ROADMAP TO RECOVERY

What happens to your body after Surgery or Injury?

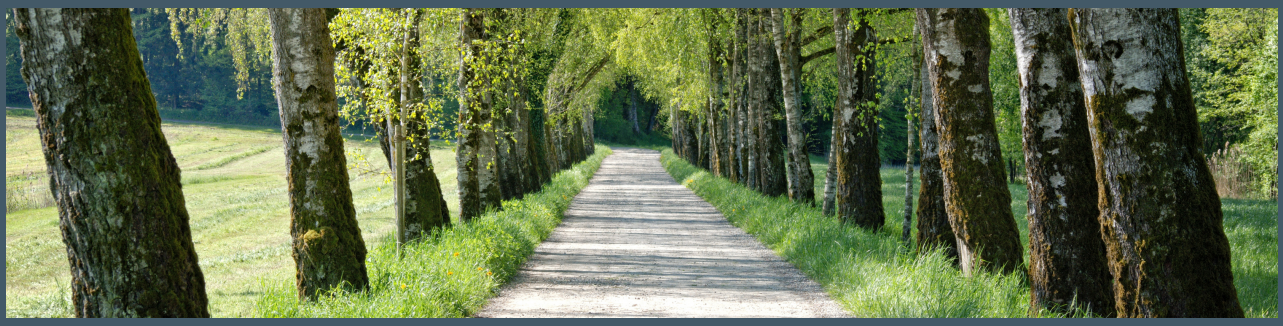
Surgery is a necessity for managing a variety of health conditions including injuries, cardiovascular disease, Cesarean delivery, and cancer.[1] In 2012, almost 313 million operations took place across the world, an increase of over 38% from 2004. The pattern was similar in the United States which accounted for almost 36.5 million of those surgeries in 2012. It is clear then that a significant number of people in the United States will undergo a surgical procedure in any given year and the expenditures associated with these procedures will continue to climb as surgical options increase and patients are unable to work during the period of recovery.

TAKE CONTROL

Surgery, in general, is a disruption to the body and triggers a series of events that are very broadly referred to as the stress response. It is a normal reaction of great importance in both nature and medicine. The natural stress response in man is designed to first protect against threats and is highlighted by the surge of hormones needed to either “fight or run”. This initial response is then followed by a response designed to promote survival, including activation of the immune system to promote wound healing and protect against infection. The surgical stress response has three key components: stimulation of the sympathetic nervous system, activation of endocrine system, and triggering of the immune system. The sympathetic nervous system can be equated to car’s gas pedal.[2] It provides the body with a burst of energy so that it can respond to danger or injury, primarily by releasing the hormone adrenaline into the bloodstream. As adrenaline circulates through the body, the heart beats faster allowing more blood to be delivered to muscles and vital organs. Other changes include dilation of the airways in the lungs so that more oxygen is taken in with every breath and release of glucose (sugar) and fats from storage sites in order to provide needed energy.

Activation of the endocrine system is primarily manifested as hormonal changes including increases in growth hormone, arginine vasopressin, cortisol, and aldosterone and decreases in insulin and thyroxine. The net effect of these hormonal changes can include a slowdown of gut motility; water and salt retention; increased energy expenditure; high glucose levels due to release from storage sites, new production from amino acids broken down from muscle protein, and insulin resistance; increased use of fats as an energy source; and increased tendency toward blood clotting.[3]

A final component of the surgical stress response is activation of the immune system, a necessary factor in recovery and wound healing. In the early postoperative period, innate immune mechanisms (immunity that is naturally present and is not due to prior exposure) are activated leading to an influx of white blood cells into the wound and the production of inflammatory mediators (cytokines and chemokines).[4] If an infectious agent had been encountered by the patient prior to surgery itself, the acquired or adaptive immune system may also be activated. The inflammatory response associated with activation of the immune system is aimed at getting rid of the infectious agent, reducing tissue damage, removal of dead cells, and start of the healing process. A key part of that healing process is an increase in anti-inflammatory agents which reduce the severity and duration of the inflammatory response. Although the stress response is highly protective by design, under certain conditions, such as surgery, instead of the sympathetic, endocrine, and immune activation being self-limiting and restorative, the response can lead to further injury. Factors affecting the likelihood of an injurious response include the magnitude of surgery, the presence of co-existing diseases particularly those affecting the lungs, heart, and kidney (e.g. diabetes), the occurrence of postoperative complications such as bleeding or infection, impaired exercise tolerance before surgery, and malnutrition.



IMPROVING OUTCOMES AND RECOVERY AFTER SURGERY AND INJURY

Over the last decade a substantial amount of research has been completed aimed at reducing perioperative stress, maintaining postoperative function and accelerating recovery after surgery. In many types of surgeries, the use of a multi-pronged approach to reduce surgical stress has been shown repeatedly to decrease rates of complications, improve recovery and shorten hospital length of stay.

PREOPERATIVE STRATEGIES

Smoking – It is well known that the risk of postoperative complications is greater in patients who smoke. In particular, infections and wound, lung, and brain complications are more common in patients who smoke. While smoking cessation for at least 4 weeks is ideal for reducing lung and wound-healing complications, shorter periods prior to surgery may still be beneficial but not to the same degree. After 8 weeks of smoking cessation, the risk is similar to those who have never smoked.

Alcohol abuse – Surgical patients who consume over 4 drinks daily have a 2-3 fold increased risk for postoperative complications (heart, lung infection, wound healing, bleeding and brain) compared to patients who consume less than 2 drinks daily. Preoperative abstinence from alcohol is recommended to reduce postoperative complications but the evidence to support this recommendation is weaker. The duration of abstinence required to reduce alcohol's negative effects varies from 2-8 weeks depending on the organ (e.g. heart vs brain vs liver).[5]

Anemia – Anemia (low red cell blood count) is seen in about 30% of patients presenting for surgery and is a risk factor for complications but so is the administration of blood-products. Optimizing the red cell count before surgery without transfusion is then the best option and this can be done by providing oral or intravenous iron or intravenous erythropoietin (a hormone produced by the kidney that stimulates red blood cell production in the bone marrow).

