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Review

Post-operative protein supplementation following orthopaedic surgery: A systematic review

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ABSTRACT

Decreased mechanical loading after orthopaedic surgery predisposes patients to develop muscle atrophy. The purpose of this review was to assess whether the evidence supports oral protein supplementation can help decrease postoperative muscle atrophy and/or improve patient outcomes following orthopaedic surgery. A systematic review was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA). PubMed (MEDLINE), Embase, Scopus, and Web of Science were searched for randomized controlled trials that assessed protein or amino acid supplementation in patients undergoing orthopaedic surgery. Two investigators independently conducted the search using relevant Boolean operations. Primary outcomes included functional or physiologic measures of muscle atrophy or strength. Fourteen studies including 611 patients (224 males, 387 females) were analyzed. Three studies evaluated protein supplementation after ACL reconstruction (ACLR), 3 after total hip arthroplasty (THA), 5 after total knee arthroplasty (TKA), and 3 after surgical treatment of hip fracture. Protein supplementation showed beneficial effects across all types of surgery. The primary benefit was a decrease in muscle atrophy compared to placebo as measured by muscle cross sectional area. Multiple authors also demonstrated improved functional measures and quicker achievement of rehabilitation benchmarks. Protein supplementation has beneficial effects on mitigating muscle atrophy in the postoperative period following ACLR, THA, TKA, and surgical treatment of hip fracture. These effects often correlate with improved functional measures and quicker achievement of rehabilitation benchmarks. Further research is needed to evaluate long-term effects of protein supplementation and to establish standardized population-specific regimens that maximize treatment efficacy in the postoperative period.

1. Introduction

Decreased mechanical loading after orthopaedic surgery predisposes patients to develop muscle atrophy.[1] This disuse atrophy is a result of a multitude of factors, including the postoperative catabolic state and loss of neuromuscular activation.[1] Muscle atrophy in the postoperative period can be difficult to overcome, and can lead to pain, weakness, decreased range of motion (ROM), increased risk of injury, and diminished quality of life.[1–3] While physical therapy can help combat postoperative muscle atrophy and its negative consequences, muscle atrophy often persists despite progressive rehabilitation.[4,5] Understanding the biochemical mechanisms of disuse musculoskeletal atrophy, as well as formulating strategies to counteract it, is therefore a high priority for improving clinical outcomes after orthopaedic surgery.[6–8]

Decreased muscle mass and function due to unloading results from the balance between protein synthesis and degradation shifting in favor of degradation and net protein loss.[9–12] This can result from reduced motor unit and mechano-transduction signaling, as well as a reduction in sensitivity to anabolic nutrient sensitive pathways.[13]As both activity and nutrition have been shown, in part, to signal through the mammalian target of rapamycin complex 1 (mTORC1) signaling pathway to stimulate anabolism, this pathway has been a key target of activity and nutrition-based therapeutic interventions.[14–18] As a result, significant efforts have been made over the past several decades to combat disuse-associated loss of muscle and function with the aid of nutritional intervention.[19–24]

Amino acids and complete protein sources have commonly been used as nutritional supplements to stimulate anabolism.[19] Whey protein is often used due to its high rate of absorption in the GI tract, as well as its

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Abbreviations

ACLR	Anterior Cruciate Ligament Reconstruction
BMI	Body Mass Index(kg/m^2)
MCMS	Modified Coleman Methodology Scoring
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO	Prospective Register of Systematic Reviews
RCT	Randomized Controlled Trial
ROM	Range of Motion
TKA	Total Knee Arthroplasty
THA	Total Hip Arthroplasty
VAS	Visual Analog Scale

high leucine content relative to other protein sources (soy, milk, etc).[25] In young adults, dosages of 20–30 g of whey protein have been commonly observed to stimulate protein synthesis.[26–28]

Leucine is an essential amino acid (required by dietary intake, not endogenously produced) known as part of the family of branched chain amino acids (BCAA; along with isoleucine & valine) and has been observed, on its own, to directly stimulate mTORC1 signaling.[24] It both serves as a substrate for protein synthesis and directly acts on mTORC1 complex assembly, as its function depends on the assembly of several key intracellular proteins.[29] This phenomenon is often referred to as the "leucine trigger" effect. In fact, the supplementation of leucine alone has acutely been observed to have stimulatory effects on protein synthesis and has been observed to preserve muscle function in bed rest/unloading studies in healthy adults.[13]Arginine is another essential amino acid that has recently been observed to play a role in intracellular mTORC1 localization and function in skeletal muscle.[30–33] In terms of indirect anabolic stimulation, arginine has also been observed to improve vasodilatory capacity (enhance nutrient delivery in skeletal muscle) and stimulate insulin release (also stimulating mTORC1 signaling).[30–33]

