Systematic Review for Protein and Creatine Supplements in Peri-operative Period in Elective Musculoskeletal Surgery-Knee and Hip Replacement

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Abstract

Background: Nutrition is increasingly becoming a greater part of medicine and in particular surgery. Pertinent nutritional clinical goals involve reducing recovery times by supplementing patients with additional nutrients and to prepare them for elective surgery so that recovery can be optimised. To assist in achieving the aforementioned outcomes within musculoskeletal surgery, supplementation with creatine and protein/Essential Amino Acids (EAA) can be a useful addition to patient care.

Methods: A systematic review was performed using EMBASE, Scopus and Medline as search engines. This yielded 200 articles of which nine were included within the analysis.

Findings: Two articles investigated creatine supplementation in orthopaedic knee surgery whilst seven focused on protein supplementation. Both creatine studies investigated pre and post-operative supplementation and found that creatine did not augment recovery of muscular strength. Whilst the six of the protein supplementation studies reported positive post-operative effects in respect to increases in strength and muscle mass. However no study matching the search criteria investigated the combination of both creatine and protein, likewise no study was found to report the speed of post-operative recovery with supplementation.

Conclusion: Supplementation with protein/EAA's is beneficial for those in the post-operative period in helping to reduce muscle atrophy and improve wound healing. There is limited evidence regarding the effects of creatine supplementation within such clinical populations, however there is a very good safety profile for both protein/EAA and creatine highlighting that supplementation is safe and can be experimented with.

Keywords: Protein • Creatine • Supplements • Knee • Hip • Elective musculoskeletal surgery • Enhanced recovery • Orthopaedic surgery • Recovery

Introduction

Nutrition balance is essential within the critically ill patient. Adequate *nutrition*al provision is vital for wound healing, restoring organ function and overcoming the increase in the metabolic demands seen by the patient. Surgical stress is also seen as one of the key circumstances where the body requires more than it's usual *nutrition* requirements therefore a considered and balanced intake of *nutrients* is necessary [1].

Oral Nutrition Supplementation (ONS) is recommended in the surgical period for all those with or at risk of under*nutrition* for one to two weeks prior to surgery [2, 3]. During hospitalisation it is common for *nutrition*al status to decline, especially after surgical trauma, impairing the post-operative recovery period, leading to poorer outcomes and patient dissatisfaction [4, 5]. ONS in the peri-operative period has been shown to decrease infection rates and length of hospital stay. Alongside this fatigue, wound healing and functional capacity has benefitted from ONS, due to satisfying the increase in for dietary protein for the stress response that can result in protein depletion leading to muscle atrophy [2]. Burgess LC, et al. investigated at the role of *nutrition*al supplements in total hip and knee replacement surgery. The authors found limited evidence for benefits of *nutrition*al supplementation. However, they did mention that there was a low risk profile and potential benefits with supplementation suggesting that they may have a role [6].

Within orthopaedic surgery post-operative muscle atrophy is a common complication. This can be a consequence of the surgery itself but it can be attributed to reduced activity pre-operatively resulting from pain, inflammation, *nutrition*al deficiencies and limited muscle activation due to injury [7]. Post-operatively this is exacerbated by the inherent catabolic inflammatory state and subsequent immobilisation that occurs leading to muscle loss and residual strength impairment [8-10]. The loss of muscle mass can hinder rehabilitation and also the return to sport when applied to athletes.

The increasing awareness of the post-operative period has led to an increased focus on post-operative rehabilitation programmes. Such programmes have focused on interventions such as electrical stimulation and early mobilisation with assisted walking to reverse muscular atrophy effects. Despite this, continued occurrence of decreased muscle mass and functional performance is commonly reported within post-operative patients in the literature [6, 9].

What is already known about nutrition and surgery?

Protein as a supplement: Deficiency in dietary protein (and other *nutrients* e.g. vitamin D and calcium) can have a negative impact on bone mass. With a low protein intake; insulin-like growth factor levels are reduced. This leads to a reduction in bone and muscle mass, increasing the risk of fracture and damage to the muscles [11]. It is thought that higher protein intakes are needed in patients with musculoskeletal issues, since to maintain and elevate protein synthesis levels in skeletal muscle and restore nitrogen balance; a net gain in protein balance is required for the body to optimally repair itself [12].

