Nutritional Support for Wound Healing

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Abstract

Healing of wounds, whether from accidental injury or surgical intervention, involves the activity of an intricate network of blood cells, tissue types, cytokines, and growth factors. This results in increased cellular activity, which causes an intensified metabolic demand for nutrients. Nutritional deficiencies can impede wound healing, and several nutritional factors required for wound repair may improve healing time and wound outcome. Vitamin A is required for epithelial and bone formation, cellular differentiation, and immune function. Vitamin C is necessary for collagen formation, proper immune function, and as a tissue antioxidant. Vitamin E is the major lipid-soluble antioxidant in the skin; however, the effect of vitamin E on surgical wounds is inconclusive. Bromelain reduces edema, bruising, pain, and healing time following trauma and surgical procedures. Glucosamine appears to be the rate-limiting substrate for hyaluronic acid production in the wound. Adequate dietary protein is absolutely essential for proper wound healing, and tissue levels of the amino acids arginine and glutamine may influence wound repair and immune function. The botanical medicines *Centella asiatica* and *Aloe vera* have been used for decades, both topically and internally, to enhance wound repair, and scientific studies are now beginning to validate efficacy and explore mechanisms of action for these botanicals. To promote wound healing in the shortest time possible, with minimal pain, discomfort, and scarring to the patient, it is important to explore nutritional and botanical influences on wound outcome.

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Introduction

Wound healing involves a complex series of interactions between different cell types, cytokine mediators, and the extracellular matrix. The phases of normal wound healing include hemostasis, inflammation, proliferation, and remodeling. Each phase of wound healing is distinct, although the wound healing process is continuous, with each phase overlapping the next. Because successful wound healing requires adequate blood and nutrients to be supplied to the site of damage, the overall health and nutritional status of the patient influences the outcome of the damaged tissue. Some wound care experts advocate a holistic approach for wound patients that considers coexisting physical and psychological factors, including nutritional status and disease states such as diabetes, cancer, and arthritis. Keast and Orsted[1] wittily state, "Best practice requires the assessment of the whole patient, not just the hole in the patient. All possible contributing factors must be explored."

Wound repair must occur in a physiologic environment conducive to tissue repair and regeneration. However, several clinically significant factors are known to impede wound healing, including hypoxia, infection, tumors, metabolic disorders such as diabetes mellitus, the presence of debris and necrotic tissue, certain medications, and

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a diet deficient in protein, vitamins, or minerals. In addition, increased metabolic demands are made by the inflammation and cellular activity in the healing wound, which may require increased protein or amino acids, vitamins, and minerals.[2]

The objective in wound management is to heal the wound in the shortest time possible, with minimal pain, discomfort, and scarring to the patient. At the site of wound closure a flexible and fine scar with high tensile strength is desired. Understanding the healing process and nutritional influences on wound outcome is critical to successful management of wound patients. Researchers who have explored the complex dynamics of tissue repair have identified several nutritional cofactors involved in tissue regeneration, including vitamins A, C, and E, zinc, arginine, glutamine, and glucosamine. Botanical extracts from *Aloe vera*, *Centella asiatica*, and the enzyme bromelain from pineapple have also been shown to improve healing time and wound outcome. Eclectic therapies, including topical application of honey, sugar, sugar paste, or Calendula succus to open wounds, and comfrey poultices and hydrotherapy to closed wounds are still in use today. Although anecdotal reports support the efficacy of these eclectic therapies, scientific evidence is lacking.

The Four Phases of Wound Healing

Tissue injury initiates a response that first clears the wound of devitalized tissue and foreign material, setting the stage for subsequent tissue healing and regeneration. The initial vascular response involves a brief and transient period of vasoconstriction and hemostasis. A 5-10 minute period of intense vasoconstriction is followed by active vasodilation accompanied by an increase in capillary permeability. Platelets aggregated within a fibrin clot secrete a variety of growth factors and cytokines that set the stage for an orderly series of events leading to tissue repair.

