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REVIEW ARTICLE

Protein-based perioperative nutrition interventions for improving muscle mass and functional outcomes following orthopaedic surgery

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Abstract
This narrative review provides an overview of protein-based perioperative nutrition interventions for improving muscle mass and functional outcomes in patients undergoing orthopaedic surgery. Globally, the number of joint replacement procedures continues to rise annually, with beneficial outcomes in terms of pain relief and quality of life. However, orthopaedic surgery is associated with a transient decline in skeletal muscle mass, strength and function, with resulting impact on balance and posture, mobility and an increased risk of falls during the perioperative period. Perioperative nutrition interventions targeted at mitigating muscle atrophy, strength loss and reduced function in response to orthopaedic surgery have primarily focused on essential amino acid and protein supplementation. Promising results have been observed in patients undergoing total knee arthroplasty, total hip replacement, surgical treatment of hip fracture and anterior cruciate ligament reconstruction. Preliminary evidence also suggests a role for perioperative β-hydroxy-β-methylbutyrate supplementation in improving muscle mass and function outcomes following orthopaedic surgery. However, translation of findings from experimental studies into clinical practice is required.

KEYWORDS
osteoarthritis, perioperative nutrition, skeletal muscle

1 | AN INTRODUCTION TO PERIOPERATIVE MEDICINE IN ORTHOPAEDIC SURGICAL SETTINGS

According to the UK National Joint Registry, a total of 147,728 joint replacement procedures were completed by the NHS in 2023 ('Home–NJR Surgeon and Hospital Profile', 2024: https://surgeonprofile.njrcentre.org.uk/). Hip replacement procedures (108,558) were most commonplace, undertaken most often in people aged over 65 years with osteoarthritis. Indeed, based on the ageing population in the UK and across the globe (Global Nutrition Target Collaborators, 2025) and given that arthritis is a disease more prevalent in older adults (Long et al., 2022), the number of joint replacement surgeries in older adults is likely to rise in future years. For example, in the United States, 850,000 total hip and 1.9 million total knee arthroplasty surgeries are predicted in 2030 (Singh et al., 2019), and in the UK, approximately 131,000 total hip and 137,000 total knee replacement surgeries are predicted in 2060 (Matharu et al., 2022). According to recent estimates from the United States, the median total healthcare expenditure calculated at 1 year post total hip or knee joint replacement surgery was $130,314 in robust older adults, increasing to $247,503 in frail patients (Ron et al., 2025).

Multiple clinical trials have reported clinically relevant improvements in pain relief and quality of life following primary hip replacement surgery, irrespective of patient age (Ayers et al., 2022; Bamman et al., 2015; Ninomiya et al., 2020; Singh et al., 2021; Yoshiko et al., 2020). However, the post-surgical period following orthopaedic surgery can also be associated with impairments in muscle mass, strength and function, leading to instability during walking, abnormal gait patterns, an increased risk of falls and reduced physical activity patterns (Ninomiya et al., 2020). Indeed, orthopaedic surgeries such as anterior cruciate ligament (ACL) reconstruction, bone fractures and joint replacements are associated with substantial and clinically relevant declines in skeletal muscle mass, strength and function over the perioperative period (Atherton et al., 2016; Hirsch et al., 2021; Kramer et al., 2019). In some instances, a compromised muscle functional capacity remains for several years after surgery (Ninomiya et al., 2020; Yoshiko et al., 2020), which presents a precarious situation for older adults, many of whom already face the challenge of age-related declines in muscle mass and function (Cruz-Jentoft et al., 2019).

