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The Scientific Rationale for Peri-Operative Vitamin & Mineral Support of Wound and Tissue Healing After Orthopaedic Surgery

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INTRODUCTION

Healing from elective orthopaedic surgery is distinct in that it affords the unique opportunity to nutritionally prepare for tissue injury beforehand in order to preemptively optimize the body's ability to heal and recover. Wound and musculoskeletal tissue repair are complex processes; they involve the interactions of different cell types, growth and inflammatory factors, and extracellular matrix components. These processes also occur in combination with factors that include a patient's baseline biologic health and other competing metabolic demands and stresses. The phases of normal tissue healing are distinct across tissue types, as well as within tissue types. These processes are none the less continuous and overlapping, progressing in a complex cascade of healing events that lead to a final patient outcome. Because the overall success and quality of tissue healing requires adequate nutrients be delivered to the area of injury, the overall health and nutritional status of the entire patient influences the ultimate potential for healing of damaged or injured tissue. Many clinical experts in wound healing therefore recommend a combined holistic and focused approach, to treat "not only the whole patient, but the hole in the patient" in an integrated, combined fashion.

There are many types of wounds with a wide range of physiologic character. Surgical wounds are distinguished as a purposeful and organized form of tissue injury, with the greater patient good as the desired outcome. Although the higher goal of surgery is the repair or restoration of some other compromise due to evolved or traumatic injury, the surgery itself is indeed a form of trauma, and necessarily results in organized tissue damage as a result. Subsequently, surgery imposes all the increased nutritional and metabolic demands on a patient that are well known to occur in the setting of trauma, in addition to the other particular demands that are specific to the operative patient. An additional principal element distinguishing surgical wounds from a more typical trauma is that surgery is carefully organized and planned; this is particular in that elective surgery affords the stated unique clinical opportunity for patients to nutritionally prepare for tissue injury beforehand in order to preemptively optimize the body's ability to heal and recover to its best possible potential.

Tissue repair and wound healing must occur in a physiologic environment that is conducive to tissue repair processes and regeneration. In the surgical patient, a multitude of factors are known to impede healing, to include hypoxia, mechanical factors, infection, neoplastic and or metastatic disease in cancer, underlying medical conditions (such as diabetes), medications (such as prednisone or other chronic steroids). This list continues to include dietary deficiencies in protein, energy sources, and micronutrient vitamins and minerals. Vitamin, mineral, and other micronutrient cofactors are of particular interest given their remarkable potential to foster and accelerate healing, and to meet the defined requirements of the peri-operative patient.

The principle objectives in incision and tissue healing after surgery are to achieve complete healing as rapidly as possible, with the greatest quality of healed tissue (biomechanical and cellular), and with the least amount of scarring to achieve optimal return to general health. Human studies have repeatedly demonstrated the clear advantages of optimizing nutrition and vitamin/mineral levels before and after surgery as a means of helping clinicians and patients meet these objectives. Researchers who have explored the complex dynamics of tissue repair have described a wide range of micronutrient factors that are required in novel levels by the surgical patient for optimal effect, and that have unique potential for interactive effect toward the demands of different types of tissue healing (i.e., skin, skeletal muscle, tendon, bone, peripheral and central nervous tissue, cardiac tissue, etc). This list includes specific forms and doses of vitamins A, B subtypes, C, D3, K1, K2, as well as minerals such as copper, zinc and others. This body of research has also identified properties of vitamins that would make for unfavorable effects or would be frankly contraindicated in the peri-operative environment at their typically-recommended daily intake levels.

At its base, it is the novel integration and application of this knowledge to the understood and unique demands of the surgical patient that serves as the evidence-based scientific foundation for a targeted vitamin and mineral regimen for the peri-operative orthopaedic patient. This targeted micronutrient effort is further encouraged by the particularly robust, beneficial micronutrient effects that are possible in the surgical patient, when the optimal doses and forms of the given micronutrients are used.

PHASES OF HEALING

Each tissue type, be it skin, bone, skeletal muscle, mucosa or otherwise has a tissue-specific cascade of healing that is typically defined in phases. Skin and deep tissue healing is a ubiquitous requirement for nearly all surgery, and as such, wound healing is discussed here as a commonality among all surgical procedures. Wound healing also provides a concrete format to demonstrate the applied vitamin and mineral strategy that can be exacted across a range of tissue types in the orthopaedic patient in particular (to include bone, tendon, ligament, muscle and other musculoskeletal tissue).

The four phases of wound healing are: 1) the injury event & hemostasis, 2) the inflammatory phase, 3) the proliferative phase, and 4) remodeling (and/or regenerative processes).

Phase I. The tissue injury event, such as with a surgical incision or suprafascial approach, initiates a response that prompts that body to clear the wound of devitalized tissue and foreign material, setting the stage for next steps. The initial vascular response involves a brief period of vasoconstriction and hemostasis. This typical six to twelve minute time of intense vasoconstriction is thereafter followed by active vasodilation and increased capillary bed permeability. There are multiple sources of growth factors, cytokines, and other micronutrient and non-micronutrient modulated factors are introduced, and set the stage for the orderly cascade of events that will lead to final tissue repair. The speed and quality of the final repair is influenced (and amplified) from the outset by the patients pre-existing levels of micronutrients, which may be preemptively optimized to meet the demands of this cascade.

Phase II. The second phase of wound healing is the inflammatory phase. It is characterized by

erythema, swelling, increased tissue temperature, and discomfort/pain. There is increased vascular permeability, and cellular response in the area of injured tissue. The early inflammatory phase is characterized by neutrophil response, and ceases after the first several days if the wound is healing properly. Several factors can drive the prolongation of this phase including hypoxia, infection, medical comorbidities (i.e., diabetes mellitus), and notably malnutrition of micronutrient deficiencies (disrupting the late inflammatory phase). In the late inflammatory phase, monocytes are converted to macrophages to destroy remaining neutrophils, scavenge devitalized tissue, and eliminate bacterial or other pathogens. These same macrophages initiate the transition from the inflammatory phase to the restorative healing phase.

