

## Trauma and Wound Healing

### Improving Healing with Nutrition

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Trauma is a stressful event caused by either a mechanical or a chemical injury. Depending on its level, trauma can have serious short-term and long-term consequences. The role of healthy nutrition, both in promoting healing and in avoiding complications associated with trauma, has long been acknowledged in trauma recovery.

Trauma varies in intensity, ranging from serious burns or traffic accidents to the gradual, cumulative trauma that occurs with repetitive overuse of muscles and joints (such as strenuous weight lifting). Minor injuries are relatively frequent, often being no more than minor irritants. However, any traumatic event, even a minor one, affects the body's natural metabolic balance and initiates a cascade of reactions aimed at repair and restoration of function.

Over the past few decades, trauma has become increasingly common (Hall J et al 1995). This may be due in part to newer, more dangerous pastimes and sports. However, we have also learned a great deal about recovering from trauma, including nutritional approaches to maximize healing.

### THE TISSUE RESPONSE TO TRAUMA

Trauma (or any injury) results in tissue damage. Immediately after traumatic injury, a pattern of local reactions and systemic changes is launched. This reparative process involves almost all organ systems.

The local response to trauma serves three goals: stop blood loss, clear tissue debris, and restore normal biological function in the affected area, with the use of scar tissue.

**Limitation of blood loss.** This begins with a brief constriction of the blood vessels to reduce blood flow to the affected area. Meanwhile, platelets are activated to form a clot or mesh of fibrin to block the bleeding blood vessels. The platelets then release substances such as histamine, serotonin, and cytokines, which activate the next stage of healing, inflammation.

**Clearing of tissue debris.** Once the bleeding is under control, the body begins to remove damaged and dysfunctional tissue through the inflammatory response. Only after the debris is completely reabsorbed can the body lay down a new tissue framework. Inflammation requires the activation of certain enzyme systems and pro-inflammatory cells that dissolve the damaged tissue.

During this inflammatory period, blood flow to the wound is increased. This vasodilation, which follows the intense vasoconstriction seen immediately after the wound is created, is mediated by chemicals such as histamine, prostaglandins, and those found in the complement cascade, which is part of the immune system response to injury. Under their influence the blood vessel walls in the area of the wound become leaky, allowing repair cells and protein-rich plasma to gather in the damaged tissues. This process results in swelling.

The plasma spilling into the wound serves multiple functions. It dilutes any irritants in the injured area and brings protein molecules called fibrinogen, which link with each other, forming a fibrin mesh big enough to occupy the entire wound. This clot helps trap foreign particles, enhances immune cell effectiveness, and forms the scaffolding over which new tissues are laid down.

Neutrophils are among the first white blood cells to arrive at the site of injury. They remove the dead and dying cells, blood clots, and the fibrin mesh to clean up the wound. Other immune cells, including monocytes, lymphocytes, eosinophils, and basophils, join the neutrophils later. Together these immune cells engulf and digest any bacteria.

### SCAR TISSUE: LONG-TERM HEALING

Once the bleeding has stopped and the body's immediate inflammatory response has been activated, long-term healing and tissue regeneration can begin. The growth of new tissue consists of three different processes:

- Angiogenesis, or creation of new blood vessels
- Formation of granulation tissue
- Remodeling of the scar to suit changing functional requirements

**Angiogenesis.** The cells lining the damaged capillaries start multiplying to form fresh blood vessels, a process known as angiogenesis. The new capillaries not only help clear the dead tissue but also support the growing cells by supplying oxygen and nutrients.

**Granulation and remodeling.** Once the wound is free of debris and new blood vessels have begun to form, repair cells called fibroblasts lay down a scaffolding of collagen. This collagen network matures into granulation tissue, which forms the foundation of scars. The granulation tissue matures as the collagen fibers become increasingly interlinked. Externally, the scar can be seen to contract and close the wound, and this process of collagen maturation and remodeling continues for a lifetime.

