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HealFast

Clinical Nutrition for Surgical and Injury Recovery

HealFast Products, Inc.
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Introduction to Clinical Nutrition for Surgery and Injury

Decades of scientific literature demonstrate that adequate nutrition and optimal outcomes are linked, not only to complications and major morbidity, but also to mortality. Undernourished pre-operative nutritional status has been linked consistently to an increase in post-operative complications including surgical site infections, longer hospital stays, slower wound healing, higher rate of mortality, amongst other complications.

Over 15 different meta analyses of trials suggest that perioperative administration of nutritional formulae contribute to a decreased rate of these same postoperative complications and consequently to a decreased length of stay in the hospital. Nutritional supplementation, however, is often underutilized in the U.S. healthcare system. There are a variety of potential reasons for this trend including questionable safety of some available ingredients, lack of nutritional training amongst providers, lack of resources and time, financial complexity in instituting proper nutrition care, concerns over lack of regulation in the over-the-counter market, and potential interactions with peri-operative and peri-trauma processes and prescribed medications with some supplement ingredients.

However, research has repeatedly demonstrated that utilizing nutritional management in the healthcare setting has high capacity for potential benefits and we believe that nutritional supplementation can address a significant unmet need by providing nutritional products that contain elements targeted to address specific clinical processes. Nutritional therapy also has the potential to be a cost-effective intervention to improve patient outcomes and avoid costly complications at low risk to the patient if formulated properly. Supplements formulated for clinical use, however, must utilize elements, dosages, and routes of administration that are validated by evidence-based research while avoiding compounds with documented adverse effects or interactions in the perio-operative and peri-injury periods. We note that given the variability in quality in the current supplement market, nutritional supplements manufactured for clinical uses need to utilize high grade, high fidelity ingredients, and be responsibly sourced and properly verified for purity and content. These supplements also need to be compounded by a qualified and reputable manufacturer in an FDA registered facility that utilizes Good Manufacturing Practice (GMP) standards and undergo extensive testing preferably by a third-party lab independent of the manufacturer.

We believe that the advantage of clinical nutrition to the patient cannot be ignored. Current challenges in the industry can be addressed with meticulous evidence-based formulation and education. This White Paper introduces to the reader the topic of clinical nutrition, it's challenges, and the scientific evidence. We aim to describe the clinical need to optimize nutrition in the

peri-operative and peri-traumatic periods and to describe the current challenges and concerns in the field of oral nutritional supplementation. We will then review the ingredients with the strongest scientific publication support that may be beneficial for a healing patient while providing a minimal risk profile.

In Summary:

- There is a clear link between optimized nutrition and clinical outcomes
- Large amount of scientific evidence suggests that perioperative administration of nutritional formulae contribute to a decreased rate of complications
- Nutritional supplementation is under-utilized in the healthcare
- There is a lack of high quality, medical grade nutritional supplements on the market
- There is large variability and safety in over-the-counter supplements
- Supplements made for clinical use need to be based on rigorous scientific evidence, utilizing elements, forms, and dose of ingredients with scientific backing
- Supplements for clinical use should undergo extensive facility testing, and be produced in accordance with FDA and GMP standards

The Need to Optimize Nutrition in a Clinical Setting

Nutritional status can have a profound effect on recovery in surgical and injury patients. This idea was first reported in 1930s, when a study showed that undernourished patients undergoing ulcer surgery had a risk of dying 10 times higher when compared with well-nourished individuals.[1]

In 1990s, a follow up prospective study of 500 patients that included 200 surgical patients, admitted to university hospital, found that 40% of patients were undernourished at the time of admission.[2] In another, separate eleven-year retrospective study, malnutrition rates were estimated to be up to 62% among the inpatient population.[3] These findings conclude that malnutrition or nutritional insufficiency is very common in clinical setting across the healthcare settings.