Exercise – Reduced exercise capacity before surgery is a risk factor for postoperative complications and long-term disability. Exercise training prior to surgery may therefore improve outcomes by allowing the body to tolerate greater levels of stress. Although moderate exercise such as walking might be easier to accomplish given sufficient time, the shorter time period from decision to surgery to actual surgery date means that a supervised high-intensity interval training programs over 3-4 weeks may be the best choice.[6] While it is clear that such exercise will improve functional capacity, studies to determine whether preoperative exercise will change postoperative outcomes are underway but have not been completed.

Nutrition – It is estimated that more than one in every three hospitalized patients is malnourished at admission and that only 3% of these patients are being properly identified and treated. The surgical stress response, which can result in muscle breakdown, increases protein requirements even further. Thus, patients at risk of malnutrition should receive high-protein oral nutritional supplements for 2-4 weeks prior to surgery.[7]

POSTOPERATIVE STRATEGIES

Prevention of nausea and vomiting – Nausea and vomiting after surgery is a common occurrence and may result in dehydration and inadequate nutritional intake leading to a prolonged hospital stay. Female patients, those with a history of nausea/vomiting or motion sickness and non-smokers are at increased risk. Thus, patients with risk factors should ideally be treated prophylactically during surgery with antiemetics (drugs used to prevent or treat nausea/vomiting).

Pain management – Adequate pain control is essential to enhanced recovery after surgery. In general, techniques that avoid or use less opioid drugs result in getting out of bed sooner, faster return of bowel function, fewer complications, and reduced length of stay. Using a combination of drugs (multimodal approach) that rely on several pain reducing mechanisms along with regional anesthesia techniques (spinal/epidural or nerve blocks, when possible) is optimal.

Early mobilization – Prolonged bed rest is associated with greater lung complications, blood clots, higher blood sugars, and decreased muscle strength. Early mobilization is therefore an important component of improving the recovery process. However, just like exercise in the preoperative period, getting out of bed and exercising some as soon as possible after surgery does increase functional capacity but the evidence that it improves outcomes remains mixed with some studies showing benefit but others that showing no change.

Nutritional care – Delays in restarting a normal diet by mouth is known to increase infectious complications and prolong the recovery period. Thus, many (but not all) patients should receive food by mouth from the day of surgery. Even when they are able to eat, the postoperative period is often characterized by lowered overall oral intake. Furthermore, during this recovery period, there is greater breakdown of muscle protein in order to increase the availability of glucose to meet energy needs. Thus, additional oral nutritional supplements are often needed.[8]

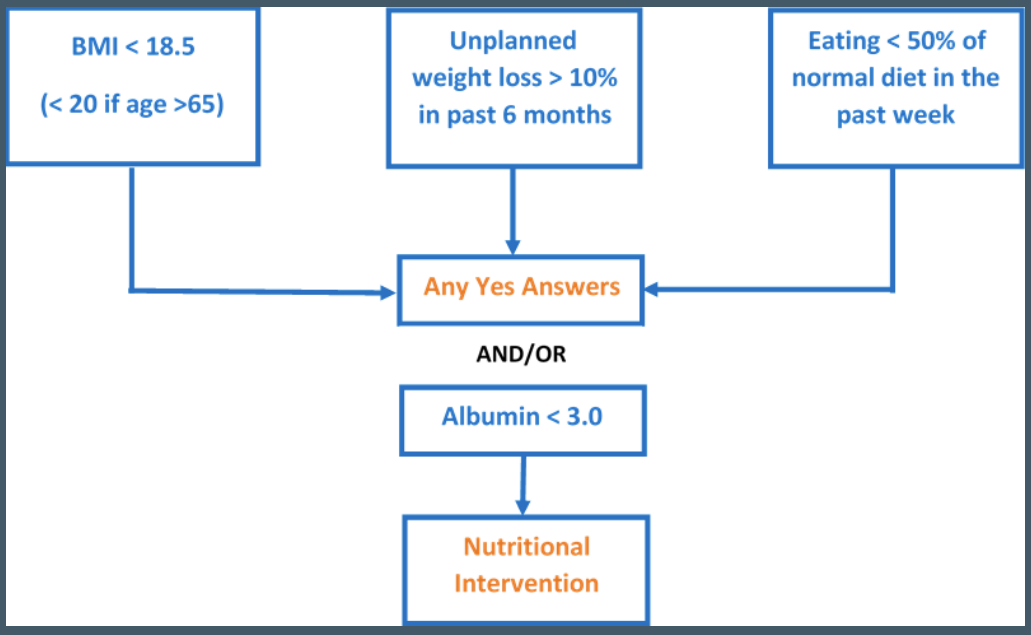
NUTRITION AS A STRATEGY TO OPTIMIZE RECOVERY AFTER SURGERY AND INJURY

THE IMPORTANCE OF PERIOPERATIVE NUTRITION

Patients with poor nutritional status prior to surgery are more likely to suffer complications after surgery including infection and death, have a greater hospital length of stay and cost of hospitalization, and are more likely to be readmitted to the hospital within 30 days after surgery.[9] But it is important to note that malnutrition is one of the few modifiable preoperative risk factors. In fact, nutritional therapy has been shown to improve outcomes in surgeries such as gut or cancer surgery, where there is a greater risk of preoperative malnutrition.