## SYSTEMIC RESPONSE TO INJURY

Four major organ systems are involved in wound healing: the sympathetic nervous system, the endocrine organs, the cardiovascular system, and an acute phase reaction involving the liver. During the immediate systemic response, the wounded person becomes alert, opium-like substances are released to decrease pain, the heart and respiratory rates quicken, blood glucose levels rise, and the basal metabolic rate speeds up. This is a stress reaction, with organ systems functioning at supraphysiological levels. A sustained level of stress takes a toll on the body's physiology unless supported by appropriate nutritional therapy.

The systemic response is produced as local chemical mediators spill into blood vessels from the wound. They activate circulating monocytes (a kind of immune cell) to release chemical messengers called cytokines. These cytokines cause the various metabolic changes seen after trauma. In cases of major trauma, there may be generalized fever; increased oxygen consumption; and increased metabolism of fats, glucose, and proteins.

As the reaction is prolonged over days or weeks, local lymph nodes and the spleen enlarge to supply immune cells.

## MALNUTRITION IN TRAUMA PATIENTS

The body needs a certain amount of nutrients to maintain a constant, healthy state. This need is determined by the basal metabolic rate. Any external or internal trauma raises the metabolic rate, and greater amounts of oxygen and nutrients are required to supply enough fuel and amino acids for repair and recovery.

Energy expenditure may rise by 10 percent to 50 percent to support the intense metabolic workload (Omerbegovic M et al 2003). Protein and amino acid requirements increase to support formation of new tissues and proliferation of immune cells, maintain lean body mass (or muscle protein), and replace the protein lost to perspiration, bleeding, and excretion.

A positive nutritional balance is reflected in rapid healing of wounds, an efficient immune response, the absence of infections or sepsis (shock), and maintenance of a lean body mass.

Population studies indicate that 9 percent to 44 percent of people with wound and surgical trauma are malnourished (Reid CL 2004). The condition often goes unrecognized and untreated in hospitals, and some studies have explored the increased risk of malnutrition during hospital stays, based on the common occurrence of clinically significant weight loss observed in hospitalized surgical patients (Fettes SB et al 2002).

Biologically, it is difficult to achieve usual levels of nutrition after major trauma because many important nutrients are channeled into the healing effort. In addition, many trauma patients suffer from altered levels of consciousness, poor appetite, reduced digestive function, compromised blood circulation, and a radical alteration of normal daily routines.

There are also pronounced changes in the way the body metabolizes nutrients and food. Under normal circumstances, carbohydrates and fat are used to produce or store energy, and protein is used for developing and maintaining lean body mass. In this nonstressed condition, 90 percent of energy is supplied by carbohydrates or fat, and proteins contribute only 5 percent to 8 percent of total calories.

By contrast, during trauma, proteins, including muscle mass, are broken down to yield as much as 30 percent of caloric needs. Even when nutrients are supplemented, proteins will be utilized to provide 20 percent to 25 percent of caloric needs.

Compared to fat, protein yields less energy per gram. The patient becomes hypermetabolic, requiring higher-than-normal levels of calories and protein. The abnormal metabolism is caused by the release of stress hormones such as cortisol and catecholamines. This hypermetabolic state contributes to rapid loss of lean body mass, even when the patient is well fed. It is critical that trauma patients maintain an adequate supply of protein and calories to protect their lean muscle mass and supply their healing body with necessary nutrients.

## COMPLICATIONS OF TRAUMA

Besides the danger posed by the trauma itself and the risk of malnutrition, patients are also at risk for complications resulting from their injury. Wound repair may be impeded by the following complications:

- **Infection.** Wound infection can occur in cases of extensive wound area, poor host defenses, and improper wound care.
- **Keloid.** Keloid is a bulky protrusion of scar tissue formed as a result of abnormal collagen synthesis. It can spread to the adjoining skin.
- **Gangrene.** Gangrene is dead wound tissue formed by the decay of body tissues. It can be caused by infection, blood clots, or lack of blood flow. This condition is most common in the extremities.
- **Rapid weight loss.** This results from protein-calorie malnutrition.
- **Compromised immune system.** The malnourished patient can quickly exhibit symptoms of decreased immune function, such as infection.