Mechanistically, it has been proposed that the direct stress response to surgery per se leads to a physiological state of whole-body protein catabolism to accommodate the increased amino acid demand for wound healing, as mediated by a complex cascade of inflammatory, immunological and metabolic events (Gillis & Carli, 2015). Depending upon the degree of surgical insult, this catabolic response can last for a few hours to several days and in some cases up to 2–4 weeks (Hill et al., 1993). Moreover, transient periods of reduced physical activity and/or complete muscle disuse in the lead up to or in the aftermath of surgery may compound the catabolic response to surgery, thereby exacerbating muscle atrophy, strength loss and impaired functional capacity (Nunes et al., 2022; Wall et al., 2013). For instance, a 3–5% decline in vastus lateralis and rectus femoris volume (as measured by magnetic resonance imaging; MRI) was reported 5 months following elective ACL reconstruction surgery in young (~27 years) patients (Norte et al., 2018). A higher rate of muscle atrophy and strength loss post-surgery is commonly sustained in older adults (Hvid et al., 2018), with a 14% decline in quadriceps muscle volume reported 2 weeks following total knee arthroplasty in older (> 65 years) patients (Dreyer et al., 2013). This observation may relate, at least in part, to an inferior muscle functional reserve pre-surgery in older adults and enhanced muscle disuse atrophy compared with their younger counterparts (Hvid et al., 2018). Moreover, large-scale prospective studies indicate that older adults experience a 5–6% reduction in lean body mass up to 1 year following hip fracture (Fox et al., 2000; Karlsson et al., 1996). Hence, an important and perhaps underappreciated feature of perioperative care relates to the preservation of muscle mass and function in orthopaedic surgery patients. Currently, this notion is especially pertinent in the UK as our healthcare system continues to recover after COVID-19, with hip and knee replacement procedures still not returned to pre-pandemic levels as of 2023 (Wainwright et al., 2024).

Highlights

- **What is the topic of this review?**
  This narrative review is focused on perioperative nutrition interventions to improve muscle mass and functional outcomes in response to orthopaedic surgery.
- **What advances does it highlight?**
  The evidence regarding effective perioperative nutrition interventions to improve muscle mass and functional outcomes relates to essential amino acid and protein supplementation.

The developing field of Perioperative Medicine aims to define and implement best practice therapeutic strategies before, during and/or after surgery to improve postoperative outcomes (de Las Casas et al., 2021). Traditional 'Enhanced Recovery after Surgery (ERAS)' initiatives have focused on immediate preoperative (with 24 hours of surgery), intraoperative and early postoperative (days after surgery) interventions (Wainwright et al., 2020). The most recent ERAS consensus statement for perioperative care in hip and knee replacement surgery frames nutrition within two contexts (Wainwright et al., 2020). First, the expert group discusses the potential role of pre-operative carbohydrate supplementation but does not recommend the implementation of this strategy based on current evidence. Second, it is highlighted that no recommendations can be made regarding postoperative nutritional care as no studies have investigated the impact of feeding or supplementation on discharge criteria. Hence, the current narrative review focuses attention on the evidence base around protein nutrition interventions in order to highlight this option, as well as shed light on nutritional interventions that still require scientific evidence before this strategy might be considered as an ERAS initiative. In contrast, 'prehabilitation programmes' should be initiated as soon as a patient is listed for a surgical intervention (Wall et al., 2023; Weimann et al., 2017). Another model of care for older surgical patients also incorporates a medical focus on co-existing comorbidities and geriatric syndromes such as frailty and cognitive impairment through using Comprehensive Geriatric Assessment and Optimisation Methodology. Nonetheless, all such perioperative approaches aim to provide a framework to facilitate patient return to a normal metabolic state and expedite recovery and have been applied to orthopaedic elective surgery (Lloyd et al., 2024).

