The Role of Amino Acid Supplementation in Orthopaedic Surgery

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ABSTRACT

The nutritional status of patients undergoing orthopaedic surgery has started to garner increasing attention in published literature. Notable previous evidence has demonstrated the negative effect of malnutrition on outcomes after orthopaedic procedures. Although there has been increased recognition of malnutrition as a risk factor for suboptimal outcomes, the use of nutritional supplementation to mitigate those risks is not well understood. The purpose of this review of most current literature on the topic is to introduce and elucidate the role of amino acid supplementation as a countermeasure to muscle loss and improvement of nutritional status in orthopaedic patients to improve results and outcomes after orthopaedic surgery.

Nutritional status has been recognized as a modifiable risk factor for improving postoperative outcomes in patients undergoing orthopaedic procedures.[1] More than half of the patients undergoing a major surgery have been shown to be malnourished or at risk of malnutrition, with evidence of nutritional status worsening over the course of a hospitalization.[2] Malnourished patients have increased risk of complications, longer lengths of stay, higher readmission rates, and higher mortality risk which in summation results in increased cost of care.[3] Phillips et al,[1] in their excellent review on screening and management of malnutrition in total joint arthroplasty patients, demonstrated that although no simple test for identifying a malnourished patients exists, a variety of laboratory markers have been previously used to identify and diagnose malnourished patients. Low serum albumin (<3.5 g/dL), low serum transferrin (<200 ug/dL), and a low total lymphocyte count (<1,500 cells/mm3) have all been reported as markers of malnutrition predictive of postoperative complications. Of these markers, albumin has been the most studied and consistently been shown to be a strong predictor of postoperative complications. When implemented in malnourished patients, nutritional supplementation has been shown to markedly reduce hospital costs by reducing rates of Intensive Care Unit (ICU) admissions, hospital-associated complications, and hospital-acquired infections.[4]

In addition to malnutrition, patients with sarcopenia, defined as progressive loss of muscle associated with natural aging, are specifically of interest to orthopaedic surgeons. Sarcopenia is highly prevalent in the elderly population, continues to increase with age and is strongly correlated with

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disability.[5] Muscle loss is further accelerated during times of injury, immobilization, and the stress of surgery. Maintaining skeletal muscle mass is essential to support whole-body protein metabolism, wound healing, physical strength, organ function, skin integrity, and immune function.[6] In populations compromised by lean body mass (LBM) loss, preserving or rebuilding LBM may reduce morbidity and mortality by enhancing muscle strength and physical function.[7]

Furthermore, optimizing nutritional status has demonstrated improved clinical outcomes and reduced postoperative complications in 'healthy' non-malnourished patients. Enhancing nutritional status resulting in improved outcomes in nonmalnourished patients reflects the increased nutritional demand caused by the stress and subsequent hypermetabolic response induced by injury and surgery. Multiple prospective randomized controlled trials have demonstrated that well-nourished patients have reduced risk of infection and decreased length of stay when provided targeted nutritional supplementation.[8,9] In patients undergoing total knee arthroplasty (TKA), for instance, a randomized double-blind placebo-controlled trial demonstrated notable reduction in muscle loss and improved strength with early functional recovery with the implementation of perioperative nutritional protocols.[10]

Despite extensive clinical data that support the link between poor nutrition and increases in postoperative complications and adverse outcomes in surgical patients, nutritional supplementation is underutilized within the practice of orthopaedics. Physician time constraints and lack of nutritional training and resources, along with a lack of standardization pose potential barriers to implementing nutritional support as a routine part of the perioperative process. The purpose of this review was to serve as a brief introduction to targeted nutritional supplementation.

Essential Amino Acids and Their Role in Mitigating Sarcopenia

Although protein intake is essential for modulation of surgical stress and enhancing recovery, surgical patients have been shown to only consume about 22 to 36% of estimated requirements.[11] Given the increased incidence of sarcopenia in older adults, the consequences of inadequate protein intake are even more essential to consider. Malnutrition in older patients is associated with worsened strength, function, independence, and increased risk of mortality.[11]

Multiple studies have demonstrated notable decreases in postoperative complications, length of stay, cost, and readmission rates in elective total joint arthroplasty and spine fusion patients who were provided a high protein diet intervention.[12,13] While whole-food sources of high-quality protein should be incorporated in all patients' diets, it can be logistically challenging to consume large amounts of protein without taking in excess calories, which can lead to unwanted weight gain. Protein supplements are more concentrated and contain a more direct form of amino acids, thus can stimulate a stronger anabolic effect than dietary protein.[14] In the perioperative setting, protein or direct amino acid supplementation can be beneficial and easier to implement.