Extreme injuries can also provoke an uncontrollable inflammatory response, overwhelming vital organ systems like the heart and lungs. This life-threatening condition, known as systemic inflammatory response syndrome, is a major problem in the management of multiple traumas. While optimal levels of inflammation can clear debris and initiate healing, these reactions need to be regulated vigilantly. The enzymes and chemicals that dissolve dead tissue can also damage living tissue. If inflammation overwhelms the control mechanism, it can reach life-threatening proportions.

### *What You Have Learned So Far...*

- Trauma is a generic term for physical or chemical injury. The intensity of trauma ranges from an acute, life-threatening event to gradual, cumulative injuries.
- The body's response to trauma involves both a local and a systemic reaction. Inflammation, blood clotting, and immune system activation are all necessary elements of healing after trauma.
- During trauma, the body functions at an enhanced physiological rate. The body's requirement for calories, protein, and nutrients is greatly enhanced, leading to a risk of malnourishment among trauma patients.
- Nutritional supplementation is critical to helping the healing process.

## ESSENTIAL NUTRIENTS FOR WOUND HEALING

Based on the extensive biological and metabolic changes that occur after trauma, nutritional supplementation is often required. The following nutritional factors have been shown to support the body's enhanced metabolic demands:

**Calories.** Wound healing consumes energy. Ordinarily, carbohydrates and fats are the main sources of energy. During the stress response, proteins are also broken down to provide energy. To prevent the loss of lean body mass, sufficient energy supply has to be maintained. After trauma, caloric requirements may be increased up to 25 to 30 calories per kilogram of body weight daily (Leininger S 2002) .

**Carbohydrates.** Carbohydrates are a rich source of cellular energy during wound healing. Carbohydrates serve a number of purposes after a wound:

- Help meet the body's heightened energy requirements.
- Aid in fibroblast movement, which is vital in wound healing.
- Enhance white blood cell activity to strengthen immune response.

**Protein.** Proteins are a vital component of collagen synthesis. Therefore, insufficient protein can affect the rate and quality of wound healing. It is well known that trauma increases the demand for protein. This requirement is further increased in the event of sepsis or stress. Wound healing requires 1.5 to 3 g per kilogram (of body weight) per day of protein, but this requirement may vary depending on the type of wound (Leininger S 2002).

**Fats.** Fats are a concentrated source of calories. Supplementation with certain fatty acids is essential. They play the chief role in cell membrane structure and function and help wound healing. It is recommended that 20 percent of calories should be obtained from fats, especially monounsaturated fats. Fats are also implicated in the synthesis of new cells; therefore, low fat levels would delay wound healing.

**Vitamin A.** Vitamin A is indispensable for normal growth and differentiation of the skin, making it significant in wound healing . The presence of vitamin A increases the strength of scar tissue. Vitamin A is required for an adequate inflammatory response and has

been used to counteract the catabolic effect that glucocorticosteroids exert on wound healing (Ehrlich HP et al 1973). The improvement in wound healing from vitamin A supplementation is also attributed to an increase in collagen cross-linking, which results in higher tensile strength (Seifter E et al 1975).

**Vitamin C.** It is well documented that wound healing requires more vitamin C than the diet alone can easily provide (MacKay D et al 2003) . As vitamin C is water soluble, it has to be taken daily. Vitamin C is important for the proper function of the enzyme procollagen hydroxylase, which generates collagen. Vitamin C forms bonds between the strands of collagen fibers and helps to provide extra strength and stability. It is also essential for the synthesis of the intracellular matrix of tissues such as bone, skin, blood vessel walls, and connective tissue. Finally, vitamin C is a potent antioxidant, and studies have shown elevated levels of reactive oxygen species (a kind of free radical) in wounds (Gupta A et al 2002; Sen CK et al 2002).

**Zinc.** Zinc is a trace mineral present in the body in only a small quantity. However, it is found in many tissues, including bone, skin, muscle, and organs, and it is required in as many as 300 enzymatic reactions. Zinc is used in DNA synthesis, cell division, and protein synthesis and mediates the maturation of T-lymphocytes ( Prasad AS 1995).The body's need for zinc increases during cell proliferation and protein secretion.