Undernourished pre-operative nutritional status has since been linked consistently to an increase in post-operative complications, such as surgical site infection, longer hospital stays, slow wound healing, higher rate of mortality, and other surgical outcomes.[4,5] On the other hand, there have also been studies that have shown that oral nutritional supplementation can reduce these very same complications, including length of stay (LOS), patient episode cost, and readmission rates.[3]

Surgical intervention itself is a complex set of processes which can result in derangements in physiological and metabolic responses, and can include decreased immunity, increased inflammation, high levels of stress hormones, increased breakdown of tissue and decreased

creation of new tissue. These changes contribute to increased protein and energy requirements after surgical intervention. When combined with prolonged preoperative and postoperative fasting and bowel preps, these factors may even increase the risk of poor post-operative nutrition status and lead to worse outcomes in relatively nourished individuals.[6]

Repleting patients with key nutrients prior to surgery and supporting their nutrition following surgery, may help patients prepare for the stress of surgical intervention and aid in a quicker post-operative recovery. In the eleven-year retrospective study mentioned above, oral nutritional supplementation prior to the procedure reduced LOS by 2.3 days, decreased episode cost by $4,734, and reduced probability of readmissions within 30 days by up to 6.9%.[3]

Nutrition Support Is Often Overlooked by HealthCare Providers

Decades of literature demonstrate that adequate nutrition and optimal outcomes are clearly linked, not only to complications and major morbidity, but also to mortality. In a recent Swiss-Austrian survey of 176 surgical departments, the faculty was asked to give opinions regarding potential benefits and use of nutrition in surgical practice. Nearly 80% of the senior leadership agreed that attention to nutrition would decrease surgical complications and 59% felt that attention to nutrition could shorten hospital stay. Despite this overwhelming affirmation that appropriate nutrition therapy can decrease complications and hospital stay, only 20% of the surgeons surveyed implemented routine screening. When asked why they did not implement routine screening, 33% responded that logistical issues were too complex and 49% felt that financial issues prevented adequate screening and intervention.[199]

In fact, surgeons and anesthesiologists routinely advise their patients to stop nutritional supplements at least two weeks prior to scheduled surgery.[7] This is due, in part, to the popularity of complementary and alternative medical treatments such as herbal remedies and their potential to have serious and potentially harmful side effects when combined with medications commonly prescribed in the perioperative and peri-trauma periods. However, there are many micro and macronutrients that are of critical importance in aiding the healing process that do not have these significant interactions and complications similar to those of herbal alternatives. Interestingly, only a few products using these ingredients exist in the market today. This is especially alarming and warrants closer evaluation given the quantity of scientific research highlighting the importance and benefits of peri-operative nutritional support.[8,9]

15 different meta analyses of trials suggest that peri-operative administration of nutritional formulae have contributed to a decreased rate of postoperative complications and consequently to a decreased length of stay in the hospital.[176-198]

In the peri-operative time frame, physicians rarely have time or adequate training to advise their patients on when or how to apply nutrition to support recovery. Nutritional supplementation, however, is a cost-effective therapy, making it inexpensive to provide with the potential to improve patient outcomes and avoid costly complications, at low risk to the patient.[1]

Accounting for the high incidence of malnutrition and undernutrition, specifically among surgical and injury patients, improving patient outcomes with supplementation would come at a low cost to healthcare providers.[1] In effect, this could help decrease health care spending while improving quality of care provided.[1] Given upcoming regulations, such as Medicare Access and CHIP Reauthorization Act of 2015 (MACRA) and Merit-based Incentive Payment System (MIPS), higher emphasis will be placed on providing quality care and reducing complications. Although there is typically little financial incentive, training, or personnel needed for lifestyle modifications and nutrition management, in light of these new policies and incentives healthcare practitioners may be further encouraged to seek out opportunities to reduce complications and potentially in-hospital length of stay. One high potential intervention involves nutritional management.

Key Nutrients to Support Injury and Surgical Healing

Surgery and injury elicits a series of reaction including release of stress hormones and inflammatory mediators, such as cytokines. Cytokine response to infection and injury has major impact on metabolism and includes catabolism of glycogen, fat, and protein with release of glucose, fatty acids, and amino acids into the circulation. The release of these substrates diverts them from their normal purpose of maintaining peripheral protein (such as muscle) mass, to the tasks of healing and immune response.[162-163] The consequence of catabolism is loss of muscle mass, which is crucial to both a short and long term functional recovery. Nutritional therapy may thus provide substrate and the energy for optimal healing and recovery and may slow down catabolic processes that lead to reduction in patient functional status.

