CHAPTER **37**

The Effects Of Nutrition On Wound Healing

Tara L. Giorgini, D.P.M.

The nutritional status of a patient can dramatically affect the body's ability to heal after injury or surgery. The wound of a nutritionally balanced patient normally heal at an optimal rate, whereas a malnourished patient is at increased risk for postoperative complications. An accurate nutritional assessment and knowledge of perioperative nutritional support will optimize the surgical outcome by promoting maximal immune response and uneventful wound healing.

PHYSIOLOGY OF WOUND HEALING

An understanding of the natural course of healing is fundamental to the care of patients with surgical or traumatic wounds. All wounds undergo an inflammatory, fibroblastic, and maturation event which contributes to final healing and functional repair. The specific phases of wound repair and duration of these cellular events consist of the substrate phase (day 1 to day 4), the proliferative phase (day 5 to day 20), and the remodeling phase (day 21 to several years).

Substrate Phase

During the substrate phase a wound demonstrates intense physiologic activity. The primary process during the substrate phase is inflammation with exudation of fibrin, the dilation of blood vessels, and the accumulation of lymphocytes, polymorphonuclear leukocytes, and macrophages.

The initial and immediate vascular response is vasoconstriction, which lasts from five to ten minutes, followed by active dilation of venules. There is extensive leaking of blood elements for about 72 hours, causing a large volume of interstitial fluid to be sequestered, thus making the tissue edematous and warm. Fibrin appears to function as a temporary glue holding the edges of the wound together.

Polymorphonuclear granulocytes are the first cells to appear, but the number rapidly declines if there is no intervening infection. Macrophages on the other hand seem to play more of a crucial role in wound nutrition due to a variety of celluar processes. The macrophage acts to microscopically debride injured tissue, and processes macromolecules into useful amino acids and sugars. The macrophage also secretes chemotactic factors which attract a greater number of macrophages, stimulate fibroblast formation, and activate for neovascularization.

Proliferation Phase

It is during this second phase of wound healing that fibroblasts proliferate and synthesize collagen, the principal component of scar tissue. The important step of collagen synthesis occurs at the ribosome level, where the amino acids proline and lysine are hydroxylated to hydroxyproline and hydroxylysine, respectively. These enzymatic reactions require a reducing agent, especially ascorbate. Without vitamin C these hydroxylations cannot occur, and only a small quantity of underhydroxylated collagen is released from the fibroblast.

Remodeling Phase

During the maturation or remodeling phase of wound healing, the random collagen fibrils reweave into an organized, tight pattern. Tensile strength of the wound increases by intermolecular cross-linking of the collagen fibers. There is a dynamic equilibrium of collagen synthesis and lysis. The lysis plays a constructive role in eliminating severely disoriented collagen fibers. These fibers can be replaced by more optimally oriented fibers, thus leading to a stronger scar. Wound breakdown can occur if collagen synthesis lags behind collagen lysis, as is the case in an individual with scurvy.

NUTRITIONAL ASSESSMENT

The physician can assess the nutritional status of the patient during the initial clinical exam. This assessment is done through the use of the patient history, physical examination, anthropometric measurements, and a careful interpretation of laboratory and immunologic studies.

History of Weight Loss

An evaluation of the patient's weight may be the single most important piece of information in assessing the patient's nutritional status. Weight loss is an important and easily attainable parameter of nutritional assessment which correlates with malnutrition and an increased risk of perioperative morbidity and mortality. Patients with an unintentional weight loss of less than 10% of their usual body weight have little risk of postoperative morbidity and mortality. However, as weight loss approaches 30% of body weight, morbidity and mortality increases dramatically, regardless of the patient's initial nutritional status.

Physical Exam

During the physical exam, the physician should make note of the texture of the patient's nails, hair and skin. Fingernails and toenails should be examined for signs of anemia, hypoxia and vitamin deficiencies. Spoon nails (koilonychia) are occasionally seen in iron deficiency anemia. Splinter hemorrhages beneath the nails, as well as petechia on the skin, are occasional manifestations of a lack of vitamin C in the diet. An icteric appearance of the skin or conjunctiva should alert the surgeon to the possibility of liver disease. Jaundice may be a manifestation of many forms of liver or biliary tract pathology. Alcoholic or hepatic liver diseases are also important possibilities to consider.

