

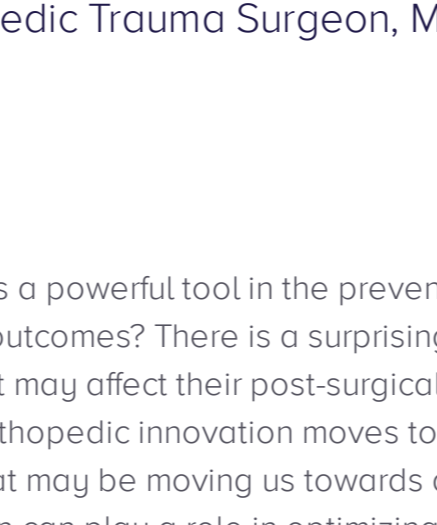


## Perioperative Nutrition: The Next Big Focus of Orthopedic Research?

September 17, 2022 | Article No. 107

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### Guest Contributor



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Fat well, be well. While not quite this simple, nutrition is a powerful tool in the preventative medicine toolkit. But does perioperative nutrition really have the potential to improve surgical outcomes? There is a surprising amount of evidence to suggest that this is the case, especially for patients with pre-existing conditions that may affect their post-surgical recovery. This relatively small but growing field of research is being predicted to have a big impact as orthopedic innovation moves towards perioperative care interventions. In this OE Insight, we reflect on the future of patient care and what may be moving us towards a focus on nutrition. We also discuss the surgical stress response, the risks associated with it, and how nutrition can play a role in optimizing healing and recovery for orthopedic patients.

### Insights

- Despite its currently siloed existence, nutrition is becoming increasingly realized as an important component of perioperative patient care. Unrecognized malnutrition can affect up to 50% of hospitalized patients.
- Pre-surgical malnutrition is commonly associated with increased risk for surgical site infections, longer hospital stays, and increased health care costs.
- Surgery initiates a cascade of inflammatory, immune, and metabolic responses which can be mitigated in several ways through nutrition.
- Carbohydrate loading, oral nutritional supplements, amino acid supplementation and immunonutrition have all been used to successfully regulate energy and protein metabolism during the surgical stress response.
- These interventions can lead to a reduced risk of postoperative complications and mortality, shorter hospital stays, and improved cost-effectiveness.
- Nutrition screening and patient pathways such as the one established by the Perioperative Enhancement Team (POET) at Duke University Hospital are working to screen surgical patients for risk of malnutrition.
- The timely and effective screening of these patients allows for appropriate nutritional interventions to be applied and the metabolic and catabolic changes associated with the surgical stress response to be mitigated.

### Towards Nutrition

In his book *Zero to One: Notes on Startups, or How to Build the Future*, Peter Thiel, outspoken investor and co-founder of PayPal, shares unconventional wisdom for entrepreneurs and makes thought-provoking predictions for the future. (1) According to Thiel, when it comes to start-ups, the key is to look for secrets – and the best place to look is where no one else is looking. Interestingly, he uses the field of nutrition as his main example:

“Most people think only in terms of what they’ve been taught; schooling itself aims to impart conventional wisdom. So, you might ask: are there any fields that matter but haven’t been standardized and institutionalized? Physics, for example, is a real major at all major universities, and it’s set in its ways. What about something like nutrition? Nutrition matters for everybody, but you can’t major in it at Harvard. Most top scientists go into other fields. Most of the big studies were done 30 or 40 years ago, and most are seriously flawed... There’s plenty more to learn: we know more about the physics of faraway stars than we know about human nutrition.” (1)

Some may add that Nutrition does, in fact, exist as a major at many established universities and is regulated in conjunction with many science-driven, national professional associations. However, perhaps what rings most true for healthcare is that nutrition is not necessarily an area of focus. According to Babjar (2019), “nutrition science is currently viewed as part of healthcare, in a separate silo” and is “not viewed as a specialty partner with everyday presence.” (2) As a result, Babjar suggests that there is much more we could know and much more we should do to address the disconnect that exists between medicine and nutrition, stating that “research on nutrition is unrecognized and lacking” and “from the office to the bedside, from cellular to clinical research, nutrition science must become part of everyday medicine.” (2) A thought also captured by Crowley et al. (2019) in their systematic review of nutrition in medical education. (3) Overall, it was found that despite its recognized centrality to the health of patients, affecting up to 50% of hospitalized patients (6), nutrition was insufficiently integrated into medical education around the world. As a result, “medical students are not supported to provide high-quality, effective nutrition care.” (3). Furthermore, there is debate within the nutritional science community as to what dietary lifestyle contributes most significantly to longevity and overall health.