Largely, surgical and injury related tissue healing is an anticipated drain on a patient's nutritional stores. Preloading with appropriate vitamins, minerals, amino acids, antioxidants, anti-inflammatories, probiotics, and trace minerals can better optimize a patient for the physiologic and metabolic stress that co-occurs with these processes. We, however, must note in our review that certain elements are best purposed pre-operatively, and some are most needed post-operatively; thus it is valuable to have differentiate the unique pre and post-operative

regimens that also take into consideration commonly used peri-operative processes, medications, events and anesthetics.

Reviewed below are the most studied nutrients that have a role in the peri-operative and peri-traumatic period. They are listed without particular order and serve as brief introductions since including all evidence on these ingredients would extend the review beyond the scope of this White Paper.

Additionally, the below discussion is purposefully focused on most evidence based, low risk ingredients. There are a number of common ingredients that may have a deleterious roles in the peri-operative and peri-traumatic period. For example, Gingko biloba, Garlic, Ginseng, Fish oil, Dong quai, and Feverfew may increase bleeding risk. Ephedra and Garlic may increase cardiovascular risk. Kava, St. John's wort, and Valerian root commonly interact with intraoperative anesthetics; and Licorice, St John's wort, Kava, Valerian, Echinacea, and Goldenseal have high potential to interact with perioperative medications. Further common Vitamins contained even in the common daily multivitamin, such as Vitamin E and Vitamin K, may post a challenges for coagulation and bleeding around time of surgery and juries.

Additionally, there are several ingredients that may be potentially beneficial in the perioperative period, namely nucleotides and omega acids, however, current studies have had mixed results, and some even suggested these to be harmful in certain circumstances. More research on these ingredients are required to further determine their roles in clinical nutrition and thus they are not discussed below..

Although not discussed explicitly below, it should be noted that more than a single form of a specific compound may exist and that all forms may not necessarily be equal in terms of physiological effect. For example, a compounds such as copper or zinc have several specific formulations with different bioavailabilities and absorption profiles resulting in different physiological actions. Some ingredients, such as the probiotics, have specific subgroups, in this case, strains, of which some are helpful to the healing and recovery process and some are not. These details are relatively well studied, but are also beyond the scope of this review.

Vitamin C

Vitamin C supplementation perioperatively or during peri-injury period is highly recommended since Vitamin C promotes healing by various mechanisms including partaking an essential role in collagen formation, providing support for the immune system, and acting as a tissue antioxidant and free-radical scavenger.

According to the U.S. Centers for Disease Control and Prevention's most recent National Report on Biochemical Indicators of Diet and Nutrition in the U.S. Population, approximately 6% of the US populations is already deficient in Vitamin C.[12] Surgical intervention further compounds the problem by lowering blood Vitamin C concentration. This reduction in Vitamin C levels is postulated to occur due to increased oxidative stress and as well as redistribution.

Decreased Vitamin C levels are significant particularly due to the fact that Vitamin C acts as an antioxidant thereby protecting cells from damage caused by free radicals which abound in times of tissue stress. Further, Vitamin C is needed for normal immune system function, iron absorption and production of collagen matrix, which is are all critical process in wound healing. Due to its many biochemical functions, Vitamin C is considered not only an essential micronutrient for maintaining health, but also an important therapeutic supplement in a variety of clinical conditions, including surgical and injury processes.[10, 11]

In a small study of patients who underwent uncomplicated gastrectomy for gastric cancer, blood concentration of Vitamin C decreased post-operatively and the reduction remained significant for seven days following surgery.[13] It was further noted that if there were associated post-operative complications Vitamin C levels are reduced even further. Although normal baseline physiological functioning requires Vitamin C for optimal metabolism, it was shown that doses much higher than the recommended daily allowance may be needed to normalize plasma and tissue Vitamin C concentration in post-operative patients.

As the body cannot synthesize Vitamin C, the main source of Vitamin C is from consumption of fruits, vegetables and plant foods.[14] Intake of these foods to the level need for recovery is often impossible in the perio-operative or peri-injury period. We note that relatively high doses of supplemental Vitamin C, combined with other trace elements, have been shown to dramatically accelerate wound healing, in some as much as 50%.