Amino acids are the building blocks of protein and play a central role in muscle protein synthesis and repair. Essential amino acids (EAAs) cannot be produced by metabolic pathways and must come from the diet. There are nine EAAs: histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine. Free form EAAs can be absorbed rapidly and used directly by muscle to trigger a greater anabolic response in comparison with dietary protein and/or protein supplements.[14] Advances in EAA research have specified the key amino acids that can lead to an increased anabolic response.

EAA supplementation has been shown to mitigate muscle wasting related to both injury-induced immobility and periods of immobilization necessitated by surgical fixation (eg, periods of non-weight bearing or partial weight bearing) commonly seen in the postinjury and postoperative period.[10,15] Aquilani et al[16] demonstrated in a randomized control trial of EAA supplementation in patients with hip fractures demonstrated that patients undergoing hip fracture surgery supplemented with EAAs had markedly enhanced functional recovery as measured by a 67% increase in a 6-min walk distance in comparison with a placebo control group. Baldissarro et al[17] randomized patients undergoing electively total hip arthroplasty to 14 day supplementation of EAAs compared with placebo and demonstrated enhanced postoperative functional recovery measured by Harris hip score in patients who were supplemented with EAAs. Studies evaluating EAA supplementation after TKA all demonstrated decreased muscle loss after surgery and improved recovery of functional mobility including rectus femoris muscle volume and quadriceps muscle strength up to 2 years after surgery.[10,15,18]

In summary, literature supports the clinical efficacy of EAA supplementation in not just mitigating sarcopenia because of immobility and immobilization but also improved functional recovery postoperatively (Table 1).

Table 1. **Highlighted Literature With Commonly Used Amino Acid Supplementation With Dosages, Duration, and Clinical Setting**

Amino Acid Supplement	Published Dosage	Duration	Clinical Setting	Result	Citation
Essential amino acids	20 g EAAs twice a day (2.2 g histidine, 2.0 g isoleucine, 3.6 g leucine, 0.6 g methionine, 3.2 g phenylalanine, 2.8 g threonine, 2.4 g valine)	1 week preoperatively 6 weeks postoperatively	Primary unilateral total knee arthroplasty	↓ decrease in mean quadriceps and hamstring volume on MRI	Dreyer et al
Essential amino acids	9 g EAAs	1 week preoperatively 2 weeks postoperatively	Primary unilateral total knee arthroplasty	↓ decrease in rectus femoris atrophy ↑ serum albumin ↓ VAS	Ueyama et al
HMB/Arg/Gln	2.4 g HMB, 14 g arginine, 14 g glutamine twice a day	5 days preoperatively 4 weeks postoperatively	Primary unilateral total knee arthroplasty	↓ decrease in quadriceps muscle strength	Nishikzaki et al
HMB/Arg/Gln	1.5 g HMB, 7 g arginine, 7 g glutamine twice a day	2 weeks postoperatively	Pelvis and extremity fracture indicated for fixation	↓ overall complications ↑ fat-free mass (body composition)	Hendrickson et al
HMB + vitamin D	3 g CaHMB, 1000 IU vitamin D twice a day	30 days postoperatively	>65 year hip fracture	↓ wound healing duration ↑ mobility at 15 and 30 days ↑ muscle strength	Ekinci et al
CrM + HMB	3-10 g/d of CrM, 3 g/d of HMB	1-6 weeks	Sports performance	↑ strength and anaerobic performance ↑ fat-free mass ↓ fat mass	Fernandez-Landa et al
Cystine, theanine	700 mg cystine, 280 mg theanine daily	2 weeks	Sports performance	↓ exercise induced neurophilia and lymphopenia	Murakami et al

EAA = essential amino acids, VAS = Visual Analogue Scale

Conditionally Essential Amino Acids—Role of L-Arginine as an Adjunct to Accelerate Wound Healing and the Anticatabolic Effects of Glutamine

Conditionally EAA (CEAAs) are non–essential amino acids that become essential during periods of physiological stress. Two well-studied CEAAs as related to healing and musculoskeletal recovery are L-arginine and L-glutamine.

Arginine functions in the body as a substrate for protein synthesis, cell proliferation, neurotransmission, vasodilation, calcium release, immune function, and wound healing.[19] Arginine depletes rapidly during times of stress; therefore, replenishing arginine levels has been considered an adjunctive treatment to accelerate wound healing.[19] Metabolically, arginine is a precursor to proline, therefore is recruited specifically for collagen synthesis. It is also a precursor to ornithine, which is critical for nitric oxide synthesis. Mechanistically, nitric oxide is a signaling molecule that triggers blood vessel dilation which leads to increased blood flow, thus supporting wound healing.