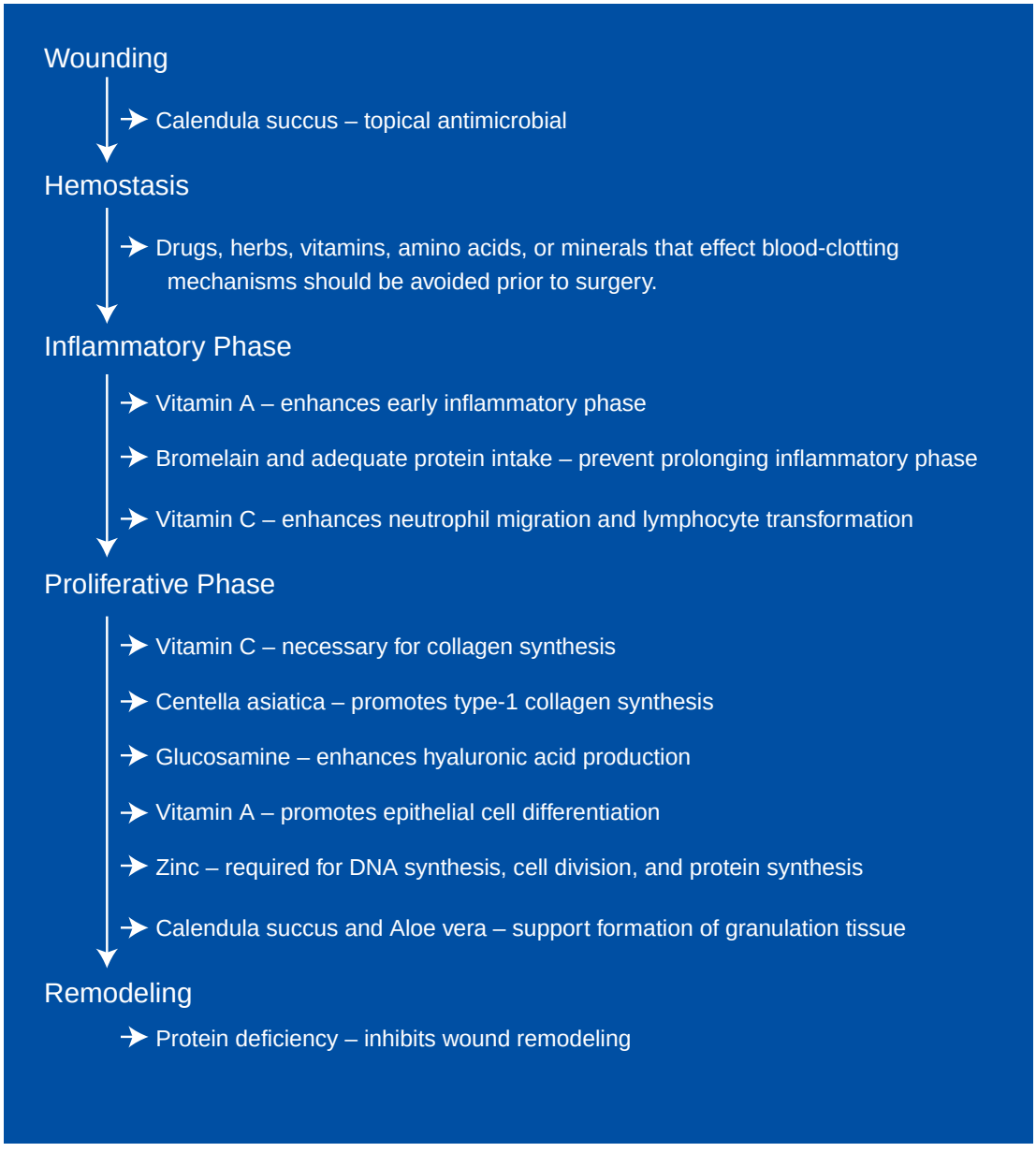
The second phase of wound healing, the inflammatory phase, presents itself as erythema, swelling, and warmth, and is often associated with pain. The inflammatory response increases vascular permeability, resulting in migration of neutrophils and monocytes into the surrounding tissue. The neutrophils engulf debris and microorganisms, providing the first line of defense against infection. Neutrophil migration ceases after the first few days post-injury if the wound is not contaminated. If this acute inflammatory phase persists, due to wound hypoxia, infection, nutritional deficiencies, medication use, or other factors related to the patient's immune response, it can interfere with the late inflammatory phase.[3]

In the late inflammatory phase, monocytes converted in the tissue to macrophages, which digest and kill bacterial pathogens, scavenge tissue debris and destroy remaining neutrophils. Macrophages begin the transition from wound inflammation to wound repair by secreting a variety of chemotactic and growth factors that stimulate cell migration, proliferation, and formation of the tissue matrix.

The subsequent proliferative phase is dominated by the formation of granulation tissue and epithelialization. Its duration is dependent on the size of the wound. Chemotactic and growth factors released from platelets and macrophages stimulate the migration and activation of wound fibroblasts that produce a variety of substances essential to wound repair, including glycosaminoglycans (mainly hyaluronic acid, chondroitin-4-sulfate, dermatan sulfate, and heparan sulfate) and collagen.[2] These form an amorphous, gel-like connective tissue matrix necessary for cell migration.

New capillary growth must accompany the advancing fibroblasts into the wound to provide metabolic needs. Collagen synthesis and cross-linkage is responsible for vascular integrity and strength of new capillary beds. Improper cross-linkage of collagen fibers has been responsible for nonspecific post-operative bleeding in patients with normal coagulation parameters.[4] Early in the proliferation phase fibroblast activity is limited to cellular replication and migration. Around the third day after wounding the growing mass of fibroblast cells begin to synthesize and secrete measurable amounts of collagen. Collagen levels rise continually for approximately three weeks. The amount of collagen secreted during this period determines the tensile strength of the wound.

Figure 1. *Nutrient Impacts on the Phases of Wound Healing*



The final phase of wound healing is wound remodeling, including a reorganization of new collagen fibers, forming a more organized lattice structure that progressively continues to increase wound tensile strength. The remodeling process continues up to two years, achieving 40-70 percent of the strength of undamaged tissue at four weeks.[2]

Figure 1 summarizes the phases of wound healing and nutrients that impact the various phases.