There are limited data evaluating protein and amino acid supplementation following orthopaedic injuries, and to our knowledge no systematic reviews have specifically evaluated protein supplementation and its effects following orthopaedic surgery. This information could help providers recommend appropriate nutritional supplementation after specific orthopaedic procedures, and it could identify areas where further research is needed. The authors aimed to identify high quality studies evaluating the use of proteins, amino acids, or peptides used to prevent or treat muscle atrophy in the postoperative period following any orthopaedic procedure. Primary outcomes included functional or physiologic measures of muscle atrophy or strength. Secondary outcomes included patient satisfaction and time to return to sport or work. We hypothesized that protein supplementation would have beneficial effects in counteracting muscle atrophy and improving functional outcomes after all types of surgery.

2. Materials and methods

2.1. Study design

A systematic review of the literature was performed following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[34] The review was registered with the Prospective Register of Systematic Reviews (PROSPERO). A search of the PROSPERO registration did not identify similar prior systematic reviews or meta-analyses. Databases were searched during April 2021 and included: MEDLINE (Pubmed), Embase, Scopus, and Web of Science. The following search query was used: "orthopaedic procedures" AND "protein" OR "amino acid" AND "dietary supplements" OR "supplementation" OR "supplement." Within PubMed, the Medical Subject Headings (MeSH) database was searched using the same query with "orthopaedic procedures" listed as a MeSH term, in order to capture all relevant surgeries indexed as orthopaedic procedures in the database.

2.2. Eligibility criteria

The principal inclusion criteria consisted of randomized controlled trials evaluating protein or amino acid regimens as an intervention to counteract muscle atrophy following orthopaedic surgery. Articles that evaluated other forms of dietary supplementation or non-orthopaedic procedures were excluded. Control groups included either placebo or a natural history control (i.e. routine post-operative protocol). The scope of surgery was intentionally left broad, to allow for a comparison of protein supplementation effectiveness across different surgical interventions. Each study's reference list was manually reviewed for additional articles to prevent unintentional exclusion of studies. Two investigators independently assessed all articles identified by the search strategy and applied the eligibility criteria.

2.3. Data extraction

The content extracted from each article included: (1) demographic data, (2) protein supplement regimen used, (3) outcomes, (4) complications, and (5) length of follow up. Primary outcomes included functional or physiologic measures of muscle atrophy or strength. Secondary outcomes included patient satisfaction and time to return to sport or work.

2.4. Data analysis

Quality assessment of studies was performed using the Modified Coleman Methodology Score (MCMS), which is the sum of fifteen components assessing the quality of study reporting and has been a standard quality assessment metric for systematic reviews in the orthopaedic literature. Heterogeneity of study design was noted including differences in protocols, measurement techniques, and outcomes measured, which prevented an adequate statistical comparison for meta-analysis.

3. Results

Following screening (Fig. 1), fourteen studies including 611 patients (224 male, 387 female) were analyzed.

Four surgical cohorts were identified: Anterior cruciate ligament reconstruction[35–38](ACLR), total hip arthroplasty[39–41] (THA), hip fractures[41–43](THA, revision THA, hip resurfacing), and total knee arthroplasty[44–48](TKA). The ACLR, THA, and hip fracture cohorts were each composed of 3 studies, while there were 5 studies in the TKA cohort (Table 1).

Average length of follow-up was 9 weeks for ACLR, 7 weeks for THA, 10 weeks for hip fracture, and 7 weeks for TKA. Protein supplementation included various combinations of essential amino acids (9 studies) in tablet form or protein powder (3 studies), and two studies utilized milk protein supplementation. Placebo supplements were most commonly an isocaloric carbohydrate tablet or powder (Table 2).

