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Peri-operative protein or amino acid supplementation for total joint arthroplasty: a systematic review and meta-analysis

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Abstract

Purpose Osteoarthritis (OA) affects weight-bearing joints, such as hips and knees, and its prevalence is rising due to factors like obesity and aging. Muscle atrophy, exacerbated by aging and surgery, increases the risk of joint instability and falls. Orthopedic surgeons explore dietary interventions to counteract these effects, with protein supplementation (PS) showing promise. This systematic review and meta-analysis assessed the effectiveness of PS in arthroplasty patients, comparing findings with sports medicine and sarcopenia literature.

Methods Following PRISMA guidelines, we searched PubMed, Web of Science, Scopus, and Embase (February 2025) for protein and amino acid supplementation studies in total knee or hip arthroplasty (TKA and THA) patients. The quality assessment used the Cochrane risk of bias and the Newcastle–Ottawa Scale. Meta-analysis calculated effect sizes for muscle atrophy and strength outcomes.

Results Nineteen studies (903 patients) evaluated oral or intravenous protein/amino acid supplementation over a mean follow-up of 55.2 days. Essential amino acids (EAA) significantly reduced muscle atrophy in quadriceps femoris muscle mass (SMD: 0.69; 95% CI: 0.44 to 0.95) and hamstring muscle mass (SMD: 1.04; 95% CI: 0.52 to 1.55). However, effects on intramuscular adipose tissue (IMAT) and muscle thickness (MT) were inconsistent. Muscle strength outcomes varied, with no significant effect on quadriceps muscle strength (QMS) or handgrip strength (HGS). Intravenous amino acid infusion improved muscle protein synthesis and reduced perioperative blood loss.

Conclusions Protein and amino acid supplementation can reduce muscle atrophy in hip or knee arthroplasty patients. While effects on muscle strength and function are mixed, intravenous supplementation offers benefits. Further standardized research is needed to confirm these findings.

Trial registration PROSPERO registration code (CRD42024555899).

Keywords Arthroplasty, Amino acid supplementation, Protein supplementation, Amino acid infusion, Essential amino acid, Branched-chain amino acids

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Background

Osteoarthritis (OA) is the prevailing progressive musculoskeletal disorder primarily impacting weight-bearing joints such as hips and knees. The prevalence of hip and knee OA has witnessed a substantial increase in recent decades and continues to rise. This can be attributed in part to the growing prevalence of obesity and other risk factors, as well as other independent causes [1, 2]. Nevertheless, following total knee arthroplasty (TKA), a considerable number of patients endure pronounced muscle atrophy and weakness, which had been reported to persist for up to 5 months and would compromise balance and functional mobility [3, 4]. Previous reports have indicated that the incidence of postoperative malnutrition can reach as high as 50% after TKA [5] and 40–80% after total hip arthroplasty (THA) [6]. Muscle atrophy is caused by senility and is exacerbated after joint reconstructive surgery [7, 8], which causes increased joint instability and susceptibility to falling. These odds add up to an increase in wear rate, aseptic loosening, periprosthetic fracture, and revision surgeries [9–11].

Orthopedic surgeons have shown interest in different dietary and exercise regimens to mitigate this. Among these, protein and amino acid supplementation have become a promising intervention to counteract muscle loss and support postoperative recovery. Protein supplementation (PS) is well-investigated in sports medicine and sarcopenia, where it enhances muscle protein synthesis, preserves muscle mass, and improves strength and function [12–17]. Essential amino acids (EAAs), such as leucine, and branched-chain amino acids (BCAAs) are particularly effective due to their role in stimulating anabolic pathways, even in older adults with anabolic resistance [14–17]. Research suggests older adults benefit from higher protein intakes (e.g., 1.2–1.6 g/kg/day) than the recommended daily allowance (0.8 g/kg/day), especially during catabolic states like surgery [18]. However, 30.3% to 65.1% of older adults with knee or hip OA have daily protein intake below this baseline, highlighting the potential role of supplementation [18]. Beyond quantity, protein quality (defined by EAA content and digestibility) is critical, with options like whey, casein, glutamine, and amino acid infusions (oral or intravenous) showing varying efficacy based on dosage, timing, and administration route [14–17]. Dietary interventions, including PS, have been integrated into the multidisciplinary approach for managing OA [19, 20].

In this systematic review and meta-analysis, we aim to evaluate the effectiveness of perioperative protein or amino acid supplementation on muscle mass, strength, and functional outcomes in patients undergoing total knee or hip arthroplasty. We compared these findings to established evidence from sports medicine and sarcopenia research to guide clinical practice and future studies.

Material and methods

Protocol and registration

The present systematic review is based on the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines. The study protocol has been registered in PROSPERO In advance.

Search strategy

We systematically searched medical electronic databases, including PubMed, Web of Science, Scopus, and Embase, in February 2025. We imposed no restrictions and collected all available journal articles up to the search date. A combination of the following keywords was used as a search strategy and narrowed down to title, abstract, and keyword search fields: ("essential amino acid*" OR "glutamine" OR "l-glutamine" OR "branched-chain" OR "BCAA*" OR "albumin infusion" OR "essential amino acid" OR "arginine" OR "l-arginine" OR "amino acid supplementation" OR "amino acid infusion" OR "protein supplementation" OR "protein infusion") AND ("arthroplasty" OR "hip replacement" OR "knee replacement").

Eligibility criteria

The population includes patients undergoing knee or hip joint replacement surgery; the intervention was consumption of protein or amino acid supplementation, and the outcome stands for surgical-related complications. Criteria for inclusion encompassed studies (1) involving patients undergoing knee or hip joint arthroplasty, (2) interventions involving oral or injectable protein or amino acid supplementation pre-, intra-, or post-surgery. We excluded case reports, case series, opinions, books, reviews, letters, conference abstracts, in-vivo, and in-vitro studies. Also, we excluded studies in which high-protein diets were used instead of supplements and studies in which the target group had specific diseases affecting protein metabolism.

Study selection

After finalizing the search, duplicates were removed, and the remaining articles were separately screened by two authors (AB and ES) based on title and abstract. The full texts of potentially relevant studies were subjected to a full-text review by two authors (AB and SK), and the first author resolved conflicts. Finally, reference lists of the included articles were reviewed for additional relevant studies.

Data extraction

To ensure accuracy, all reviewers extracted and summarized key information from the included articles so that at least two individuals extracted and summarized the data from each article. The following information was extracted by the authors: author name, date of publication, region of study, type of study, type of arthroplasty, inclusion and exclusion criteria, age, sex, body mass index (BMI), dietary information, the number of participants in each group, the type of protein, amino acid, or placebo given to each group, dosage, route of administration, repetition, overall dose, timing (before, during, or after surgery), period of supplementation intake, exercise or physical therapy details and all outcomes measured. After addressing and resolving any conflicting findings, the final dataset was obtained.