Yet, the future is always bright. As Babjar writes, “research and healthcare delivery of nutrition has the opportunity to transform.” (2)

In a recent OrthoJoe conversation regarding a new study published in the *Journal of Bone and Joint Surgery (JBJS)*, Mohit Bhandari, founder and editor in chief of OrthoEvidence (OE), and Marc Swintkowski, editor in chief of JBJS, discuss the growing importance of perioperative care research, like nutrition, and highlight its role in advancing the field of orthopedics. (4) (Link: [OrthoJoe Falsehood 39](#))

“Big innovations now are not going to come from implant design... Real advances are going to come from perioperative care. What does that look like? That’s going to be anything from when you get surgery, to how you condition for surgery, to what sort of rehab you get, and absolutely this is pretty exciting, that you can maintain lean mass [through perioperative nutrition]... Perioperative care is gaining more and more importance as an area of real focus for surgical outcomes.” (4)

Mohit Bhandari

“It’s really not a new nail, or a different neck shaft angle in an implant, or a head size anymore, it’s preoperative considerations and postoperative rehabilitation that’s going to advance our field collectively.” (4)

Marc Swintkowski

The JBJS article being discussed by Hendrickson et al. (2022), investigated conditionally essential amino acid supplementation for trauma patients with pelvic or extremity fractures that were indicated for operative fixation. (5) It’s one of many new clinical trials in a line of research focusing on perioperative nutrition to improve surgical outcomes. According to the OE Ongoing Trial tool, a tool that is powered by data from clinical trials.gov, there are currently 45 ongoing clinical trials investigating perioperative nutrition for orthopedic patients. Of the 41 trials reporting a specific indication, the most commonly investigated conditions were sarcopenia (24.5%) and fracture (19.5%). Of the 28 trials reporting anatomical region, 32.2% related to lower extremity and 28.6% related to the hip. Currently, nutrition-related Advanced Clinical Evidence (ACE) reports in the OE database are read mainly by orthopedic surgeons (46.5%) and physiotherapists (26.3%), especially those pertaining to fracture (75%).

### The “Surgical Cascade”

Surgery stimulates what Hirsch et al. (2021) have described as a “cascade of inflammatory, immune, and metabolic responses that result in a hypermetabolic-catabolic state.” (6) In an effort to meet energy demands and promote wound healing, there is significant upregulation of glucagon, cortisol, and proinflammatory cytokines. (6) This upregulation leads to significant catabolism of hepatic and muscle glycogen and upregulated gluconeogenesis in the liver, causing elevated blood glucose levels. (6)(7) Elevated catabolic hormone levels also interfere with insulin secretion, leading to post-surgical insulin resistance which further contributes to the hyperglycemic state, something that can last from several days to weeks after surgery. (6)(7) Upregulated gluconeogenesis also increases the demand for amino acids, especially those which are conditionally essential. (Callout: “Certain amino acids are considered conditionally essential because the body cannot synthesize them in sufficient quantities during certain physiological periods of growth, including pregnancy, adolescent growth, or recovery from trauma.” (8)), such as glutamine and arginine; a need that is met by decreased protein synthesis and increased protein catabolism. (6)(7)

The magnitude of this stress response also depends on the magnitude of surgery being performed. For patients undergoing more major surgery, such as total joint replacement or open fracture fixation, this stress response will be elevated and metabolic changes will take longer to normalize following surgery. (7)(13) According to Finnerty et al. (2013), while this response is initially beneficial to the patient, “the exaggerated and prolonged inflammatory, metabolic, and catabolic responses induce clinical complications, delay recovery, and increase mortality.” (7)

