Effects of nutrition on wound healing

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Optimal wound healing and its close relationship to a patient's positive nutritional balance is well known. For years, physicians have attempted to improve the metabolic status of patients after surgery or trauma. Currently, major emphasis is placed on perioperative nutritional status and its effect on postoperative wound healing. The intricacies of metabolism and healing are areas of current active research, in an effort to advance the quality of patient care. For the head and neck surgeon, wound healing is of paramount concern in areas of tumor extirpation, head and neck reconstruction, and maximization of postoperative functional recovery. To better explain why adequate nutrition is important in postoperative wound healing, we will provide a brief synopsis of nutrition and its relationship to wound healing. (OTOLARYNGOL HEAD NECK SURG 1994;110:557-9.)

WOUND HEALING CASCADE

Wound healing can be divided into immediate (inflammatory), acute (proliferative), and chronic (remodeling) phases. Immediately after a wound occurs, the plasma-clotting cascade is activated, and platelets and neutrophils are recruited through chemical mediators. Mononuclear phagocytes and lymphocytes are attracted next. Blood flow to the wound must be adequate, and bacterial presence must be minimal. In the proliferative phase, macrophages and platelets secrete factors that cause angiogenesis with reestablishment of blood flow across the wound edges. If small vessels are damaged, as in irradiation and diabetes, this process is impaired. Platelet- and macrophage-mediated fibroblastic proliferation and migration occur next with the initiation of connective tissue formation. Additionally, inflammatory cells and platelets release factors causing the basal epithelial layer to detach, migrate vertically, and attempt to epithelialize the wound gap, provided no impediments exist.

In the chronic phase of wound healing, a scar matrix is produced that gradually matures. Fibroblasts begin to lay down type III and type IV collagen, provided that the local wound millieu is permissive. Vitamin C, elemental oxygen, copper, and iron are all necessary for collagen formation. The requirement for elemental oxygen is exploited during hyperbaric therapy for wound healing because collagen synthesis increases under such circumstances. Maximal collagen synthesis occurs during the first 2 weeks, and its deposition is primarily the third and fourth weeks after wound formation. Proteoglycans and other matrix mucopolysaccharides are deposited within the first 4 weeks. Myofibroblasts, present within the first 3 weeks, are responsible for wound contraction, and collagenase activity coexists with collagen deposition. Increased tissue strength through increased collagen cross-linking gradually results during the next 6 months.[1]

NUTRITION IN HEAD AND NECK CANCER PATIENT

In otolaryngology, the head and neck cancer patient can provide a challenge with respect to wound healing. Three major areas of concern for malnutrition exist. First, odynophagia and dysphagia prevent appropriate oral intake. Second, baseline poor nutrition is not uncommon in head and neck cancer patients because of other factors (i.e., an unbalanced diet or alcoholism). Third, the neoplasm itself depletes the patient's overall nutritional status. Objective laboratory indexes of the nutritional status of patients have been suggested. These include serum albumin levels, serum transferrin levels, cutaneous anergy testing, total lymphocyte count, and triceps skin-fold measurements.[2] If these values are decreased before surgery, a regimented protocol for nutritional support is strongly recommended (either enterally or parenterally) before surgery, so that postoperative healing can be maximized and wound complications minimized.[3] The goal of such supplementation is to ensure normal protein synthesis after surgery. Enteral feeding with a small-bore

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Received for publication Oct. 2, 1993; accepted Dec. 3, 1993.
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0194-5998/94/$3.00 + 0 23/1/53299

Table 1. Nutritional supplementation in wound healing

Substance	Role in wound healing	Supplementation
Amino acids	Protein building blocks	Standard enteral or parenteral nutrition 40 kcal maximum including 2 gm/kg protein maximum
Lipids	Membrane assembly; assists immune responses	Same as above
Carbohydrates	Prevents gluconeogenesis from protein stores	Same as above
Vitamin A	Assists epithelialization; membrane labilizer	10-25,000 IU/day acutely
Vitamin C	Necessary for collagen maturation and wound strength	500 mg 2-3 times/day
Trace elements (iron, copper, zinc, magnesium)	Role controversial; may contribute to overall healing	Zinc sulfite 220 mg 3 times/day

feeding tube is one common route of instituting such treatment.[4]

MAJOR NUTRITIONAL COMPONENTS FOR WOUND HEALING

Familiarity with the contributions of protein, carbohydrate, lipid, and vitamin metabolism aids in the understanding of the relationship between nutrition and wound healing. In overtly malnourished patients, delayed wound healing and increased susceptibility to infections are evident. In addition, the malnourished patient has increased anabolic activity in vital organs (e.g., liver) at the expense of decreased metabolism in skin and muscle.[5] In head and neck reconstruction, appropriate healing of muscle and skin is paramount because poor nutrition can result in wound dehiscence, fistula formation, and carotid rupture.