Risk of bias assessment

For quality assessment of randomized controlled trials (RCTs), Cochrane risk of bias tool (ROB), and case-control study, The Newcastle–Ottawa Scale (NOS) was used.

Statistical analysis

We performed a random-effects meta-analysis to assess the effect of PS on quadriceps muscle strength (QMS) and muscle atrophy in patients undergoing arthroplasty by calculating the effect size and corresponding confidence intervals (95%CI). Furthermore, a fixed-effect model was applied for outcomes with low heterogeneity ($I^2 \leq 25\%$). The effect size of our interest in this analysis was Standard Mean Difference or SMD (by Hedges, 1981) using the mean differences from baseline for both supplemented and non-supplemented groups and SD of these mean differences. We have intervention and control groups and mean and SD values of pre and post-operation for each group. So we calculated the mean changes from baseline and SD of the mean changes for each group using the following formula:

$$\text{SD change} = \sqrt{(\text{SD2baseline} + \text{SD2 final} - (2 \times r \times \text{SDbaseline} \times \text{SDfinal}))}$$

SD change represents the SD of the mean changes from baseline, SD baseline represents the SD of pre-op in each group, SD final means the SD post-op in each group, and r represents the correlation between the pre-op and post-op measurements. The first step in calculating the correlation (r in the formula) was to contact the corresponding authors of the included studies to request their data sets or the correlation between the baseline and the final measurements because this correlation value is not generally mentioned in the studies. If the corresponding authors did not share the requested data, we assigned a value of 0.7 to the r in the formula to calculate the SD change. Finally, if there were further missing data in a study, we did not include the study in the meta-analysis. Heterogeneity and inconsistency were assessed using chi-squared ($\chi 2$ or Chi2) and I2 statistic. Sensitivity analyses were performed to evaluate the influence of individual studies on the overall effect size for analyses with high heterogeneity. Egger's regression test was also performed to assess publication bias. P values less than 0.05 were considered statistically significant. All analyses were performed using the R software (version 4.3.2 (2023-10-31)), using the "meta" and "metafor" packages.

Results

Search result

We conducted searches across multiple databases; after removing duplicate entries, we were left with 254 studies for further consideration. Following title/abstract screening and full-text review, 19 articles fulfilled our inclusion criteria [21–39] (Fig. 1).

Study characteristics

These studies were conducted across different countries, with six studies from Japan [28, 30–33, 37], five from the USA [21, 23, 26, 29, 35], two from Italy [24, 27], two from Sweden [25, 34], two from the UK [36, 38], one from China [39], and one from Iran [22]. In total, 903 patients, 578 of whom were female, were included. 12 articles focused on the arthroplasty of the hip joint [22–28, 31–34, 36], while six examined the knee joint [21, 29, 30, 35, 37, 39], and one study focused on both hip and knee joint [38]. 14 articles employed an oral intervention [21, 23, 24, 27–33, 35, 37–39], and five utilized IV intervention [22, 25, 26, 34, 36]. Furthermore, out of the 19 articles, six studies used EAA as the intervention [21, 24, 29, 33, 35, 37], while the remaining studies employed various other types of amino acids. The mean follow-up time was 55.2±84.9 days, ranging from 1 day to 365 days. One article was a case-control study [32], while the remaining were all RCTs (Table 1).

Risk of bias assessment

The domains of selection, which encompass random sequence generation, allocation concealment, and the reporting domain, were more frequently classified as having an unclear risk of bias. Most of the studies were classified as having a low risk of bias, and none of the articles reached a high risk of bias in any of the assessed domains. The case-control study scored eight on the NOS quality assessment [32]. The details of the quality assessment are provided in Fig. 2.