Milk based proteins have been found to stimulate greater amino acid uptake and net protein deposition compared to soy-based proteins [12]. Specifically, whey proteins, which contain all 9 Essential Amino Acids (EAA) are considered most effective for time efficient protein assimilation, synthesis and the prevention of muscle atrophy [13, 14]. In addition, EAA are a key stimulator for protein synthesis and therefore important in achieving a net protein balance, which allows for conditions of muscular adaptation and remodelling to occur [15]. They can either be found within complete animal based proteins or can be given as free-form EAA bolus. Two specific amino acids-arginine and lysine-have been shown to stimulate osteoblast proliferation, activation and differentiation, highlighting the potential importance of EAA supplementation for clinical populations [5].

Creatine as a supplement: Creatine is a naturally occurring non-protein amino-acid compound found primarily in red meat and seafood [16]. Supplementation is common within athletes with the aim of increasing muscular strength and high-intensity exercise performance. Supplemental creatine is known to enhance the ability to maintain muscular force and power output in healthy subjects, by preventing the depletion of intramuscular phosphocreatine but also: decreasing protein degradation, antioxidant protection and shuttling energy from the mitochondria to the cytosol [16, 17]. The intention of supplementation is to increase total body stores of phosphocreatine, so that when repeated contractions occur the process of intramuscular depletion is delayed [18]. Supplementation with creatine has been shown to be beneficial in non-orthopaedic populations by enhancing recovery and aiding injury prevention [15].

Aim

The aim of this review was to investigate the current literature surrounding peri-operative protein and creatine supplementation and establish whether combined protein and creatine supplementation is feasible for use during MSK surgery and whether it has the potential for a meaningful impact on post-operative outcomes and rehabilitation.

Literature Review

The key words used in the search engines were: "protein" "supplementation", "creatine" "amino acid" and "surgery" with Medline, Embase and Scopus used as the electronic databases. The reference lists of screened articles were also searched to identify additional articles. The PRISMA pathway can be found below (Figure 1).

Inclusion and exclusion criteria

Studies were included if they were published in the English language, published in a peer reviewed journal and were clinical studies investigating protein or creatine supplementation in elective orthopaedic patients. Exclusion criteria consisted of review articles, cadaveric studies, computer simulations, paediatric studies.

Study selection

Dillan Mistry (DM) performed the literature search and reviewed titles and abstracts with full texts then assessed for availability and against the inclusion criteria. Articles were then assessed for eligibility by two authors (DM and PL).

Data extraction

A standardised spreadsheet was created to extract pertinent information from the selected studies. This included: type of study, participants, procedures, indications, gender, age, follow-up, outcome measures and conclusions.

Results

In total nine studies were selected within this review. Two investigating the use of creatine supplementation and seven investigating protein/EAA supplementation. Six studies were randomised control trials with a double-blind approach, with one taking an unblinded approach [19] (Table 1).

All nine studies investigated knee pathology comprising of ACL pathology and arthroplasty. All studies compared supplementation with either creatine or protein against placebo, with also comparing to isocaloric carbohydrate as a third condition [12]. Average ages in the creatine group 49.9 years (36.0 to 63.7) and protein/EAA 37.72 years (25.9 to 75.9) two studies in the protein group didn't provide ages [15, 20]. A total of 43 patients received creatine supplementation (25 males and 18 females) whilst 145 received protein or EAA (male 89 and female 37-did not give numbers on gender) (Table 2) [20].

The two studies investigating creatine supplementation both involved pre-operative and post-operative supplementation. Both studies used post-operative supplementation of 5 g/day whilst pre-operative loading supplementation protocols differed. Tyler TF, et al. gave 20 g/day for one week whilst gave 10 g/day for 10 days [17, 18]. However, both these strategies are within the parameters of effective creatine loading protocols. Duration of treatment also differed with treating for 84 days whilst treated for 40 days [15, 17, 18]. However, in both cases the results indicated that creatine supplementation did not have an effect on post-operative rehabilitation. (Table 3).

Of the seven studies investigating protein/EAA supplementation, two studies examined pre and post-operative supplementation, interestingly both featuring provision of EAA [20, 21]. In contrast, 12. Holm L, et al. looked at post-operative carbohydrate and protein (combined milk and soy sources) supplementation and used whey protein supplementation [12, 15]. The two studies investigating EAA supplementation, provided EAA seven days pre- and post-operatively for two weeks and six weeks [20, 21]. Total doses were also different in these studies; 3 g three times a day and 20 g twice a day [20, 21]. In both cases the overarching conclusion was that supplementation post operatively helped to reduce muscle atrophy and led to enhanced muscular integrity.