**Water.** Meeting hypermetabolic needs may leave the body dehydrated. Not only is it essential to maintain hydration, but the need for hydration increases if a wound is draining or if a person is on an air-fluidized therapy bed. Trauma patients' daily requirement of water may range from 1500 to 2000 mL/day (Leininger S 2002).

## THE THERAPEUTIC ROLE OF NUTRITION

The hypermetabolic effects of stress may require special or high-dose nutrients for enhanced wound healing and uneventful recovery. The nutrients affecting the wound healing process include arginine, glutamine, inositol, choline, carnitine, alpha lipoic acid, and coenzyme Q10 (Patel GK 2005)

**Arginine.** Arginine fuels the cellular immune response and fights against bacterial challenges. It is an essential precursor to protein synthesis at the wound site and increases local wound immune function. Researchers have found that in the case of trauma and surgery, arginine requirements increase to 17 to 25 g of oral arginine per day, in contrast to the usual 5 g per day (Barbul A et al 1991; Kirk SJ et al 1993). Enhanced wound healing has been observed with large doses of arginine (Patel GK 2005).

**Glutamine.** Glutamine is a key substrate for fast-growing and multiplying cells, including white blood cells. Glutamine stimulates the proliferation of fibroblasts, thereby helping in wound closure. It is the major amino acid lost during any tissue injury, implying that it has a significant role in the preservation of lean body mass. According to researchers, glutamine possesses anabolic properties. These properties are effective in wound healing only when present in amounts 2 to 7 times greater than required in healthy persons (Roth E et al 1990).

**Bromelain.** Bromelain is a proteolytic enzyme derived from pineapple stem. This anti-inflammatory enzyme possesses the ability to break down or dissolve proteins. This property can be utilized to reduce muscle and tissue swelling, especially following injuries or surgery (MacKay D et al 2003). Use of oral bromelain over the postoperative period results in faster resolution of swelling and decreased dependence on analgesics in fracture patients (Kamenicek V et al 2001). Similar results have been recorded after dental surgery (Tassman G et al 1964) and musculoskeletal trauma (Masson M 1995).

**Glucosamine.** Glucosamine provides the raw material needed to repair the connective tissue found in skin, tendons, ligaments, and joints (McCarty MF 1996; Zupanets IA 2002). Animal studies show that levels of glucosamine increase in injured tissue during healing (Lehto M 1985). Although human studies on the effect of glucosamine during wound healing have not yet been published, recent reviews of perioperative nutrition recommend glucosamine 1500 mg daily until healing is complete (MacKay D et al 2003).

**Aloe vera.** The healing properties of aloe vera have been known for centuries. Used as a topical application, aloe stimulates collagen synthesis and has been shown to promote wound healing (Chithra P et al 1998a). Animal studies have demonstrated beneficial effects of aloe vera in healing frostbite, electrical injuries, and diabetes (Miller MB et al 1995; Chithra P et al 1998b; Davis RH et al 1987; Davis RH et al 1988). Aloe vera improves the permeability of cell walls, boosts nutrient influx into the cells, and removes toxins from the cells (Vogler BK et al 1999).

**Curcumin.** An extract of the spice turmeric, curcumin is used to reduce inflammation and treat wounds and skin ulcers. Research shows that it has antioxidant properties and other health benefits (Nirmala C et al 1999). It also improves the formation of new skin and the migration of immune cells that are necessary for healing at the wound site (Sidhu et al 1999). Specifically, it has been shown to enhance muscle regeneration in muscle injury (Thaloor D et al 1999).

**Omega-3 fatty acids.** Omega-3 fatty acids, including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), are anti-inflammatory and have wide-ranging effects. They stimulate the immune system by enhancing T-cell and natural killer cell activity. Because the body's need for fats increases under conditions of stress, the omega-3 fatty acids play an important role in the healing process.

## BOOSTING GROWTH FACTORS

Growth factors are small proteins that enable cells to communicate. There are seven major growth factor families: epidermal growth factor, transforming growth factor-beta, insulin-like growth factor 1, interleukins, platelet-derived growth factor, fibroblast growth factor, and colony-stimulating factors.