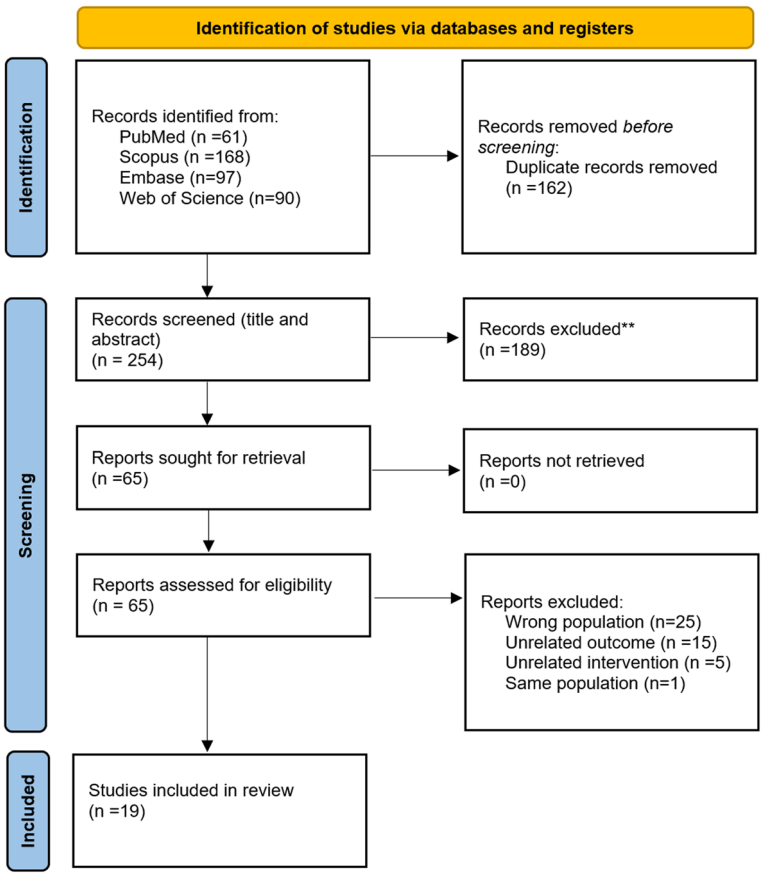

Fig. 1 PRISMA flow chart

Muscle mass and atrophy

Seven studies have reported on the effects of PS on muscle mass and atrophy, which utilized different measurements to assess these variables and reported their findings using various parameters [21, 28, 30, 31, 35, 37, 39]. EAA, along with age and sex, is an independent factor in preserving muscle atrophy after TKA [37]. EAA consumption significantly affected muscle atrophy in the quadriceps, hamstring, and adductor muscles. Additionally, taking EAA resulted in a significantly higher intramuscular adipose tissue (IMAT) change rate in both legs [21, 35]. Ninomiya et al. found no significant effect of whey protein on IMAT or muscle thickness (MT) [31]. However, Li et al found whey protein and rehabilitation training significantly improved leg circumference as a correlative value to skeletal muscle mass [39]. Furthermore, using HMG/Arg/Gln could reduce rectus femoris muscle atrophy; but the difference compared to the placebo group was insignificant [30]. Ikeda et al reported that BCAA and training significantly affect muscle mass [28] (Table 2). Our meta-analysis showed that PS significantly improved quadriceps femoris muscle mass (SMD: 0.69; 95% CI: 0.44 to 0.95) and hamstring muscle mass (SMD: 1.04; 95% CI: 0.52 to 1.55). However, the effect on upper arm muscle mass was negligible (SMD: 0.12; 95% CI: −0.60 to 0.83). The overall effect size for muscle mass across all muscle groups was 0.70 (95% CI: 0.48 to 0.92), suggesting a beneficial effect of PS (Fig. 3). Subgroup analyses revealed TKA studies had stronger reductions in muscle atrophy (SMD: 0.82) than THA (SMD: 0.43) (Fig. 4). Short-term follow-up (1–6 weeks) showed greater muscle atrophy reduction (SMD: 0.81) than long-term (>6 weeks; SMD: 0.59) (Fig. 5).

Muscle strength and function

For the assessment of muscle strength, surgeons utilized measures such as quadriceps muscle strength (QMS), hamstring muscle strength (HMS), and HGS. Seven studies have examined the effects of PS on QMS, with the isometric method predominantly used for measurement [21, 28, 30, 31, 35, 37, 39]. Two articles found no correlation between EAA and muscle strength [35, 37]. however, another study observed high QMS improvement rates after using BCAA in both operated and contralateral legs [28]. Dreyer et al the only research measuring QMS at different knee extension angles showed increases at both

Table 1 Study characteristics

Author	country	Study groups (I1/I2/C)	Sample size (I1/I2/C)	age (I1/I2/C)	BMI I1/I2/C	female (I1/I2/C)	Supp (dose/form)	Exercise session/time	arthroplasty	Follow-up	Outcomes measures
Alipour 2022 [22]	Iran	17 AA/Saline	18/18	56±19.6/60±17.3	NR	NR	500cc/IV	NR	THA	1 d	core temperature/ MAP/HR
Askanazi 1980 [23]	USA	AA/AA+GLU/GLU	7/8/7	56±9/57±9/ 54±14	NR	2/4/3	70 g/PO	NR	THA	5 d	plasma, muscle AA
Baldassarro 2016 [24]	Italy	EAA/Maltodextrin	30/30	67.9±7.3/ 65.6±9.5	29.8±4.2/ 27.5±3.9	16/20	8 g/PO	24/45′	THA	14 d	plasma AA/HB/ Transferrin/HHS/ Inflammation rate
Blomqvist 1995 [25]	Sweden	Glutamine/α-Ketoglutarate/c	10/10/13	68±1/66±2/68±2	25.5±1.0/ 24.9±1.3/ 25.3±1.0	3/7/6	0.28 mg. kg/IV	NR	THA	1 d	plasma, muscle AA/ ribosome parameters/ blood hormone
Church 2021 [26]	USA	travasol10%/ standard care	9/13	52.2±2.8/ 55.5±3.2	28.2±1.8/ 29.5±1.2	2/6	135 mg.kg.h/IV	NR	THA	1 d	FSR/FBR/Muscle net balance
De sire 2020 [27]	Italy	AA/C	10/10	80.33±6.72/ 77.65±8.40	NR	9/8	8 g/PO	10/40′	THA	60 d	serum myostatin
Dreyer 2013 [21]	USA	EAA/Alanine	16/12	68 ± 5/70 ± 5	34 ± 7/29 ± 3	11/8	40 g/PO	NR	TKA	42 d	quadriceps/hamstring area
Dreyer 2018 [35]	USA	EAA/Alanine	19/20	64.41 ± 0.94	29.78 ± 1.20	NR	40 g/PO	98/NR	TKA	42 d	quadriceps/hamstring area
Evans 2003 [36]	UK	Albumin/Gelofusine/Haemaccel/ Saline	13/14/14/14	69.2/73.9/73.8/ 69.1	NR	10/7/10/3	2L/IV	NR	THA	NR	Blood aggregation/ agglutination /serum albumin/BT/ APTT
Ikeda 2019 [28]	Japan	BCAA/starch	18/13	75.2±4.9/ 75.6±6.6	21.9±4.0/ 25.5±3.7	18/13	3.4 g/PO	28/60′	THA	30 d	knee extension strength/AMA/ HGS/hip abduction strength
Ikeda 2022 [32]	Japan	Normal strength/ Muscle weakness	71/91	64.4±8.6/ 67.1±9.7	23.2±3.2/ 24.9±4.5	59/78	NA	NR	THA	365 d	hip abductor muscle strength/ knee extension muscle strength/ the 10-m timed gait test/HHS/Energy expenditure
Invernizzi 2020 [33]	Japan	EAA/C	16/16	80.33± 6.72 77.65±8.40	23.05±4.77/ 23.15±5.33	13/14	8 g/PO	10/40′	THA	14 d	HGS/TUG/ILOA
Khalid 2024 [38]	UK	Protein/C	33/31	75±5/75±5.5	NR	25/21	20 g/PO	84/NR	THA/TKA	84 d	WOMAC/EQ-5D/ ICECAP-O/Physical activity level/protein screener55+/

Table 1 (continued)

Author	country	Study groups (I1/I2/C)	Sample size (I1/I2/C)	age (I1/I2/C)	BMI I1/I2/C	female (I1/I2/C)	Supp (dose/form)	Exercise session/time	arthroplasty	Follow-up	Outcomes measures
Li 2024 [39]	China	Whey protein/ Maltodextrin	36/36	66.53 ± 4.14/67.50 ± 3.87	24.98 ± 3.44/25.39 ± 2.48	24/27	30 g/PO	60/NR	TKA	84 d	Knee extension muscle strength/ VAS/ ROM/AKS/leg circumference/
Muyskens 2019 [39]	USA	EAA/alanine	19/22	64.95±1.35/ 63.82±1.29	29.71±1.00/ 30.66±2.13	20/17	40 g/PO	NR	TKA	42 d	energy expenditure/muscle histology/gene expression/muscle stem cell
Ninomiya 2023 [31]	Japan	Whey protein/C	29/29	70.28 ± 3.26/ 70.86 ± 3.69	22.22 ± 2.74/ 23.09 ± 2.02	29/29	11 g/PO	168/NR	THA	84 d	hip abductor muscle strength/ knee extensor muscle strength/ HGS/quadriceps MT/IMAT/TUG-t/ HHS/hip pain/JHEQ point/Alb/Hb/CRP
Nishizaki 2015 [30]	Japan	HMG+L-arginine+ L-glutamine/ orange juice	13/10	71.1/69.8	NR	NR	40.8 g/PO	15/NR	TKA	42 d	energy expenditure/knee extension strength/ length of hospital stay/rectus femoris cross-sectional area/body weight
Ueyama 2023 [37]	Japan	EAA/lactose powder	30/30	75.9/75.8	NR	23/27	9 g/PO	NR/120′	TKA	28 d	serum alb/RFA/knee pain/quadriceps muscle diameter
Widman 2002 [34]	Sweden	AA/acetated Ringer	22/24	67±7/67±6	25.64/ 26.09	11/12	2.268 g.h/IV	NR	Primary HA	NR	Body temperature/ Blood loss