Perioperative strategies have also been shown to be effective in reducing length of hospital stay and healthcare costs and have improved time to pre-surgery levels of physical fitness, mobility and independence. For instance, a comprehensive systematic review recently evaluated the effectiveness of preoperative resistance exercise training in total knee replacement patients, demonstrating a benefit on post-operative knee function and range of motion in the early (1–3 months) period (Wu et al., 2022). However, orthopaedic surgery often requires a period of partial or complete immobility; hence, in practice, exercise training may not always be viable as a pre- or rehabilitation strategy in orthopaedic patient groups, and other interventions should be investigated. Nutrition interventions, albeit most widely established within the context of perioperative parenteral nutrition (Grimes et al., 1987), have also been reported to reduce the length of hospital stay and experiences of severe complications following major orthopaedic surgery (Briguglio & Wainwright, 2025). Current standard clinical nutrition practices for surgery primarily focus on screening and prevention of malnutrition, pre-surgical fasting protocols and combating post-surgical insulin resistance (Hirsch et al., 2021), leaving recommendations regarding personalised oral macronutrient composition and timing in relation to surgery less well established (Briguglio & Wainwright, 2022, 2025; Briguglio et al., 2023). Therefore, the over-arching aim of this narrative review is to discuss the efficacy of protein-based perioperative nutritional interventions, with a focus on oral feeding rather than parenteral nutrition, to mitigate the decline in muscle mass, strength and function following orthopaedic surgery, with context-specific applications (i.e., due to sport or fall-related bone fractures, joint replacements in osteoarthritic patients, etc.) across the life course.

2 | PERIOPERATIVE NUTRITION FOR ORTHOPAEDIC SURGERY

The efficacy of nutritional interventions to mitigate the muscle atrophy response to orthopaedic surgery has primarily been extrapolated from proof-of-concept experimental studies conducted using simple/uncomplicated models of muscle disuse (i.e., not confounded by an underlying illness) in healthy volunteers (Deane et al., 2024), rather than complicated models of disuse in patient groups undergoing orthopaedic surgery (Figure 1). In brief, randomised controlled trials (RCT) conducted using a simple/uncomplicated disuse model have revealed a lack of clear evidence regarding the benefit of nutritional interventions and most commonly protein or amino acid ingestion in mitigating muscle atrophy in response to muscle disuse in healthy volunteers (for a recent review refer to Hughes et al., 2024). Notwithstanding, clinical trials investigating the efficacy of oral (as opposed to parenteral) perioperative nutrition strategies to mitigate muscle atrophy in response to orthopaedic surgery in patient groups have primarily focussed on protein or amino acid based perioperative interventions, as reviewed in Hirsch et al. (2021). The scientific basis for these trials is underpinned by elaborate metabolic studies in patient groups scheduled for hip (Church et al., 2021) or ACL reconstruction (Howard et al., 2022) surgery that conducted acute measurements of muscle protein turnover, rather than chronic changes in muscle mass, strength and function. Hence, translation to clinically relevant outcomes should be considered with caution. Nonetheless, using a proof-of-concept RCT, the administration of a pre-operative infusion of amino acids was effective in stimulating muscle protein synthesis (MPS) rates and attenuating muscle protein breakdown (MPB) rates during the surgical period in a cohort of middle-aged elective hip arthroplasty patients (Church et al., 2021). Accordingly, net muscle protein balance (aggregate difference between MPS and MPB over a given time period) was improved and the muscle catabolic response to hip replacement surgery was attenuated in the patient group that received the preoperative amino acid infusion during surgery compared with a standard care group (Church et al., 2021). These data are consistent with clinical trials in which the interoperative and postoperative infusion of amino acids has been shown to increase net muscle protein balance in elective colorectal surgery patients (Donatelli, Schricker, Mistraletti et al., 2006, Donatelli, Schricker, Parrella et al., 2006). However, it should be noted that no control group was included in either study (Donatelli, Schricker, Mistraletti et al., 2006, Donatelli, Schricker, Parrella et al., 2006), and hence it is difficult to draw firm conclusions regarding the impact of the amino acid infusion. Moreover, it is conceivable that the intravenous infusion of amino acids compared to oral ingestion of amino acids may elicit divergent physiological responses. For example, amino acid infusions elicit more rapid and pronounced plasma amino acid concentrations, whilst oral amino acid ingestion elicits a greater postprandial insulinaemia (Abdulla et al., 2019). Hence, whilst these preliminary studies show promise in terms of a perioperative nutrition strategy, translation to real world application of supplemental or dietary interventions remains unclear.