### Patient Risks

One primary concern for patients, especially those with specific pre-existing conditions such as diabetes, is that uncontrolled post-surgical insulin resistance can lead to impaired immune function and wound healing, thus increasing the risk of infection and mortality. (6) Moorthy et al. (2019) also found women, older, more obese, and hypertensive patients tended to be at higher risk of developing postoperative hyperglycemia. (26) A study by Sato et al. (2016) found that, for both diabetic and non-diabetic patients undergoing cardiac surgery, a 50% decrease in insulin sensitivity resulted in a 5-6-fold increase in the risk of complications and a 10-fold increase in the risk of severe infection. (9) In orthopedic trauma patients with no history of diabetes, Kurunaka et al. (2010) found that a mean perioperative glucose level greater than 220 mg/dL was associated with a seven times higher risk of infection. (14)

Another concern for surgical patients is the elevated protein catabolism and eventual breakdown of skeletal muscle that occurs in order to provide the amino acid precursors for gluconeogenesis, wound healing, and immune function. (6) This increased protein metabolism has the potential to impede healing and increase morbidity, especially for patients with limited protein stores, such as those with low lean body mass and protein-energy malnutrition (PEM). (6)(7) A study by Zhang et al. (2022) found that patients with PEM had a 1.5-fold risk of in-hospital mortality. Additionally, these patients had a longer hospital stay and higher total hospital costs compared to those without PEM. (10) A study by Greene et al. (2010) found that patients who were malnourished, with a serum albumin <3.5 g/dL, had a seven-fold greater risk of major wound complication. (15). Further, malnutrition can be seen in 50% or more of those patients admitted with a hip fracture and undergoing operative treatment. This has further been associated with increases in mortality in this patient population. (27) (28) Another issue comprising the postoperative nutritional state is that significant skeletal muscle atrophy can occur as a result of immobilization, commonly seen after orthopaedic operations. The loss of muscle volume can impact strength, functionality, and impair recovery, especially over longer periods of immobilization. (6) A study by Kiroe et al. (2020) found that in healthy, young, male patients who underwent 7 days of unilateral knee immobilization with a knee brace, total thigh volume decreased by 5.5%. This decrease in volume was also accompanied by significant decreases in leg extensor (+19%), leg press (-21%), and calf strength (-8%). (11) This deterioration of skeletal muscle is even more pronounced in older patients, with a study by Dreyer et al. (2015) estimating that atrophy in patients over 65 years of age recovering total knee arthroplasty occurred at around 1% per day. (12)

### Nutritional Interventions

The potential to mitigate these surgical risks by modulating this stress response through appropriate nutrition is precisely what makes preoperative nutritional interventions so enthralling. For the most part, nutritional strategies are aimed at meeting nutritional needs perioperatively, working to manage post-surgical insulin resistance and reduce muscle atrophy. (6)

#### Pre-Operative Carbohydrate Loading

According to a 2012 meta-analysis by Awad et al., oral carbohydrates administered 2-4 hours pre-anesthesia resulted in reduced postoperative insulin resistance as well as a reduced hospital stay compared to patients undergoing a normal fasting protocol. However, significant heterogeneity was found in the 21 included studies and therefore quality of evidence was considered low to moderate. (16) The authors also mention that these proposed benefits of preoperative carbohydrate loading may also extend to decrease protein catabolism and reduce the loss of lean body mass. (16) Preoperative carbohydrate loading is now a component of the enhanced recovery after surgery (ERAS) paradigm, challenging the pre-existing guideline that recommended a period of prolonged fasting prior to anaesthesia. (17)

#### Oral Nutritional Supplements

Oral nutritional supplements (ONS) are typically high energy, high protein beverages that also contain many other important macronutrients. (18) They leverage the different actions of carbohydrates and improve a malnourished patient’s condition, optimize protein glucose levels, stimulate protein synthesis, and improve surgical outcomes. (6) A study done by Xie et al. (2022) found that ONS can help to improve nutrient intake, weight, and body mass index in patients screened for potential nutrition risk. (19) Botello-Carretero et al. (2010) found that perioperative ONS in patients undergoing surgery for hip fracture helped to decrease the (9) in serum albumin experienced post-operatively and decrease the risk of postoperative complications. (20) Another study by Eneroth et al. (2006) also found benefits of ONS for hip fracture patients, finding that ONS administered consecutively for 10 days reduced the risk of fracture-related complications from 70% in the control group, to just 15%. (21) According to Hirsch et al. (2021), ONS have also been found to reduce the net cost associated with hospitalization by an average of 12.2% and that these cost savings were associated with reduced complications (-35%) and length of stay (-2 days). (6)