ASSESSMENT OF NUTRITIONAL STATUS BEFORE SURGERY

A number of screening tools are available and the perioperative nutrition screen (PONS – see figure below) is one that is easy to apply in the preoperative period. This tool uses body mass index (BMI - a measure that combines height and weight), recent change in weight, recent decrease in food intake, and preoperative blood albumin level (a rough measure of nutritional state that is commonly tested before surgery). A nutritional intervention is recommended if there are 1 or more positive responses on the PONS.



NUTRITIONAL NEEDS SPECIFIC TO SURGICAL PATIENTS

The surgical stress response results in whole-body catabolism (breakdown of complex molecules to smaller ones). This is seen principally as the wasting of muscle, releasing amino acids to allow the synthesis of proteins known as acute phase reactants and production of glucose needed as an energy source.[10] In addition, perioperative fasting can worsen the surgical stress response, weaken gut function, and amplify protein losses. Thus, patients who are malnourished or undernourished or muscle-depleted are particularly vulnerable and need nutritional supplementation. In brief, nutritional supplements targeting preservation of muscle function, energy production, wound healing, pain, and immune function are key to maximize recovery after surgery.

IMPROVING PERIOPERATIVE NUTRITION

Preoperative – Since protein requirements are increased by the surgical stress response, current recommendations are that patients should receive at least 1.2-2.0 grams of protein/kilogram of body weight/day.[9] Studies show that 25-30 grams of protein in a single meal results in the most protein synthesis and is optimal when repeated multiple times per day.[11] Patients who are screened at risk for poor nutritional status should receive a high-protein oral nutritional supplement containing at least 18 grams protein/dose, 2-3 times/day for a minimum of 7-14 days. In addition, in many (but not all) patients and in order to minimize the detrimental effects of fasting, clear fluids can be taken up to 2 hours prior to anesthesia. Similarly, at least 45 grams of a carbohydrate drink as a clear liquid taken 2-3 hours before surgery may, in many surgeries, improves insulin sensitivity (typically decreased by the surgical stress response) and results in better blood sugar control. The addition of specific nutritional elements such as vitamin D, hydroxymethylbutyrate, zinc, and bromelain, that can reduce postoperative muscle breakdown, support immune function, optimize gut function, and reduce pain and swelling should also be considered.

Postoperative – For most surgeries, early resumption of oral intake is recommended as tolerated. Once again, protein supplementation is needed during the recovery period to maintain lean muscle mass. This can be accomplished using a high-protein diet (1.5-2.0 grams/kilogram of body weight/day) or oral nutritional supplements. Nutritional supplementation, which again include elements like vitamin D, hydroxymethylbutyrate, zinc, and bromelain should continue for a minimum of 4-8 weeks after surgery and possibly up to 3-6 months after surgery in those who are severely malnourished. It is important to remember that the protein intake goal is more important than total calorie intake during this period of healing and recovery.

NUTRITIONAL SUPPLEMENTS TO MAXIMIZE RECOVERY AFTER SURGERY AND INJURY

Understanding the changes produced by the stress response to surgery and injury, we focused on the 5 essential ingredients needed to overcome the nutritional deficits specific to surgery and injury. These 5 supplements discussed below support energy production, strengthening of muscles, immune function, and response to pain – all essential for maximizing recovery from surgery or injury.

BROMELAIN – NUTRITIONAL SUPPORT FOR WOUND HEALING AND PAIN

Normal wound healing

Normal wound healing requires a multidimensional set of interactions with a variety of mediators in the body including immune cells, inflammatory mediators and extracellular macromolecules, such as collagen, enzymes, and glycoproteins, that provide structural and biochemical support to surrounding cells. The goal, of course, is to heal a wound as quickly as possible with the least amount of pain and result in a fine scar with high resistance to disruption under tension (tensile strength). The four phases of normal wound healing include hemostasis, inflammation, proliferation, and remodeling.[12]

The initial phase is the stopping of blood flow which involves both the constriction of blood vessels at the site of the wound as well as the formation of a clot. Blood cells called platelets are an integral part of a blood clot and they secrete a variety of growth factors and inflammatory mediators that initiate the process of tissue repair. The second phase, the inflammatory phase, is characterized by redness, swelling, warmth, and pain and is mediated by an increase in blood vessel permeability which allows white blood cells to migrate into the surrounding tissue to clear debris and bacteria. The proliferative phase follows and is defined by the formation of new blood vessels and connective tissue (especially collagen) and a process by which new skin and mucous membranes replace superficial cells damaged or lost in the wound. The last phase of wound healing is wound remodeling, where the new collagen fibers are reorganized to yield greater tensile strength. This remodeling process can continue for almost two years, although 70% strength is achieved after just four weeks.[13]

What is bromelain?

Bromelain is the name given to a family of proteolytic enzymes that are extracted from the stems and immature fruits of the pineapple plant.[14] Proteolytic enzymes break the long chainlike molecules of proteins into shorter fragments and eventually into their components, amino acids. This enzyme activity is evaluated by how the commercial preparation of bromelain breaks down a compound like gelatin – e.g. gelatin digesting units per gram (GDUs/g). Although the proteolytic activity is responsible for many of its beneficial effects, some of the favorable effects are associated with other components contained in bromelain that are not proteolytic. Bromelain is currently categorized as a dietary supplement, and generally recognized as safe by the U.S. Food and Drug Administration (FDA).

How does bromelain help wound healing?