Patches of dermatitis on the face or near the corners of the eyes may be a manifestation of niacin or vitamin B6 (pyridoxine) deficiency. Patients who are anemic may present with pale palpebral conjunctiva. If a patient complains of night blindness during the review of systems, one should suspect a vitamin A deficiency. A sore mouth in general, as well as bleeding gingivae, may represent a deficiency in ascorbic acid. Reddened lips or the presence of cheilosis in a patient could be signs of vitamin B2 (riboflavin) deficiency. Complaints of a painful tongue (glossitis) may be the manifestation of a dietary deficiency of vitamin B12 (cyanocobalamine) or folate. A smooth tongue should not be considered a normal presentation. Loss of papillae gives the tongue a red slick appearance, and suggests a deficiency of vitamin B12, iron, or niacin.

Anthropometric Measurement

Body (anthropometric) measurements are used as an assessment of nutritional status. The most commonly used are triceps skin fold (TSF) and mid-arm muscle circumference (MAMC). TSF can be considered a measure of body fat stores, since 50% of body fat is located in the subcutaneous tissue. This assessment is performed by simply grasping a fold of skin on the posterior aspect of the mid- upper arm, pulling it away from the underlying muscle, and measuring its thickness with Lange or Harpenden calipers. These measurements can be compared with standardized tables to determine the degree of abnormality. Studies suggest that abnormally low values are helpful in predicting the risk of postoperative morbidity. TSF measurements less than 80% (or 13.2 mm) should arouse suspicion of and further evaluation for an associated nutritional deficiency.

The measurement of muscle mass, an indirect measure of protein stores, can be indirectly assessed by measuring the mid-arm muscle circumference (MAMC). The circumference (C1) of the mid-upper arm is converted to the MAMC with a simple calculation (MAMC = C1 - (3.14 TSF). Again, observed measurements of less than 80% (or 18.6 cm) of the predicted value should prompt further nutritional evaluation.

Laboratory

Body protein stores may be assessed through a measurement of the creatinine-height index (CHI). Creatinine, a product of muscle metabolism, is normally excreted in the urine. The excretion of creatinine should be proportional to the amount of lean body mass, provided that the renal function is normal. This study requires the measurement of total creatinine in a collection of a 24-hour urine sample. These values, evaluated against height, can then be compared to an ideal value. This test is more sensitive than MAMC as a measurement of body protein.

Laboratory measurement of serum albumin is used more frequently in nutritional evaluation. A value below 3.5 gm/100 ml represents a mild protein deficiency state. Albumin has a relatively long serum half-life (20 days) and may not reflect the presence of an acute nutritional deficiency. However, this test can be used reliably as a screening technique for sub-acute or chronic nutritional deficiency.

Measurement of serum transferrin levels may be valuable in the assessment of patients with chronic or acute nutritional problems, because it has a short half-life (8 days,) and is synthesized as a high-priority protein. Serum transferrin levels can be approximated by measurement of the total iron-binding capacity (TIBC) and using a conversion factor (transferrin = (0.8 TIBC) - 43). Serum transferrin levels of less than 150 ug, or a TIBC of less than 250 micrograms should arouse suspicion of nutritional deficiency. Prealbumin (half-life of 2 days) and retinol-binding protein (half-life of ten hours) levels are additional biochemical indicators of visceral protein depletion, and an early detection of protein deficiency.

Immunologic Studies

During nutritional replenishment of patients who have protein calorie malnutrition (PCM), immunoglobulins are the class of proteins that are synthesized with the highest priority. Therefore, the evaluation of immunocompetence is an important aspect of nutritional evaluation.

Anergic patients who fail to demonstrate a response to delayed hypersensitivity testing to the usual recall test antigens (mumps, *Candida*, trichophyton) are likely to have a nutritional deficiency and are at increased risk of developing perioperative complications. Interestingly, in cancer patients who develop postoperative infection, the presence of an abnormal response to delayed hypersensitivity testing is more predictive of postoperative septic episodes than are measurements of albumin, serum iron, or retinol-binding protein.

An additional simple immunologic measure of nutritional deficiency is a total lymphocyte count less than 1,800 cells/mm3. This number is derived from a WBC differential. It is calculated from the following formula: TLC = WBC x % lymphocytes/100.

