Nutrition and Wound Healing: An Update

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Summary: Nutrition has always been noted to be one of the major influences on the successful outcome of wound healing. The exuberant cellular and biochemical events that constitute the wound-healing cascade require energy, amino acids, oxygen, metals, trace minerals, and vitamins for successful completion. Many nutritional deficiencies impact on wound healing by impeding fibroblast proliferation, collagen synthesis, and epithelialization. There are also nutrients that can enhance wound-healing responses. It is imperative for physicians to obtain a complete nutritional history and consider nutritional intervention as a means of affecting the course of healing. This review examines many of the advances that have occurred in understanding nutrition/wound interactions. (*Plast. Reconstr. Surg.* 127 (Suppl.): 38S, 2011.)

The close link between nutrition and wound healing has been known since biblical times. Since then, clinical experience and rigorous scientific studies have confirmed the importance of nutrition to the healing wound. The internal wound environment—specifically, the availability of protein, nutrients, vitamins, cofactors, and caloric energy necessary to synthesize matrix and to build, break down, and remodel healing wounds—is essential for successful healing. This article presents an update on new developments in the field of nutrition and wound healing and is not an exhaustive review of the field.

Trauma, surgical or accidental, causes significant metabolic perturbations characterized by mobilization of amino acids from muscle and other organs, gluconeogenesis, and hypermetabolic responses. Many of these metabolic responses are mediated by the wound itself by means of afferent nerve fibers that perceive pain, inflammation, and changes in pH.[1] It is of interest to note that at a time of severe catabolism in the host, the wound is able to "commandeer" resources for successful healing, which is an anabolic process. However, the hormonal/cytokine/growth factor characteristics of the wound that facilitate this process have not been defined.

Malnutrition is well recognized as a risk factor for healing and needs to be recognized and possibly corrected preoperatively. In contrast, most operations in well-nourished patients are successful, with uncomplicated healing responses, even if nutritional intake is absent or curtailed for 7 to 10 days. Evaluation of preoperative nutritional status is an important consideration because improper administration or implementation of nutritional therapies can result in increased patient morbidity and unnecessary health care costs.

A complete history and physical examination should be performed on each patient. This alone has been found to be 80 to 90 percent accurate in evaluating patient nutritional status, and the addition of multiple or complex biochemical, immune, or anthropometric measurements does not increase greatly the accuracy of nutritional assessment.[2] Malnutrition may be expected if the history reveals unintentional weight loss (20 percent weight loss is indicative of severe malnutrition), if the patient appears cachectic with obvious muscle wasting, or if the patient has a history of or reason for alimentary malabsorption. These factors along with any comorbid conditions such as diabetes, other endocrinopathies, or renal or liver failure must be noted, as they will guide nutritional management. Some biochemical markers that have been used as aids in diagnosing malnutrition include measurement of serum proteins (albumin, <3.5 mg/dl; prealbumin, <15 mg/dl; and transferrin, <200 mg/dl), nitrogen balance, total cholesterol, and creatinine. Baseline assessment documenting the status of these markers should be obtained before implementing any nu-

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Received for publication May 25, 2010; accepted August 23, 2010.

DOI: 10.1097/PRS.0b013e318201256c

Disclosure: *The authors have no financial interest to declare in relation to the content of this article.*

tritional therapy, and optimization of nutritional status should be tailored to each patient's unique history, abnormality, and expected therapy.

Malnutrition (which can occur in as many as half of hospitalized patients) predisposes patients to increased septic complications, prolonged ventilator dependence, pneumonia, and impaired or failed wound healing.[3,4] Determining who would truly benefit from nutritional supplementation is still a matter of some debate, but there is evidence that preoperative nutritional support reduces infectious complications and anastomotic breakdown in severely malnourished patients undergoing major elective surgery.[5] Postoperative nutritional support should be considered in patients expected to be unable to eat for a period of at least 2 weeks.[6] The efficacy of preoperative and/or postoperative nutritional intervention in reversing the effect of malnutrition on wound healing is not well defined; one study suggested that even brief periods of nutritional intervention can fully restore collagen synthetic ability in malnourished humans.[7]

In malnourished preoperative patients or in postoperative patients unable to tolerate a diet (or unable to meet nutritional and caloric needs) for a protracted period, enteral or parenteral feeds should be started or, if held, resumed as early as possible. There have been multiple prospective studies to demonstrate that enteral feeding is superior to parenteral feeding in reducing morbidity from septic complications (e.g., pneumonia, abdominal abscesses, line sepsis) in those patients requiring nutritional supplementation.[8,9] Unfortunately, the enteral route is not always available or well tolerated by patients. In these circumstances, parenteral nutrition should be used as a means of maximizing the intake of proteins and calories necessary for satisfactory wound healing. However, parenteral nutrition does not afford the patient the apparent immunologic benefits of enteral feeding and should therefore be either replaced by enteral feeds when possible or augmented with enteral feeds as tolerated. Furthermore, it should be noted that parenteral nutrition carries the potential for intravenous line complications, including the morbidity associated with line insertion and the ever-present potential for line sepsis.