Phase III. The proliferative phase of wound healing that follows is characterized by tissue re-epithelialization and granulation. The length of this phase is variable as it is largely and directly related to the extent and relative volume of injured tissue. Growth factors and chemotactic factors are released from macrophages and platelets. This, in turn, prompts the activation of wound fibroblasts which then produce and prompt substances further essential to wound repair, such as various collagen types (tissue dependent), hyaluronic acid, chondroitin sulfate, dermatan and heparin sulfate. Together, these form the described connective tissue matrix that is required for cell migration. Vascular and capillary in-growth is also critical to this phase, in order to provide a means to meet increasing local metabolic demands as healing progresses. The relative vascularity and collagen formation are highly dependent on micronutrient support, with often dramatic potential to modulate the tensile strength and overall quality of healing tissue, as well as more generalized biomechanical quality and compliance and other factors.

Phase IV. The final phase of wound healing is remodeling. This includes the addition and reorganization of collagen fibers and other tissue to optimize wound tensile strength and tissue quality. There is capacity for this phase to continue up to two years, though 40-70% of tensile strength (versus undamaged tissue) is usually recognized in the first four weeks. These first four weeks, therefore, represent the critical healing window, upon which all further healing is entirely dependent.

Macronutrition with appropriate levels of lipids, protein, and carbohydrates is important in all phases of post-operative wound healing and is well understood in this setting.[1]

From the standpoint of optimized vitamin, mineral and co-factor micronutrition in the setting of surgical wound healing, the above can be considered by matching the four phases of wound healing to the nutrients that most impact each of the phases. The injury and hemostasis phase is matched best with those compounds that should be avoided prior to surgery, with most concerns being related to impact on clotting cascade and as a source of excessive bleeding. This notably includes forms of vitamin E, as well as non-vitamin herbal supplements and medicines. There is a clear positive role for optimized vitamin K in the inflammatory phase. The inflammatory phase can be positively modulated by increased doses and forms of vitamin A (supports early inflammatory phase events), vitamin C (fosters lymphocyte transformation and neutrophil migration), vitamin D, and others. The proliferative phase enhanced by vitamin A (cell differentiation), multiple B vitamins, vitamin C (collagen synthesis and crosslinking, vascular healing), Zinc (cell division and DNA synthesis), Copper and others. The remodeling phase is positively influenced by elevated doses of vitamin C (collagen remodeling), vitamin K (cell growth), and others.

AN OVERVIEW OF VITAMINS AND MINERALS MOST IMPORTANT TO SURGICAL RECOVERY & HEALING (WITH THEIR RELATIVE EFFECTS AND OPTIMAL DOSES)

Vitamin A

Vitamin A is the broad term for a large number of related compounds, though retinol and retinal are often referred to as 'pre-formed" vitamin A. Beta-carotene and other carotenoids that can be converted by the body into retinol are referred to as "provitamin A carotenoids". Literally hundreds of different carotinoids are synthesized by plants, though only about 10% are pro-vitamin A carotinoids. A substantial evidence-base supports the role for vitamin A as a peri-operative nutritional supplement.[33]

Retinoic acid and its isomers can act as hormones to affect gene expression, subsequently having a wide range of influences at a baseline physiologic level. It is likely that vitamin A, vitamin D and thyroid hormone dynamically interact to influence gene transcription. Through the activation, suppression, or transcription of specific genes, retinoic acid plays a major role in cellular differentiation, facilitating specialization of cells for highly specific physiologic roles. This includes a significant role in wound and tissue healing or regeneration. Many of the physiological effects linked to vitamin A function appear to result from this role in cellular differentiation.

Vitamin A is also commonly regarded as the anti-infective vitamin, because it is required for normal functioning of the immune system. Retinol and its metabolites are well known to maintain the function and integrity of the skin and mucosa which serve as a first line of defense against infection. Several studies in animal models have documented the beneficial effects of optimal vitamin A intake on wound strength and strength of tendon repairs after surgery (and they are discussed in more detail below). Vitamin A and retinoic acid hold a central role in the differentiation of the lymphocytes, white blood cells that are critical for healthy immune response. Activation of T-lymphocytes, the primary regulatory cells of the immune system, appears to require all-trans-binding of retinoic acid receptors. Some authors have gone so far as to regard Vitamin A deficiency as a nutritionally acquired immunodeficiency disease.

Vitamin A has a critical role in red blood cell production. Precursor stem cells are dependent on vitamin A retinoids for normal differentiation into healthy red blood cells. Vitamin A also appears to facilitate the mobilization of iron from body storage site to forming red blood cells for incorporation into hemoglobin molecules (the oxygen-transporting molecule in red blood cells).

Vitamin A has important interactions with vitamin D, zinc and iron in the surgical patient. Vitamin A deficiency may exacerbate iron deficiency anemia, which is clearly a potentially important issue from the standpoint of the surgical patient. Vitamin A supplementation has definitive beneficial effects on iron deficiency anemia, and improves iron nutritional status in multiple groups to include children and pregnant women. The combination of vitamin A and iron seems to synergistically reduce anemia more effectively than either supplemental iron or vitamin A alone. In kind, animal studies have shown that iron deficiency adversely decreases available plasma and liver levels of vitamin A.