Prognostic Nutritional Index

Many studies indicate that malnourished patients are at an increased risk of surgical morbidity and mortality. One study quantified the relative risks using the predictive indicators of visceral protein depletion (albumin, transferrin), abnormal TSF, and anergy. The prognostic nutritional index (PNI) quantifies the risk of postoperative complications utilizing preoperative nutritional evaluation, as follows:

$$\text{PNI}(\%) = 158 - 16.6\ (\text{albumin}) - 0.78\ (\text{TSF}) - 0.20\ (\text{transferrin}) - 5.8\ (\text{delayed hypersensitivity}).$$

Using this categorization, patients were placed into three risk categories: low (PNI < 30), intermediate (30 < PNI > 59), and high (PNI > 60). Surgical complications occurred in 11.7%, 36.8%, and 81% respectively.

NUTRIENTS

Successful wound healing depends, in part, on the presence of adequate nutritional stores provided by a balanced diet of protein, carbohydrate, fat, vitamins, and minerals. Correlations can be made between the presence or absence of these nutrients and wound healing.

Protein

A deficiency of protein contributes to poor wound healing. Physiologically, protein depletion prolongs the substrate phase of healing and impairs fibroplasia. Studies demonstrate a diminution of fibroblastic proliferation, proteoglycan and collagen synthesis, neoangiogenesis, and wound remodelling in the presence of hypoproteinemia. When protein deficiency is prolonged, edema and wound dehiscence may develop secondary to low serum albumin.

Efforts have been made to identify specific amino acid influences on wound healing. Methionine has been found to be critical in wound repair. In protein-depleted animals, the addition of methionine has shown to reverse the prolongation of the substrate phase of healing and accelerate the rate of fibroplasia. Methionine is converted to cystine, which appears essential for reversing the effects of protein depletion. Cystine may be needed as a co-factor in enzyme systems responsible for collagen synthesis. Even more important, since the formation of disulfide bonds appears to be critical for the proper alignment and attachment of peptide chains forming the triple helix of tropocollagen, sulfur-containing amino acids such as cystine may be the most important protein constituent in the wound healing process.

Additional studies found a reduction in histidine-deficient animals and restoration of the healing process to normal with histidine supplementation. It was postulated that histidine, which is converted to histamine, is needed in large amounts during wound healing. Arginine is also suggested as an agent that promotes wound healing.

Carbohydrates and Fat

Glucose is needed as an energy source for white cell function. Adequate anti-inflammatory and phagocytic activity by white cells is necessary during the substrate phase of healing to prepare the wound for fibroplasia. Without adequate quantities of glucose, resistance to infection is decreased, and collagen synthesis is impaired.

Fats are essential constituents of cell membranes and thus necessary for the synthesis of new cells. However, no significant impairment of wound healing is associated with essential fatty acid deficiency.

Diabetes is the most common condition that may be accompanied by delayed or poor healing of wounds due to defective carbohydrate and fat metabolism. Unavailability of glucose or failure of glucose to enter cells interferes with anaerobic as well as aerobic metabolism. One study found that insulin deficiency, even in the absence of microvascular disease, suppressed collagen reposition in wounds.

Adequate amounts of carbohydrates and fats are required to prevent excessive metabolism of amino acids for caloric needs. When amino acids are used to meet caloric requirements, the adverse effects discussed under protein deficiency may occur.

Vitamins

Several vitamins have been shown to play a role in wound healing. Vitamin C (ascorbic acid) is the best understood. A Vitamin C deficiency causes scurvy, and contributes to abnormal wound healing. Fibroblast function is impaired when ascorbic acid is deficient. The hydroxylation of lysine and proline during collagen synthesis requires ascorbic acid, oxygen, alpha-ketoglutarate, and iron, all of which act in conjunction with lysyl and prolyl hydroxylases, the enzymes that catalyze these reactions. In the absence of ascorbic acid, these enzymes stay in an inactive sub-unit form, and unhydroxylated protein is subject to proteolysis. Signs of impaired collagen formation include poor wound healing and fragility and rupture of capillaries. Scorbutic guinea pigs are able to close uninfected open skin wounds at a normal rate, but they do so by the process of wound contraction, which is a contractile phenomenon of specialized fibroblasts (myofibroblasts) which do not require collagen formation.