I1 intervention 1, *I2* intervention 2, *C* control, *sup* supplementation, *HB* hemoglobin, *MAP* mean arterial pressure, *HR* heart rate, *AA* amino acid, *GLU* glucose, *EAA* essential amino acid, *AMA* upper arm muscle cross-sectional area, *HHS* Harris hip score, *FSR* fractional, *WOMAC* The Western Ontario and McMaster Universities Osteoarthritis Index, *EQ-5D* EuroQol-5 Dimension 5-level, *ICECAP-O* ICECAP-O: ICEpop Capability Measure for Older People, *VAS* visual analog scale, *AKS* American knee society scale

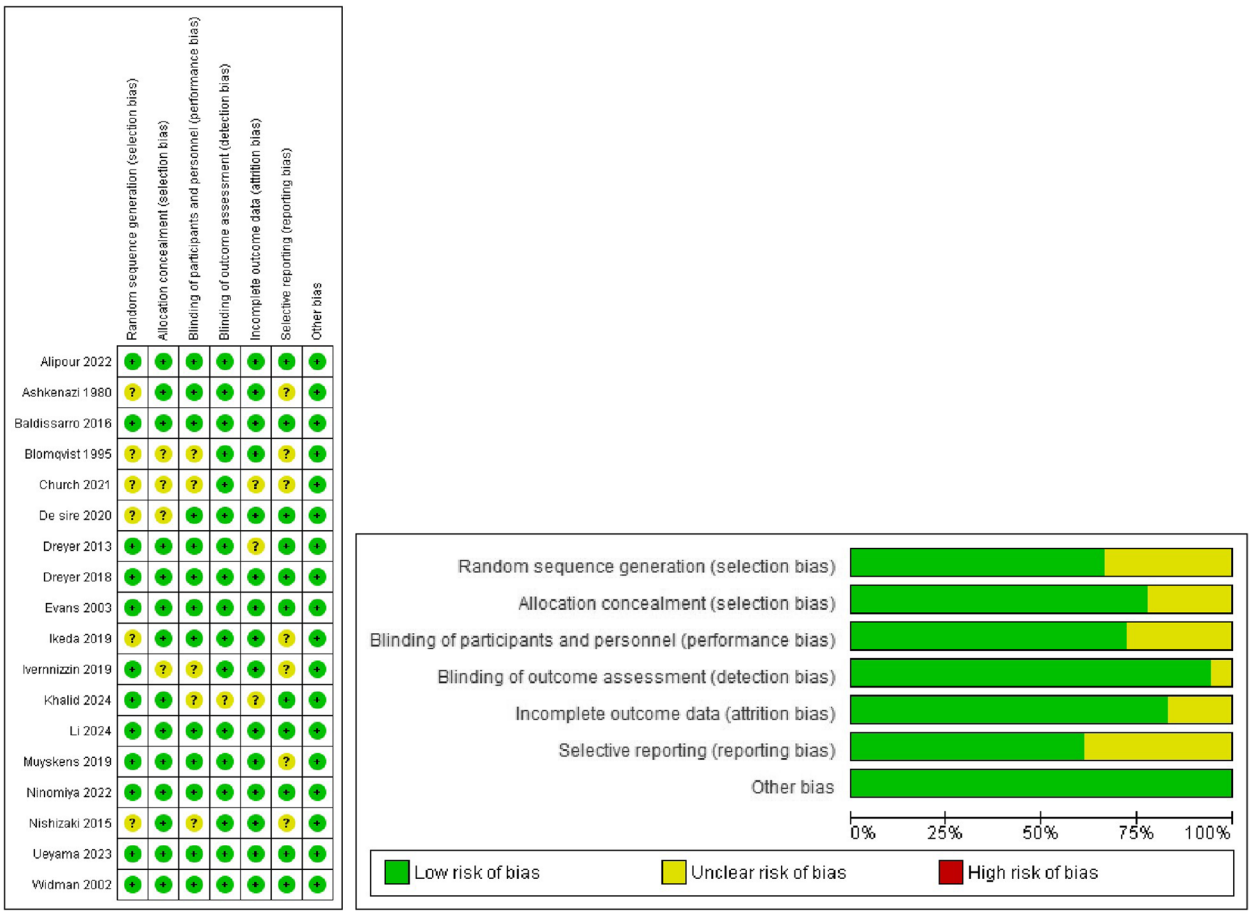

Fig. 2 Risk of bias summary and graph

45 and 60 degrees for the operated leg and a significant strength increase at 45 degrees in the EAA group [21]. One study found a positive effect of HMG/Arg/Gln on QMS in the operated leg two weeks post-operation, but this effect was not significant by the end of the follow-up period [30]. Ninomiya et al. concluded that whey protein significantly affected QMS on both sides and HMS on the contralateral side [31]. Similarly, Li et al found significantly higher muscle strength with using whey protein [39] (Table 3). Additionally, five studies reported no effect of PS on HGS [28, 31, 33, 35, 37]. Details of these findings are organized in Table 4. A random-effects model was used to analyze the effect of PS on QMS across seven studies. The pooled effect size was 0.9341 (95% CI: −0.2911, 2.1592), indicating a non-significant trend toward improvement in QMS (z = 1.4943, $p = 0.1351$) with substantial heterogeneity among the studies, with an estimated $tau^2 = 2.5912$ (SE = 1.5789) and $I^2 = 95.48\%$ with subgroup analyses revealed high QMS heterogeneity in TKA ($I^2 = 96\%$) but more consistent effects in THA ($I^2 = 0\%$) (Fig. 6). Follow-up duration did not significantly moderate results ($p > 0.39$) (Fig. 7). Sensitivity analysis was conducted to assess the robustness of the QMS results by systematically removing one study at a time. The results are summarized in Supplementary Table 2.

