals who abuse alcohol are at high risk for zinc deficiency, and zinc supplementation should be considered if they present with a non-healing wound. Diabetics are at high risk for developing hypomagnesemia that can subsequently lead to neuropathy and platelet dysfunction, both well-known contributors to foot ulceration. A well-controlled 2018 study demonstrated that a 12-week regimen of magnesium supplementation in diabetics with foot wounds significantly decreased ulcer size compared to placebo.[14] Additionally, the study group demonstrated enhanced glucose metabolism and decreased inflammatory markers such as high-sensitivity C-reactive protein.

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Copper

Copper is an essential nutrient needed for host defense mechanisms, red and white cell maturation, iron transport, cholesterol and glucose metabolism, and wound closure; however, its main utilization in wound care is as an adjunct to wound dressings because of its antifungal and antimicrobial properties.[15,16] Iron and selenium supplementation have been studied, but results are either inconclusive as in the case of selenium, or even indicative of being detrimental to wound healing.[17,18]

Amino Acids

Certain amino acids, such as arginine and glutamine, are essential for normal wound closure and supplementation, with these amino acids essential in cases of malnutrition.[19] Supplementation above the recommended maximum daily allowance has not proven to improve wound healing. Arginine is a precursor of nitric oxide that has a potent vasodilatory effect, increasing blood flow to the distal extremities. Arginine is also involved in the synthesis of collagen

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and the release of insulin-like growth factor (IGF-1), essential for epithelialization. Despite these demonstrated positives, little research has been done to prove the impact of arginine supplementation on wound healing. In rat models, arginine supplementation increased collagen deposition in subcutaneous tissues and amplified wound breaking strengths.[20]

This phenomenon could be explained specifically by the impact of nitric oxide, as nitric oxide knockout rat models had no difference in wound breaking strengths or collagen deposition after arginine supplementation.[21] (a knockout rat is a rat whose DNA has been genetically engineered so that it does not express particular proteins.) However, arginine supplementation does increase protein balance of skin wounds despite inhibition of nitric oxide synthase.[22] As promising as animal studies have been, these benefits have not been shown in human models, and all wounds examined were acute as opposed to chronic. Several studies have shown the benefits of a nutritional cocktail that contained arginine on pressure ulcer healing; however, it is difficult to attribute this solely to arginine.[23-26]

Leigh, et al. showed that pressure ulcers did not respond to arginine in a dose-dependent manner, as there was no change in pressure ulcer healing when comparing 4.5g and 9g supplements.[27] With no known human studies investigating the effect of arginine supplementation on healing of chronic wounds it is debatable whether arginine supplementation has any positive effect on the healing of chronic wounds in humans.[27]

While the role of arginine in wound healing remains unclear, there is even less certainty regarding the impact of glutamine. Glutamine is abundant in plasma and an important inflammatory mediator. It also induces production of certain cytoprotective heat shock proteins that help decrease infection rates.[28] Kesici, et al. showed that well-nourished rats showed no difference in hydroxyproline deposition, a strong marker for collagen synthesis and subsequent wound closure after glutamine supplementation was administered. The authors deduced that glutamine supplementation in healthy subjects does not accelerate wound healing.[29]

Conversely, Jalilimanesh, et al. found improved wound contraction and expedited complete wound closure of second-degree burns following glutamine supplementation.[31]

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Studies on amino acid supplementation are promising and further studies are indicated.

Probiotics

The extensive utilization of probiotics has also led to speculations regarding their role in diabetic wound healing. Probiotics have been theorized to improve immune function and metabolic control, and to abolish pathogenic microbes.[32] These properties make probiotics an appealing supplement for aiding diabetic wound closure. An analysis of 12 weeks of probiotic supplementation demonstrated decreased length, width, and depth of diabetic foot ulcers compared to a placebo group.[33] This could be explained by the direct antimicrobial effects of probiotics as well as their impact on the patient's antioxidant status. While this study's findings were promising, the impact of probiotics on insulin metabolism and lipid profiles has been inconclusive.[33-35]

Despite the growing interest in nutrient supplementation as an adjunct to wound closure protocols, the fundamental building blocks of carbohydrates, proteins, fats, and fluids must be present as a baseline. Before any nutrient supplementation should be considered, a clinician must first ensure that their patients are sufficiently nourished with basic macronutrients. Calorie restriction has severe impact on wound closure as calorie deficits can prompt cortisol production, which leads to subsequent protein catabolism and increased inflammatory responses.[36]