AMINO ACIDS AND WOUND HEALING

Amino acids are important for wound healing. In the past three decades, there has been increased recognition that several amino acids have the 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. Rats fed chow supplemented with 1 percent arginine have enhanced wound breaking strength and collagen synthesis when compared with chow-fed controls.[10] Similar findings were noted in parenterally fed rats given an amino acid mixture containing high doses (7.5 g/liter) of arginine in rats.[11]

Two studies have been conducted so far on the effect of arginine supplementation on collagen accumulation in healthy human subjects. Using a micromodel where collagen accumulation occurs in a subcutaneously placed segment of polytetrafluoroethylene tubing, young healthy human volunteers (25 to 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 hydrochloride (24.8 g of free arginine) daily for 14 days.[12] In a subsequent study of healthy elderly humans (67 to 82 years), daily supplements of 30 g of arginine aspartate for 14 days resulted in significantly enhanced collagen and total protein deposition at the wound site when compared with placebo controls.[13] This study also evaluated the epithelialization of a split-thickness wound created on the upper thigh of each subject and found that arginine supplementation had no effect on this healing response. More recently, another well-designed randomized study confirmed that arginine supplementation does not enhance epithelial healing response in split-thickness skin graft donor sites.[14]

Improved collagen synthesis has also been noted in humans given dietary supplementation with arginine, glutamine, and β-hydroxy-β-methylbutyrate.[15] β-Hydroxy-β-methylbutyrate is a metabolite of the amino acid leucine and has been shown to magnify the exercise-related positive changes in performance and increase muscle mass to a greater extent than exercise alone. Older adults underwent subcutaneous implantation of two small, sterile, polytetrafluoroethylene tubes. Daily supplementation of the three nutrients led to a significant increase in collagen deposition in the polytetrafluoroethylene tubes without an effect on total protein accumulation. Ornithine, a metabolite of arginine in the urea cycle, and ornithine ketoglutarate have been shown

to also enhance wound collagen deposition in animals, although no studies in humans have yet been carried out.[16,17]

There are several mechanisms by which arginine can enhance wound healing (Table 1). All or some of them may be operational, but the exact mechanism of action remains undetermined. Either way, arginine does provide a safe means of increasing wound collagen synthesis.

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. In young rats, healing of skin, stability of sutures in gut anastomoses, and reepithelialization of partial-thickness burns have all been shown to be compromised in the setting of essential fatty acid deficiency.[18] Impaired wound healing has also been documented in humans with essential fatty acid deficiencies.[19]

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 antiinflammatory properties by inhibiting eicosanoid production and other mediators such as platelet-activating factor, interleukin-1, and tumor necrosis factor-α.[20–22] Animals consuming diets enriched with omega-3 fatty acids had weaker wounds than controls 30 days after injury. The weaker wounds did not contain less collagen; rather, it is thought that the omega-3 supplementation impaired the quality, crosslinking, or spatial orientation of collagen fibrils.[23] The use of parenteral fish oil in rats treated with dexamethasone had no impact on wound hydroxyproline levels (index of collagen deposition) or histologic evaluation; given the fact that the healing response was severely blunted by steroid use, this study does not rule out a possible deleterious effect of fish oil on wound healing.[24] Recent study using a human suction blister model noted that consumption of omega 3-fatty acids raised blister fluid interleukin-1 levels and decreased healing time.[25]

From the above, it is safe to conclude that use of fish oil supplements adversely impacts the healing response and that surgeons should inquire preoperatively whether their patients use such supplements. How long before surgery such supplements should be stopped to reverse the impact on wound healing is not known.

Table 1. Possible Mechanisms of Action of Arginine on Collagen Synthesis

Provides precursor for proline biosynthesis through the arginine→ornithine→glutamic semialdehyde→proline pathway
Enhanced wound nitric oxide synthesis, which enhances angiogenesis and collagen synthesis
Enhanced T-cell function, which increases wound healing
Increased pituitary release of growth hormone

VITAMINS

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 crosslinking. The symptoms of scurvy reflect this impaired synthesis of collagen and connective tissue and include bleeding into the gingiva, skin, joints, peritoneum, pericardium, and adrenal glands. More generalized symptoms include weakness, fatigue, and depression. Histologic findings include minimal collagen deposition, decreased angiogenesis, and significant hemorrhage. Electron microscopy of fibroblasts from scorbutic patients reveals a dilated and disordered rough endoplasmic reticulum with diminished polysome content. Ascorbic acid is a specific co-substrate for the enzymes 4-prolyl hydroxylase and lysyl hydroxylase; biochemically, it is a reducing agent required for the conversion of proline and lysine to hydroxyproline and hydroxylysine, which are critical to collagen crosslinking and mechanical strength.[26] Vitamin C deficiency, in addition to impairing wound healing, has also been associated with an increased susceptibility to wound infection. If wound infection does occur in the setting of vitamin C deficiency, it is apt to be more severe.