Vitamins and Minerals Essential to Wound Healing

Vitamin A

Vitamin A is required for epithelial and bone tissue development, cellular differentiation, and immune system function. Substantial evidence supports the use of vitamin A as a perioperative nutritional supplement.[5] In addition to facilitating normal physiological wound repair, Ehrlich and Hunt have shown vitamin A reverses the corticosteroid-induced inhibition of cutaneous and fascial wound healing.[6-8] Vitamin A has also corrected non-steroid induced, post-operative immune depression[9] and improved survival in surgically-induced abdominal sepsis.[10] Levenson et al suggest vitamin A benefits the wound by enhancing the early inflammatory phase, including increasing the number of monocytes and macrophages at the wound site, modulating collagenase activity, supporting epithelial cell differentiation, and improving localization and stimulation of the immune response.[10,11]

Animal studies show vitamin A may increase both collagen cross-linkage and wound-breaking strength. Greenwald et al inflicted surgical flexor profundus damage and immediate repair on adult chickens. They found chickens that ate a diet supplemented with vitamin A (150,000 IU/kg chicken chow) demonstrated wound-breaking strength more than double that of controls fed standard chicken chow.[12] In addition, rats with dorsal skin incisions and concurrent comminuted femoral fractures exhibited delayed cutaneous healing. Supplemental vitamin A enhanced wound healing in these animals, demonstrated by increased breaking strength of the dorsal skin incisions in rats fed supplemental vitamin A compared to the non-supplemented group. The authors believe the improved wound healing is a result of an increased rate of collagen cross-linkage.[13]

Levenson and Demetrio recommend vitamin A supplementation of 25,000 IU daily before and after elective surgery.[14] Research supports perioperative vitamin A supplementation in patients known to be immune depleted or steroid treated. Surgical patients with sepsis and those with fractures, tendon damage, or vitamin A deficiency may also benefit from perioperative vitamin A supplementation. Additional research is necessary to establish the effectiveness of universal perioperative vitamin A supplementation in healthy individuals.

Concern among some practitioners regarding the potential toxicity of higher doses of vitamin A has led to uneasiness about using it perioperatively. The vast majority of toxicity cases have occurred at daily vitamin A dosages of 50,000-100,000 IU in adults over a period of weeks to years.[15] Short-term supplementation of 25,000 IU daily appears to be safe for most non-pregnant adults. Caution must be exercised in supplementing vitamin A in patients for whom the anti-inflammatory effect of steroids is essential, such as in rheumatoid arthritis or organ transplants, as well as in pregnant women and women of childbearing age.[5]

Vitamin C

Ascorbic acid is an essential cofactor for the synthesis of collagen, proteoglycans, and other organic components of the intracellular matrix of tissues such as bones, skin, capillary walls, and other connective tissues. Ascorbic acid deficiency causes abnormal collagen fibers and alterations of the intracellular matrix that manifests as cutaneous lesions, poor adhesion of endothelium cells, and decreased tensile strength of fibrous tissue.[16] Clinical manifestations of ascorbic acid deficiency include bleeding gums, poor immunity, easy bruising and bleeding, and slow healing of wounds and fractures.[17] Ascorbic acid is necessary for the hydroxylation of proline and lysine residues in procollagen, which is necessary for its release and subsequent conversion to collagen. Hydroxyproline also stabilizes the collagen triple-helix structure.[18] In addition to collagen production, ascorbic acid enhances neutrophil function,[19] increases angiogenesis,[20] and functions as a powerful antioxidant.[21]

Although ascorbic acid is required for reparation of damaged tissue, researchers have demonstrated the benefit of vitamin C only in vitamin C-deficient individuals using low doses of

ascorbic acid.[22] In a study by Hodges et al, four subjects (ages 33-44) were depleted of vitamin C for 99 days to induce scurvy. On day 100, a 5-cm incision was made in the left thigh of each subject and they began the oral administration of 4, 8, 16, or 32 mg ascorbic acid daily. Healing was measured by histological and electron microscope technique. It was shown that 4 mg daily of vitamin C was just as effective as 32 mg daily for wound healing in these vitamin C-deficient subjects.[22] The efficacy of using vitamin C to improve wound healing in non-deficient individuals remains uncertain. It should be noted, however, that even the highest dose in this study (32 mg) is below the RDA for vitamin C. Higher doses and larger differences between doses might have yielded more significant differences.

Humans lack the ability to store vitamin C, and certain populations are more likely to be deficient in ascorbic acid, including the elderly, alcoholics, drug abusers, and under-nourished individuals.[23] Subclinical vitamin C deficiency is being recognized increasingly in the general population. Published cases show that restricted eating patterns, prolonged hospitalization, severe illnesses, and poor dietary intake in both children and adults cause deficiency with significant clinical consequences.[4,24-26] In one study 12 patients with post-surgical diffuse hemorrhage, each exhibiting normal coagulation parameters, were found to have low plasma ascorbic acid levels. Each patient received 250-1,000 mg oral vitamin C daily. Within 24 hours of vitamin C administration there was no further evidence of bleeding or need for subsequent blood transfusions in any patient. The authors concluded vitamin C deficiency should be included in the differential diagnosis for nonspecific bleeding in surgical patients.[4]

In mammals, ascorbic acid is necessary for a normal response to physiological stressors, with the need for ascorbic acid increasing during times of injury or stress.[27] Studies have shown the physiological stress of intense exercise generates excess reactive oxygen species (ROS), increasing the demand on the antioxidant defense system.[28-30] A similar elevation of ROS has been noted within wounds; therefore, substances that increase tissue antioxidants are thought to benefit healing.[31-33] Events leading to wounds, including trauma and surgery, are perceived as physiological stressors that have also been correlated with a decrease in plasma ascorbic acid.[34,35] Thus, the acute stress experienced by trauma or surgery patients may unmask marginal vitamin C deficiencies, leading to deficiency symptoms.