Ehrlich and Hunt's work has shown that vitamin A has ability to reverse or dramatically counteract the corticosteroid-induced inhibition of cutaneous and fascial wound healing.[20,21,29] A number of animal studies well document the enhanced strength of skin wounds and bone with targeted vitamin A protocols.[10,26,51,52] Levinson et al suggest that vitamin A benefits healing most by enhancing the early inflammatory phase, including increasing the number of monocytes and macrophages at the wound site, modulating collagenase activity, supporting epithelial cell differentiation, and

improving localization and stimulation of the immune response.[38]

With the above in mind, form-ratios and targeted levels of vitamin A as optimized for the orthopaedic surgery patient will strongly support:

- Normal gene expression,
- Immune function, and
- Iron / red blood cell / hemoglobin metabolism,
- Mitigation of diabetes and (chronic) steroid use on wound healing
- Ideal biomechanics, strength and compliance of integumentary tissue (skin, fascia, connective tissue)

Vitamin A dosing recommended for the surgical patient: 5000 IU (required retinol (as retinyl acetate) limited to an optimal 750 IU (15%), combined with 4250 IU (85%) of beta-carotene.

Recommended Dietary Allowance (RDA): 2333 IU daily for women and 3000 IU for men.

Some authors advocate significantly higher dosing protocols as beneficial with levels in the 10,000-50,000 IU/day orall or 10,000 IU/day IM, though regimens of this nature would require direct physician oversight on a per patient basis. (JK. 2010) (The Stechmiller paper suggests 10,000-50,000 IU/d orally or 10,000 IU/d IM. For those on corticosteroids, 10,000-15,000 IU/d orally is suggested).

Vitamin B1 (thiamine)

Thiamine (B1) was isolated and characterized in the 1930's and was among the first compounds to be recognized as a vitamin. Thiamine has important molecular function as a co-enzyme functioning in roles focused on the production of ATP and energy from (macronutrient) foods, and in healing processes by its transketolase-associated role in DNA and RNA synthesis.

It is known to have increased requirement in times of stress, such as during periods of intensive physical training and other strenuous activity, during times of infection, and similarly, during times of generally increased metabolic demand. The related clinical importance for increased levels of thiamine in the peri-operative patient thus becomes apparent.

Several lines of study have provided a strong evidence-base to support that vitamins B1 (thiamine), B6 (pyridoxine) and B12 (cyancobalamin) have analgesic and anti-inflammatory capacities in both human and animals.[22,25,39,43,59] There is also animal evidence to support a central and peripheral neuro-protective effect for thiamine, as might be of particular importance during intracranial, spinal, or extremity surgery.[55]

Thiamine levels increased from typical daily recommended intake to be optimized for the orthopaedic surgery patient will support:

- Avoidance of deficiency given the increased thiamine requirements as known to accompany physical stress, as following surgical trauma or other tissue injury.
- Optimal energy / ATP production (to meet the elevated metabolic requirements of healing tissue)
- Ideal nucleic acid production capability as particularly required during reparative cell growth and differentiation during healing after surgery.

Vitamin B1 (thiamine) recommended for the surgical patient: 50mg/day

This notably increased dose will meet the above goals, and recognizing the safety margin implicit in that the FDA Food and Nutrition Board has not set a tolerable upper limit, as there are no known toxic effects with long-term daily doses up to 200mg/day).

RDA: 1-1.2mg/day.

Vitamin B2 (riboflavin)

Riboflavin is a water soluble B vitamin with several established antioxidant functions and known supportive roles in the metabolic functioning of B1, niacin, and folic acid. It has an important role in iron metabolism, and there are human studies demonstrating that optimizing riboflavin nutrition status supports restoration of circulating hemoglobin levels. It is therefore of particular importance in the peri-operative setting in order to optimize hemaglobin before surgery, and to meet increased related demands and facilitate iron metabolism post-operatively (in response to the incumbent demands of intra-operative blood loss).

There is also an evolving body of literature to describe the role for riboflavin and other B vitamins in bone metabolism, and fracture risk [60,61] as may be of additional consideration in the setting of reconstructive orthopaedic surgery and spine surgery procedures.

Vitamin B2 (riboflavin) recommended for the surgical patient: 50 mg/day

No toxic or adverse effects of high-dose riboflavin intake in humans are known. The higher doses most appropriate to the peri-operative patient have been found to intensify the urine bright or "neon" yellow, though this is a harmless effect.

RDA: 1-1.3mg/day.

Vitamin B3 (niacin)

Niacin is the water-soluble B vitamin that is also known as vitamin B3. Nicatinamide is the amide form of B3, and is the active derivative of niacin that is used by the body to form the co-enzymes nicatinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADP). On the cellular level, humans gain most of their energy from different types of oxidation-reduction reactions, and as many as 200 enzymes require niacin co-enzymes NAD and NADP for electron transfer to complete these fundamental energy-deriving processes. These are critical in the cellular metabolism of fats, proteins, carbohydrates, alcohols, fatty acids and cholesterol [8], and are particularly important in meeting the markedly increased metabolic demands incumbent to healing tissue after surgery.

During disorders or circumstances of medical stress that include immune system dysfunction, diabetes, age-related diseases and surgical stress, nicotinamide is a robust cytoprotectant that regulates cellular inflammatory activation, early apoptotic phosphotidylserine exposure, and late degradation of DNA.[41] It is involved and governs a set of unique cell pathways that are believed to be primary in determining cellular survival and longevity.[41]

Effects of optimally-dosed niacin in the surgical patient, include those as outlined above in addition to observed neuroprotective effects [3,12,23] support of vascular integrity, and preservation of cerebral and endocardial endothelial cell integrity, and other similar effects.[14,50]

Niacin levels increased from typical daily recommended intake to be optimized for the orthopaedic surgery patient will support:

- Ideal capacity of management of oxidative stress and cellular survival in traumatized tissues (to particularly include oxidatively-sensitive tissues such as nervous and cardiac tissue)
- Optimal inflammatory cell modulation (as critical during early-phase wound healing)
- Cellular energy management during times of peak metabolic demand during healing

Vitamin B3 (niacin) recommended for the surgical patient: 25 mg/day

Although this level is only 25% above the typical daily RDA value, it is regarded as sufficiently elevated to meet the outlined goals as specific to the majority of surgical patients, while concurrently avoiding the potential for flushing as a side effect (in keeping with the tolerable upper intake level of 35 mg/day as per Food and Nutrition Board recommendations).