Bromelain helps with wound healing by 1) reducing existing tissue swelling through the enzymatic breakdown of blood clots, resulting in increased tissue permeability and reabsorption of edema fluid into blood circulation 2) improving the tissue permeability of antibiotic drugs and resulting in higher antibiotic levels 3) stimulation of white blood cells to kill bacteria 4) increasing anti-inflammatory mediators 5) decreasing pain and 6) decreasing healing time.[12, 14] Studies in patients with acute sinusitis, face and head trauma, trauma of the lower extremity, childbirth, and oral surgery support these findings. For example, in dental surgery patients, bromelain was found to decrease swelling in the early and late stages after surgery. In addition, pain was reduced in the treatment group, likely by decreasing mediators of pain.[15] Based on the available evidence, bromelain was approved in Germany for acute post-operative (ENT surgeries) and post-traumatic conditions of swelling.[16]

How does bromelain help pain?

Bromelain has both a direct influence on pain by decreasing pain mediators such as bradykinin, as well as indirect effects through its anti-inflammatory actions (e.g. reduction in edema, debris and immune complexes).[17] Bromelain was first reported to be of value as an analgesic/anti-inflammatory for use in rheumatoid arthritis and osteoarthritic patients in 1964. Subsequent studies have continued to support the use of bromelain to manage pain in patients with osteoarthritis.[18] Bromelain also appears to be effective in reducing swelling, bruising, and pain in women having episiotomy (a surgical cut made at the opening of the vagina during childbirth).[19]

What is the suggested dose of bromelain?

There is no standard dose for bromelain. Recommended dosing generally ranges between 80 and 320 mg/day but because it is relatively nontoxic, daily doses up to 2000 mg have been used. Since the proteolytic activity (and therefore the medicinal effect) of bromelain can degrade based on storage conditions and processing of pineapples, it is not practical to substitute bromelain supplements with oral consumption of raw pineapple fruit.[20] Even though it's extracted from pineapple, eating pineapple or drinking its juice doesn't provide a large enough dose.

HYDROXYMETHYLBUTYRATE (HMB) – ENHANCING RECOVERY BY PRESERVING MUSCLE FUNCTION

What is HMB?

Hydroxymethylbutyrate (HMB) is an active metabolite of the essential amino acid leucine. HMB is found in very small amounts in foods such as avocado, citrus fruit, cauliflower, and catfish.[21] HMB is made from leucine in the muscle and liver cells but only 5% of the leucine is converted to HMB, yielding very small amounts (0.2-0.4 grams in a 70 kg person) on a daily basis.

How does surgery alter muscle function?

The surgical stress response results in whole-body catabolism (breakdown of complex molecules to smaller ones). This is seen principally as the wasting of muscle, releasing amino acids to allow the synthesis of proteins known as acute phase reactants and production of glucose needed as an energy source.[10] In addition, perioperative fasting can worsen the surgical stress response, weaken gut function, and amplify protein losses.

In addition, perioperative fasting can worsen the surgical stress response, weaken gut function, and amplify protein losses. In patients with critical illness who may be also confined to bed rest, a vicious cycle is present with bed rest promoting muscle breakdown and the resultant muscle wasting and weakness preventing much needed ambulation and physical activity. It has been reported that patients in the acute care setting can lose about 2% of their muscle mass per day but with longer hospital stays, they can lose as much as 50% muscle mass.[22] Loss of muscle mass has significant consequences, including muscle weakness, fatigue, risk of pulmonary complications (e.g. longer need for a ventilator, pneumonia), and prolonged hospitalization as a consequence of a slower recovery.

How does HMB work?

The effects of HMB resulting in an improvement of physical performance, stamina, or recovery are related to the inhibition of protein break-down, increased protein synthesis, stimulation of growth hormone, increase of muscle stem cells, and decreased cell death.[23]

Does HMB supplementation alter outcomes?

HMB enhances recovery following exercise training and has been shown to increase lean body mass and functionality in the elderly.[24] In a study evaluating the effect of HMB (3 grams/day) versus placebo in healthy older adults placed on 10 days of complete bed rest, lean body mass was preserved in patients treated with HMB, in contrast to placebo patients, who lost 2 kilograms of body weight.[25] Similarly, in patients undergoing total knee replacement, muscle strength was preserved with HMB supplementation[26] and in patients with a hip fracture, HMB accelerated wound healing, decreased the period of immobility, and increased muscle strength.[27] HMB as part of protein supplementation also resulted in improved nutritional status, muscle strength, and 50% lower mortality at 90-days after-discharge in older malnourished hospitalized patients.[28]

What is the suggested dose of HMB?

The commonly recommended dose of HMB is up to 3 grams per day. However, this amount is difficult to obtain from usual diet because of the low transformation rate of leucine to HMB (see above) and therefore, supplementation is needed. Chronic consumption of HMB appears to be safe in both the young and the elderly and HMB appears to be most effective when taken for at least 2 weeks prior to training.[24]

NADH – A COFACTOR NEEDED FOR ENERGY PRODUCTION

What is NADH?

Nicotinamide adenine dinucleotide (NAD) is a cofactor (a substance whose presence is essential for activity) for a number of cellular processes including energy production, DNA repair, gene expression, antioxidant activity, brain dopamine production, and immunological functions.[29] Because of its role in DNA repair and gene expression, NAD, through its activity on the sirtuin family of enzymes, may play a pivotal role in extending the life of the cell and therefore, slowing the aging process.[30] NAD can exist in two forms: NAD+ and NADH (also referred to as the reduced form of NAD).

How does NADH create energy?