Most multivitamin preparations available in the U.S. contain approximately 200 mg of Vitamin C. However, in uncomplicated surgery patients, more than 500 milligrams per day of Vitamin C supplementation may be required to support wound healing. Further, Vitamin C can have additional impact on other physiological functions, for example, in cardiac surgery patients, Vitamin C supplementation may prevent post-operative atrial fibrillation.[15,16] Recently, it was shown that oral Vitamin C supplementation, in association with beta-blockers, is even more effective in preventing post-operative atrial fibrillation than beta-blockers alone.[17,18]

Roles of Vitamin C are truly multifaceted. In 2016, a systematic review and meta analysis in showed that there is even evidence that preoperative dose of Vitamin C can be used as an adjunct for reducing postoperative morphine consumption, and that there is high-level evidence

supporting perioperative Vitamin C supplementation for complex regional pain syndrome (CRPS I) prevention after extremity surgery. [164]

Overall, the importance of Vitamin C to patients are clear in that well controlled clinical trials in sepsis, trauma and major burns testing high-dose Vitamin C have shown clinical benefit with nearly non-existent risk profile.[165]

Citrus Bioflavonoids

Citrus Bioflavonoids are a collection of compounds typically found in citrus fruits which have a great variety of benefits, including functions as strong antioxidants, with potential properties such as anti-tumor agents and cardiovascular support. Importantly, they have a strong ability to improve Vitamin C absorption, which in itself a very strong benefit. These compounds additionally provide a broad spectrum of documented benefits in cases of heart disease, cancer, vision disorders, allergies, and viral infections. Certain flavonoids, notably diosmin and hesperidin, have been used routinely in Europe for many years to treat varicose veins, hemorrhoids, edema, bruising, and wounds.

Two separate European studies indicate that oral application of flavonoids to patients with leg ulcers (a common complication of chronic venous insufficiency) greatly increases healing rates. When this formulation was given for two months to a group of individuals who were suffering from leg ulcers, their ulcers healed faster and to a greater degree than those of a control group that received a placebo instead.[19] A larger, randomized study recently completed in Poland confirmed these results and highlighted the supportive role that flavonoids play in the wound-repair process.[20]

Another recent study demonstrated that infected wounds heal more quickly if treated with flavonoids.[21] This study, performed on guinea pigs, showed that either topical or oral application of diosmin/hesperidin was effective in accelerating the healing of infected wounds which resulted in the suggestion that may also have antibacterial or immune supportive functions.

Diosmin and hesperidin may have many other beneficial properties in wound healing.[22] On a molecular level, flavonoids have been shown to inhibit the synthesis of prostaglandins, a feature that likely contributes to their anti-inflammatory effect.[23] The combination of all these properties at the site of a wound is important in creating an environment that favors tissue repair.

Vitamin B Complex

Vitamin B Complex is a series of vitamins that work together in many metabolic reactions. There is ample and decisive evidence that deficiency in any vitamins in the B complex can significantly decrease capacity for tissue regeneration and healing and induce many deleterious metabolic effects. Vitamin B complex is thought to have many benefits and is particularly known for its integral role in energy productions and has just recently been recognized for its benefits in the healing process. It is integral to all major wound healing processes. [41]

Vitamin B complex is thought to speed up wound healing, increase protein synthesis and the number of repair cells at the wound, prevent excessive inflammation, protect against oxidative stress, and increase tissue blood flow. [37, 38, 39, 40]

Vitamin	Name	Molecular Function
Vitamin B_1	Thiamine	Thiamine plays a central role in the release of energy from carbohydrates. It is involved in RNA and DNA production, as well as nerve function.[166]
Vitamin B_2	Riboflavin	Riboflavin is involved in release of energy in the in several metabolic reactios as well as the catabolism of fatty acids.[167]
Vitamin B_3	Niacin	Niacin plays animportant role in energy transfer reactions in the metabolism of glucose, fat and alcohol.[168l] It is also a oenzyme in lipid and nucleic acid synthesis.[169]
Vitamin B_5	Pantothenate	Pantothenic acid is involved in the oxidation of fatty acids and carbohydrates. Coenzyme A, which can be synthesised from pantothenic acid, is involved in the synthesis of amino acids, fatty acids, ketone bodies, cholesterol,[170] phospholipids, steroid hormones, neurotransmitters, and antibodies.[171]
Vitamin B_6	Pyridoxine	Pyridoxine serves as a cofactor in many enzyme reactions mainly in amino acid metabolism including biosynthesis of neurotransmitters.
Vitamin B_8	Biotin	Biotin plays a key role in the metabolism of lipids, proteins and carbohydrates. It is a critical co-enzyme involved in the synthesis of fatty acids and in gluconeogenesis; It is also involved in synthesis of several amino acids
Vitamin B_9	Folate	Folate acts as a co-enzyme in the form of tetrahydrofolate (THF), which is needed for normal cell division, especially in times of tissue growth, which are times of rapid growth. Folate also aids in the production of red blood cells.[173]
Vitamin B_{12}	Cobolamine	Vitamin B12 is involved in the cellular metabolism of carbohydrates, proteins and lipids. It is essential in the production of blood cells in bone marrow, and for nerve sheaths and proteins.[174] Vitamin B12 functions as a co-enzyme in intermediary metabolism for the methionine synthase reaction with methylcobalamin.[175]