The recommended dietary allowance for vitamin C is 60 mg/day; the clinical spectrum of its administration varies widely. In surgical patients, the dosage varies widely. Burn victims require as much as 1 to 2 g/day to restore urine and tissue levels to normal. 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.[27]

Vitamin A deficiency impairs wound healing. Subsequently, vitamin A was shown to enhance wound healing even in nondeficient states. More importantly, vitamin A, administered either topically or systemically, reverses the antiinflammatory effects of corticosteroids on wound healing.[28,29] Vitamin A has also been proposed as therapy for

wound healing impaired by diabetes, tumor formation, cyclophosphamide, 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, doses of vitamin A as high as 25,000 IU/day (five 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.

Vitamin E maintains and stabilizes cellular membrane integrity, primarily by protection against destruction by oxidation. As an antioxidant, it has been proposed that vitamin E could reduce injury to the wound by excessive free radicals.[30] The liberation of free radicals from inflammatory cascades in necrotic tissue, tissue colonized with microbial flora, ischemic tissue, and chronic wounds can result in depletion of free radical scavengers such as vitamin E. This process is believed to be at work in patients with chronic lower extremity wounds.[31] The antiinflammatory properties of vitamin E are similar to those of steroids. Vitamin A can reverse the wound-healing impairment induced by vitamin E. Vitamin E has also been shown to affect various host immune functions, often in a negative fashion.

As with fatty acids, preoperative assessment should include a careful evaluation of vitamin supplementation history, as the potential for unexpected side effects exists. The use of vitamin A as a treatment for the steroid-induced impairment in wound healing remains a valuable adjunct.

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 used in the development 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 dermatologic 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/dl have been associated with decreased fibroblast proliferation and collagen synthesis. These defects are readily reversed with repletion of zinc to normal levels. Zinc levels can be depleted in settings of severe stress and 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 recommended daily allowance for zinc is 15 mg. It should be stressed that no studies have demonstrated any improvement in wound healing after the administration of zinc to patients who are not zinc deficient.

Iron is required for the hydroxylation of proline and lysine; 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 causes, 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.

HERBAL SUPPLEMENTS

Many patients take daily nutritional supplements that may affect wound healing (Table 2).[32] Among herbal supplements, garlic, ginseng radix rubra, curcumin, and ginger extract have been shown to influence wound healing. Saponin, derived from ginseng, markedly improved wound healing in diabetic and aging rats by enhancing granulation tissue formation.[33] Similarly, garlic in-

Table 2. Effects of Herbal Supplements*

Supplement	Use	Side Effects
Ginger	Helps alleviate respiratory ailments	Bleeding
Ginseng	Decreases blood sugar in diabetics	Insomnia, hypoglycemia, hypertension, headaches
Echinacea	Natural antibiotic/ immunostimulant	Immunosuppression, poor healing of chronic wounds
Bromelain	Reduces swelling/ inflammation, débridement	Bleeding
Ephedra	Stimulant	Hypercoagulable state, tachycardia

*Adapted from Broughton G II, Crosby MA, Coleman J, Rohrich RJ. Use of herbal supplements and vitamins in plastic surgery: A practical review. *Plast Reconstr Surg.* 2007;119:48e–66e.

creases wound angiogenesis.[34] A combination of curcumin and ginger was found to increase collagen and decrease matrix metalloproteinase-9 levels in an abrasion wound given to steroid-pretreated rats.[35] Other supplements may have deleterious effects, such as bromelain. Although bromelain may have benefits as a débriding and antiinflammatory agent, it is also a potent inhibitor of platelet aggregation and may cause bleeding. Dong quai ("female ginseng") has been shown to have Coumadin-like properties and interferes with clotting. Echinacea, which has been studied for a potential role in wound healing, has been shown to be immunosuppressive.[35] Overall, obtaining a careful nutritional history, including the use of health supplements, is important in preparing patients for surgical intervention.

CONCLUSIONS

It is clear that nutrition plays a critical role in wound healing. Starting with careful assessment preoperatively, nutrition offers a meaningful means of impacting wound healing. As T. K. Hunt declared, "wound nutrition is whole body nutrition," and as such, nutritional rehabilitation is an important intervention. Furthermore, specific nutrients can be used judiciously to influence specific aspects of the healing response.

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