#### Amino Acid Supplementation

The main goal of amino acid supplementation is to mitigate muscle atrophy after surgery. (22) A study by Dreyer et al. (2018) found that an essential amino acids (EAA) supplement, amino acids that can only be obtained through diet (consisting of histidine, isoleucine, leucine, lysine, methionine, phenylalanine, threonine and valine), reduced the loss of muscle volume when administered 7 days preoperatively and 6 weeks postoperatively in patients recovering from total knee arthroplasty. However, there were no differences found in functional outcomes between the EAA group and control. (22) Investigating supplementation with conditionally essential amino acids (CEAA) (including arginine, cysteine, glutamine, tyrosine, glycine, ornithine, proline, and serine), Hendrickson et al. (2022) found that patients indicated for operative fixation of extremity and pelvic fractures, CEAA led to significantly less complications compared to control (30.5% vs 43.8%). Additionally, fat free mass (FFM) was maintained in the CEAA group compared to the control group, which saw FFM decrease 6 weeks postoperatively. (5)

#### Immunonutrition

Immunonutrition supplements were created to help modulate immunity and contain a mix of amino acids such as arginine and glutamine, fish oil, and nucleotides. (23) A study by Gonçalves et al. (2021) investigating immunonutrition for TKA and THA patients found that immunonutrition decreased length of stay, reduced postoperative infectious and non-infectious complications, and lowered rates of transfusion or intensive care unit stay. (23) These findings are similar to findings from Alito et al. (2016) that also showed immunonutrition, in this case combined with accelerated postoperative recovery protocol, led to a decreased length of stay and lower postoperative C-reactive protein levels in THA patients. (24)

### Nutrition Optimization Protocol

To address the higher postoperative mortality, morbidity, length of stay, readmission rates, and hospital costs associated with malnutrition, the Perioperative Enhancement Team (POET) Nutrition Clinic has been established at Duke University Hospital. (25) The protocol begins with the use of the Perioperative Nutrition Screen (PONS), which was developed to specifically screen for perioperative nutrition risks using the validated screening tools such as the Malnutrition Universal Screening Tool (MUST) that were originally developed to screen for malnutrition in patients already in hospital. (25) The following are the four main screening items in the PONS, with any yes answer requiring the patient be further assessed by a registered dietician:

- BMI < 18.5 (or <20 for patients >65)
- Weight loss > 10% in the last 6 months without trying
- Oral intake < 50% of normal diet in the last week
- Serum albumin < 3.0 g/L

Using PONS allows for quick and efficient preoperative malnutrition risk identification for preoperative nutrition intervention. (25) If placed in the high-risk nutrition path, patients will be preoperatively administered a high protein ONS 2-4 weeks in advance of surgery. Seven days before surgery, patients receive immunotherapy. Perioperatively, patients will undergo carb loading two hours before surgery. Postoperatively, patients will receive immunonutrition for another 7 days followed by a high protein ONS for the next 3 weeks. If patients are placed in a low nutritional risk pathway, they receive much the same nutritional supplementation with the exception of the preoperative ONS. (25)

“It is hoped that simple pathways like this, with some substituting of targeted ONS supplements made for diabetic and renal dysfunction patients when indicated will simplify perioperative nutrition care... It is key to note the nutrition care of the surgical patient will be greatly enhanced by the presence of an RD on the surgical team who can participate in the pre- and post-operative care of the patient... We believe multidisciplinary preoperative nutrition programs will improve nutrition screening, nutrition care, and outcomes for the over 50 million patients having surgery in the US (and around the world). Furthermore, we hypothesize that major cost savings will be realized when preoperative nutrition screening and care are made an essential part of training surgical patients for the “marathon of their lives.” (25)

Williams et al. (2020)