The second metabolic study is a pilot RCT that manipulated dietary protein intake (1.2 vs. 1.9 g kgBM^{-1} day^{-1}) during a 2-week period of muscle disuse prior to primary ACL reconstruction in a small cohort (n = 3 protein, n = 3 control) of young men (Howard et al., 2022). MPS rates were increased in the high protein diet group over this pre-operative period, indicating a potential benefit of increasing dietary protein intake during inevitable periods of complete muscle disuse or markedly reduced levels of physical activity prior to orthopaedic surgery. To this end, no metabolic studies have investigated the muscle anabolic response to oral (rather than parenteral) protein or amino acid feeding during the post-operative rehabilitation period within the context of orthopaedic surgery. In addition, limited conclusions can be drawn from these studies (and indeed studies in uncomplicated models of disuse) since they do not capture the entire perioperative period, inclusive of pre-, during and post-operative periods, or combine acute metabolic readouts with clinically relevant measurements of muscle function. As such, this area warrants further investigation to enhance our understanding of the metabolic cascades underpinning the entire surgical process. Nevertheless, these data provide the scientific rationale to undertake large-scale RCTs into oral protein-based feeding strategies to mitigate decrements in muscle mass, strength and function in the context of orthopaedic surgery.

3 | ESSENTIAL AMINO ACID SUPPLEMENTATION

Longitudinal studies into the efficacy of essential amino acid (EAA) supplementation as a perioperative nutrition strategy have generally

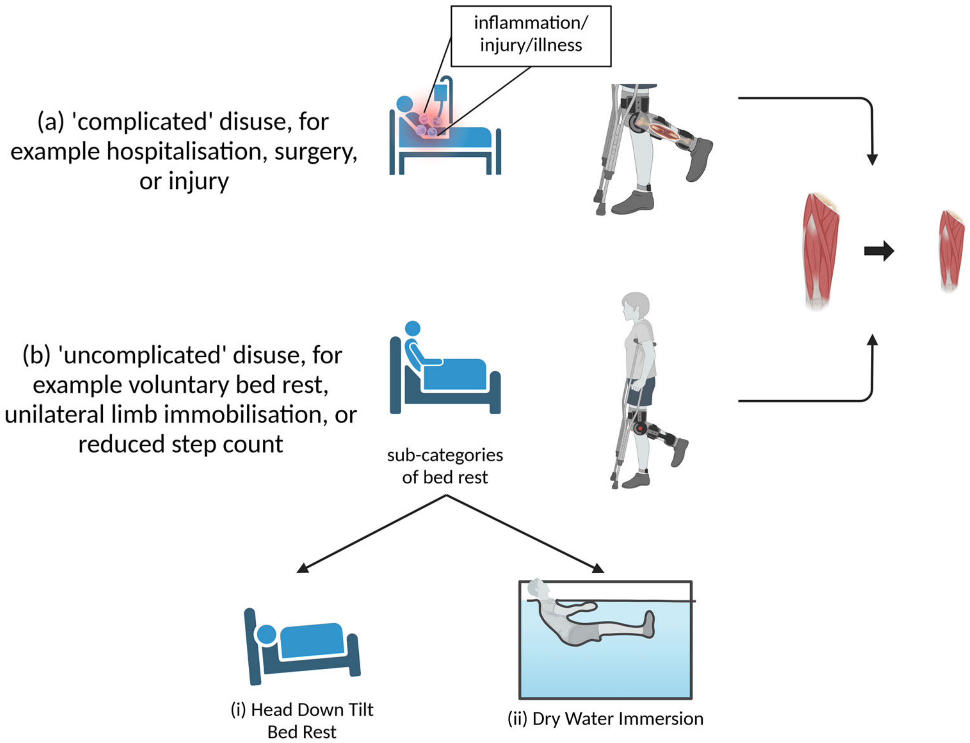

FIGURE 1 Different disuse scenarios. Complicated disuse refers to periods of disuse due to injury, hospitalization, or diseased states. Uncomplicated disuse refers to periods of disuse due to voluntary bed rest or inactivity, without a prior disease or injury state. Image created with BioRender.com.