Cutaneous healing wounds have been found to have lower ascorbic acid content than intact tissue. Levels of vitamin C were compared to normal skin in two-, four-, seven-, and 14-day-old wounds in animals. Vitamin C levels decreased approximately 60 percent post-wound and had not exhibited full recovery by day 14.[36] In addition, low levels of antioxidants, including ascorbic acid, accompanied by elevated levels of markers of free radical damage have been detected in elderly rat cutaneous wounds exhibiting delayed healing. Eighteen-month-old wounded male rats were compared to 3-4 month-old rats pre-wound and seven days post-wound. Normal skin of aged and young rats showed no difference in ascorbic acid content; however, a 59-percent decrease in ascorbic acid content was observed in wound tissues of aged animals compared to its content in young adult wounds.[37] Rasik and Shukla propose the delay in wound healing of older rats is at least partially a result of increased free radical damage.[37]

The programmed sequences of the cellular and molecular processes occurring during wound repair are also dependent on immune function. Infection resulting from impaired immunity is one of the most commonly encountered and clinically significant impediments to wound healing.[3] In addition, cellular immunity and dysregulation of cytokines can impair wound healing.[38] Ascorbic acid has been shown to improve immune function in humans.[39-42] Human volunteers who ingested 2-3 g ascorbate daily for several weeks exhibited enhanced neutrophil motility to chemotactic stimulus and stimulation of lymphocyte transformation.[43] Neutrophil motility and lymphocyte transformation were also stimulated by 1 g intravenous ascorbic acid in six healthy volunteers. Alterations in these activities were related to serum ascorbic acid levels.

The combined effect of ascorbic acid on collagen synthesis, antioxidant status, and immunomodulation make it an appropriate supplement for wound repair protocols. Research provides evidence for the use of low doses of vitamin C in vitamin C-deficient individuals, but many practitioners believe larger doses of ascorbic acid in non-deficient individuals are indicated for optimal wound repair. Levenson and Demetriou recommend supplementing 1-2 g ascorbic acid daily from wound onset until healing is complete.[14] Such doses may be justified due to the lack of adverse effects at these levels[44] combined with the potential for deficiency in certain individuals. In addition, the transient increase in metabolic requirements for vitamin C resulting from the physiologic stress of trauma or surgery and the metabolic requirement of vitamin C for collagen synthesis are indications for higher doses of vitamin C in non-deficient individuals.

Zinc

Approximately 300 enzymes require zinc for their activities. Zinc is an essential trace mineral for DNA synthesis, cell division, and protein synthesis,[45] all necessary processes for tissue regeneration and repair. Zinc deficiency has been associated with poor wound healing and decreased breaking strength of animal wounds,[46] which can result from decreased protein and collagen synthesis during healing found in zinc-deficient animals.[47] Senapati and Thompson found zinc levels were 50-percent higher in muscle and skin from abdominal wounds of rats during wound healing, but mild deficiency reduced this accumulation.[48]

Zinc demands are thought to be the highest from time of wounding throughout the early inflammatory phase. Sequential changes in zinc concentrations were studied in the incisional wound model in the rat. Zinc levels increased from wounding and peaked on the fifth day – at a time of high inflammation, granulation tissue formation, and epidermal cell proliferation.[49] Zinc concentrations returned to normal by the seventh day, when inflammation had regressed. It has been suggested that increased local demand for zinc resulting from surgery and wounding exposes otherwise marginal zinc deficiencies in humans.[48]

Perioperative zinc supplementation is recommended for zinc-depleted patients.[23] Data is lacking to show zinc supplementation improves healing in non-deficient individuals; however, zinc deficiency in humans is widespread, and injured and stressed individuals are more prone to developing deficiencies. Ehrlich et al suggest zinc is lost in significant amounts after surgery because of fistulas, stress, and diarrhea.[50] Zinc deficiencies have also been identified in individuals with deep partial- or full-thickness burns and chronic venous leg ulceration.[51,52]

Further research is needed on the efficacy of zinc supplements for wound healing. Justification for perioperative zinc supplementation includes the absence of adverse effects at moderate doses (15-30 mg daily) and evidence that zinc deficiency impairs wound healing. Zinc supplementation of 15-30 mg daily is recommended perioperatively to prevent unmasking of marginal deficiencies. Higher levels of zinc supplementation may be necessary in patients with malnutrition, malabsorption, chronic diarrhea, or other risk factors of zinc deficiency.

Vitamin E

Vitamin E is popular among consumers for skin care and to prevent scar formation. It functions as the major lipophilic antioxidant, preventing peroxidation of lipids and resulting in more stable cell membranes. The antioxidant-membrane stabilizing effect of vitamin E also includes stabilization of the lysomal membrane, a function shared by glucocorticoids.[53] Systemic vitamin E and glucocorticoids inhibit the inflammatory response and collagen synthesis, thereby possibly impeding the healing process. The effect of vitamin E on wound healing is complex; it may have alternate effects in different types of wounds and in the presence of other nutrients, as well as different functions for water soluble versus lipid soluble preparations of vitamin E.