Eight papers have assessed the effects of PS on muscle function [21, 24, 31, 33, 35, 37–39]. Various assessments have been utilized with commonly used ones, including the Harris Hip Score (HHS), Timed Up and Go test (TUG-t), the 6-minute walk test, The Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC), and American Knee Score (AKS). Ninomiya et al. found no significant difference in HHS and TUG-t test scores between exercise alone and exercise combined with whey protein [31]. In contrast, Invernizzi et al and Baldassarro et al reported that patients who received EAA performed significantly better in the TUG-t test and HHS [24, 33]. Dreyer et al. observed no statistically significant difference in TUG and 6-minute walk test scores using EAA [35]. However, in another study by Dreyer et al. EAA showed significant improvement in the TUG test but not in the 6-minute walk test [21].

Table 2 Muscle mass and atrophy

Muscle	Study	Specific Muscle	Measurement tool/unit	Intervention				Control			
				Pre-op		Post-op		Pre-op		Post-op	
				Involved leg	Uninvolved leg	Involved leg	Uninvolved leg	Involved leg	Uninvolved leg	Involved leg	Uninvolved leg
Quadriceps femoris	Dreyer 2013 [21]	Rectus femoris	MRI/cm^3	120 ± 11	140 ± 12	110 ± 11	136 ± 12	133 ± 13	150 ± 16	108 ± 9	135 ± 14
	Dreyer 2018 [35]	NA	MRI/AU	48.66 ± 3.45	55.49 ± 3.87	43.87 ± 2.93	54.41 ± 3.65	44.81 ± 3.09	49.98 ± 3.05	38.31 ± 2.39	46.44 ± 2.94
	Ueyama 2023 [37]	Rectus femori	Ultrasound/ mm^2	258.0 ± 88.7	NA	326.0 ± 91.53	NA	305.2 ± 97.2	NA	345.7 ± 97.1	NA
	Nishizaki 2015 [30]	Rectus femoris	CT scan/cm^2	528±164	502±87	572±171	548±130	542±164	577±140	506±164	533±168
	Ninomiya 2023 [31]	Rectus femoris + vastus intermedius	Ultrasound/ mm	27.05 ± 6.92	32.64 ± 7.26	31.62 ± 6.84	36.48 ± 6.43	28.51 ± 7.24	32.84 ± 6.52	29.79 ± 6.90	33.21 ± 5.49
	Li 2024 [39]	NA	Tape measure/ cm	44.6 ± 0.93	NA	45.3 ± 0.83	NA	44.1 ± 1.12	NA	44.2 ± 1.08	NA
Hamstrings	Dreyer 2013 [21]	NA	MRI/cm^3	142 ± 13	147 ± 13	129 ± 11	142 ± 12	154 ± 17	150 ± 15	126 ± 16	137 ± 14
	Dreyer 2018 [35]	NA	NA	69.32 ± 4.05	69.37 ± 4.19	63.76 ± 3.41	67.50 ± 3.75	63.86 ± 3.33	63.64 ± 3.33	55.93 ± 2.91	58.75 ± 3.05
intermuscular adipose tissue (IMAT)	Dreyer 2013 [21]	NA	NA	66 ± 7	62 ± 8	69 ± 8	61 ± 7	46 ± 7	40 ± 5	44 ± 6	39 ± 5
	Ninomiya 2023 [31]	NA	NA	65.10 ± 14.35	59.15 ± 10.96	59.67 ± 10.26	54.56 ± 9.09	54.48 ± 10.97	61.92 ± 7.12	62.27 ± 14.50	56.11 ± 9.43
AMA	Ikeda 2019 [28]	NA	NA/cm^2	48.4±11.6		47.0±11.6		61.3±19.9		58.5±12.8	

QM quadriceps muscle, *IMAT* intermuscular adipose tissue, *HM* hamstring muscle, *AU* arbitrary unit, *F-U* follow-up, *AMA* upper arm muscle cross-sectional area

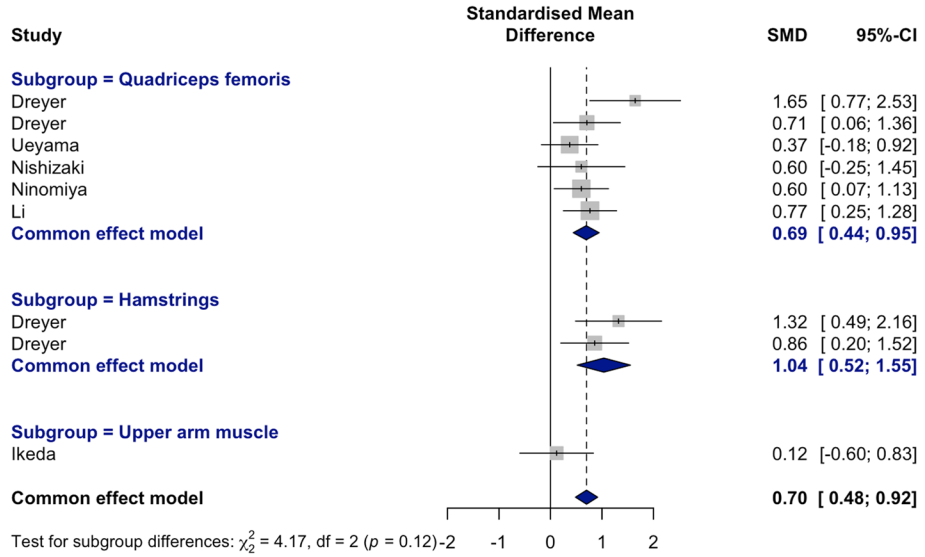

Fig. 3 Forrest plot for muscle atrophy in different muscle groups

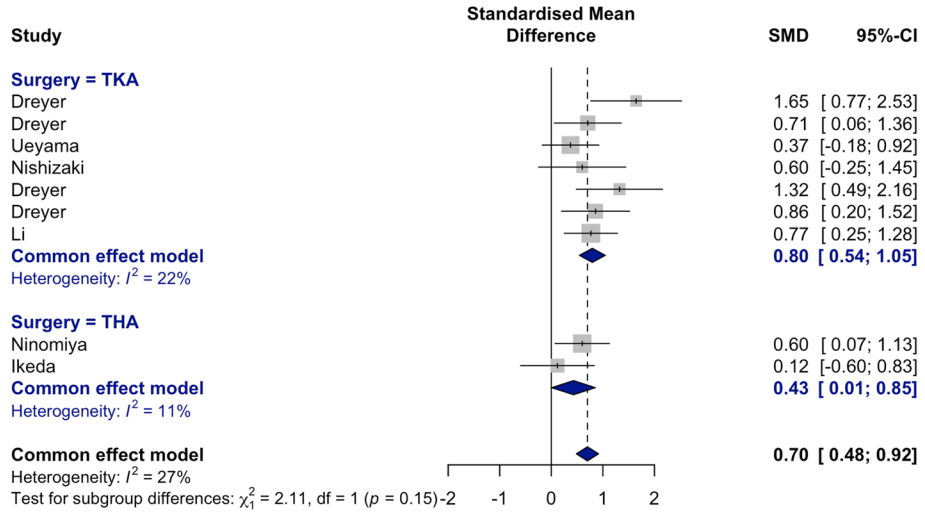

Fig. 4 Subgroup analysis of muscle atrophy after total knee or total hip arthroplasty

Similarly, Ueyama et al. reported no significant difference in the 6-minute walk test with EAA [37]. Li et al found a significantly higher AKS after using whey protein [39]. Additionally, Khalid et al found a slightly higher median WOMAC score in the PS group compared to the control group [38] (Table 5).