Protein supplementation was reported to have beneficial effects across all types of identified surgeries. The primary benefit was decreased muscle atrophy measured by muscle cross sectional area. The most significant difference in muscle atrophy was observed in the final week of follow-up for 11/14 studies (average follow up was 8 weeks). Eight of the fourteen studies also demonstrated improved functional measures (Table 2), including increased muscle function measured by isokinetic muscle strength. Of note, most participants were involved in some form of formal physical therapy for varying durations after surgery, but this was not standardized across all studies. There were no significant increases in side effects reported comparing protein supplementation cohorts to controls. Of the included investigations, only 2 studies (both for

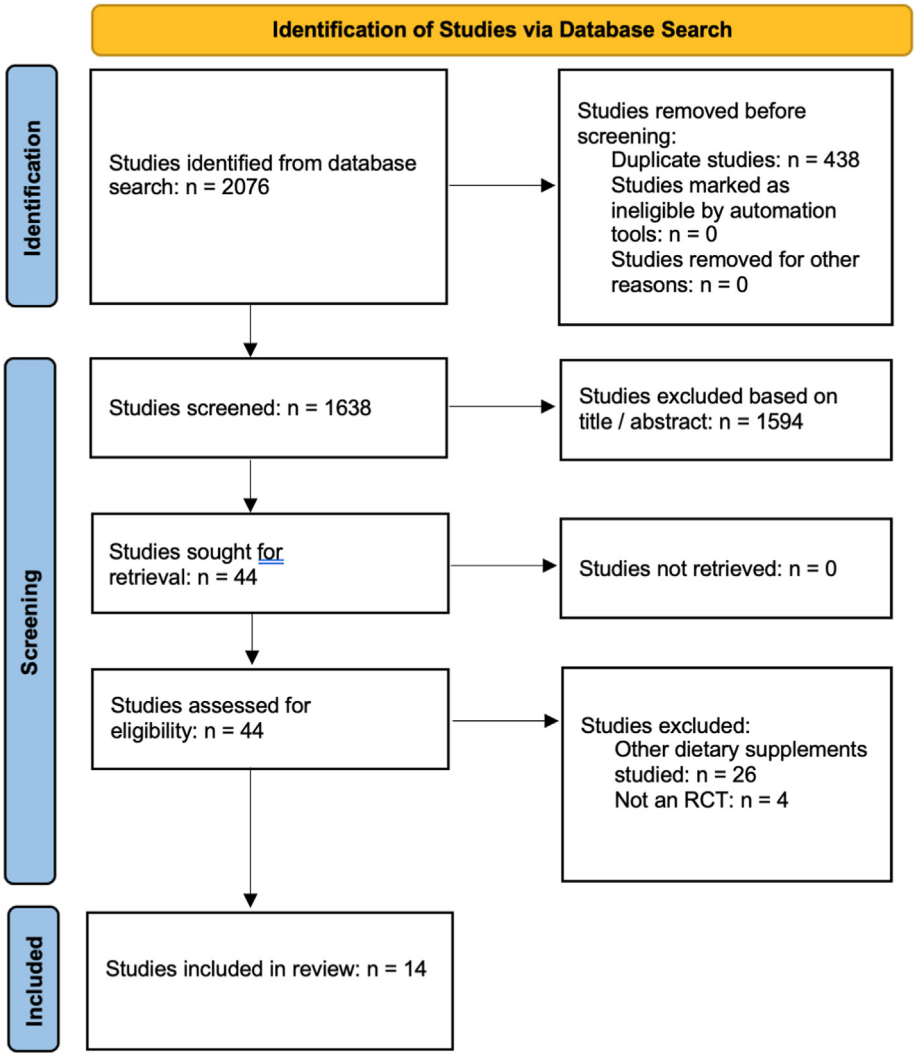

Fig. 1. Search strategy for identification of studied articles.

hip fracture) had participants follow a standardized diet, in order to better control baseline protein intake.[41,42] Average MCMS scores for each surgical cohort were as follows: ACLR 55 (fair), TKA 55 (fair), THA 46 (poor), hip fracture 44 (poor).

4. Discussion

The results of this systematic review of fourteen RCTs suggest that protein supplementation in the post-operative period following orthopaedic surgery may be an effective intervention to combat muscle atrophy. Specifically, protein supplementation was found to have a significant effect on muscle cross-sectional area and isokinetic muscle strength, which was most notable in the final follow-up week for 11/14 studies. Several of the studies examined here also reported improved functional measures and quicker achievement of rehabilitation benchmarks. Of note, all 14 studies utilized different protein regimens, so it is difficult to recommend a specific, maximally effective regimen based on this review. Therefore, further RCTs with greater methods of standardization will be required to improve targeting and to further develop guidelines for populations who may stand to benefit from nutritional intervention.