Animal studies of vitamin E supplementation on surgical wounds show conflicting results. Greenwald et al showed flexor tendon repair in chickens treated with vitamin E had breaking strength less than half that of controls measured

after days 7 and 45 from surgical repair.[12] Another animal study showed impaired collagen synthesis in rats treated with vitamin E after wounding.[54] The researchers cite the glucocorticoid-like effect of vitamin E as the cause of the negative results. However, these effects are mitigated by vitamin A, as vitamin A is a lysomal destabilizer that reverses several of the deleterious effects of glucocorticoids.[8]

Paradoxical results found by Galeano et al showed a hydrophilic vitamin E preparation positively impacted delayed wound healing in diabetic mice. Increased breaking strength and collagen content of the wound was found in treated animals. These authors speculate inhibition of lipid peroxidation accounted for the positive results.[55] In addition, prophylactic administration of vitamin E has been shown to increase breaking strength and normalize healing of wounds exposed to preoperative irradiation[56] and to decrease the development of intraperitoneal adhesions in animals.[57]

Since the discovery of vitamin E as the major lipid-soluble antioxidant in skin, it has been used topically for a wide variety of skin lesions. Anecdotal reports claim topical vitamin E is valuable for speeding wound healing and improving cosmetic outcome of burns and other wounds, including surgical scars. Such claims are disputed by two human clinical trials. In a double-blind study of 15 patients with surgically-induced wounds, emollient lotion and emollient lotion mixed with vitamin E were applied to healing wounds. The wounds were randomly divided into two parts and the different topical applications were applied to the same half of each wound twice daily. Physicians and patients independently evaluated the scars for cosmetic appearance on weeks 1, 4, and 12. In 90 percent of cases, topical vitamin E either had no effect, or actually worsened the cosmetic appearance of scars.[58] In addition, 33 percent of the patients studied developed contact dermatitis to topical vitamin E. A response to this study, published in *Dermatologic Surgery*, pointed out that d-alpha tocopherol is an extremely unstable compound, rendering details of its source, formulation, storage condition, and stability over time critical to interpretation of this study. It was also noted that breakdown products and contaminants could account for the inflammatory response encountered.[59] In a second, larger blinded study, the effects of topical steroids, vitamin E, or the base cream carrier for these substances on scar outcome of 159 post-operative patients were evaluated. Both topical steroids and topical vitamin E failed to impact scar thickness, range of motion, or ultimate cosmetic appearance.[60]

The available data on vitamin E and wound healing could lead to several possible conclusions: (1) systemic vitamin E may have a negative impact on surgical wounds due to its lysosomal-stabilizing properties; (2) vitamin A may mitigate these negative effects; and (3) hydrophilic and hydrophobic preparations of vitamin E may have different actions related to wounds. The benefit of topical vitamin E on surgical wound healing and scar formation remains inconclusive and, although anecdotal reports support topical use of vitamin E for scar therapy, research shows it may have a negative effect on scarring and wound outcome.

Other Dietary Supplements and Wound Healing

Bromelain

Bromelain is a general name given to a family of proteolytic enzymes derived from *Ananas comosus*, the pineapple plant. Throughout the 1960s and 1970s a series of studies found the effects of orally administered bromelain include the reduction of edema, bruising, pain, and healing time following trauma and surgical procedures.[61-64] More recently, researchers from the Czech Republic found that patients with long bone fractures administered a proteolytic enzyme combination containing 90 mg bromelain per tablet had less post-operative swelling compared to patients given placebo.[65] Fractures were treated by surgically inserting rods through the long axis of the fractured bone (intramedullary fixation) or by constructing an external framework of pins and rods going through the skin and muscle to connect to the fractured bone (external fixators). The treatment group was given three 90-mg tablets

three times daily for three days after surgery and, subsequently, two tablets three times daily for two weeks. On the fourteenth post-operative day the limb volume of the treatment group was reduced by 17 percent compared with nine percent in the control group. The total number of analgesics consumed by the treatment group was also significantly reduced in comparison to the control group.[65]

Studies by Tassman et al show bromelain reduced swelling, bruising, pain, and healing time in patients following dental surgeries.[63,66] In a double-blind study of dental surgery patients, bromelain was found to decrease swelling to 3.8 days, compared with seven days in patients given placebo. In addition, duration of pain was reduced to five days in the treatment group, compared to eight days in the placebo group.[63]

In an uncontrolled trial, bromelain was reported to positively influence swelling, pain at rest and during movement, and tenderness in patients with blunt injuries to the musculoskeletal system.[67] Although bromelain has been shown to reduce post-operative and trauma-related pain, this is probably related to its anti-inflammatory action rather than a direct analgesic effect.[68]

Aside from its documented anti-inflammatory activity, bromelain is of interest to surgeons because of its ability to increase resorption rate of hematomas. Bromelain's influence on hematoma resorption was demonstrated using artificially induced hematomas in humans. Hematomas in the treatment group resolved significantly faster than controls when oral bromelain was given at the time of hematoma induction and for seven days thereafter.[69]

Seltzer investigated two different doses of bromelain in patients undergoing rhinoplasty. Fifty-three patients were randomized to receive either one of two doses of bromelain or placebo. In patients receiving placebo, swelling and ecchymosis persisted for seven days, compared to two days in both bromelain groups.[70] However, a randomized trial of 154 facial plastic surgery patients receiving either 400 mg bromelain daily or placebo for one day before and four days after surgery found no statistically significant differences in edema between the two groups.[71]

Tassman et al noted that, while post-surgical oral bromelain administration was effective in reducing pain, swelling, and healing time, a protocol using pre- and post-surgical bromelain is recommended.[63] Studies have shown bromelain prevents aggregation of blood platelets in patients with high platelet aggregation values, which has led to recommendations by physicians and surgeons to avoid oral bromelain prior to any surgical procedure. In one human trial, bromelain was administered orally to 20 volunteers with a history of heart attack or stroke, or with high platelet aggregation values. Bromelain decreased platelet aggregation in 17 of the subjects and normalized values in eight of the nine subjects who previously had high aggregation values.[72] Contrary to this, other human studies have shown oral bromelain to be free of any significant effects on clotting parameters.[73,74] In one study, 47 patients with various disorders leading to edema and inflammation found no significant effects of oral bromelain (40 mg four times daily for one week) on bleeding, coagulation, and prothrombin time.