During the past several decades, the contribution of protein metabolism in relation to adequate wound healing has been investigated. In starved animals, a lag period in the healing of surgical abdominal wounds is apparent.[6] This delay in the initiation of healing has been primarily attributed to impaired protein metabolism. Furthermore, angiogenesis is delayed during the proliferative phase of wound healing with poor nutritional status. Wound contraction is also impaired in malnourished patients. Moreover, both bacterial phagocytosis by neutrophils and cellular immune responses are impeded in the malnourished patient. This fact supports the reason for anergy testing of patients before surgery. When various amino acids are withheld from the diet of wounded animals, weight loss after injury is increased and skin healing is impaired. Key amino acids, such as arginine[7] and those containing sulfur,[8] are thought to be involved in optimal wound healing.

Carbohydrate metabolism has also been investigated with regard to wound healing. This has been primarily in the context of diabetes mellitus. With decreased carbohydrate availability from malnutrition or diabetes, increased amino acid degradation occurs because of diversion of amino acid carbon to gluconeogenesis. Furthermore, the pentose shunt, which is required for the formation of ribose sugars (to form the nucleic acid backbones for DNA synthesis), is impaired with decreased carbohydrate availability.

Decreased lipid availability can negatively effect wound healing. When essential fatty acids are deficient, there is a decreased availability of 18-carbon fatty acids for synthesis into arachidonic acid.[1] It has been postulated that decreased prostaglandin synthesis (from arachidonic acid) may result in blunted immune responses in the wound and in the organism. However, other data suggest that they may not be required.

Several water- and fat-soluble vitamins serve as important cofactors in the wound healing response. Of this group, vitamin C and vitamin A have the most important roles in the reparative process. Vitamin C is needed for the hydroxylation of both proline and lysine in collagen synthesis. Vitamin A is a cellular membrane labilizer. Lack of vitamin A has been correlated with decreased collagen synthesis, decreased epithelialization, and increased incidence of wound infections.[9] In fact, all connective tissue synthesis in the wound matrix is impaired or inefficient without vitamin C or vitamin A. With increased vitamin A, the number of macrophages in the wound is increased, with increased macrophage phagocytic activity. In addition, increased cell-mediated immunity has been correlated with increased vitamin A. Vitamin K deficiencies can impair the acute response in wound healing because the initial events involve vitamin K–dependent clotting factors.[9]

From the above discussion, it is obvious that normal wound repair requires the presence of numerous nutritional factors. Optimizing a patient's nutritional status before surgery is crucial to the

surgical management of patients undergoing major head and neck surgery. Parenteral and enteral nutrition have now made it possible to restore a normal nutritional state to patients malnourished by their disease.

NUTRITIONAL CLINICAL STUDIES

Since the early 1980s, investigators have closely followed the nutritional status of patients, applied supplemental nutrition when necessary (or experimentally), and measured objective parameters of wound healing by qualitative and quantitative means. These human studies mostly involved patients undergoing abdominal surgery. Similar principles exist between all malnourished patients, regardless of the cause of their malnutrition. Therefore these experimental findings can be extrapolated to head and neck patient populations. Most studies compared patients who were at varying levels of malnutrition or who were given different feeding regimens. Such clinical investigations measured changes in hydroxyproline content of Gore-tex tubing implanted in patients as a standardized measure of wound healing. In one study, when malnourished patients were given adequate nutrition within 24 hours of their surgery, enhanced wound healing was evident.[10] In addition, if standard total parenteral nutrition was administered to malnourished patients for 1 week before surgery, their ability to synthesize collagen (as judged by hydroxyproline content in Gore-tex tubes) was *even higher* than in patients judged to have normal nutrition.[11] Moreover, these patients possessed an increased ability to synthesize collagen when compared with patients receiving total parenteral nutrition after surgery. Improved collagen synthesis was apparent *before* laboratory parameters associated with improved nutrition became manifest. Others have observed increased wound healing and decreased weight loss with parenteral nutrition.[12]

Some investigators propose that by adding branched-chain amino acids (in higher concentrations than normally supplied), wound healing can be augmented. However, the clinical applicability of this concept is not clearly established.[13] More recently, the use of polypeptide growth factors such as growth hormones, somatomedins, and insulin-like growth factors[14] has been proposed to improve wound healing. Investigators have suggested that exercise and deeper sleep in patients can increase the endogenous levels of such substances.[15]

Currently, no firm nutritional formula or route of administration has been widely accepted as an optimal method to replete malnourished patients before surgery. Controversy exists as to which parameters most accurately reflect the nutritional status of patients. However, strong evidence suggests that patients exhibiting recent weight loss, decreased serum albumin or transferrin level, and impaired immunity are at risk for increased wound complications after head and neck surgery. As a result, preoperative enteral or parenteral nutrition should be given to such patients. Early postoperative feeding is beneficial to all patients who are undergoing the healing process. Suggestions for nutritional supplementation are listed in Table 1.

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