The conversion of NAD+ to NADH, and vice versa, are essential reactions in creating ATP (adenosine triphosphate).[31] ATP is the main carrier of energy that is used for all cellular activities. When ATP is enzymatically converted to adenosine diphosphate (ADP), energy is released. In order to generate ATP, the food that we eat is directed through three processes: glycolysis, the Krebs Cycle, and the electron transport chain. In glycolysis and the Krebs cycle, NADH molecules are formed from NAD+. On the other hand, in the electron transport chain (a series of proteins and organic molecules found in the inner membrane of the mitochondria), all of the NADH molecules are subsequently split into NAD+, H+, and electrons. These electrons are passed from one member of the transport chain to another in a series of reactions and the energy released in these reactions is then used to make ATP. Glycolysis and the Krebs cycle produce 2 ATP molecules each while the electron transport chain transfers energy into as many as 32 ATP molecules.[32]

Health effects of reduced nicotinamide adenine dinucleotide (NADH)

While nicotinamide adenine dinucleotide (NAD+) or reduced nicotinamide adenine dinucleotide (NADH) is an essential metabolic cofactor that is central to energy metabolism, NAD+ concentrations in cells decline with aging and is linked to numerous aging-associated diseases, including loss of muscle tissue and frailty, metabolic disease such as high blood sugar, and cognitive decline.[33] Many of these diseases may be slowed down by replenishing NAD+ levels and therefore, targeting NAD+ levels has emerged as a potential therapeutic approach to moderate ageing-related disease, and extend the human healthspan and lifespan.

Potential health benefits of boosting NAD+ levels vary by body tissue and include:[33-35]

- Brain - Improved brain function and protection from degeneration of the nervous system, especially of neurons in the brain
- Vasculature (blood vessels) - Increased formation of new blood vessels and improved blood flow
- Liver - Improved liver function and reduced fatty liver disease
- Muscle - Reduced atrophy, enhanced mitochondrial function (energy production), increased insulin sensitivity and increased physical activity
- Pancreas - Increased insulin secretion and reduced inflammation
- Fat tissue - Reduced dyslipidemia (defined as elevated total or low-density lipoprotein cholesterol levels, or low levels of high-density lipoprotein cholesterol) and prevention of insulin resistance
- Inflammageing (age-related increase in the levels of pro-inflammatory markers in blood and tissues) - Reduced inflammation and improved immune cell function

Strategies that boost NAD+ levels include lifestyle changes, such as increasing exercise, reducing number of calories consumed, eating a healthy diet and following a consistent daily pattern of healthy sleeping habits and mealtimes. Another approach is the use of inhibitors or activators to boost NAD+ production and the use of dietary supplements.[33]

Does NADH supplementation alter outcomes?

The majority of the current data are from animal studies where increasing NAD levels has been shown to improve mitochondrial (location where energy production occurs) function, waste disposal, and DNA repair while decreasing oxidative stress, inflammation, and aging.[36] In a small study of patients with Chronic Fatigue Syndrome, NADH was shown to reduce fatigue.[37] In disorders of brain aging such as Parkinson's Disease, NADH supplementation improved disabilities related to movement.[30, 36] Similarly, NADH may improve cognitive function.[30, 36] Several clinical studies have shown promising results but others have shown little or no benefit, suggesting that benefits may be highest in those with low tissue NAD+ concentration at baseline. In a recent, 10-week, randomized, placebo-controlled, double-blind study (highest quality study), increasing NAD+ levels improved skeletal muscle insulin signaling and sensitivity in postmenopausal prediabetic women who were overweight or obese.[38] An addition benefit was that genes related to muscle remodeling and regeneration were also up-regulated. These findings demonstrate the safety and effectiveness of NAD+ supplementation, although additional research is needed.

What is the suggested dose of NADH?

Although higher doses have been safely administered, common dosing ranges from 5-20 milligrams per day.

THE IMPORTANCE OF VITAMIN D FOR MUSCULOSKELETAL HEALTH

What is vitamin D?

Vitamin D is a fat-soluble vitamin that is naturally found in a few foods and also produced by the body when ultraviolet (UV) rays from sunlight start the formation of vitamin D in the skin.[39] In foods and dietary supplements, vitamin D has two main forms, D2 (ergocalciferol) and D3 (cholecalciferol), that differ only in their chemical structures. However, the majority of evidence indicates that vitamin D3 raises blood levels to a greater extent and maintains these higher levels longer than vitamin D2, even though both forms are well absorbed in the gut.[40] Most people are also able to get some of their vitamin D needs through exposure to sunlight. Type B UV (UVB) radiation in sunlight penetrates uncovered skin and converts 7-dehydrocholesterol in the skin to previtamin D3, which then becomes vitamin D3. UVB radiation does not penetrate glass, however, so exposure to sunshine indoors through a window does not produce vitamin D. Older people and people with dark skin are less able to produce vitamin D from sunlight.[41]

What are the functions of vitamin D?

Vitamin D supports calcium absorption in the gut and maintains adequate blood levels of calcium and phosphate to allow the normal bone development process of deposition of minerals on the bone matrix. It is also needed for bone growth and bone remodeling, following injury. In addition, Vitamin D is involved in the reduction of inflammation as well as regulation of neuromuscular and immune function, and glucose metabolism.[41] Finally, Vitamin D is needed for the normal development and growth of muscle fibers and low vitamin D levels can negatively affect muscle strength and lead to muscle weakness, fatigue, and pain.[41, 42]

Does vitamin D supplementation alter outcomes?

Although there is considerable debate over the definitions, Vitamin D deficiency is defined by the Endocrine Society as a level < 20 ng/ml while Vitamin D insufficiency is defined as a level of 21–29 ng/ml.[43] Applying these definitions, the occurrence of vitamin D insufficiency in the general population is as high as 50 to 80%.[44] A systematic review of studies examining Vitamin D levels and outcomes after surgery reported that the majority (but not all) the studies showed significantly worse outcome in patients with low vitamin D status.[45] In a small study, preoperative supplementation of Vitamin D in spine surgery patients decreased inflammation and the intensity of pain after surgery.[46] Vitamin D supplementation might also play an important role in prevention of skeletal muscle injuries following exercise.[47, 48]

What is the suggested dose of Vitamin D?