Vitamin C also plays a role in resistance to infection. When *Staphylococcus aureus* is injected into scorbutic guinea pigs, resulting abscesses are much larger than those that develop when non-scorbutic animals are similarly injected. Neutrophil function is impaired in ascorbic acid deficiency because this vitamin is required for reduction of oxygen to "superoxide (O_2^-)." In white blood cells, "superoxide" acts as an antibacterial and helps generate other bactericidal agents.

There is no convincing evidence that wound healing is accelerated by the administration of vitamin C when tissue levels are normal. Ascorbic acid deficiency may develop rapidly in seriously ill or injured patients because it is not stored in appreciable amounts. Large doses of ascorbic acid are administered to severely burned patients, however, only 250 to 500 milligrams daily are needed for patients about to undergo major surgery.

Vitamin A deficiency has been shown to retard epithelization, closure of wounds, the rate of collagen synthesis, and the cross-linking of newly formed collagen. Incisions have been reported to heal more rapidly in normal patients when given supplemental vitamin A.

Vitamin A has a labilizing effect on lysosomal membranes, as opposed to glucocorticoids, which are known to promote stabilization of cell membranes. Several studies have shown that in patients receiving systemic steroids, vitamin A can counteract the inhibitory effects of the steroids. Vitamin A may also aid in wound healing through its suppressive action on certain infections as evidenced by its effect on the thymus gland. If a normal animal is given supplementary vitamin A, enlargement of the thymus gland occurs with increased production of thymic DNA, RNA, and protein. Also, if vitamin A is administered to a stressed animal, thymic atrophy and adrenal hypertrophy that would develop are prevented. Patients who have suffered severe injury, or have prolonged interference with food intake should receive supplements of 25,000 international units per day.

Vitamin K is required for synthesis of prothrombin and clotting factors II, VII, IX, and X. Vitamin K deficiencies may result from excessive bleeding and hematoma formation, further leading to impaired healing and possible wound infection. Vitamin K deficiency should be anticipated and corrected when present in patients suffering from liver disease or disorders of fat digestion and absorption.

Vitamin E has also been implicated in the wound-healing process, although its role may be considered negative. The effect of vitamin E is similar to glucocorticoids in that it stabilizes cell membranes, thus interfering with collagen synthesis and wound healing. This effect may be beneficial in the clinical setting to retard or prevent the appearance of hypertrophic scar or keloid formation.

B vitamins act as co-factors in a variety of enzyme systems in protein, carbohydrate, and fat metabolism. Markedly delayed wound healing occurs in rats with dietary restriction of riboflavin, pyridoxine, and biotin. The granulation tissue produced under such conditions is much less dense and more vascular and cellular than that found in control animals. Antibody formation and some white blood cell function is impaired when deficiencies of pyridoxine, pantothenic acid, and folic acid exist.

Minerals

Clinical evidence of impaired wound healing is lacking for most trace elements, except for zinc. Low zinc levels have been associated with slow wound healing. Restoration of depleted zinc levels to normal ones has been found to result in normalized healing rates. A study showed that in otherwise healthy young patients, surgically unopposed defects heal at twice the rate of control subjects when 220 mg zinc sulfate supplements are added to each of three daily meals.

Zinc appears to be a component of DNA and RNA polymerases, and thus probably has an important role in cell division. Zinc may also be required for several stages of Vitamin A metabolism, and may adversely affect wound healing by interfering with the availability of vitamin A.

Although zinc deficiency is rare, it may occur in patients who have suffered a severe injury, infection, disorder of the digestive tract, or prolonged, non-supplemented intravenous hyperalimentation. Serum zinc levels less than 100 micrograms/100 ml may herald wound problems, and 200 milligrams of zinc sulfate may be given daily in divided doses.

Iron, in addition to vitamin C, is very important for the hydroxylation of proline and lysine. Therefore, iron is necessary for effective collagen synthesis. It is debatable whether iron deficiency further compromises wound healing by virtue of anemia. Iron deficiency is easily corrected, and diagnosis is by monitoring serum levels.