It is noteworthy that the studies pertaining to bromelain and platelet aggregation are over 30 years old. The potential benefit of pre- and post-surgical oral bromelain on hematoma resorption, pain, inflammation, and healing time justifies the need for concise, well-designed clinical trials evaluating different doses of bromelain on clotting parameters. Until further data is available regarding bromelain's action on platelets, oral bromelain administration should be withheld or used with caution before surgery.

Glucosamine

Hyaluronic acid is an important part of the extracellular matrix and one of the main glycosaminoglycans secreted during tissue repair. Production of hyaluronic acid by fibroblasts during the proliferative stage of wound healing stimulates the migration and mitosis of fibroblasts and epithelial cells. Glucosamine appears to be the rate-limiting substrate for hyaluronic acid synthesis.[75] *In vitro* studies suggest the mechanism of glucosamine on repair processes involves stimulation of the synthesis of glycosaminoglycans and

Table 1. *Perioperative Nutritional Protocol*

Nutrient	Dose	Action
Vitamin A**	25,000 IU daily	Enhances early inflammatory phase of wound healing; supports epithelial cell differentiation; improves localization and stimulation of immune response.
Vitamin C**	1-2 g daily	Synthesis of collagen, proteoglycans, and other organic components of the intracellular matrix; tissue antioxidant; supports immune response.
Zinc**	15-30 mg daily	Required for DNA synthesis, cell division, and protein synthesis.
Glucosamine**	1,500 mg daily	Enhances hyaluronic acid production in the wound.
Protein**	Minimum of 0.8 g/kg body weight daily	Prevents delayed healing and surgical complications.
Bromelain (use post-surgery only)	500-1,000 mg daily	Reduces edema, bruising, pain, and healing time.

** Use from two weeks prior to surgery until healing is complete

collagen.[76] Animal studies have shown the content of glycosaminoglycans within the site of partially ruptured muscles increased maximally five days after trauma and decreased thereafter.[77] This suggests the timing of glucosamine supplementation may determine its therapeutic impact on wounds.

Clinical trials using glucosamine for perioperative support are lacking. However, the administration of oral glucosamine both before as well as the first few days after surgery or trauma might enhance hyaluronic acid production in the wound, promoting swifter healing and possibly fewer complications related to scarring.

Protein and Wound Healing

Adequate protein intake is essential for proper wound healing. Protein depletion appears to delay wound healing by prolonging the inflammatory phase; by inhibiting fibroplasia, collagen

and proteoglycan synthesis, and neoangiogenesis (proliferation phase); and by inhibiting wound remodeling.[78,79]

Experimental protein depletion in animals caused a decrease in the tensile strength of wounds. Rats fed a diet deficient in protein exhibited decreased wound integrity and strength versus control animals.[80] In a study of 108 human patients with experimental wounds, individuals with either low serum protein or serum albumin had significantly weaker wounds than those with normal protein values.[81]

Protein calorie malnutrition increases morbidity and mortality in the surgical/trauma patient. Many studies have found hospitalized patients in a state of malnutrition at admission. Thus, it is important to increase protein intake to optimize healing and immune function, and to prevent post-surgical complications in these individuals.[82-84]

Protein supplementation of elderly patients with liquid protein formulas significantly enhanced healing of pressure ulcers. The change in ulcer area was significantly correlated with the amount of protein in the diet.[85]

The surgical or trauma patient exists in a state of metabolic stress, with the severity of the stress depending on the severity of the wounded state. An injured patient requires more protein than a non-injured patient because of the increased metabolic activity of wound healing, acute-phase protein production in response to stress, and amino acid mobilization from muscle used for hepatic gluconeogenesis.

In a non-injured state, adults require approximately 0.8 g dietary protein/kg body wt/day. Elderly patients have a higher protein requirement (1-1.2 g/kg body wt/ day) due to a decreased ability to synthesize proteins. The surgical/trauma patient can require significantly more protein. Minor surgery may not significantly increase the protein requirement; however, if the patient is already protein malnourished, wound healing will be adversely affected unless dietary protein intake is increased. Major surgery can increase protein requirements 10 percent, while a patient with multiple traumas may need 75-percent more protein. Burn wounds cause tremendous metabolic stress and have the greatest impact on protein requirements, increasing protein need 75-100 percent.[86]

Table 1 summarizes nutrients recommended for perioperative nutritional support.

Amino Acids in Wound Healing

It is well accepted that sufficient protein is necessary for wound healing. This appears to be due to the increased overall protein need for tissue regeneration and repair. Researchers have investigated the effects of specific amino acids on the healing process and determined that arginine and glutamine appear to be necessary for proper wound healing.