The Food and Nutrition Board at the National Academies of Sciences, Engineering, and Medicine has established that the maximum daily intake unlikely to cause adverse health effects (i.e. upper limit) for adults older than 18 years is 100 micrograms or 4000 International Units.[39]

ZINC – A NUTRITIONALLY ESSENTIAL MINERAL FOR IMMUNITY AND WOUND HEALING

What is zinc?

Zinc is the second most abundant trace metal in the human body with a total amount in the body of 2-4 grams. Zinc levels are higher in the bone and eyes than in the blood and since zinc cannot be stored, it has to be taken up daily from food or as a nutritional supplement in order to assure a sufficient supply. Foods that contain zinc include oysters, red meat, poultry, beans, nuts, seafood (crab, lobster), and whole grains. Zinc deficiency is very common with almost 2 billion people being affected worldwide, particularly in developing countries. Even in developed countries, zinc deficiency is common in the elderly.[49]

What are the functions of zinc?

Zinc is involved in numerous processes including growth and development, stabilization of cell membranes, cell proliferation and cell death, protein synthesis, DNA formation, > 300 enzymatic reactions, immune function, and wound healing.[50]

With regards to immune function in the period early after surgery, injury, or sports, innate immune mechanisms (immunity that is naturally present and is not due to prior exposure) are activated leading to an influx of white blood cells into the wound and the production of inflammatory mediators (cytokines and chemokines).[4] If an infectious agent had been encountered by the patient prior to surgery itself, the acquired or adaptive immune system may also be activated. Zinc deficiency decreases the activity of the cells of the innate immune system, including granulocytes, monocytes, and macrophages resulting in weakening of important immune functions such as chemoattraction (movement of immune cells toward the site of infection) and phagocytosis (process by which immune cells engulf other bacteria or other infectious particles) or cytotoxicity (killing of infected cells).[51] Zinc deficiency also impairs the cells (T-cells, B-cells) of the adaptive immune system by inducing a decrease in the numbers of these cells and in antibody production.[50]

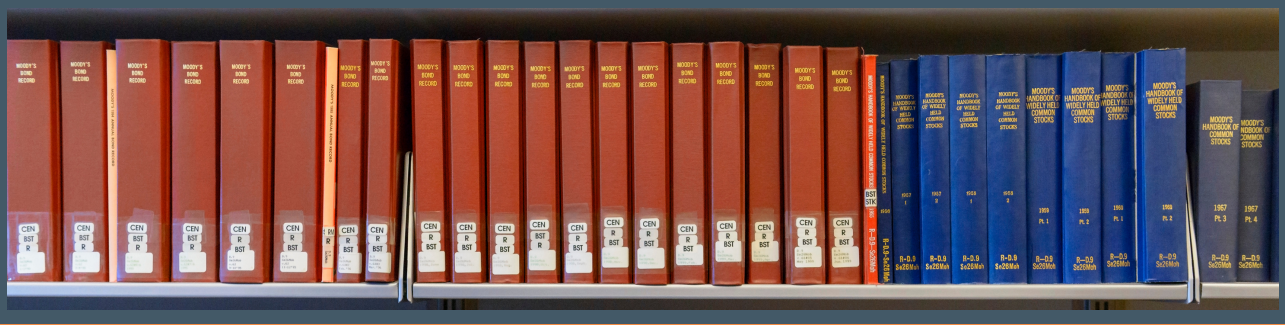
Zinc also plays a major role in regulating every phase of the wound healing process including blood coagulation, immune response and inflammation, repair of cell membranes, restoration of skin tissue, formation of new blood vessels, and scar formation.[52] It is required for collagen and protein synthesis and cell proliferation - essential elements for tissue regeneration.

What is the suggested dose of zinc?

The recommended dietary allowance for adult men and women is 11 mg/day and 8 mg/day of zinc, respectively. The Upper Intake Level (maximum daily intake unlikely to cause harmful effects on health) for zinc is 40 mg daily for all males and females over 19 years of age.[53]

REFERENCES:

1. Weiser TG, Haynes AB, Molina G, et al. Size and distribution of the global volume of surgery in 2012. Bull World Health Organ. Mar 1 2016;94(3):201-209F. doi:10.2471/BLT.15.159293
2. Understanding the stress response. Accessed April 4, 2020. https://www.health.harvard.edu/staying-healthy/understanding-the-stress-response
3. Barber MD, Fearon KCH. The physiological response to surgical trauma. In: Dunn GP, Johnson AG, eds. Surgical Palliative Care. Oxford University Press; 2004.
4. Dabrowska AM, Slotwinski R. The immune response to surgery and infection. Cent Eur J Immunol. 2014;39(4):532-7. doi:10.5114/ceji.2014.47741
5. Bradley KA, Rubinsky AD, Sun H, et al. Alcohol screening and risk of postoperative complications in male VA patients undergoing major non-cardiac surgery. J Gen Intern Med. Feb 2011;26(2):162-9. doi:10.1007/s11606-010-1475-x
6. Whittle J, Wischmeyer PE, Grocott MPW, Miller TE. Surgical Prehabilitation: Nutrition and Exercise. Anesthesiol Clin. Dec 2018;36(4):567-580. doi:10.1016/j.anclin.2018.07.013
7. Williams DGA, Molinger J, Wischmeyer PE. The malnourished surgery patient: a silent epidemic in perioperative outcomes? Curr Opin Anaesthesiol. Jun 2019;32(3):405-411. doi:10.1097/ACO.0000000000000722
8. Gustafsson UO, Scott MJ, Hubner M, et al. Guidelines for Perioperative Care in Elective Colorectal Surgery: Enhanced Recovery After Surgery (ERAS((R))) Society Recommendations: 2018. World J Surg. Mar 2019;43(3):659-695. doi:10.1007/s00268-018-4844-y