Proteins

Proteins are required for collagen synthesis, inflammatory cell formation, and wound contraction. Proteins are active throughout each phase of wound healing and must be present in ample quantities to ensure competent matrix deposition and maintenance of oncotic pressure. Breslow, et al. observed that patients with pressure ulcers who consumed the most amount of proteins and calories healed the most efficiently and did not gain a significant amount of weight, suggesting that energy is being preferentially utilized for ulcer healing and not being stored.[37]

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Fat Intake

Adequate fat intake is necessary as fats serve as the vehicle for fat-soluble vitamins A, D, E, and K. Specific fats such as omega-6 fatty acids are precursors to prostaglandins and leukotrienes, while also having a robust impact on inflammatory cell proliferation and migration.[38] Many older patients have little interest in drinking and are in a state of constant dehydration. While not directly contributing to caloric nourishment, fluid intake is still vital and serves to maintain skin turgor and promote tissue oxygenation. Fluids must be sufficiently restored, particularly in the setting of a draining wound such as venous stasis or lymphatic wound. Before nutrient supplementation should even be considered, a clinician must first ensure that their patients are sufficiently nourished with basic macronutrients.

Biochemical Lab Values

Biochemical lab values have been historically used to predict nutritional status. Albumin and pre-albumin are widely used by physicians to assess malnourishment. These values can be affected by factors such as hydration, medications, congestive heart failure, and liver disease, and may not always give the entire picture. To aid in evaluating laboratory data, the medical community has begun shifting towards the utilization of indices for nutritional assessments.

Mini Nutritional Assessment

One widely used tool is the Mini Nutritional Assessment (MNA) which was originally designed for elderly individuals in the United States but has been proven to be effective in any demographic. This index utilizes a scoring system that quantifies factors such as BMI, weight loss, and mobility. The MNA has been reported to have a 96% sensitivity, 98% specificity, and a 97% positive predictive value for predicting under-nutrition, and is a practical tool for clinicians.[39]

Other similar tools exist such as the Malnutrition Screening Tool, and the Malnutrition Universal Screening Tool, but the MNA seems to have the broadest applicability currently. While these assessments are useful, there are certain demographics that may still be at nutritional risk regarding wound healing. For example, impoverished individuals are often calorically nourished but may still be deficient in certain nutrients which may interfere with wound closure. Thorough clinical assessment and the proper utilization of lab values are imperative to ensure malnourishment does not go untreated, as its impact on chronic wounds can be devastating.

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Not all nutritional supplementation is benign and can be detrimental if utilized when not indicated. Omega-3 fatty acids were previously thought to be beneficial for wound healing because of their anti-inflammatory properties. However, studies have shown that omega-3 fatty acids reduce long-term wound strength. Initial analysis demonstrated improved epithelialization during the early phases of healing, but the benefits quickly faded as the wound bed became weaker than the placebo during the maturation phase.[40]

There is controversy regarding the effect of vitamin E as well. Because it inhibits the absorption of vitamin A, it is contraindicated in vitamin A deficiency. Because of the vasodilatory effect of increased

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nitric oxide with arginine supplementation in a septic patient, it may lead to increased risk of septic shock. Even nutraceuticals are not completely benign, and despite the utility of nutritional supplementation in non-healing wounds, they should not be given aimlessly.

Undiagnosed nutritional deficiencies are likely responsible for the chronicity of a surprisingly high number of non-healing wounds.

The keys to nutritional management of wound patients in a clinical environment are identification and knowledge. Identifying a malnourished or high-risk individual and responding appropriately can be the difference between rapid closure and a complicated non-healing wound. Ensuring that patients are sustaining sufficient intake of calories, proteins, and fluids is crucial.

Vitamins, minerals, and other micronutrients require a substantial baseline of these macronutrients. However, with proper caloric intake, the supplementation of certain nutrients has been shown to have a profound impact on wound healing. Undiagnosed nutritional deficiencies are likely responsible for the chronicity of a surprisingly high number of non-healing wounds. Repletion of these nutrients can lessen the burden of chronic wound management for clinicians and patients. On the other hand, knowing which nutrients provide a therapeutic effect, even in well-nourished patients, should not be ignored.

Nutrients such as vitamin C and arginine have shown promise in their ability to aid wound closure, and their applicability may be broader than what was previously thought. Appropriate use of nutritional supplements should be a mainstay in any clinical setting where wounds are commonplace, and podiatric wound care specialists have the opportunity to be at the forefront of this advancement. **PM**

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