Arginine

Arginine is a non-essential amino acid that plays a key role in protein and amino acid synthesis. It is acquired from the diet and derived endogenously from citrulline in a reaction catalyzed by the enzyme arginine synthetase. Adequate tissue arginine appears to be essential for efficient wound repair and immune function.[87]

Arginine (17 g/day) was given to 30 elderly patients (>65 years of age) who sustained an experimental surgical injury. Supplemented patients demonstrated significantly greater hydroxyproline (a sign of collagen deposition) and protein accumulation at the wound site, compared to non-supplemented controls. Lymphocyte response, signifying greater immune activity, was elevated in the supplemented group, as was insulin-like growth factor-1, which is a control molecule for wound repair.[88] Other studies have found similar results.[89,90]

Glutamine

Glutamine is used by inflammatory cells within the wound for proliferation and as a source of energy.[91,92] Fibroblasts use glutamine for these same purposes, as well as for protein and nucleic acid synthesis. Because optimal functioning of these cells is paramount to the healing process, glutamine is a necessary component of the process of tissue repair. Glutamine is a non-essential amino acid that can become a "conditionally es-

sential" amino acid in certain circumstances, including tissue injury.[93] Glutamine is released from skeletal muscle following injury or surgery, which can cause a relative deficiency of glutamine in skeletal muscle and the gut, as intestinal uptake is frequently diminished as well.

Studies utilizing oral glutamine pre- and post-surgery, and in burn patients, have shown mixed results. Oral feeding of glutamine in surgery patients did not affect plasma glutamine or nitrogen turnover. Intravenous glutamine in surgery patients as an alanine-glutamine dipeptide showed consistently better post-operative results, as seen by significantly decreased length of hospital stays (average of four days or less).[92] A significantly smaller incidence of pneumonia, bacteremia, and sepsis was noted in patients with multiple trauma given enteral glutamine feedings.[94] Whether glutamine supplementation will enhance wound healing in less severely injured individuals is not known.

A mixture of arginine (14 g/day), glutamine (14 g/day), and beta-hydroxy-beta-methylbutyrate (HMB) (3 g/day) was given to 18 elderly (>70 years) individuals who then underwent experimental implantation of sterile polytetrafluoroethylene tubes that could later be excised and studied for fibroblastic migration and collagen deposition. Supplementation with this mixture resulted in significantly greater wound collagen deposition than in 17 controls not supplemented.[95]

Table 2 summarizes nutrients recommended for post-surgery or trauma care.

Table 2. *Post-surgery or Trauma Protocol*

Nutrient	Dose
Bromelain	500-1,000 mg daily
Vitamin A	25,000 IU daily
Vitamin C	1-2 g daily
Zinc	15-30 mg daily
Protein	Minimum 0.8 g/kg body weight daily
Glucosamine	1,500 mg daily

Recommended from wounding until healing is complete.

Botanical Medicines in Wound Healing

Centella asiatica and Aloe vera

Centella asiatica and *Aloe vera* have been used for decades as folk remedies for burns, wounds, and scars. Improved wound healing has been reported from topical or internal application of these two botanical medicines. Continued use of these plants as healing agents has led to scientific investigation of their efficacy as wound healing agents.

Centella asiatica (gotu kola) has been documented to aid wound healing in several scientific studies.[96-99] One of the primary mechanisms of action of Centella appears to be the stimulation of type-1 collagen production.[100] Animal studies have consistently shown topical application of *Centella asiatica* to a sutured wound significantly increased the breaking strength of the wound.[96,99,101,102] Asiaticoside, a saponin extracted from *Centella asiatica*, is thought to be one of its

active constituents. Shukla et al showed a 0.2-percent asiaticoside solution applied topically twice daily for seven days to punch wounds in guinea pigs resulted in 56-percent increase in hydroxyproline, 57-percent increase in tensile strength, increased collagen content, and better epithelialization compared to controls. Using the same punch wound model the researchers demonstrated an oral dose of 1 mg/kg for seven days produced a 28-percent reduction in wound area and a significant increase of tensile strength and hydroxyproline content of the wound.[102]

Topical treatment with *Aloe vera* has been shown to improve healing in frostbite and electrical injury in animals.[103,104] In addition, *Aloe vera* has improved the healing of wounds in both normal and diabetic rats.[105,106] Topical application and oral administration of *Aloe vera* to rats with healing dermal wounds increased the collagen content of the granulation tissue as well as the degree of cross-linkage. Collagen increased 93 percent with topical treatment and 67 percent with oral treatment compared to controls. The increase was attributed to increased stimulation by *Aloe vera* of collagen synthesis or increased proliferation of fibroblast synthesis of collagen, or both.[107] In a similar study, the effects of oral and topical *Aloe vera* on full thickness dermal wounds in rats exhibited an increase in glycosaminoglycan components of the extracellular matrix and, in particular, hyaluronic acid and dermatan sulphate levels.[107]

Aloe vera and *Centella asiatica* have been widely used for a host of curative purposes including facilitating wound repair. In spite of their wide use as folk remedies the biochemical basis for their action or influence on tissue repair is just beginning to be understood. Human clinical trials are needed to determine safety and benefits of perioperative oral administration of these botanicals. Topical application of both *Aloe vera* and *Centella asiatica* extracts to healing wounds or surgical scars appears to be safe and facilitates improved wound repair.

Eclectic Wound Therapies

Humans have always been faced with the dilemma of how to treat wounds. Many diverse and interesting approaches to wound management have been applied throughout medical history. Thirty years ago physicians believed pus in a wound was laudable and anxiously awaited its arrival;[108] surgeons today attempt every conceivable means to prevent its presence. Although scientific validation is absent, some wound-care therapies applied by eclectic physicians are still considered valuable and effective therapies today.