IV infusion

Five studies infused the amino acids intravenously [22, 25, 26, 34, 36]. Evans et al. found that colloid infusion caused temporary changes in platelet and coagulation parameters without affecting blood loss during hip arthroplasty [36]. Church et al. focused on total hip arthroplasty (THA) and discovered that perioperative amino acid infusion restored muscle net protein balance by augmenting muscle protein synthesis [26]. Widman et al. demonstrated that amino acid infusion promoted thermogenesis during anesthesia, reducing perioperative blood loss [34]. Alipour et al. specifically studied amino acid infusion in hip surgery patients with spinal anesthesia, observing a significant reduction in core body temperature without affecting mean arterial pressure or heart rate [22]. Finally, Blomqvist et al. explored the effects of glutamine and a-ketoglutarate, finding that glutamine

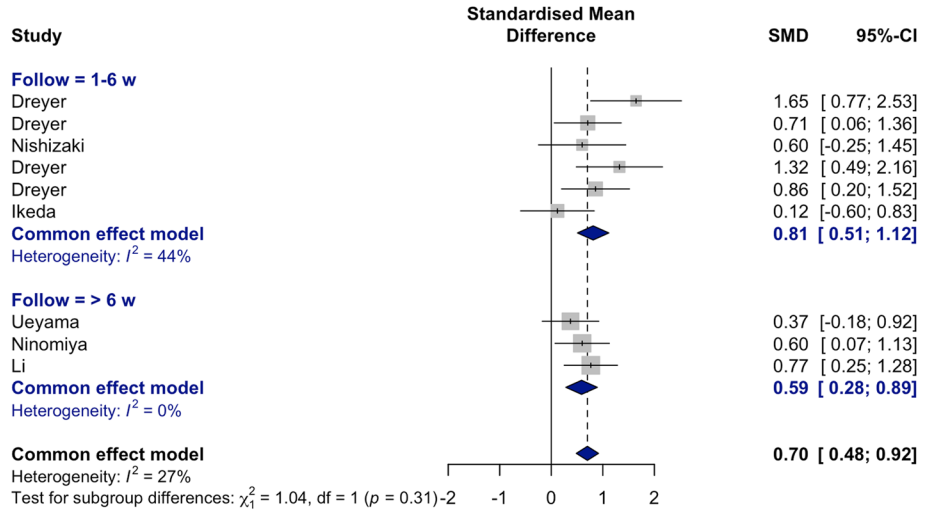

Fig. 5 Subgroup analysis of muscle atrophy in short-term (less than 6 weeks) and long-term (more than 6 weeks) follow-up durations

Table 3 Quadriceps muscle strength

Study	Unit	Intervention				Placebo			
		operated leg		non-operated leg		operated leg		non-operated leg	
		pre-op	post-op	pre-op	post-op	pre-op	post-op	pre-op	post-op
Nishizaki 2015 [30]	Nm/Kg	1.1±0.3	W2:0.9±0.4 W4:1.0±0.4 W6:1.0±0.4	1.3±0.4	W2: 1.3±0.3 W4:1.3±0.4 W6:1.2±0.3	1.1±0.62	W2:0.7±0.9 W4:0.9±0.9 W6: 0.9±0.6	1.3±0.7	W2:1.1±0.6 W4:1.3±0.6 W6: 1.2±0.5
Dreyer 2013 [21]	N	45°:87 ± 9 60°:89 ± 9	W2 45°:45 ± 6 W2 60°:41 ± 6 W6 45°:81 ± 7 W6 60°: 81 ± 7	45°:100 ± 7 60°:109 ± 9	W2 45°:100 ± 10 W2 60°:109 ± 10 W6 45°:104 ± 9 W6 60°: 110 ± 11	45° :87 ± 15 60°97 ± 16	W2 45°:36 ± 7 W2 60°:33 ± 8 W6 45°:69 ± 9 W6 60°: 65 ± 8	45°:112 ± 16 60°:126 ± 18	W2 45°:100 ± 12 W2 60°:105 ± 12 W6 45°:99 ± 12 W6 60°: 112 ± 14
Ninomiya 2023 [31]	Nm/Kg	0.96±0.36	1.19±0.35	1.11±0.40	1.36±0.40	0.87±0.31	0.97±0.33	1.02±0.32	1.13±0.26
Ikeda 2019 [28]	Kgf/Kg	0.24±0.10	0.31±0.08	0.37±0.13	0.43±0.13	0.26±0.06	0.31±0.08	0.31±0.09	0.33±0.09
Dreyer 2018 [35]	N	102.71 ± 9.50	93.63 ± 9.29	113.32 ± 11.16	121.56 ± 11.93	79.95 ± 13.68	81.80 ± 10.54	108.29 ± 12.08	101.89 ± 11.80
Ueyama 2023 [37]	N	130.8 ± 66.7	M48:177.9 ± 62.1	N/R	N/R	136.3 ± 62.0	M48:157.3 ± 60.7	N/R	N/R
Li 2024 [39]	Nm	45.26 ± 1.67	83.22 ± 1.92	N/R	N/R	45.01 ± 1.43	78.06 ± 1.45	N/R	N/R

Table 4 Handgrip strength (HGS)

Study	Arthroplasty	Follow-up	Intervention		Placebo	
Ninomiya 2023 [31]	THA	8 W	21.60±3.93	22.57±3.84	20.83±4.13	21.00±4.11
Ikeda 2019 [28]	THA	N/R	17.4±5.2	18.4±4.3	18.6±5.0	19.3±4.3
Dreyer 2018 [35]	TKA	6 W	28.95 ± 2.39	w2:30.47±2.32/ w6:30.74 ± 2.43	28.35 ± 1.89	w2:30.00±1.90/ w6:28.03 ± 1.87
Ueyama 2023 [37]	Unilateral TKA	2 Y	20.1 ± 4.4	M48:22.5 ± 4.4	20.9 ± 7.2	M48:22.5 ± 7.7