RDA: 14-16 mg/day, and tolerable upper limit is 30-35 g/day (dependent upon age/gender). Excess may result in flushing and GI distress.

Vitamin B5

Vitamin B5, or pantothenic acid, is a component of coenzyme A (Co-A) which is an essential enzyme in a number of life sustaining reactions. Co-A is required for a number of molecular reactions that generate energy from carbohydrates, fats and proteins. It is required for synthesis of essential fats, cholesterol, steroid hormones, neurotransmitter (acetylcholine) synthesis and others. The heme molecule of hemoglobin requires Co-A for synthesis.

A number of authors have reported a role for B5 supplementation in the quality and rapidity of wound healing. [4,24,27,58] The relative importance of vitamin B5 to the surgical patient with respect to these improved wound healing benefits is clear. Aprahamian and colleagues (Aprahamian M 1985) reported their results in an investigation of pre-operative and post-operative supplemental vitamin B5 in an animal wound healing model, reporting gross, histological and biomechanical measures. They noted significant advantage in the B5 supplemented group with both an accelerated and increased in cellular response, as well as a remarkable mechanical increase in tissue resistance that was most obvious after the second post-operative week. Further study as to the mechanism of this response is reported by Weimann and Hermann's in vitro work on the effects of pantothenic acid (B5) on the migration, proliferation, and protein synthesis of human dermal fibroblasts as a wound healing model.[58] They noted a significant positive effect on rapidity and quality of healing, with a reported cellular response accelerated by over 30%. They conclude that vitamin calcium d-pantothenic acid (vitamin B5) accelerates wound healing by increasing the number and travelling distance of migrating cells, and hence their speed of action. Cell division is increased and protein synthesis is favorably altered to facilitate the wound healing process.

Vitamin B5 (pantothenic acid) levels increased from typical daily intake (as optimized for the surgical patient) will facilitate:

- Essential Co-A directed energy metabolism as required of healing tissue
- Restorative production of heme, hemoglobin and new red blood cells in response to operative blood loss anemia
- Proven accelerated wound healing with improved wound tensile strength and overall soft-tissue biomechanical integrity.

Recommended vitamin B5 intake in the peri-operative patient: 50 mg/day

Pantothenic acid is not known to be toxic in humans, and a tolerable upper limit has not been set by the Food and Nutrition board of the Institute of Medicine. An isolated study reports issues with diarrhea in those taking extremely high doses of vitamin B5 on the order of 10-20 grams of calcium d-pantothenate daily.

RDA: 5mg/day.

Vitamin B6

Vitamin B6 has an essential role in over 100 enzyme reactions, catalyzing a wide range of reactions throughout the body. It has a primary role in mobilizing glycogen energy stores to meet increased metabolic demands, as when healing, and is fundamental in converting protein to usable energy forms through gluconeogenesis. It is important for immune function, red blood cell formation and function, nervous system function, nucleic acid synthesis (as during post-operative reparative cell division), and hormone function (through the alteration of gene transcription). B6 also has an important role in human bone metabolism, with support of proper cancellous bone structure and biomechanics.[28]

Low vitamin B intake has been shown to measurably impair immune function, especially in elderly patients, increasing risk of post-operative infection and other compromise. Restoration of vitamin B6 levels has been shown to result in normalization of lymphocyte proliferation and interleukin-2 production, further confirming that adequate vitamin B6 intake is important for optimal immune system function [42] as during the normal early phases of wound and other tissue healing. One study noted that the levels of B6 required to reverse immune system impairments in the elderly were notably higher than the current FDA recommended daily allowance.[42]

In the same regard, Cheng and recently reported results of his study of vitamin B6 supplementation in increasing immune response in clinically stressed and critically ill hospitalized patients. A significant improvement in molecular and cellular immune response was achieved with large-dose B6 supplementation (50-100 mg.day), supporting their conclusion that such an approach could compensate for depressed immune function in critically ill patients.[11]

Badner and colleagues investigated a role for B6 in mitigating myocardial ischemia with nitrous oxide anesthesia, studying 53 patients undergoing elective total knee or total hip replacement.[6] They found that pre-emptive utilization of vitamin B6 and B12 (in elevated doses) was significantly preventive, and concluded that a one week course of oral B vitamins can prevent increase in homocysteine from nitrous oxide, and by implication myocardial ischemia as well.

Vitamin B6 levels measurably increased from typical daily intake, and as optimized for the orthopaedic surgery patient will foster:

- Optimized immune function in the medically-stressed surgical patient
- Mitigation of myocardial ischemia with nitrous-oxide anesthesia regimens
- Support of peri-operative red blood cell function and production
- Support of nucleic acid synthesis during restorative tissue healing
- Support of proper cancellous bone structure and biomechanical function (as particularly related to bone & joint or spinal reconstructive procedures).

Recommended vitamin B6 intake for the surgical patient: 100 mg/day

Long-term intake of B6 at levels of 500 mg/day has been shown to be related to rare instances of sensory neuropathy. The Food and Nutrition board recommends an upper tolerable limit of B6 of 100 mg/day, and there are no reports of beneficial reports in levels beyond.