In addition to evaluating the effectiveness of protein supplementation following various orthopaedic procedures, another important goal of this review was to identify specific areas where evidence is lacking. We observed that most of the literature has focused on patient populations that are older and at greater risk of nutritional deficiency, such as those undergoing joint replacement surgery. Importantly, muscle protein synthesis after nutritional supplementation has been shown to be less responsive in elderly patients due to aging associated anabolic resistance whereby sensitivity of anabolic pathways to nutrition are diminished compared to younger populations.[49] Therefore, it is possible that patients at risk of being nutrient deficient or nutrient-insensitive (i.e. older adults, those with type-II diabetes) may gain more benefit from protein supplementation strategies. In terms of the younger patient population, outside of ACLR, no RCTs have evaluated protein supplementation following arthroscopic procedures of the knee or any other joint. In addition, no studies have evaluated protein supplementation following upper extremity procedures.

Even within the ACLR literature, several important limitations preclude the development of a standardized protocol for implementing protein supplementation in this patient population, and there remains a substantial need for high quality RCTs. First, only one study recorded patients' protein intake outside of the supplementation regimen.[35] This is especially important in the ACLR cohort as these patients are often younger and often participating in athletics where they may have a higher protein and/or caloric need and intake. By accounting for baseline protein intake, the true amount of "supplemental" protein to recommend to patients would be better elucidated, which could assist in developing individualized protocols. This is critical as protein supplementation has been shown to have minimal effects on muscle adaptations in young men

Table 1
Study Demographics and Patient Characteristics.

Author/ Year	Surgery	Study Design	Study Sample Size	Treatment Group Size	Control Group Size	Sex (M/ F)	Age (Average ± *SD* [Range])	BMI Overall	BMI Treatment Group	BMI Control Group	Side Effects	Modified Coleman Methodology Score
Holm et al. 2006	ACL Reconstruction	Double Blinded RCT	26	8 PC*, 9 IC*	9 PL*	16 M/ 10F	N/A (18–35)	N/A	**PC Group**: 24.7 ± 1.1 **IC Group**: 26.0 ± 1	**PL Group**: 25.6 ± 1.2	None reported	52
Laboute et al. 2013	ACL Reconstruction	Double Blinded RCT	45	22	23	32 M/ 13F	N/A (18–45)	N/A	25 ± 3.3	25.6	None reported	56
Kim et al. 2017	ACL Reconstruction	Open RCT	30	15	15	30 M	25.4 ± 6.1	N/A	25.2	25.1	None reported	56
Ferrando et al. 2013	Total Hip Arthroplasty	Open RCT	16	8	8	11 M/ 5F	**Control Group**: 55 ± 7 (45–65) **Treatment Group:** 55 ± 8 (45–68)	N/A	N/A	N/A	None reported	42
Baldissarro et al. 2016	Total Hip Arthroplasty	Double Blinded RCT	60	30	30	24 M/ 36F	66.6 ± 8.4	N/A	29.8 ± 4.2	27.5 ± 3.9	None reported	46
Ikeda et al. 2019	Total Hip Arthroplasty	Single Blinded RCT	31	18	13	31F	75.4 ± 5.8	N/A	21.9 ± 4	25.5 ± 3.7	None reported	49
Nishizaki et al. 2015	Total Knee Arthroplasty	Open RCT	23	13	10	11 M/ 12F	70.5 (65–80)	N/A	N/A	N/A	None reported	52
Dreyer et al. 2013	Total Knee Arthroplasty	Double Blinded RCT	28	16	12	9 M/ 19F	69 ± 0.96	N/A	34 ± 7	29 ± 3	None reported	56
Dreyer et al. 2018	Total Knee Arthroplasty	Double Blinded RCT	39	19	20	14 M/ 25F	64.4 ± 0.9 (53–76)	29.8 ± 1.2	N/A	N/A	None reported	52
Muyskens et al. 2019	Total Knee Arthroplasty	Double Blinded RCT	41	19	22	14 M/ 27F	64.3 ± 0.9 (53–76)	N/A	29.7	30.7	None reported	56
Ueyama et al. 2020	Total Knee Arthroplasty	Double Blinded RCT	60	30	30	10 M/ 50F	**Treatment Group:** 75.9 (58–92) **Placebo Group**: 75.8 (65–87)	N/A	25.4	24.2	None reported	59
Schurch et al. 1998	Hip Fracture	Double Blinded RCT	82	41	41	8 M/ 74F	80.7 ± 7.4	N/A	24.2 ± 4.4	24.4 ± 3.5	**Nausea:** 4 Treatment 4 Control **Diarrhea:** 2 Treatment 1 Control	**44**
Botella-Carretero et al. 2008	Hip Fracture	3 Arm Open RCT	90	30, 30	30	35 M/ 55F	**Treatment Group 1:** 83.1 ± 6.3 **Treatment Group 2:** 84.6 ± 5.7 **Control Average:** 83.7 ± 7.9	N/A	**Treatment Group 1**: 24.2 ± 3.0 **Treatment Group 2**: 23.7 ± 3.5	23.6 ± 2.4	**Vomiting or Diarrhea:** 7 Treatment Group 1 10 Treatment Group 2 5 Control Group	**44**
Rondanelli et al. 2020	Hip Fracture	Double Blinded RCT	40	19	21	10 M/ 30F	**Treatment Group:** 81.9 ± 8.3 **Control Group:** 84.8 ± 8.6	24 ± 5.4	N/A	N/A	None reported	46