Vitamin A

Vitamin A is required in cell growth (especially tissue and bone formation), which is very important in the healing process that takes place after surgery and injuries. It is known to activate production of connective tissue, including collagen (promotes tissue synthesis), and helps new blood vessels grow, which is necessary for nourishing newly formed tissue. It increases collagen cross-linking and wound breaking strength. [44, 45, 46, 47]

Vitamin A increases the *initial* inflammatory response in wounds, thus facilitating the migration of cells that assist with wound healing at the cite. Importantly, it reverses corticosteroid-induced inhibition of cutaneous wound healing. [42, 43]

Vitamin A also enhances resistance to infection by stimulating the body's immune function.

Bromelain

Another well-known and popular healing adjunct is Bromelain, an extract from pineapple. [58-60.] Various studies indicate that Bromelain reduces swelling, bruising, pain after surgery and physical injuries, as well as healing time. Bromelain is often used in conjunction with Quercetin. [61-87]

A wide range of therapeutic benefits have been claimed for bromelain; such as reversible inhibition of platelet aggregation, angina pectoris, bronchitis, sinusitis, surgical traumas, thrombophlebitis, pyelonephritis and enhanced absorption of drugs, particularly of antibiotics. [88-101]

Recent results from preclinical and pharmacological studies recommend bromelain as an orally given drug for complementary tumor therapy. Especially promising are reports on animal experiments claiming an antimetastatic efficacy as inhibition of growth and invasiveness of tumor cells. [101-109]

Bromelain also has potential to eliminate burn debris and to accelerate wound healing and in several studies Bromelain supplementations significantly increased the resorption rate of hematomas. [110-119]

Quercetin

Quercetin, a plant pigment naturally found in foods such as onions, is a so called bioflavonoid. It promotes decreased histamine release in the body and thus acts like an anti-inflammatory as well as an anti-oxidant. Usually after surgery inflammation is a common response, and often unfavorable response if excessive or prolonged.

Quercetin supplementation is also known to enhance wound healing, as Quercetin incorporates into the collagen matrices.

Quercetin, particularly in conjunction with Bromelain may help reduce bruising, swelling and scarring.[25, 26]

Probiotics

Probiotics are widely known for their specific healing benefits regarding certain surgeries, as well as other broader beneficial effects in general.

Surgery patients often receive antibiotic treatment. The use of perioperative broad-spectrum antibiotics has become the standard of care for most major surgeries. Antibiotics are used to reduce postoperative infection risk. This practice has been validated in the literature and is now considered an essential part of the surgical process. While considered essential to surgical success and safety, antibiotic use does contribute to postoperative morbidity. Significant gastrointestinal flora disruption can occur, leading to decreased resistance to pathogens known to cause antibiotic associated diarrhea, such as Clostridium difficile. Studies have shown that the use of antibiotics known to disturb the gastrointestinal flora is associated with clinical symptoms, such as diarrhea, in as many as 30% of patients.[27, 28]

Research has shown that the use of probiotics can help to restore gut microecology through various mechanisms including: receptor competition, competition for nutrients, inhibition of epithelial and mucosal adherence of pathogens, introduction of lower colonic pH favoring the growth of nonpathogenic species, stimulation of immunity, and/or production of antimicrobial substances.[29,30]

In fact it is common practice in Britain for hospitals to routinely use probiotic supplements to reduce the incidence of antibiotic-resistance and hospital-acquired infections. Studies show that probiotic supplementation leads to a significant reduction of bacterial infection rates. Several probiotics strains also have well documented efficacy data in treatment of antiobiotic associated diarrhea.