RDA: 1.2-1.7 mg/day.

Vitamin B12

Vitamin B12 is unique in containing a metal ion (cobalt) and also has the largest and most complex molecular structure of all the vitamins. Vitamin B12 has a number of actions, to include those on the peripheral and central nervous systems, bone marrow and osseous tissue, skin, mucous membranes, and blood vessels.[30] Of these, the affects related to nervous system function and maintenance are those most relevant to the surgical patient. The importance of supplement support in the surgical patient is further compounded, as B12 deficiency is estimated to affect 10-15% of people over the age of 60.[7]

A number of studies have investigated the role for B12 for neurologic support before and after nerve tissue injury. Okada and colleagues reported the use of high dose vitamin B12 in rat sciatic nerve injury model, demonstrating improved histological nerve regeneration as well as functional recovery.[49] In sum, this body of literature provides support for the utilization of high-dose B12 for both neuroprotective and other effects in the peri-operative patient. This would reasonably be of particular merit for patients undergoing

procedures for neurologic compromise, such as carpal tunnel release, or cervical spine or lumbar spine decompression.

No toxic or adverse effects have been associated with large intakes of vitamin B12 from food or supplements, and no tolerable upper intake level is set by the Food and Nutrition Board in the most recent revision of the RDA.

Recommended vitamin B12 intake for the surgical patient (without known B12 deficiency): 100 mcg/day

This is specifically critical for those pursuing surgery for or potentially involving neurologic compromise, and/or for those patients 60 years old or greater.

RDA: 2.4 mcg/day for vitamin B12.

Biotin

Biotin is a water soluble vitamin, and took nearly four decades of research after its discovery to be recognized as a vitamin. It is often regarded as a B-complex vitamin. It is known to be important co-factor of enzymes required for fatty acid oxidation and synthesis, gluconeogenesis, and metabolism of certain amino acids. Biotin deficiency is uncommon, although high doses of pantothenic acid are knows to compete with intestinal and cellular uptake for biotin (given their similar molecular structures). As higher dose pantothenic acid is important in facilitating rapid wound healing and tissue strength in the surgical patient, biotin should be supplemented as well to prevent potential for competitive biotin deficiency in this setting.

Biotin recommended for the orthopaedic surgery patient: 300 mcg/day

When taken along with a regular diet, this dose will meet the above requisites (and in keeping with RDA recommendations and safety).

RDA: 25-30 mcg/day, and the tolerable upper limit has not been established.

Folate

Folate (or folic acid) is a water-soluble B vitamin, with a singular enzyme cofactor role in mediating the transfer of one-carbon units. This notably includes a prominent action in nucleic acid metabolism, amino acid metabolism, immune function and inflammatory response, [19] all of which are of additional importance in the healing continuum after surgery.

Folate has commonplace application pre-pregnancy in the prevention of neural tube defects and other neurologic anomalies, though a body of more recent work has documented that folic acid can enhance neurologic growth and repair mechanisms even the adult patient.[31] This has particular implication for use in neurosurgery, spine surgery, and common peripheral neurodecompressive procedures such as carpal tunnel release. These same mechanisms are believed to account for the documented effect of folic acid in protecting against falls in studies of balance in the elderly.[54] This, too, has appreciable particular application in the peri-operative setting, particularly in the elderly, osteoporotic patient that is remobilizing after an orthopaedic procedure or other surgery.

Supplemental folate increased from typical daily intake, and optimized for the surgical patient will support:

- Best immune function and wound healing response
- Potential for neural repair and re-growth
- Decreased fall risk in the elderly, who are at greatest risk in this regard peri-operatively

Folate intake recommended for the surgical patient: 400-1000 mcg/day

RDA: 400mcg/day, with a tolerable upper limit of 800-1000mcg/day.

Vitamin C

Ascorbic acid, better known as vitamin C, is a water soluble vitamin that humans require through dietary sources. This is of particular interest, as humans are unlike most mammals that are able to produce their own vitamin C systemically.

Vitamin C is critical in the synthesis of collagen, a ubiquitous structural component of connective tissue, ligaments, tendon, bone, cartilage, capillary walls and blood vessels. Vitamin C has a very important role in tissue healing after injury such as in the setting of surgery – particularly orthopaedic procedures that are typically focused on the tissue types most dependent on collagen integrity.

Vitamin C also plays a role in the synthesis of norepinephrine, an important neurotransmitter critical to brain and nerve function. Additionally, vitamin C is required for the human body to synthesize carnitine, a molecule that is required for energy conversion by means of transport of fat to intracellular mitochondria.

Vitamin C is also known to function as an antioxidant, even in low doses. This action protects healthy tissue and cells from injury by the by products of normal metabolism or as generated through exposure to toxins, medicines, pollutants and other similar substances.

Vitamin C has a wide range of established clinical effects to include vasodilation effects, decreased hypertension, and mitigation long-term effects in diabetes. Several studies have provided evidence that wound healing in subjects not deficient in vitamin C can be accelerated with supplement levels above that as recommended for routine daily intake by the FDA. Others have also demonstrated a reduction in wound contracture rate, further supporting the directed application of vitamin C in the peri-operative setting.

The minimum RDA for vitamin C continues to be based primarily on prevention of deficiency disease, with little regard to chronic disease issues as outlined above. A minimum RDA for an adult is on the order of 75 mg/day, though most supplements provide levels in comfortable excess (appreciating that tolerable safe upper limits are in the 1800mg/day range and above for adolescents and adults).

Forms and levels of vitamin C as optimized for the orthopaedic surgery patient will support:

- Best healing of bone, tendon, ligament, skin, capillaries and vessels, and other collagen-rich tissues, with recognition that there is a very wide margin of safety for this water soluble vitamin.
- Protective antioxidant effects and their potential benefits on injured, healing tissues.