Patient demographic information are presented for surgery type, study design, sample size, sex (male, M; female, F), body mass index (BMI), and side effects. Interventions: Protein; protein + carbohydrate (PC); isocaloric control (IC); placebo control (PL).

Table 2
Study Interventions and Patient Outcomes.

Author/ Year	Surgery	PT or Exercise Protocol	Outcome Measures	Significant Primary Outcomes	Treatment Group Supplement Used	Control Group Supplement Used	Study Length	Summary of Outcomes
Holm et al. 2006	ACL Reconstruction	TID for 12 weeks	Quadricep cross-sectional area, isokinetic strength (peak strength, time to reach peak strength), quadricep muscle biopsy	**Quadricep Cross Sectional Area:** Significant difference between PC group and IC group at distal, middle, and proximal locations. **Muscle Biopsy: Strength:** ↑ 13%± 3% in PC group.	**PC* Group:** 10 g protein from skim milk, 7 g carbohydrate, 3.3 g fat. **IC* Group:** 17 g carbohydrate, 3.3 g fat	1.4 g carbohydrate and 1 g fat	12 weeks	Protein supplementation has a positive effect on both muscle hypertrophy and strength (torque) in ACL rehabilitation.
Laboute et al. 2013	ACL Reconstruction	Daily muscle strengthening exercises and physiotherapy	Thigh circumference, isokinetic testing, single-leg long jump, body fat	**Thigh Muscle Circumference at 10 cm from Patella:** ↑ 1.2 cm ± 1.4 for entire population. Treatment group ↑ 1.7 cm ± 1.3 compared to ↑0.69 cm ± 1.2 in control group. **Thigh Muscle Circumference at 15 cm from Patella:** ↑ 1.3 cm ± 1.6 for entire population. Treatment group ↑ 1.6 cm ±0.9 compared to ↑ 1.16 cm ± 1 in control group.	Leucine tablets 330 mg (1.5 g protein, 0.12 g carbohydrate, 0.01 g fat) QID	Tablet of same appearance, size and color without leucine.	2.7 weeks	Leucine supplementation did not improve muscle strength recovery of injured limb. Thigh circumference increased in leucine group.
Kim et al. 2017	ACL Reconstruction	Standardized progressive 12 week protocol	Isokinetic quadricep muscle strength	**Treatment Group** had significant improvement in strength at 60°/sec and 180°/sec after 12 weeks.	20 g whey protein before and after training sessions. 40 g total whey protein postoperatively for 12 weeks.	No control supplement.	12 weeks	Protein supplementation had a positive effect on muscle hypertrophy and strength in quadriceps after ACL reconstruction.
Ferrando et al. 2013	Total Hip Arthroplasty	Patient-specific protocol	**Primary**: Muscle strength (quadricep) **Secondary:** Functional status	**Treatment Group** ↑ 35% in muscle strength at 8 weeks.	15 g EAA supplement TID (0.225 g histidine, 1.455 g isoleucine, 5.46 g leucine, 2.28 g lysine, 0.45 g methionine, 0.915 g phenylalanine, 1.275 g threonine, 1.5 g valine, 0.09 g tryptophan, 1.35 g arginine)	No placebo for control group.	8 weeks	Greater improvement in quadricep strength in EAA group without an associated increase in muscle mass. No difference in functional measures.
Ikeda et al. 2019	Total Hip Arthroplasty	Standardized protocol	**Primary:** Muscle strength (hip abduction, knee extension)	**Treatment Group** knee extension on operative side improvement (147.7) compared to control group (114.4).	Daily BCAA supplement: 3.0 g of amino acids (1.2 g leucine, isoleucine and valine and 1.8 g lysine)	1.2 g starch (no amino acids)	1 month	Knee extension and muscle mass improvement with BCAA supplementation and rehab.
Baldissarro et al. 2016	Total Hip Arthroplasty	Standardized BID protocol	**Primary:** Harris Hip Score	**Treatment Group Harris Hip Score:** Improved from 41.8 ± 1.15 to 76.37± 6.6 and was significant when compared to control group.	4 g EAA supplement BID (leucine 1.25 g, isoleucine 0.625 g, valine 0.625 g, threonine 0.35 g, phenylalanine 0.02 g, cysteine 0.15 g.	Maltodextrin BID	2 weeks	Improved HHS in EAA group and increased circulating amino acids after 2 weeks.
Dreyer et al. 2013	Total Knee Arthroplasty	Standardized BID inpatient protocol	**Primary:** Changes in muscle volume **Secondary:** functional mobility, pain	**Treatment Group Muscle Volume at 2 weeks:** ↓ 3.4%± 3.1% quadricep volume compared to ↓ 14.3%± 3.6% in control group. **Treatment Group Muscle Volume at 6 weeks:** ↓ 6.2%± 2.2% compared to ↓ 18.4%± 2.3%.	20 g EAA BID 1 week pre-operatively and continuing 2 weeks post-operatively	Nonessential amino acids BID 1 week pre-operatively and 2 weeks post-operatively	7 weeks	Increased mid-thigh intermuscular adipose tissue in nonoperated leg, change in hamstring strength from baseline to 2 weeks and from baseline to 6 weeks.
Dreyer et al. 2018	Total Knee Arthroplasty	Standardized BID inpatient protocol	**Primary:** Changes in muscle volume (quadricep,	**Treatment Group Quadricep Muscle Volume at 6 weeks:** ↓ 8.5%± 2.5% muscle	20 g EAA BID 1 week pre-operatively and continuing 2 weeks	20 g placebo BID 1 week pre-operatively and continuing 2	7 weeks	The EAA group experienced a significantly less decrease in mean

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Table 2 (*continued*)