Growth factors have a number of functions in wound healing (Steenfos HH 1994):

- Forming granulation tissue
- Increasing connective tissue by creating new blood supply
- Promoting remodeling and growth of new skin
- Attracting proteins and immune cells to fight infection

Studies have shown that various growth factors are diminished after trauma. For instance, serum levels of insulin-like growth factors are decreased during critical illness (Timmins A et al 1996). Nutrients that stimulate the secretion of growth factors may assist

recovery from trauma. Various supplements have been studied for the ability to boost growth factors, including the amino acid arginine, omega-3 fatty acids, and nucleotides (Daly JM 1992).

Arginine, a semiessential amino acid, helps in wound healing and recovery from stress. In addition, arginine enhances the immune response of trauma patients. In a study of healthy people and surgical and intensive care unit patients, arginine was shown to increase lymphocyte and monocyte proliferation and to enhance helper T cell formation (Kirk SJ et al 1990). Arginine also increases intestinal calcium absorption and collagen synthesis.

Ornithine alpha-ketoglutarate (OKG) is a salt formed of two molecules of ornithine and one molecule of alpha-ketoglutaric acid. OKG is a promising anticatabolic agent that promotes wound healing and protein synthesis. Researchers have hypothesized that OKG works by upregulating glutamine and arginine production (Cynober L 1991).

Glutamine supplementation in critically ill patients has been shown to improve gut-associated lymphoid tissue function and enhance the immune defense against infection (Jones C et al 1999).

## LIFE EXTENSION FOUNDATION RECOMMENDATIONS

After an injury, it is very important to maintain an adequate supply of calories to support the increased metabolic state. The following guidelines are suggested:

- 55 percent of calories should come from carbohydrates, mainly complex carbohydrates that can be found in whole-grain foods.
- 20 percent of calories should come from fats. The addition of EPA/DHA omega-3 fatty acids can help supply these essential fatty acids.
- 25 percent of calories should come from protein. The addition of whey protein to the diet can help guarantee that adequate protein is ingested.

It is also very important that trauma patients stay properly hydrated. They should drink plenty of water throughout the day.

In severe wound conditions, physicians sometimes use hyperbaric oxygen therapy.

In addition, the following vitamins and nutrients may aid the healing process:

- **Vitamin A**—5000 to 10,000 international units (IU) daily
- **Vitamin C**—1000 milligrams (mg) daily
- **Zinc**—50 mg daily
- **L-arginine**—9000 to 18,000 mg daily
- **L-ornithine**—1000 mg daily
- **Glutamine**—1000 to 3000 mg daily
- **Bromelain**—500 mg daily
- **Glucosamine** —1500 mg daily
- **Aloe vera**—follow label directions
- **Curcumin**—800 to 1600 mg daily
- **Omega-3 fatty acids**—1400 mg EPA and 1000 mg DHA daily

## TRAUMA SAFETY CAVEATS

An aggressive program of dietary supplementation should not be launched without the supervision of a qualified physician. Several of the nutrients suggested in this protocol may have adverse effects. These include:

### Aloe vera

- Do not ingest aloe vera if you have Crohn's disease, an intestinal obstruction, an acute inflammatory intestinal disorder (such as ulcerative colitis or appendicitis), or any abdominal pain of unknown origin.
- When used as a laxative, aloe vera can cause abdominal pain or discomfort.
- Ingesting aloe vera can cause swelling, kidney disorders, heart irregularities, and bone loss.
- Long-term intake may lead to a potassium deficiency and has been associated with an increased risk of colon cancer.

## **Bromelain**

- Consult your doctor before taking bromelain if you are taking anticoagulants or antithrombotic agents. Bromelain can thin the blood.
- Bromelain can cause gastrointestinal symptoms such as nausea and diarrhea.
- Bromelain can cause bleeding from the uterus between menstrual periods (metrorrhagia) and excessive uterine bleeding during menstruation (menorrhagia).