A clinical study relating to collagen deposition evaluated the effect of 2 weeks of CEAA supplementation demonstrated a 67% increase in subcutaneous collagen deposition compared with a control group.[20] Potential benefits of this collagen response from CEAA supplementation in the setting of orthopaedic soft-tissue procedures such as anterior cruciate ligament reconstruction and rotator cuff repair would be of great value in promoting healing and merit further investigation. In addition, L-arginine has been shown to support immune function postoperatively and is correlated with lower rates of surgical site infection.[21] Arginine has also been shown to improve exercise performance. A double-blind Randomized Control Trial (RCT) in athletes demonstrated that arginine supplementation correlated with markedly higher increases in VO2 max testing compared with placebo.[22]

Glutamine is used as an energy source after a stress response and protects against excessive inflammatory injury by inducing the expression of heat shock proteins, which provide cellular protection in states of inflammation, injury, and stress. Glutamine supplementation has also been suggested to support muscle recovery in athletes such as professional basketball players given its anabolic properties.[23] In addition, glutamine is the primary fuel source for rapidly dividing cells, such as epithelial cells during wound healing. Glutamine has potent anticatabolic properties and is a rate-limiting agent for new muscle protein synthesis.[7] Glutamine has been shown to be an important nutritional need in catabolic states and has been noted to have positive effect on healing of traumatically fractures bones through attainment of positive nitrogen balance in small animal models.[24]

The combination of CEAA supplementation has been previously studied in orthopaedic surgery patients. Nishizaki et al[25] demonstrated enhanced postoperative quadriceps muscle strength recovery after TKA in patients supplemented with a combination of CEAAs L-arginine and L-glutamine with beta-hydroxy-beta-methyl butyrate (hydroxy methyl butyrate (HMB)), because of possible synergistic effects. Hendrickson et al[26] demonstrated in a randomized control trial that CEAA supplementation with 7 g of arginine and 7 g of glutamine twice daily for 2 weeks postoperatively reduced postoperative complications and muscle wasting after fracture fixation without any reported adverse events related to amino acid supplementation.

In summary, CEAA supplementation appears to play a role in assisting wound healing and preventing muscle wasting across multiple studies and thus should be considered a target for adequate nutritional supplementation in orthopaedic patients (Table 1).

Beta-Hydroxy Methyl Butyrate Supplementation in Preserving Lean Body Mass

HMB is a metabolite of leucine, a branched-chain essential amino acid. HMB has several metabolic functions including protein metabolism and muscle hypertrophy and insulin modulation. Typical dietary intake of HMB ranges from 0.25 to 1 g daily. HMB has been used by athletes because its ergogenic effects can enhance performance and build muscle mass. More recent research has focused on the use of HMB to mitigate muscle loss in posttraumatic and postsurgical patients.[27] The ergogenic effects of HMB supplementation are likely to result in mitigation of protein metabolism and the regulation of enzymes associated with protein catabolism during times of stress such as orthopaedic injuries and surgical procedures.[27]

HMB has been shown to stimulate protein synthesis by activating the mammalian target of rapamycin pathway, upregulating the repair rate of muscle and tendon tissue, and mitigating myofibrillar degradation, thereby minimizing muscle loss.[28] HMB supplementation also appears to be safe, with no deleterious effects on levels of cholesterol, blood glucose, and biomarkers of liver and kidney function. Baier et al[29] demonstrated in a yearlong study with HMB supplementation demonstrated safety and efficacy in increasing protein turnover and lean tissue in elderly patients. Ekinci et al[30] used an enteral product containing 3 g of calcium-HMB and 1000 IU vitamin D in addition to standard postoperative nutrition in a randomized control trial of patients after hip fracture fixation, and found increased rates of wound healing, shorter periods of immobilization, reduced dependence to bed rest and associated complications to bed rest, and increased strength without any reported supplement associated adverse events.

Given its safety and efficacy, HMB may be an ideal supplement during periods of immobilization in patients with orthopaedic injuries and after orthopaedic surgical procedures (Table 1).

Creatine Monohydrate Enhances Bone Remodeling and Mitigates Muscle Atrophy

Creatine is an organic compound that is synthesized in the body from the amino acids including arginine, methionine, and glycine. Approximately 95% of all creatine is stored within skeletal muscle, and intramuscular stores of creatine can be increased by supplementation.[31] Creatine's primary function is to prevent adenosine triphosphate depletion but has been shown to provide other positive benefits of health, including increased LBM, reduced protein degradation, antioxidant-mediated protection, and support of energy transfer from the mitochondria to the cytosol.[32] Creatine monohydrate (CrM) is the most studied and bioavailable form of creatine.