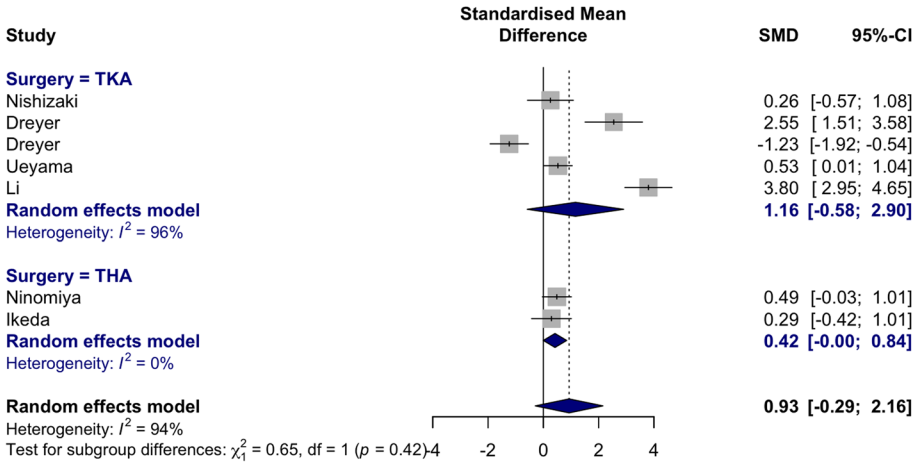

Fig. 6 Forrest plot for QMS after total knee or total hip arthroplasty

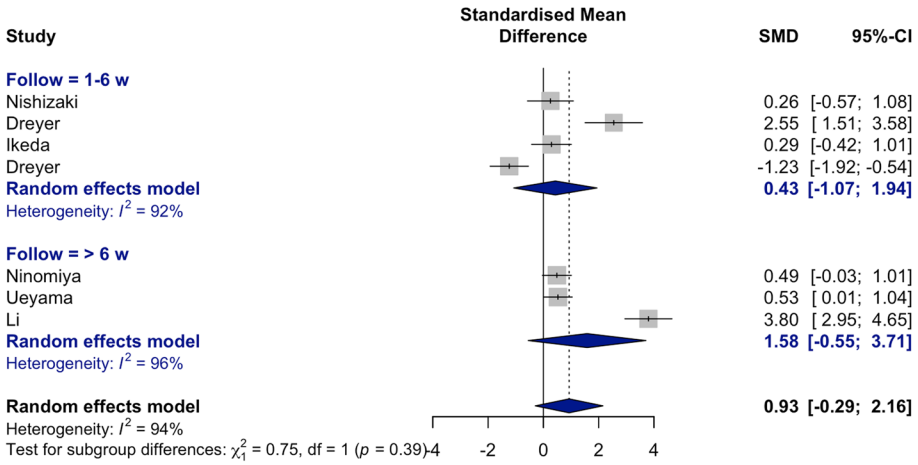

Fig. 7 Subgroup analysis of QMS in short-term (less than 6 weeks) and long-term (more than 6 weeks) follow-up durations

Table 5 Timed Up and Go test (TUG-t)

Author	Sample size C/I	Control		Intervention		Arthroplasty
		pre	post	pre	post	
Invernizzi 2019 [33]	15/16	18.85	16.03	19.31	15.57	THA
Ninomiya 2023 [31]	29/29	10.64 ± 3.96	9.30 ± 2.53	10.56 ± 3.46	8.88 ± 1.65	THA
Dreyer 2018 [35]	20/19	11.40 ± 0.68	10.90 ± 0.85	9.88 ± 0.46	9.87 ± 0.44	TKA
Dreyer 2013 [21]	12/16	NA	31.9 ± 10.2 %	NA	_4.0 ± 9.5%	TKA

infusion prevented glutamine level decreases. In contrast, total free amino acid concentration decreased overall [25]. (A detailed table of changes in each amino acid level is presented in Supplementary-table-1).

Publication bias

Publication bias was assessed using Egger's regression test for both QMS and muscle atrophy. For QMS, the test results indicated no significant publication bias (z = 1.4241, p = 0.1544) (Fig. 8). Similarly, for muscle

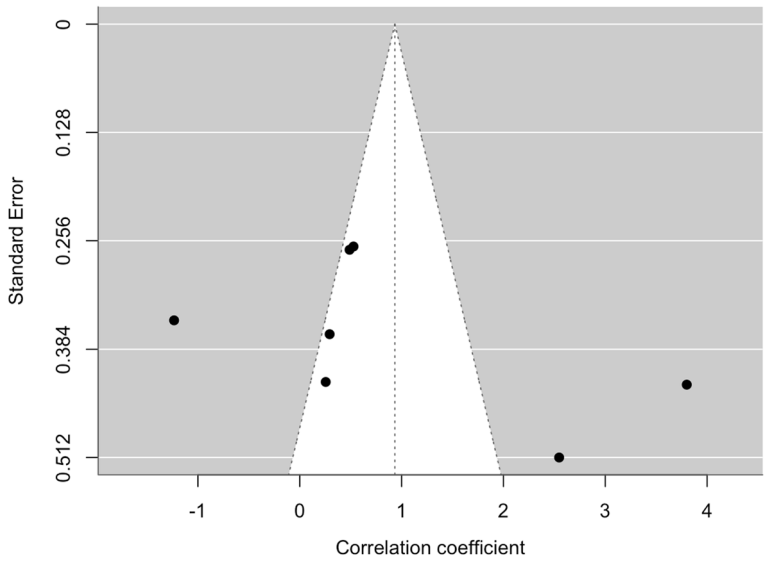

Fig. 8 Funnel plot Muscle atrophy

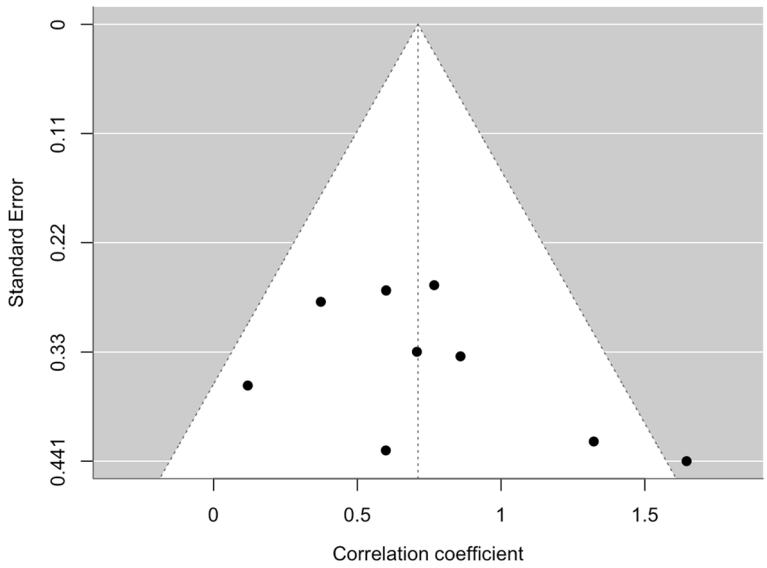

Fig. 9 Funnel plot for QMS

atrophy, Egger's test also showed no significant bias (z = 1.5601, $p = 0.1187$) (Fig. 9).