Copper is contained in lysly oxidase, which is an enzyme important in the formation of covalent cross-linkages which strengthens scar tissue. Copper deficiency has only been reported in cases of long-term intravenous alimentation in which copper supplementation has been omitted. However, American diets have been shown to be deficient in both copper and zinc.

POSTOPERATIVE NUTRITIONAL SUPPORT

Starvation, whether it be brief (24-72 hours) or prolonged (greater than 72 hours), frequently accompanies surgery, which may produce fever, pain, discomfort and/or nausea. It is important for patients to realize the necessity of maintaining a proper intake of fluids, calories, and protein to promote an adequate healing response.

Adequate fluid intake is most important during the first 24 hours after surgery. It is during this period that the body is experiencing the greatest effect of the endocrine response to the stress of surgery. The total 24-hour fluid maintenance requirement is calculated to be 2500 ml.

The patient's protein and calorie requirement can be estimated from ideal body weight. Knowing the body weight, the recommended daily protein intake varies between 1.0 and 2.5 grams of protein/kg. The recommended calorie intake is calculated on the basis of protein needs and ranges from 24-40 kcal/gm of protein (the higher range being used for more severe catabolic states, i.e., multiple fractures, burns, sepsis). A knowledge of the patient's nutritional and fluid requirements, as well as the existence of any previous deficits in the patient's nutritional status prior to surgery, will allow the surgeon to determine a diet which will optimally support the patient through the wound healing process.

SUMMARY

Proper wound healing requires specific nutritional requirements which must be met to allow optimal repair of tissues. It is important for the surgeon to have an understanding of the presurgical nutritional state of the patient in order to adequately plan for and prevent any complications which might arise due to poor healing of tissues. At the time of the initial clinical exam, the surgeon should perform a thorough history and physical exam, as well as certain measurements and tests. If a nutritional deficit exists, it should be corrected prior to surgery by using a balanced diet with supplements of the deficient nutrient. Postoperative nutritional support is needed to maintain an adequate protein calorie intake in order to promote satisfactory wound healing.

BIBLIOGRAPHY

Berlinger NT: Wound Healing. *Otolaryngol Clin North Am* 15(1):29-34, 1982.

Broden G, Bark S, Nordenvall B, Backman L: Nutritional Assessment and Postoperative Morbidity. *Acta Chir Scand* suppl 520:27-32, 1984.

Chvapil M, Koopmann CF: Age and Other Factors Regulating Wound Healing. *Otolaryngol Clin North Am* 15(2):259-269, May 1982.

Ehrlichman RJ, Seckel BR, Bryan DJ, Moschell CJ: Common Complications of Wound Healing. *Surg Clin North Am* 71(6):1323-1351, 1991.

Harris DR: Healing of the Surgical Wound. *J Am Acad Dermatol* 1(3):208-214, 1979.

Hirsch S, de Obaldia N, Petermann M, Covacevic S, Burmeister R, Liorens P, Iturriaga H, Bunout D: Nutritional Status of Surgical Patients and the Relationship of Nutrition to Postoperative Outcome. *J Am Coll Nutr* 11(1): 21-24, 1992.

Keithley JK: Wound Healing in the Malnourished Patients. *AORN J* 35(6): 1094-1099, 1982.

Orr JW, Shingleton HM: Importance of Nutritional Assessment and Support in Surgical and Cancer Patients. *J Reprod Med* 29(9): 635-647, 1984.

Marshman R, Coupland GAE: Nutritional Status and Postoperative Complications in an Australian Hospital. *Aust NZ J Surg* 50(5): 516- 519, 1980.

Navia JM, Menaker L: Nutritional Implications in Wound Healing. *Dent Clin North Am* 20(3):549-567, 1976.

Pollack SV: Wound Healing: A Review. *J Dermatol Surg Oncol* 5(8): 615- 619, 1979.

Roy LB, Edwards PA, Barr LH: The Value of Nutritional Assessment in the Surgical Patient. *J Parenter Enteral Nutr* 9(4): 170-172, 1985.

Ruberg RL: Role of Nutrition in Wound Healing. *Surg Clin North Am* 64(4): 705-713, 1984.

Schumann D: The Nature of Wound Healing. *AORN J* 35(6): 1068-1077, 1982.

Schumann D: Preoperative Measures to Promote Wound Healing. *Nurs Clin North Am* 14(4): 683-697, 1979.