Vitamin C intake recommended for the surgical patient: 400 mg/day.

Appreciating the scientific support that 400 mg of vitamin C per day is sufficient for most people to fully saturate plasma and circulating cells with vitamin C in young, healthy non-smokers, a dose in the range of 400 mg of vitamin C per day is recommended as ideal for most patients peri-operatively.

RDA: 75 mg/day for women and adolescents, 90 mg/day for adult men.

Vitamin D3

Vitamin D is a fat-soluble vitamin that is essential for maintaining normal calcium metabolism. Cholecalciferol, vitamin D3, can be synthesized in the skin upon exposure to sunlight (UVB radiation), or can be obtained from dietary intake.

Many of the effects of vitamin D are mediated at the cellular level through a nuclear transcription factor know as the vitamin D receptor (VDR). The ultimate steps in this vitamin D mediated cascade modulate the transcription of specific genes; more than 50 individual genes in various tissue types are known to be regulated by 1, 25-dihydroxy vitamin D.

Vitamin D is well known for its roll in efficient calcium utilization and regulation in the body, and maintenance of serum calcium levels within a tightly controlled range is critical for normal nervous system function, bone growth, and maintenance of proper bone density.

Vitamin D is also important as an inhibitor of cell proliferation, and a supporter of cell differentiation. These effects have been studied observationally with respect to prevention or certain types a cancer; early promising results have prompted even more rigorous and controlled studies which are ongoing presently. These effects on cell proliferation (division) and differentiation (specialization) also bear important implications for adequate vitamin D levels when it comes to optimizing conditions for wound or tissue healing.

Vitamin D is an important modulator of immune system function, particularly with respect to the cellular mediated responses. Most of the cells of the immune system (to include T-cells, macrophages, dendritic cells, etc) express the vitamin D receptor. There is a growing body of scientific study to support the importance of vitamin D in enhancing innate immunity and inhibit the development of autoimmunity. This potential for enhancing immune function also has clear importance as relative to elective surgery, and preventing subsequent infection.

Vitamin D plays a role in insulin secretion, though this role is not well understood. Animal models and limited human study suggest that low vitamin D levels have adverse secondary effects on glucose tolerance in Type II diabetes mellitus (NIDDM). This has related implications for wound healing in the diabetic patient undergoing surgery as poorly controlled diabetes can compromise wound and soft tissue healing potential.

Adequate intake has been defined by the Food and Nutrition board to be in the range of 200-600 IU per day, depending on age and gender. The 1997 adequate intake levels established by the Food and Nutrition Board of the Institute of Medicine are felt by most experts to still be far too low to appreciate best potential benefit of this vitamin. This has been progressively supported by evolving study, leading most experts (to include the American Academy of Pediatricians and others) to recommend significantly higher daily intake of vitamin D (see below).

Most present supplements contain vitamin D3 (cholecalciferol) which is more biologically potent than vitamin D2 (ergocalciferol).

Levels of D3 (as the preferred form) as optimized for the surgical patient will support:

Optimal dosing for the surgical patient requires appreciation that the most relevant literature supports an adult or adolescent intake level of at least 2000 IU (two thousand IU) / day in a normal state. Even higher levels have shown benefit in certain sub-groups of patients in observational studies (diabetes, some cancers, risk of fracture from osteoporosis, multiple sclerosis). Surgery has unique demands which would support intake in excess of 2000 IU per day for a controlled, short peri-operative course as a most conservative measure.

Note that toxicity typically requires extremely high levels of vitamin D, with some experts suggesting 40,000 IU per day as a benchmark level of concern. Research published since 1997 suggests that the upper intake level is overly conservative and that vitamin D toxicity is highly unlikely in healthy people at intake levels less than 10,000 IU per day.

Vitamin D recommended for the surgical patient: Vitamin D3 (cholecalciferol):
1000-5000 IU/day

RDA: No values have been established. However adequate intake (AI) values from the FDA have been set at 200 IU for < 50-yr-old, 400 IU for 50-70-yr-old, and 600 IU for > 70-yr-old.

Vitamins K1 & K2

Vitamin K is a fat-soluble group of vitamins with primary effect as related to protein functioning in the normal clotting cascade, though the vitamin K family has a much broader range of effects that extend well beyond those related to blood clotting. There are two broad forms of vitamin K: vitamin K1, and vitamin K2. Vitamin K2 is synthesized by bacteria in a range of forms, while vitamin K1 is synthesized primarily by plants as phylloquinone. Phylloquinone represents the major dietary form of vitamin K, and has effects that are distinct from the effects of vitamin K2. The mail role of vitamin K1 is in clotting and in reparative cell growth, both important factors in the scope of surgery and wound healing. The primary role for vitamin K2 is in cell growth and in bone mineralization, as well as other actions. Overt vitamin K1 deficiency can result in impaired coagulation with increased bleeding times and operative bleeding. Fortunately, this is not common, but would be of obvious issue in the per-operative setting. The role for vitamin K2 with respect to osteoporosis, fracture healing and bone metabolism is rapidly evolving, with markedly increasing clinical application for fracture treatment and prevention in Europe and Japan.

Much has been written about the opposed effects of vitamin K1 and blood thinners (such as warfarin/Coumadin) that are sometimes used after total hip replacement, hip hemiarthroplasty, and other similar procedures. A post-operative course of Coumadin (warfarin) is sometimes used in these settings to help minimize the risk of lower extremity blood clots, deep venous thrombosis (DVT), and pulmonary embolus.