9. Wischmeyer PE, Carli F, Evans DC, et al. American Society for Enhanced Recovery and Perioperative Quality Initiative Joint Consensus Statement on Nutrition Screening and Therapy Within a Surgical Enhanced Recovery Pathway. Anesth Analg. Jun 2018;126(6):1883-1895. doi:10.1213/ANE.0000000000002743
10. Gillis C, Wischmeyer PE. Pre-operative nutrition and the elective surgical patient: why, how and what? Anaesthesia. Jan 2019;74 Suppl 1:27-35. doi:10.1111/anae.14506
11. Paddon-Jones D, Campbell WW, Jacques PF, et al. Protein and healthy aging. Am J Clin Nutr. Jun 2015;101(6):1339S-1345S. doi:10.3945/ajcn.114.084061
12. MacKay D, Miller AL. Nutritional support for wound healing. Altern Med Rev. Nov 2003;8(4):359-77.
13. Stadelmann WK, Digenis AG, Tobin GR. Physiology and healing dynamics of chronic cutaneous wounds. Am J Surg. Aug 1998;176(2A Suppl):26S-38S. doi:10.1016/s0002-9610(98)00183-4
14. Maurer HR. Bromelain: biochemistry, pharmacology and medical use. Cell Mol Life Sci. Aug 2001;58(9):1234-45. doi:10.1007/PL00000936
15. Liu S, Zhao H, Wang Y, Zhao H, Ma C. Oral Bromelain for the Control of Facial Swelling, Trismus, and Pain After Mandibular Third Molar Surgery: A Systematic Review and Meta-Analysis. J Oral Maxillofac Surg. Aug 2019;77(8):1566-1574. doi:10.1016/j.joms.2019.02.044
16. Herbal Medicine: Expanded Commission E. Accessed May 26, 2020. http://cms.herbalgram.org/expandedE/Bromelain.html?ts=1590527157&signature=fee9d442ff048493e9faabc463894a68
17. Brien S, Lewith G, Walker A, Hicks SM, Middleton D. Bromelain as a Treatment for Osteoarthritis: a Review of Clinical Studies. Evid Based Complement Alternat Med. Dec 2004;1(3):251-257. doi:10.1093/ecam/neh035
18. Akhtar NM, Naseer R, Farooqi AZ, Aziz W, Nazir M. Oral enzyme combination versus diclofenac in the treatment of osteoarthritis of the knee--a double-blind prospective randomized study. Clin Rheumatol. Oct 2004;23(5):410-5. doi:10.1007/s10067-004-0902-y
19. Howat RC, Lewis GD. The effect of bromelain therapy on episiotomy wounds--a double blind controlled clinical trial. J Obstet Gynaecol Br Commonw. Oct 1972;79(10):951-3. doi:10.1111/j.1471-0528.1972.tb12194.x

20. Muhammad ZA, Ahmad T. Therapeutic uses of pineapple-extracted bromelain in surgical care - A review. J Pak Med Assoc. Jan 2017;67(1):121-125.
21. Landi F, Calvani R, Picca A, Marzetti E. Beta-hydroxy-beta-methylbutyrate and sarcopenia: from biological plausibility to clinical evidence. Curr Opin Clin Nutr Metab Care. Jan 2019;22(1):37-43. doi:10.1097/MCO.0000000000000524
22. Hasselgren PO. beta-Hydroxy-beta-methylbutyrate (HMB) and prevention of muscle wasting. Metabolism. Jan 2014;63(1):5-8. doi:10.1016/j.metabol.2013.09.015
23. Kaczka P, Michalczyk MM, Jastrzab R, Gawelczyk M, Kubicka K. Mechanism of Action and the Effect of Beta-Hydroxy-Beta-Methylbutyrate (HMB) Supplementation on Different Types of Physical Performance - A Systematic Review. J Hum Kinet. Aug 2019;68:211-222. doi:10.2478/hukin-2019-0070
24. Wilson JM, Fitschen PJ, Campbell B, et al. International Society of Sports Nutrition Position Stand: beta-hydroxy-beta-methylbutyrate (HMB). J Int Soc Sports Nutr. Feb 2 2013;10(1):6. doi:10.1186/1550-2783-10-6
25. Deutz NE, Pereira SL, Hays NP, et al. Effect of beta-hydroxy-beta-methylbutyrate (HMB) on lean body mass during 10 days of bed rest in older adults. Clin Nutr. Oct 2013;32(5):704-12. doi:10.1016/j.clnu.2013.02.011
26. Nishizaki K, Ikegami H, Tanaka Y, Imai R, Matsumura H. Effects of supplementation with a combination of beta-hydroxy-beta-methyl butyrate, L-arginine, and L-glutamine on postoperative recovery of quadriceps muscle strength after total knee arthroplasty. Asia Pac J Clin Nutr. 2015;24(3):412-20. doi:10.6133/apjcn.2015.24.3.01
27. Ekinci O, Yanik S, Terzioglu Bebitoglu B, Yilmaz Akyuz E, Dokuyucu A, Erdem S. Effect of Calcium beta-Hydroxy-beta-Methylbutyrate (CaHMB), Vitamin D, and Protein Supplementation on Postoperative Immobilization in Malnourished Older Adult Patients With Hip Fracture: A Randomized Controlled Study. Nutr Clin Pract. Dec 2016;31(6):829-835. doi:10.1177/0884533616629628