CrM supplementation combined with resistance training enhances gains in strength in both young and elderly patients, and its role in improving LBM with its safety of use as a supplement has been previously demonstrated.[33] Although several studies have documented potential benefits of CrM and hydroxy methyl butyrate (HMB) separately, newer evidence suggests a potential synergy between the two supplements when taken concurrently. In a recent systematic review, Fernandez-Landa et al showed that the use of 3 to 10 g of CrM daily combined with 3 g of HMB daily lead to positive effects on measures of strength, anaerobic performance, and lean body mass in comparison with individual supplementation of CrM and HMB, respectively.[34]

In summary, CrM either in isolation or in addition to HMB could be a potentially advantageous supplement in orthopaedic patients (Table 1).

Catabolic Stress Reduction Through Cystine/Theanine Supplementation

Cystine is a non–essential amino acid contained in many food materials including meat and is converted to cysteine by thioredoxin before being incorporated into cells. Theanine is decomposed to glutamic acid and ethylamine in the body. After entering cells, cysteine and glutamic acid are used together with glycine for the synthesis of GSH, one of the substances with the strongest antioxidant effects in the body and important for adjusting immune function.[35] Therefore, cystine and theanine have been termed as stress-reducing amino acids.

A reduction of the catabolic stress of surgery itself is one of the most important elements in enhanced recovery after surgery perioperative management protocols. Regarding perioperative nutritional optimization, enhanced recovery after surgery recommendations include the following four elements: removal of the preoperative fasting period, carbohydrate loading up to 2 hours before surgery, early initiation of postoperative oral ingestion, and promotion of intestinal motility. The usefulness of early initiation of enteral nutrition in the perioperative period for nutritional optimization is widely recognized, but similar stress-reducing effects of the orally ingested amino acids, cystine and theanine, which induce an increase in glutathione (GSH), have been reported.[36]

Supplementation with the amino acids cystine/theanine exhibit notable stress-reducing effects through anti-inflammatory and immune-modulating properties. These potent immune-modulating effects have been studied in various settings including postsurgical patients and high-level athletes.[37,38] For instance, Miyachi et al[37] published a randomized single-blind parallel group study in patients undergoing gastrectomy and demonstrated that ingestion of cystine (700 mg) and theanine (280 mg) for 10 days from 5 days before surgery inhibited a postoperative increase in resting energy expenditure; promoted recovery from changes in interleukin-6, C-reactive protein, lymphocyte ratio, and granulocyte ratio; and inhibited an increase in body temperature. Markedly increased C-Reactive Protein (CRP) levels, increased neutrophil counts, and decreased lymphocyte count in athletes after strenuous exercise has been studied, and excessive inflammation and immune suppression after exercise were reduced by administration of cystine and theanine.[38]

These results suggest that cystine and theanine can suppress excessive inflammation and increase the immune response after invasive processes, such as exercise or surgery. The goal of a comprehensive perioperative nutritional therapy should address not only supplementation of protein elements and lost energy but also specifically include early reduction of the stress response of surgery. The dose in clinical studies is 700 mg of cystine and 280 mg of theanine, well-tolerated, compliance with ingestion is high, and their use is versatile and safe.[37]

In summary, supplementation of amino acids such as cystine and theanine for patients undergoing orthopaedic surgery could stand to benefit from reduction in catabolic stress reduction through novel nutritional pathways which should be studied (Table 1).

Summary

Nutritional status is a modifiable risk factor that is underutilized in the recovery from orthopaedic surgery. The increased stress and hypermetabolic response to injury and surgery can lead to depletion of essential nutrients and metabolites. This hypercatabolic state triggers the body to break down skeletal muscle to support the increasing demand for these nutrients and metabolites. There is evidence to support improving nutritional status by supplementation in many populations including the malnourished, elderly, and 'healthy' individuals. Targeted nutritional supplementation may mitigate muscle degradation and promote collagen synthesis and wound healing. Nutritional supplementation can reduce the rate of postoperative complications regardless of baseline nutritional status.

There is currently a gap between the evidence and clinical practice, which supports the need for further research, education, and validation of the clinical implications of perioperative and peri-injury nutritional supplementation. There might be a role for increased utilization of registered dieticians and certified nutrition specialists to either design custom perioperative nutritional plans for malnourished patients undergoing orthopaedic surgery or to establish institutional protocols for standardized perioperative nutritional protocols for all patients. Strategic implementation of protocols supported by evidence of clinically effective supplements would likely lead to improved clinical outcomes and decrease the financial burden that is tied to complications of injury and surgery.

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