It is important to recognize that excessive vitamin K and widely variable daily dietary intake of vitamin K can each make the predictable management of warfarin challenging after surgery. This is true even when warfarin is dosed using leading-edge genetically-specific dosing protocols to optimize blood thinner programs for a given individual. Accordingly, The American Academy of Orthopaedic Surgeons and other groups recommend that patients taking blood thinners such as warfarin after hip surgery or total knee replacement should avoid excessive dietary intake of vitamin K as a means of helping to minimize these concerns. However, the dominant focus in warfarin management has shifted from the given level of vitamin K intake, to concern related to the relative day-to-day variability in intake a primary concern.

Most clinical experts accordingly recommend a diet to include a regular and non-variable daily intake of vitamin K as a best strategy to safely balance the potential difficulties with excessive vitamin K against the known important advantages of an adequate daily oral intake of vitamin K1 and K2 (to promote bone mineralization and reparative cell growth). These vitamin K effects have particular importance after reconstructive orthopaedic and spinal procedures, especially with surgery or joint implants requiring bone in-growth or bone healing. An exogenous source of oral vitamin K2 is also important peri-operatively since the limited primary source of endogenous vitamin K2 is intestinal bacterial flora which may be disrupted by usual peri-operative antibiotics; there are not dense food-based sources of vitamin K2.

Although vitamin K is a fat-soluble vitamin, the body has little potential for vitamin K storage, so regular consistent daily intake is required to support its role in bone healing and cell growth. Finally, the human body's inability to store vitamin K is exaggerated further when patients are taking warfarin, as warfarin itself disrupts the body's vitamin K recycling system.

The above balanced goals in mind, most clinical experts presently recommend a:

» A relatively constant and non-variable daily dietary supplement intake of vitamin K1 and K2 (to support post-surgical reparative cell growth and bone mineralization)

- Achieving the above with vitamin K amounts that are tailored to meet the higher demands as specific to surgery, particularly bone and joint procedures.
- This would especially include patients on warfarin or other vitamin K antagonists that cause known disruption of the body's vitamin K recycling system, as these patients are most prone to deficiency without daily intake.

Vitamin K recommended for the orthopaedic surgery patient:

K1 = 500mcg/day

K2 = 5-15mcg/daily (preferably as MK-4, menatetranone)

The above important goals are best met by a directed, pharmaceutically-pure vitamin K1 & K2 supplementation program (that will provide a predictable, stable daily dose of vitamin K), in conjunction with a patient recommendations for non-excessive, consistent volume, once a day whole-food intake of leafy greens (ie, one salad of consistent size, once a day).

Foods that are known to be unusually high in vitamin K best avoided and most include kale, collards, turnip greens, Swiss chard, raw parsley, broccoli, spinach, Brussels sprouts and soybean oil. Recommendations of this nature should be reasonably included as part of pre-operative total joint replacement patient education programs ("Joint School" or "Joint Camp" programs) or in similar settings requiring peri-operative management of vitamin K antagonists.

RDA: 90 mcg/day (for men and women > 18 yrs old)

Manganese

Manganese is known to have diverse physiologic effects, many of which remain incompletely understood. Known functions include those related to its anti-oxidative effect, cellular metabolism, bone and cartilage growth and health[35], and wound healing. Manganese is responsible for prolidase activation, which in turns produces proline, an amino acid that plays a pivotal role in collagen formation and stability. Both topical (manganese mineral salts) and oral applications have been described with respect to wound healing in particular.[9,46]

Chebassier presented insights in 2004 in looking at the stimulatory effect of both boron and manganese on keritinocyte migration as related to wound healing. Their work documented a 20% acceleration of wound closure as compared to the matched control. Further analysis prompted their conclusion that the documented acceleration in wound healing was prompted by an increased keritinocyte migration response (as opposed to proliferation).[9]

Recommendation for manganese in the peri-operative patient: 1.5 mg/day
(limited to 3 months peri-operatively before a return RDA levels)

A single case report for supplement-related oral manganese toxicity describes a person taking high-dose mineral supplements for a period of years. It is a singular isolated report (without correlate), and there are certainly no know instances of toxicity for those taking elevated mineral supplement levels for shorter durations (months).

RDA: not established, but AI levels range from 1.6-2.3mg/day depending upon age and gender. The tolerable upper limit is 11 mg/day for adults.

Zinc

Zinc is an essential trace mineral, and over 300 enzymes require zinc for their activities. These numerous cellular zinc-dependent processes include catalytic, structural, and regulatory roles in DNA synthesis, cell division, protein synthesis, cell signaling, anti-oxidant function and beyond.[5]

Zinc has been widely researched for its effects on wound healing [36,45], and zinc deficiency is well associated with poor wound healing and decreased biomechanical integrity of healing wounds and soft tissue.[2] These effects have been attributed to decreased collagen and protein synthesis, affecting a broad range of healing tissues to include skin, muscle, tendon, ligament and bone. In skin, zinc has been shown to enhance healing by facilitating keritinocyte migration through several mechanisms, to include integrin modulation.[57] Zinc demands are believed to be highest during phase I of wound healing (immediately following injury) [36], emphasizing the importance of preemptively optimized zinc levels in the surgical patient. It has been suggested that the marked demand for zinc after surgery and wounding exposes marginal relative zinc deficiencies that would have otherwise have been without clinical impact in humans.[53]

The wound healing properties may extend to include vascular tissue repair as well. Kaji et al reported their in vitro work investigating the role for zinc in promoting the repair of wounded monolayers of cultured vascular endothelial cells. Both the appearance and number of cells was markedly improved in the zinc-treated group, with other results suggesting that zinc promotes the visualized repair process of damaged vascular endothelium through the lipoxegenase pathway (that modulates the cellular response to endogenous bFGF).[34]

Recommendation for zinc in the surgical patient: 25-40 mg/day

This is an elevated dose versus the RDA, and is targeted to meet the expected increased demands imposed by surgical wounding as outlined, when taken pre-operatively. This is of additional importance, appreciating present sentiment that zinc deficiency in humans is common and under-recognized. The elevated peri-operative dose recommended peri-operatively is far below the levels associated with mild GI side effects that are reported in isolated individuals taking 50-150mg/day of supplemental zinc. Prolonged excessive zinc intake can interfere with copper and iron absorption and metabolism.