reported favourable outcomes with regards to mitigating post-surgical declines in skeletal muscle mass, strength and/or function in orthopaedic patient groups (George et al., 2023; Reider et al., 2023). A series of clinical trials have been conducted at the University of Oregon in this area (Dreyer et al., 2013, 2018; Muyskens et al., 2019, 2020). These studies utilised a randomised, double blinded, placebo-controlled experimental design and recruited a relatively large cohort of middle-aged (n = 39) and older (n = 28) total knee arthroplasty patients to ingest 20 g of EAA (equivalent to ~40 g protein) or a placebo (non-essential amino acid (NEAA) mixture or alanine) twice daily for 7 days before and 2 (Dreyer et al., 2013) or 6 (Dreyer et al., 2018) weeks after surgery. This elegant research design included a within-subjects control study arm with measurements of muscle (quadriceps) volume (using gold standard MRI), strength and function also conducted on the contralateral, non-operated leg. A consistent finding across studies was that EAA ingestion attenuated the magnitude of muscle atrophy by 5–12% when measured at 2- or 6-weeks post-surgery, although the preservation of muscle mass with EAA ingestion did not consistently translate to improvements in strength and functional mobility over the 6-week rehabilitation period (Dreyer et al., 2013, 2018). The absence of an exercise component within the perioperative medicine strategy likely explains, at least in part, the lack of improvements in strength and function. Interestingly, although the degree of muscle atrophy was more substantial during the early versus later post-surgical period (as has been previously reported; Hardy et al., 2022), the favourable effect of the EAA intervention was comparable between post-surgery time points. The evidence base regarding the peri-operative role of EAA supplementation also extends to RCTs in hip fracture and hip arthroplasty patients, whereby improvements in muscle mass (Hendrickson et al., 2022), strength (Borsheim et al., 2008; Ferrando AA et al., 2013) and function (Aquilani et al., 2019; Baldissarro et al., 2016; Invernizzi et al., 2019) have consistently been reported during the post-surgical period. Hence, there is accumulating evidence that EAA supplementation represents an intervention that potentially improves outcomes following orthopaedic surgery.

4 | PROTEIN SUPPLEMENTATION

Guidelines for surgical patients generally recommend an adequate preoperative dietary protein intake in excess of 1.2 g $kgBM^{-1}$ day^{-1} (Wischmeyer et al., 2018), which is substantially higher than the RDA for protein of ~0.8 g $kgBM^{-1}$ day^{-1}. However, it has been suggested that even higher protein intakes may be warranted for individuals during injury scenarios (Tipton, 2010) and studies into optimal protein recommendations for orthopaedic surgery patients are needed (McKendry et al., 2024). Interestingly, protein intakes of <0.6 g $kgBM^{-1}$ day^{-1} have been reported in older patients during a 6-day period of hospitalisation following total hip or knee arthroplasty (Weijzen et al., 2019) which, although higher than reported for abdominal surgery patients (Hardy et al., 2023), remains lower than deemed adequate. Accordingly, the preponderance of longitudinal studies have investigated the effects of postoperative protein supplementation on more subjective clinical outcomes during rehabilitation, rather than more objective muscle-specific endpoints in older hip fracture patients (Espaulella et al., 2000; Schurch et al., 1998; Tidermark et al., 2004). For instance, improvements in activities of daily living and quality of life were reported in patients randomised to 20 g/day of protein supplementation (a protein-rich formula, Fortimel) versus control (standard care) when measured at 6 months post-hip surgery (Tidermark et al., 2004). Moreover, a separate RCT conducted muscle-specific measurements in young ACL reconstruction patients and reported that the combined ingestion of protein and carbohydrate (10 g protein from skimmed-milk and soybeans, 7 g carbohydrate) augmented improvements in muscle mass and strength outcomes following 12 weeks of resistance training rehabilitation (Holm et al., 2006). Hence, the evidence base pertaining to the longer-term postoperative effect of protein supplementation appears promising. However, it must be acknowledged that studies investigating longer-term interventions may no longer be impacting the post-surgical period but rather be investigating the impact of nutritional supplementation on exercise training interventions during rehabilitation. Hence, future studies are warranted to determine the optimal post-surgical time over which to implement nutritional interventions in the context of rehabilitation. Nonetheless, several RCTs have been conducted investigating protein or amino acid supplementation in orthopaedic patient groups, indicating a beneficial effect on muscle function and quality of life outcomes. As such, these interventions may be worth considering in the first instance for clinicians with the goal of implementing dietary recommendations for orthopaedic patients. Moreover, follow-up studies are warranted to investigate the effect of perioperative protein supplementation on more sensitive physiological measurements of muscle mass, strength and function in orthopaedic patient groups.