28. Deutz NE, Matheson EM, Matarese LE, et al. Readmission and mortality in malnourished, older, hospitalized adults treated with a specialized oral nutritional supplement: A randomized clinical trial. Clin Nutr. Feb 2016;35(1):18-26. doi:10.1016/j.clnu.2015.12.010
29. Braidy N, Berg J, Clement J, et al. Role of Nicotinamide Adenine Dinucleotide and Related Precursors as Therapeutic Targets for Age-Related Degenerative Diseases: Rationale, Biochemistry, Pharmacokinetics, and Outcomes. Antioxid Redox Signal. Jan 10 2019;30(2):251-294. doi:10.1089/ars.2017.7269
30. Braidy N, Liu Y. NAD+ therapy in age-related degenerative disorders: A benefit/risk analysis. Exp Gerontol. Apr 2020;132:110831. doi:10.1016/j.exger.2020.110831
31. Canto C, Menzies KJ, Auwerx J. NAD(+) Metabolism and the Control of Energy Homeostasis: A Balancing Act between Mitochondria and the Nucleus. Cell Metab. Jul 7 2015;22(1):31-53. doi:10.1016/j.cmet.2015.05.023
32. Melkonian EA, Schury MP. Biochemistry, Anaerobic Glycolysis. StatPearls. 2020.
33. Covarrubias AJ, Perrone R, Grozio A, Verdin E. NAD(+) metabolism and its roles in cellular processes during ageing. Nat Rev Mol Cell Biol. Feb 2021;22(2):119-141. doi:10.1038/s41580-020-00313-x
34. Hepler C, Bass J. Supplements to treat prediabetes. Science. Jun 11 2021;372(6547):1147-1148. doi:10.1126/science.abj0764
35. Katsyuba E, Romani M, Hofer D, Auwerx J. NAD(+) homeostasis in health and disease. Nat Metab. Jan 2020;2(1):9-31. doi:10.1038/s42255-019-0161-5
36. Lautrup S, Sinclair DA, Mattson MP, Fang EF. NAD(+) in Brain Aging and Neurodegenerative Disorders. Cell Metab. Oct 1 2019;30(4):630-655. doi:10.1016/j.cmet.2019.09.001
37. Forsyth LM, Preuss HG, MacDowell AL, Chiazze L, Jr., Birkmayer GD, Bellanti JA. Therapeutic effects of oral NADH on the symptoms of patients with chronic fatigue syndrome. Ann Allergy Asthma Immunol. Feb 1999;82(2):185-91. doi:10.1016/S1081-1206(10)62595-12
38. Yoshino M, Yoshino J, Kayser BD, et al. Nicotinamide mononucleotide increases muscle insulin sensitivity in prediabetic women. Science. Jun 11 2021;372(6547):1224-1229. doi:10.1126/science.abe9985

39. NIH. Vitamin D Fact Sheet for Health Professionals. Accessed March 14, 2021. https://ods.od.nih.gov/factsheets/VitaminD-HealthProfessional/
40. Logan VF, Gray AR, Peddie MC, Harper MJ, Houghton LA. Long-term vitamin D3 supplementation is more effective than vitamin D2 in maintaining serum 25-hydroxyvitamin D status over the winter months. Br J Nutr. Mar 28 2013;109(6):1082-8. doi:10.1017/S0007114512002851
41. Medicine IO. Dietary Reference Intakes for Calcium and Vitamin D. The National Academies Press; 2011:1132.
42. Sinha A, Hollingsworth KG, Ball S, Cheetham T. Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. J Clin Endocrinol Metab. Mar 2013;98(3):E509-13. doi:10.1210/jc.2012-3592
43. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. Jul 2011;96(7):1911-30. doi:10.1210/jc.2011-0385
44. Rosen CJ. Clinical practice. Vitamin D insufficiency. N Engl J Med. Jan 20 2011;364(3):248-54. doi:10.1056/NEJMcp1009570
45. Iglar PJ, Hogan KJ. Vitamin D status and surgical outcomes: a systematic review. Patient Saf Surg. 2015;9:14. doi:10.1186/s13037-015-0060-y
46. Krasowska K, Skrobot W, Liedtke E, et al. The Preoperative Supplementation With Vitamin D Attenuated Pain Intensity and Reduced the Level of Pro-inflammatory Markers in Patients After Posterior Lumbar Interbody Fusion. Front Pharmacol. 2019;10:527. doi:10.3389/fphar.2019.00527
47. Pilch W, Kita B, Piotrowska A, et al. The effect of vitamin D supplementation on the muscle damage after eccentric exercise in young men: a randomized, control trial. J Int Soc Sports Nutr. Nov 11 2020;17(1):53. doi:10.1186/s12970-020-00386-1
48. Zebrowska A, Sadowska-Krepa E, Stanula A, et al. The effect of vitamin D supplementation on serum total 25(OH) levels and biochemical markers of skeletal muscles in runners. J Int Soc Sports Nutr. Apr 9 2020;17(1):18. doi:10.1186/s12970-020-00347-8
49. Maywald M, Wessels I, Rink L. Zinc Signals and Immunity. Int J Mol Sci. Oct 24 2017;18(10)doi:10.3390/ijms18102222

50. Bonaventura P, Benedetti G, Albarede F, Miossec P. Zinc and its role in immunity and inflammation. Autoimmun Rev. Apr 2015;14(4):277-85. doi:10.1016/j.autrev.2014.11.008
51. Maares M, Haase H. Zinc and immunity: An essential interrelation. Arch Biochem Biophys. Dec 1 2016;611:58-65. doi:10.1016/j.abb.2016.03.022
52. Lin PH, Sermersheim M, Li H, Lee PHU, Steinberg SM, Ma J. Zinc in Wound Healing Modulation. Nutrients. Dec 24 2017;10(1)doi:10.3390/nu10010016
53. Zinc. Accessed May 14, 2020, https://ods.od.nih.gov/factsheets/Zinc-HealthProfessional/

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