Honey and sugar or sugar paste have been used to treat wounds for decades. Both are considered to be antimicrobial and have been associated with scarless healing in some cavity wounds.[109] Hyaluronic acid consists of disaccharide chains made from modifications of the monosaccharide glucose. One possible mechanism in scar prevention is that glucose in honey or derived from sugar may be converted into hyaluronic acid at the wound surface, forming an extracellular matrix that promotes wound healing.[109] Fetal wounds heal without scar formation and the extracellular matrix of fetal wounds is rich with hyaluronic acid and lacks excessive collagen.[109] The glucose in honey or derived from sugar may facilitate a balance between hyaluronic acid and collagen, similar to that found in fetal wounds.

Preparations of fresh juice from *Calendula officinalis* preserved in alcohol, known as Calendula succus, are used topically to promote wound healing. Naturopathic doctors utilize Calendula succus to cleanse wounds after minor surgical procedures and throughout the healing process. External Calendula succus is listed in *The Complete German Commission E Monographs* for promoting wound healing. Topical application is thought to have anti-inflammatory and granulatory action.[110]

Knitbone and bruisewort are common names for *Symphytum officinalis* (comfrey) that give clues to its traditional uses. The active ingredient in comfrey is thought to be allantoin, which is reported to promote cell division and the growth of connective tissue, bone, and cartilage. Comfrey poultices are applied externally on intact skin

for bruises, sprains, and fractures. Medical literature regarding comfrey is limited to its potential liver toxicity when taken internally. However, many anecdotal reports claim comfrey is extremely effective at promoting swift healing in bruises, sprains, and fractures. External application to intact skin does not appear to have the same toxicity concerns as internal consumption.

Table 3 summarizes botanicals and other topical treatments for wound healing.

Table 3. *Topical Wound Care*

Topical preparation	Action
Aloe vera	Increases collagen content and degree of collagen cross-linkage within the wound.
Centella asiatica	Stimulates type-1 collagen production.
Honey or sugar paste	Glucose converted into hyaluronic acid at the wound surface forming an extracellular matrix that promotes wound healing; also considered antimicrobial.
Calendula succus	Anti-inflammatory and promotes granulation.
Symphytum officinale	Promotes cell division and the growth of bone, cartilage, and other connective tissues; applied topically to closed wounds.

Adequate tissue perfusion, blood flow, and oxygen levels are required for wound healing. Tissue perfusion delivers oxygen and nutrients to regenerating tissue. The synthesis of fibroblasts and the enzymatic hydroxylation of proline and lysine residues on the forming collagen chains are dependent, in part, on the availability of oxygen.[111] Hydrotherapy utilizes external hot and cold applications of water to manipulate the quantity of blood flow through a given tissue. Adequate blood flow brings oxygen, nutrients, and red and white blood cells to target tissues. This basic physiological manipulation of blood flow can support the wound healing process. Hydrotherapy is an inexpensive and powerful adjunct to wound care; however, there are some limitations to applying hydrotherapy to open wounds, burns, and in patients with peripheral neuropathies.

Discussion

Wound healing proceeds quickly and efficiently in a physiologic environment conducive to tissue regeneration and repair. Nutritional status of patients at the time of trauma or surgery influences the biochemical processes necessary for the phases of normal healing to occur. Undernourished or malnourished individuals heal less efficiently and are at greater risk for complications during and after surgery. Part of treating the whole patient and not just the "hole in the patient" is appreciating the complex interactions and the nutrients involved in the wound-healing process. The relationship between malnutrition and poor wound healing is well documented,[112-114] while the impact of optimal levels of dietary and supplemental nutrient intakes for wound healing is relatively unknown.

Promotion of good nutrition is recommended, particularly in populations at risk for marginal and frank nutritional deficiencies, including the elderly,[115] severely injured,[116] smokers,[117,118] patients with maldigestion or poor assimilation,[3] and hospitalized patients[119] before elective surgery. Evidence supporting supplementation of nutrients known to benefit the healing process in healthy

individuals is lacking. Several journal reviews cite a high prevalence of complementary and alternative medicine (CAM) use by surgical patients.[120-126] The authors of these articles caution against the use of CAM therapies because of potential adverse reactions, the most common being potential vitamin, mineral, herb, or amino acid interactions with platelet aggregation or anesthetics or other pharmaceuticals given perioperatively.[124-126] The potential benefit of nutrients is seldom discussed.

Evidence exists that vitamins A and C, zinc, arginine, glutamine, glucosamine, bromelain, *Aloe vera*, and *Centella asiatica* may be beneficial to wounded or surgical patients; however, many patients will be advised to avoid them. More extensive, well-defined, blinded clinical trials to evaluate the safety, efficacy, and drug interactions of these potential beneficial substances are needed.

From the current available data it would appear that an adequate protein supply, as well as supplementation of 25,000 IU vitamin A, 1-2 g vitamin C, 15-30 mg zinc, 3-15 g arginine, 3-15 g glutamine, and 1,500 mg glucosamine per day prior to and after surgery would benefit adult patients. Wounded patients could also benefit from these nutrients from wounding until healing is complete. Post-operative topical application of *Aloe vera* and *Centella asiatica* extracts may facilitate the creation of a flexible, fine scar with high tensile strength at the wound site. In addition, 750-1,000 mg bromelain post-operatively may reduce edema, bruising, pain, and healing time following trauma and surgical procedures. Several eclectic wound therapies have survived through the centuries and are still in use today. Scientific research is needed to validate safety and efficacy of these eclectic therapies.

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