Author/ Year	Surgery	PT or Exercise Protocol	Outcome Measures	Significant Primary Outcomes	Treatment Group Supplement Used	Control Group Supplement Used	Study Length	Summary of Outcomes
			hamstring) **Secondary:** functional mobility and strength	atrophy compared to ↓ 13.4%± 1.9% in control group**. Treatment Group Hamstring Muscle Volume at 6 weeks:** ↓ 7.4%± 2.0% compared to ↓ 12.2%± 2.3%.	post-operatively. EAA composed of: 2.2 g histidine, 2.0 g isoleucine, 3.6 g leucine, 3.2 g lysine, 0.6 g methionine, 3.2 g phenylalanine, 2.8 g threonine, 2.4 g valine	weeks post-operatively. Placebo composed of 20 g alanine.		quadriceps and hamstring volume bilaterally. No significant differences in function.
Nishizaki et al. 2015	Total Knee Arthroplasty	Standardized protocol	**Primary:** Knee extension strength, rectus femoris cross sectional area	**Treatment Group Maximal Quadricep Strength:** Control group significantly decreased at 14 days (1.1–0.7), but the intervention group did not (1.1–0.9).	HMB (2,400 mg)/ Arg (14,000 mg)/ Gln (14,000 mg) with an average of 63.7 g(4.2) daily. Starting 5 days preoperatively and 28 days after surgery BID.	Orange juice (280 mg daily). Starting 5 days preoperatively and 28 days after surgery BID.	6.7 weeks	Decreased loss of quadriceps muscle strength after TKA
Muyskens et al. 2019	Total Knee Arthroplasty	Standardized protocol	**Primary:** Muscle biopsy (vastus lateralis)	**Treatment Group** had increased number of satellite cells at time of operation that decreased to be similar to the control group at the 1/2-week post-operative biopsy.	EAA composed of: histidine 2.2 g, isoleucine 2.0 g, leucine 3.6 g, lysine 3.2 g, methionine 0.6 g, phenylalanine 3.2 g, threonine 2.8 g, valine 2.4 g BID for 1 week preoperatively continuing 6 weeks postoperatively.	Placebo group received alanine 20 g BID 1 week preoperatively continuing 6 weeks postoperatively	7 weeks	EAA supplementation decreased muscle atrophy after TKA along with inflammatory markers. Increased satellite cells at time of operation from 7 day EAA supplementation preoperatively.
Ueyama et al. 2020	Total Knee Arthroplasty	Standardized protocol	**Primary:** Muscle cross sectional area (rectus femoris and quadriceps) **Secondary:** serum albumin level, VAS pain, mobility, recovery of ADLs.	**Treatment Group Muscle Measurements 3 Weeks from Baseline:** Rectus femoris cross-sectional area ↑ 119%(79%–179%) compared to ↑ 102%(63%–186%) in control group. Quadricep muscle diameter ↑ 127%(78%–192%) compared to ↑ 111%(72%–179%) in control group. **Treatment Group Muscle Measurements 4 Weeks from Baseline:** Rectus femoris cross-sectional area ↑ 116%(71%–206%) compared to ↑ 97%(68%–155%) in control group. Quadricep muscle diameter ↑ 123%(86%–171%) compared to ↑ 97%(68%–155%) in control.	