RDA: 8 mg/day for women and 11 mg/day for men.

Vitamin E

The term vitamin E actually describes at least twelve discreet compounds, though of these, the tocopherols, and alpha-tocopherol in particular, are those with greatest nutritional significance in humans. The topic of vitamin E and wound healing is of some controversy. Together, the best available literature addressing vitamin E and wound healing leads to several possible conclusions: 1) systemic vitamin E may have a negative impact on surgical wounds as secondary to its lysosomal-stabilizing properties, 2) vitamin A may have a role in mitigating some of these potentially adverse effects, and 3) hydrophilic and hydrophobic preparations of vitamin E may have distinct effects as related to healing.[40]

Of potentially greater issue in the operative setting are the vitamin E effects related to increased intra-operative hemorrhage. There are multiple reports of increased bleeding as attributed to vitamin E effects [13,32], particularly with higher-dose vitamin E, and most authors join the American Academy of Anesthesiology, American Academy of Orthopaedic Surgeons, American College of Surgeons and others in recommending against peri-operative vitamin E supplementation. This has been offset by more recent studies indication that moderate-dose supplemental vitamin E protocols can maintain the integrity of physiologic benefit from vitamin E, while obviating the bleeding issues associated with higher doses.[16] At least one study investigated the effect of supplemental vitamin E on bleeding time in healthy volunteers using two weeks of 800 IU/day in healthy volunteers; this is a dose substantially above the recommended daily intake of 30 IU/day, though no significant effect on bleeding time was noted. Though this is encouraging for those that might benefit from elevated vitamin E

dosing, a risk-benefit analysis of available studies would favor avoiding vitamin E peri-operatively from a safety standpoint at this time. Our subsequent recommendation remains tempered on the side of caution for peri-operative patients until further research proves to the contrary. This prudent approach is similar to that is also supported for avoidance of herbal medicines and compounds in the peri-operative setting. Herbal medicines can have great benefit, and are often remarkably potent pharmacologically, though many herbal compounds are known to strongly and unpredictably potentiate the effects of general anesthetic, increase bleeding, and other varied effects that are simply unsafe in the critically-balanced operating room environment.[48]

Recommended vitamin E intake for the surgical patient: 7.5 mg/day

This low-dose regimen is sufficient to mitigate the low short-term potential for deficiency issues, while simultaneously absolutely minimizing potential for adverse anti-platelet of coagulation concerns attributed to higher-dose supplemental vitamin E programs.

RDA: 15 mg/day (22.4 IU/day). Established tolerable upper limits are 1000 mg/day (1500 IU/day). However, a meta-analysis of 135,967 patients enrolled in a total of 19 clinical trials by Miller ER 2005 demonstrated that vitamin E supplementation of over 400 IU/day was significantly linked to an increase in all cause mortality. (Miller ER 2005)

TIMING OF PERI-OPERATIVE VITAMIN AND MINERAL SUPPORT PROGRAMS

The pre-operative and post-operative time frames for a targeted peri-operative supplement optimization program that includes the above will vary considerably based upon the nature and magnitude of the surgery being planned, the patient's baseline health status, compounding medical issues, and other factors. In general and for most patients, a:

1. two to four week pre-surgical program, and
2. four to six week post-surgical regimen

will predictably meet the intended goals outlined above. These goals include fostering complete healing as rapidly as possible, with the greatest quality of healed tissue (biomechanical and cellular), and with the least amount of scarring to achieve optimal return to general health. There is also likely merit, though less so, for an isolated four to six week post-operative course for the patient having undergone urgent or emergent surgery (or in other situations in which an optimized pre-operative preparative vitamin and mineral course was not possible). Modifications to the above based upon patient health and other factors are reasonable considerations on an individualized basis.

Any other supplements should be stopped so as to not overlap with the outlined regimen optimized for surgery. This would particularly include discontinuing any herbal remedies or medicines, which most surgeons and anesthesiologists recommend be stopped for at least 2-3 weeks prior to surgery.

CONCLUSION

It is well accepted that ideal nutrition is often critical to proper healing of the surgical patient. This includes appropriate protein & lipid intake, carbohydrate intake, and other macro-nutritional factors, as well as the broad and often more complex micro-nutritional factors that are discussed as the focus of this work. Abundant nutritional information characterizing the role for vitamins and minerals in the support of wound and other types of tissue healing have been scientifically evolving for at least the past forty years. Even so, this body of information has been scattered widely over time and application in a manner unfavorable and frankly obscure to considering a directed, organized, comprehensive micronutrient approach for the peri-operative patient. However, once this body of knowledge is properly organized, aligned, integrated and applied to the specific goals of surgical recovery, a compelling basis and strategy for the use of peri-operative vitamins and mineral support for the surgical patient is clear.

If the principle objectives in incision and tissue healing after surgery are to achieve complete healing as rapidly as possible, with the greatest quality of healed tissue (biomechanical and cellular), and with the least amount of scarring to achieve optimal return to general health, then there is sound medical evidence to reasonably support the use of a targeted peri-operative micronutrient supplement program as outlined here. Use of such a specific vitamin and mineral supplemental nutrient regimen is further supported by both the safety of such a regimen in the operative / peri-operative window, and by the relatively low expense as relative to the wide array of potential benefits.

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