Other studies show that the incidence of postoperative infections (including Pneumonia and Cholangitis), the duration of postoperative hospital stay, and the length of antibiotic therapy were all lower among patients receiving probiotics.

Probiotics, when used following surgery, can accelerate recovery through improved immunity, as well as reduce the risk of postoperative infection and antibiotic-associated diarrhea. The existing

body of evidence supports the use of Lactobacillus species, either alone or in combination with other genera.[31]

Amino Acids: Arginine and Glutamine

Amino acids play a crucial role in protein synthesis and muscle tissue repair. Specifically, L-arginine is an amino acid that has been shown to stimulate wound healing, while L-glutamine restores cellular energy stores. In clinical studies, patients given L-arginine supplementation after major surgery benefited from a faster recovery of immunological parameters and fewer infectious complications.[32]

Randomized clinical trials of patients undergoing surgery for hip fracture demonstrated that providing pre- and post-operative energy-protein supplements resulted in better recovery plasma proteins and fewer post-operative complications, even among patients with normal pre-operative nutritional status.[33, 34] In addition, a recent study showed that amino acid supplementation assisted with surgical recovery in patients who had undergone total knee arthroplasty, as demonstrated by attenuated muscle atrophy and accelerated return to functional mobility.[35]

Glutamine

Glutamine is the most abundant amino acid in the body and accounts for 60% of the intracellular amino acid pool. This amino acid is considered to be conditionally essential as a deficiency can occur rapidly after injury. Glutamine is used as an energy source after the stress response. In addition, glutamine is the primary fuel source for rapidly dividing cells like epithelial cells during healing.

Glutamine has potent antioxidant activity and also has direct immunological function by stimulating white cell proliferation through its use as energy. Glutamine has anticatabolic and anabolic properties also and is the rate-limiting agent for new protein synthesis. [48-51]

Because of its many roles in the wound, it is of particular concern when there is a rapid fall in both intracellular and extracellular glutamine levels, to a deficiency state, in the presence of a major wound.[52]

Glutamine protects against excessive inflammatory injury by inducing the expression of heat shock proteins, which provide cellular protection in states of inflammation, injury, and stress. Furthermore, glutamine can modulate and preserve gut function, which is compromised in severe stress.[53]

Glutamine, besides being an important metabolic fuel, can also be considered an important nutritional mediator of the inflammatory response. It does appear to decrease wound infection

and it does improve healing in experimental studies. Further, prospective, controlled, and randomized clinical trials show decreased mortality and infectious morbidity in burn patients given glutamine supplements.[54-57]

Arginine

As a single agent, Arginine is the best-studied component of immunonutrition, with copious evidence showing that Arginine is beneficial to wound healing. [120-122]

Arginine, while normally a non-essential amino acid, becomes an essential nutrient during periods of physiological stress. However, during these periods Arginine is rapidly depleted, and this can affect the immune system response in injured states and during other disease processes. [123-125]

Arginine is critical for collagen synthesis, improving our immune function, and wound healing abilities. [125-128]

Numerous studies show that Arginine supplementation, administered either orally or parenterally, accelerates wound healing by increasing collagen deposition in wounds. [128-131]

Not only does Arginine increase collagen accumulation, but it also causes increased activity of peripheral blood lymphocytes. It improves epithelial reconstitution after intestinal injuries and also has been shown to nearly double improvements in pressure ulcer healing times. [125-134]

Metabolically, Arginine is a precursor to Proline, and is thus recruited specifically for collagen synthesis. It is also a precursor for ornithine, which is critical for polyamine synthesis, and for nitric oxide. In fact, Arginine is the sole metabolic substrate for the synthesis of Nitric Oxide, which plays a role in wound collagen synthesis and regulation of blood blow. [135]

For example, inhibition of NO synthesis during healing results in weaker wound recovery and decreased collagen synthesis. This is commonly found in cases of diabetes and malnutrition. [125-129]

Trace Minerals

Zinc

Zinc is a cofactor of many enzymes, including some that are needed to repair wounds. It is also an antioxidant and has significant antibacterial properties. Even a mild deficiency of zinc can interfere with optimal recovery from everyday tissue damage and more serious trauma.