3 g EAA TID one week preoperatively and 2 weeks postoperatively (isoleucine 603 mg, leucine 684 mg, lysine 756 mg, methionine 603 mg, phenylalanine 405 mg, threonine 405 mg, tryptophan 207 mg, valine 603 mg, arginine 630 mg, histidine 315 mg, starch 1089 mg)	Placebo (lactose powder 9 g) 1 week preoperatively and 2 weeks postoperatively	8 weeks	EAA supplementation prevented rectus femoris muscle atrophy and accelerates functional recovery after TKA.
Schurch et al. 1998	Hip Fracture	No protocol reported	**Primary:** Bone density, bone remodeling markers and muscle strength **Secondary:** Function	**Bone Mineral Density of Proximal Femur Treatment Group**: Difference of ↑ 2.42% (0.26%–4.59%) representing attenuated loss of bone mineral density. **Serum IGF-1 (Bone Remodeling) Treatment Group:** ↑ 51.5%(18.60%–84.4%) compared to control.	20 g Protein supplementation daily (90% milk proteins)	Isocaloric placebo (maltodextrin)	24 weeks	Protein supplementation increased IGF-1 and decreased loss of bone mineral density at the proximal femur.

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Table 2 (*continued*)

Author/ Year	Surgery	PT or Exercise Protocol	Outcome Measures	Significant Primary Outcomes	Treatment Group Supplement Used	Control Group Supplement Used	Study Length	Summary of Outcomes
Botella-Carretero et al. 2008	Hip Fracture	Details not reported	**Primary:** Serum albumin/Retinol Binding Globulin and BMI **Secondary:** Functional measures, post-operative complications	None	**Treatment Group 1**: Commercial protein powder (Proteina vegenat med) with 9 g of protein QID **Treatment Group 2:** Commercial enternal nutrition with 18.8 g BID	No intervention, observed normally nourished or mildly undernourished patients.	1.8 weeks	Supplementation had positive effect on post-operative complications in undernourished patients.
Rondanelli et al. 2020	Hip Fracture	Inpatient standardized protocol	**Primary**: Pain (VAS) **Secondary:** Daily therapy length	**VAS:** Decreased significantly compared to control at 15 days Intervention: -47.5% Control: -37.1%	6.6 g EAA sachet taken with water or milk BID for 4 weeks (1500 mg leucine, 1000 mg lysine, 750 mg glutamine, 550 mg valine, 450 mg isoleucine, 450 mg glycine, 350 mg serine, 250 mg threonine, 250 mg phenylalanine, 350 mg tyrosine, 350 mg histidine, 125 mg methionine, 75 mg tryptophan)	Isocaloric placebo (maltodextrin)	4 weeks	EAA effective in reducing pain levels and time to resolution of pain. The decrease in pain was associated with increased length of daily physical therapy.