## **Curcumin**

- Do not take curcumin if you have a bile duct obstruction or a history of gallstones. Taking curcumin can stimulate bile production.
- Consult your doctor before taking curcumin if you have gastroesophageal reflux disease (GERD) or a history of peptic ulcer disease.
- Consult your doctor before taking curcumin if you take warfarin or antiplatelet drugs. Curcumin can have antithrombotic activity.
- Always take curcumin with food. Curcumin may cause gastric irritation, ulceration, gastritis, and peptic ulcer disease if taken on an empty stomach.
- Curcumin can cause gastrointestinal symptoms such as nausea and diarrhea.

## **EPA/DHA**

- Consult your doctor before taking EPA/DHA if you take warfarin (Coumadin). Taking EPA/DHA with warfarin may increase the risk of bleeding.
- Discontinue using EPA/DHA 2 weeks before any surgical procedure.

## **Glucosamine**

- Consult your doctor before taking glucosamine if you have diabetes. It is unknown if glucosamine will increase insulin resistance in humans but glucosamine has been shown to increase insulin resistance in healthy animals and in animals with diabetes. Animals given intravenous glucosamine were found to have a significantly decreased rate of glucose uptake in their skeletal muscle (this effect was not observed, however, in animals given oral glucosamine).
- If you have diabetes, are overweight, or have difficulty with glucose tolerance and take glucosamine under medical advisement, monitor your blood glucose level frequently. Your doctor will need to adjust your medication levels accordingly.
- Glucosamine can cause gastrointestinal symptoms such as nausea and diarrhea.

## **L-Arginine**

- Do not take L-arginine if you have the rare genetic disorder argininemia.
- Consult your doctor before taking L-arginine if you have cancer. L-arginine can stimulate growth hormone.
- Consult your doctor before taking L-arginine if you have kidney failure or liver failure.
- Consult your doctor before taking L-arginine if you have herpes simplex. L-arginine may increase the possibility of recurrence.

## **L-Glutamine**

- Consult your doctor before taking L-glutamine if you have kidney failure or liver failure.
- L-glutamine can cause gastrointestinal symptoms such as nausea and diarrhea.

## **L-Ornithine**

- Do not take L-ornithine if you have an ornithine aminotransferase deficiency.
- High doses of L-ornithine can cause gastrointestinal symptoms such as nausea and diarrhea.

## **Vitamin A**

- Do not take vitamin A if you have hypervitaminosis A.
- Do not take vitamin A if you take retinoids or retinoid analogues (such as acitretin, all-trans -retinoic acid, bexarotene,

etretinate, and isotretinoin). Vitamin A can add to the toxicity of these drugs.

- Do not take large amounts of vitamin A. Taking large amounts of vitamin A may cause acute or chronic toxicity. Early signs and symptoms of chronic toxicity include dry, rough skin; cracked lips; sparse, coarse hair; and loss of hair from the eyebrows. Later signs and symptoms of toxicity include irritability, headache, pseudotumor cerebri (benign intracranial hypertension), elevated serum liver enzymes, reversible noncirrhotic portal high blood pressure, fibrosis and cirrhosis of the liver, and death from liver failure.

## Vitamin C

- Do not take vitamin C if you have a history of kidney stones or of kidney insufficiency (defined as having a serum creatine level greater than 2 milligrams per deciliter and/or a creatinine clearance less than 30 milliliters per minute).
- Consult your doctor before taking large amounts of vitamin C if you have hemochromatosis, thalassemia, sideroblastic anemia, sickle cell anemia, or erythrocyte glucose-6-phosphate dehydrogenase (G6PD) deficiency. You can experience iron overload if you have one of these conditions and use large amounts of vitamin C.

## Zinc

- High doses of zinc (above 30 milligrams daily) can cause adverse reactions.
- Zinc can cause a metallic taste, headache, drowsiness, and gastrointestinal symptoms such as nausea and diarrhea.
- High doses of zinc can lead to copper deficiency and hypochromic microcytic anemia secondary to zinc-induced copper deficiency.
- High doses of zinc may suppress the immune system.

For more information see the Safety Appendix

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