5 | *β*-HYDROXY-*β*-METHYLBUTYRATE

Beyond protein and/or EAA ingestion, another perioperative nutrition strategy in terms of mitigating the decline in muscle mass, strength and function following orthopaedic surgery includes *β*-hydroxy-*β*-methylbutyrate (HMB) supplementation (Marshall et al., 2020). HMB is a metabolite of leucine catabolism in the liver (van Koevering & Nissen, 1992) and skeletal muscle that has been shown to stimulate MPS and attenuate MPB rates in reference to in vitro cell culture models (Eley et al., 2007) and in vivo human clinical trials (Wilkinson et al., 2013, 2018). Accordingly, improvements in muscle mass and strength with 2–3 g/day of HMB supplementation have been reported in older adults (Flakoll et al., 2004) and, most notably, an attenuated decline in muscle mass in response to 10 days of bedrest in older adults (Deutz et al., 2013). Moreover, in an RCT, pre- and postoperative supplementation with a combination of HMB, arginine and glutamine was shown to expedite the restoration of quadriceps strength in older adult total knee arthroplasty patients (Nishizaki et al., 2015). However, while a recent meta-analysis that investigated the impact of HMB on a broad range of clinical conditions reported a beneficial effect on muscle mass and strength, the effect sizes were small (Bear et al., 2019). In addition, no studies were considered low risk of bias, and many of the included studies did not investigate HMB in isolation, but rather alongside other supplements. Therefore, while there may be a potential clinical benefit of HMB, it is difficult to delineate if this effect is due to HMB alone. Hence, it would be recommended that further high-quality clinical trials should be undertaken to further investigate the efficacy of HMB interventions before it is considered by clinicians in the context of perioperative nutrition for orthopaedic patients.

6 | CONCLUSION

Experimental and clinical studies suggest EAA supplementation is a promising perioperative nutritional strategy to mitigate declines in muscle mass, strength and function following orthopaedic surgery, with some evidence suggesting a role for protein and HMB supplementation. The National Institutes of Health (NIH) National Center for Advancing Translational Sciences defines translational research as 'the process of turning observations in the laboratory, clinic and community into interventions that improve the health of individuals' (NCATS Overview, National Center for Advancing Translational Sciences, 2024: https://ncats.nih.gov/about/ncats-overview/strategic-plan/overview-of-ncats). To explore and translate findings from experimental studies of perioperative nutrition for patients undergoing orthopaedic elective surgery into clinical practice requires careful consideration of several factors. These factors include working with patients and other stakeholders to understand: (i) the prevalence of underlying nutritional and muscle disorders, (ii) acceptability and feasibility of pre-, intra- and postoperative nutritional interventions, and (iii) outcomes that matter to this patient group and the healthcare economy. In addition, there is a need for careful consideration of the research methodologies to be employed that are most likely to lead to timely change in practice. For example, randomised clinical trials and/or implementation-effectiveness studies and there is a need for evaluation of cost effectiveness of single component and/or multicomponent interventions (e.g., nutrition alone or nutrition and exercise). Accordingly, patient and public involvement and engagement (PPIE) activities and feasibility studies that provide a signal of efficacy and potential for implementation (translation into clinical practice) are crucial first steps in progressing this exciting field of perioperative nutrition in orthopaedic surgery.

AUTHOR CONTRIBUTIONS

Alix K. Hughes and Oliver C. Witard were responsible for the concept of the review. All authors contributed to the design and writing of the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All persons designated as authors qualify for authorship, and all those who qualify for authorship are listed.

CONFLICT OF INTEREST

None declared.

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