Data are presented for surgery type, physical therapy (PT) or exercise intervention, listed outcome measures, significant primary outcomes, treatment and control supplements used [Protein; protein + carbohydrate (PC); isocaloric control (IC); placebo control (PL); Essential amino acids (EAA); Branched-chain amino acids (BCAA); Leucine; carbohydrate; fat; maltodextrin; non-essential amino acids], study duration, and study conclusions. Additional abbreviations: visual analog scale (VAS), SID (once daily dose), BID (two daily doses), TID (three daily doses), QID (four daily doses).

who have sufficient baseline dietary protein intake.[50]

Second, there was wide variation in the types of protein supplements used, most evident in the ACLR cohort. Holm et al.[35] evaluated protein in the form of skim milk and soybean product, while Kim et al.[37] chose whey protein for supplementation. These factors are important as protein source affects absorption rate and amino acid flux, which may acutely contribute to differences in nutrient sensing and signaling.[25] While the majority of studies in the other cohorts evaluated essential amino acid supplementation, in the ACLR cohort only Laboute et al.[36] evaluated EAAs using leucine. Further research is needed to evaluate whole protein sources, peptide sources (hydrolysates), EAAs, and specific amino acid supplementation as there may be advantages to each for a given patient population based on absorption rates, bioavailability, total amino acid intake, and caloric requirements. For example, in instances where excess amino acid intake may be deleterious due to compromised kidney function, low-dose supplementation of key amino acids such as leucine rather than whole protein sources may be advantageous to mitigate muscle loss while reducing risk.[29]

Among the studies that attempted to quantify muscle mass as an objective outcome variable of protein supplementation, all studies utilized thigh cross sectional area as a representative measure. This is subject to both manual error during measurement, as well as physiologic confounders such as hydration status or body composition.[51] The use of imaging technology such as dual energy x-ray absorptiometry (DEXA) may serve as a more objective measure of muscle mass as it can report to the nearest gram of tissue for a given region of interest.[52]

Finally, it is important to note that there is a broader context of factors that play a role in recovery after various orthopaedic procedures. The varying demographics, medical comorbidities, and baseline functional status of the patient populations that typically undergo each procedure included in this review play a unique role in overall recovery and return to function. In addition, the rehabilitation protocols are very different among each surgery. As varying rehabilitation strategies may differentially improve functional recovery after each orthopaedic procedure,[52–54] further research is needed to determine the role protein supplementation may play in the context of these rehabilitation approaches.

This systematic review is not without limitations. The scope of the study was left broad as there were multiple surgery types and protein regimens included, which make the conclusions less precise. Average MCMS scores were in the fair to poor categories, limiting the conclusions that can be drawn from the studies, as well as highlighting the need for future better-quality studies. As described above, physical therapy and exercise protocols were included, but they were not standardized among studies. Finally, the included studies all evaluated short-term outcomes of protein supplementation. Further RCTs are needed to evaluate longer-term outcomes (i.e., 6–12 months for ACL reconstruction) and specific supplementation protocols following various orthopaedic procedures. This would allow for better customization of nutritional interventions and identification of patient populations who may benefit the most.

5. Conclusions

Protein supplementation appears to have beneficial effects on mitigating muscle atrophy in the postoperative period following ACLR, THA, TKA, and surgical treatment of hip fracture. This response often correlates with improved functional measures and quicker achievement of rehabilitation benchmarks. Further research is needed to establish standardized supplementation regimens and guidelines for improving clinical outcomes in the postoperative period.

Submission statement

All authors have read and agree with manuscript content. While this manuscript is being reviewed, the manuscript will not be submitted elsewhere for review and publication.

Authors' contributions

A.G. served as primary manuscript writer and assisted with performing systematic review. B.M.H assisted with writing manuscript and

performing systematic review. B.S.L. facilitated study design and performed manuscript review. J.D.H. facilitated study design and performed manuscript review. P.C.M facilitated study design and performed manuscript review.

Conflict of interest

The authors have no interests that are in direct conflict with the conduction of the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.smhs.2023.08.002.

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