The hypermetabolic state associated with surgery and injuries leads to a marked increase in loss of zinc, and a risk for a zinc deficiency state has adverse effects on the healing process including a decrease in epithelial rate, wound strength, and decreased collagen strength.

One controlled trial found the healing time of a surgical wound was reduced by 43% with oral supplementation zinc. Zinc also plays a vital role in the immune system and can reduce inflammation, bacterial growth, and scar tissue creation, whereas a deficiency can certainly worsen recovery. [24]

Selenium

Selenium has strong antioxidant roles. There is some suggestion that it may expedite wound healing in burn patients. A prospective, randomized controlled trial investigated the effect of large intravenous doses of trace elements (copper, selenium, and zinc) on patients with major burns and found that cutaneous concentrations of those trace elements were increased, antioxidant status (as measured by normalization of plasma glutathione peroxidase level) was improved, and wound healing was benefited as measured by decreased graft requirement. [136] The antioxidant properties of selenium benefit wound healing. [137, 138, 139] Further, selenium is commonly deficient in patients in the hospital setting. [140]

Copper

Copper has a complex role in various cells, modulating several cytokines and growth factor mechanisms of action, and it is essentially involved in all stages of the wound healing process. [141-156]. Old and recent literature shows that the activity of PDGF, VEGF, and Angiogenin is copper-dependent. Copper peptides, specifically, are small protein fragments that, along with copper, stimulate collagen production and can improve the effectiveness of antioxidants and can escalate the amount of protein synthesis in collagen and elastin thus also supporting wound healing processes.

Magnesium

Magnesium has vast metabolic impact in regards to recovery. [157] It aids in muscle relaxation, soreness, and cramping.[158, 159] Although magnesium is not a primary analgesic in itself, it enhances the analgesic actions of more established analgesics as an adjuvant agent. The role of magnesium for perioperative analgesia has been investigated by many authors and it was found in a randomized control trial that administration of magnesium pre-operatively can reduce pain scores and decrease amount of opioids needed to control pain. [160] This finding has been repeated and generalized in multiple studies in both IV and oral formulations. Magnesium can also improves endothelial function, especially in patients with atherosclerosis. [161]

Addressing the Need for Clinical Nutrition

There a significant amount of clinical data to support that poor nutritional status is linked to increases in post-operative complication and adverse outcomes in surgical patients. Literature supports that nutritional therapy can reduce these same risks and improve outcomes. Extensive clinical research have validated the supportive role of nutritional elements in peri-operative or peri-injury time frames. Despite the relative abundance of scientific research, there is a striking lack of high-quality, pharmaceutical- grade nutritional supplements and mediceuticals that are specifically designed to support the nutritional status of these patients.

Nutritional supplements can address this significant unmet need by providing nutritional products that contain elements targeted to address specific clinical and medical conditions, while using elements, dosages, and routes of administration that has been validated by evidence-based research and avoiding compounds that have documented adverse effects or interactions in the perio-operative and peri-injury periods.

With variability in quality the current supplement industry, great care must be taken in manufacturing a supplement for clinical use. The supplement for this purpose must utilize high grade, high fidelity ingredients, responsibly sourced and properly verified for purity and content. These supplements also need to be compounded by a qualified manufacturer in an FDA registered facility that utilizes Good Manufacturing Practice (GMP) standards and need to undergo extensive testing for heavy metals, pesticides, and microbial contaminants, preferably by a third-party lab independent of the manufacturer.

Furthermore, optimal interventions for nutrition therapy should be comprehensive, spanning the entire perioperative or peri-injury period, and target various parts of the process with specific nutrients that benefit the underlying set of processes. Recent advances in perioperative care have emphasized the concept of “prehabilitation” to provide pre-operative intervention such as physical therapy and nutritional support to best prepare the patient prior to surgery. In fact, research has shown that adding nutritional formulas during the week of surgery enhances recovery and return to baseline function.[36]

The breadth of research in the field of clinical nutrition needs to be applied. Current evidence suggest that many nutrients can be compounded at relatively low cost, provide a favorable safety profile, all with significant potential to improve patient care, optimize recovery, and reduce complications.

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