Discussion

Efficacy of PS for hypertrophy of the elderly, dosage and duration

PS to achieve muscle hypertrophy can be discussed regarding the target population, adequate dosage, sufficient duration of intervention, timing, efficacy of different compounds, and combination with resistance training. In a systematic review and meta-analysis of 17 RCTs, Liao et al. investigated the impact of combined PS and resistance training on lean muscle mass of older people; they concluded that PS improves body composition and function [40]. Conversely, Morton et al.'s study employed meta-regression and subgroup analysis, revealing that PS during resistance training becomes less effective as age increases. Moreover, it does not significantly augment changes in lean body mass among older individuals [41]. The different assumptions might be due to the inclusion of unhealthy older people. Studies suggest that older people benefit from increased dietary

protein consumption during catabolic health conditions, e.g., arthroplasty, due to anabolic resistance to muscle protein synthesis [42, 43]. Nunes et al. investigated the impact of increasing daily protein intake on lean body mass in healthy individuals; their meta-analysis suggests that subjects aged ≥65 years consuming 1.2–1.59 g of protein/kg/day and younger individuals (<65 years old) ingesting ≥1.6 g of protein/kg/day significantly increase lean body mass [44]. Other studies have confirmed that a total protein intake of 1.5 to 1.6 g/kg/day has significantly increased muscle strength and volume in elderly individuals with sarcopenia [45–47]. Ninomiya et al. only gave 11 g/day of whey protein, which is insufficient stimulation, although baseline protein intake was not measured [31]. On the other hand, Muyskens et al. had 40 g/day of EAA, which seems sufficient, but the supplementation lasted only for 7 days. Protein synthesis is a slow process and requires longer intervention periods to see any significant changes [48]. Studies on sarcopenia indicate that a six-month follow-up has a better impact on improving muscle strength and increasing muscle volume than a three-month follow-up [49].

Quality of the protein

The protein requirements of older adults exhibit heightened reliance on both the quantity and quality of dietary protein. Protein quality is calculated by EAA profile and protein digestibility using established metrics such as the protein digestibility-corrected amino acid score (PDCAAS) or the digestible indispensable amino acid score (DIAAS) [50]. Regarding the different PS options, studies in the field of arthroplasty are focused mainly on EAAs, including leucine [29–32, 35, 41, 43, 45]. This is plausible because the leucine content in the protein intake of the elderly plays a critical role in maintaining and regaining muscle mass [51]. Ueyama et al. gave 9 g/day of EAAs, providing 0.68 g of leucine [45], and Ikeda et al. supplemented their patients with 3 g/day BCAAs containing 1.2 g of daily leucine [28]. Studies indicate that providing at least 2.5 grams of leucine per meal positively impacts muscle protein synthesis [52, 53]. Leucine content varies across different protein sources, with whey protein containing the highest, approximately 12%, making it one of the best choices due to its affordability relative to isolated amino acids [49, 54, 55]. Ninomya et al. used 11 g/day of a whey protein blend with 2.3 g (21%) of leucine [31].

Exploring other fields of surgery

The importance of hamstring and quadriceps strength on anterior cruciate ligament (ACL) injuries, ACL reconstruction outcomes, and rehabilitation is well established [56], augmenting these efforts with PS shows promising results [57]. Other fields of surgery have conducted similar investigations; for example, in colorectal cancer, Burden et al. used a supplement drink with 24 g/day of protein for at least 10 days before surgery but showed no evidence of reducing the complications [58]. We hypothesize this is because of a very low duration of the supplementation period and insufficient dosage [42–44]. Regarding bariatric surgeries, studies have demonstrated that consuming protein leads to a more significant decrease in body fat mass, a more considerable decrease in body weight, and an increase in relative muscle mass in the lower limbs [59–61].

Limitations and suggestions

One limitation of this systematic review was the unavailability of all the detailed statistical analyses, so we used a standard value for our correlation analysis. Some of our included studies were underdosed, insufficiently followed, and commonly augmented with exercise or other nutritional supplements, making it hard to conclude the efficacy of PS alone [24, 28, 31, 33, 34, 37]. Another one was the high heterogeneity in QMS meta-analysis, which indicates that the effect of PS may vary significantly depending on factors such as study design, participant characteristics, or type of protein used. We suggest that future research focus on longer PS durations. It's essential to address the baseline protein intake of the individual and then supplement it to sufficient grams per kg of body weight and evaluate the cost-effectiveness of protein compounds, such as whey protein and EAAs.

Conclusions

This systematic review and meta-analysis suggest that peri-operative protein and amino acid supplementation significantly reduces muscle atrophy in total knee or hip arthroplasty patients. Intravenous delivery also enhances muscle protein synthesis and cuts blood loss. Despite variable strength and function outcomes, supplementation is a key intervention, though further standardized research is warranted.

Abbreviations

OA	Osteoarthritis
PS	Protein supplementation
EAA	Essential amino acids
IMAT	Intramuscular adipose tissue
BCAA	Branched-chain amino acid
TKA	Total knee arthroplasty
THA	Total hip arthroplasty
TJA	Total joint arthroplasty
MT	Muscle thickness
QMS	Quadriceps muscle strength
HMS	Hamstring muscle strength
HGS	Handgrip strength

Supplementary Information

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Supplementary Material 1.

Authors' contributions

All authors contributed substantially to this study. Also, all authors read and approved the final manuscript. Amir Mehrvar and Mohammad Noroozi conceptualized and supervised the study and reviewed and revised the final draft. Yashar Khani developed the methodology, administered the steps, reviewed and edited the final manuscript, and validated the data extraction sheet. Study selection, risk of bias assessment, data extraction, and writing the original draft were done by Ali Salmani, Elias Sadooghi Rad, Shaghayegh Karami, Mohammad Elahi, Alireza Bahrami Samani, and Iman Elahi Vahed. Iman Elahi Vahed conducted the meta-analysis.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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