Regarding the other five studies investigating protein supplementation, all focused on the post-operative supplementation period ranging from 2 weeks through to 12 weeks. Holm L, et al. provided a 10 g daily bolus (with 7 g carbohydrate) and dosing 40 g daily [12, 15]. Both studies showed that supplementation gave a positive impact for reducing muscle atrophy and improving muscle strength. Of the remaining 3 studies, two used specific amino acids 22. Laboute E, et al. investigated the effects of a Leucine supplement, whilst Eraslan researched glucosamine as a supplement finding that it did not improve the rehabilitation outcomes of athletes after ACL reconstruction [22, 23]. However did find that Leucine supplementation appeared to promote muscle recovery in the affected

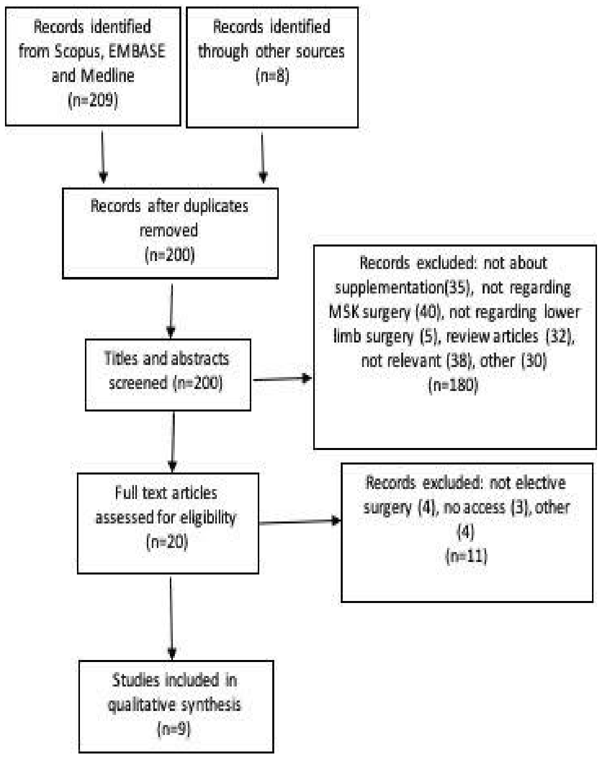

Figure 1. The Prisma Pathway.

Table 1. Study Characteristics [12, 15, 17-23].

Article Number	Author	Year	Type of study	Indication for treatment
1	Tyler, et al.	2004	Randomised Double Blind Prospective Clinical Trial	ACL reconstruction
2	Roy, et al.	2005	Randomised Double Blind Parallel Group Study	Total knee arthroplasty
3	Holm, et al.	2005	Randomised Double Blind Study	ACL injury
4	Ueyama, et al.	2020	Double-Blind Placebo Controlled Randomised Control Trial	OA - Total knee arthroplasty
5	Dreyer, et al.	2018	A Randomised Double Blind Placebo Controlled Trial	Total knee arthroplasty
6	Kim, et al.	2017	Research Study	ACL reconstruction
7	Laboute, et al.	2013	Double blinded randomised control trial	ACL reconstruction
8	Eraslan, et al.	2015	Randomised control trial	ACL reconstruction
9	Lopez-Vidriero, et al.	2019	Unblinded randomised control trial	ACL reconstruction

Table 2. Patient Demographics and Supplementation from selected studies [12, 15, 17, 18, 20-23]

Article Number	Author	Year	Supplement given	Dose	No of Participants	Male	Female	Age
1	Tyler, et al.	2004	Creatine	20 g/day for 1/52; 5 g/day thereafter	25	16	9	36 ± 1.2
2	Roy, et al.	2005	Creatine	10 g/day 10 days before surgery and 5 g/day 30 days post-surgery	18	9	9	63.7 ± 10.0
3	Holm, et al.	2005	Protein and carbohydrate	10 g protein and 7g Carbohydrate after exercise	8	5	3	25.9 ± 1.2
4	Ueyama, et al.	2020	EAA	3 g TDS, 1 week before and 2 weeks after TKA	30	7	23	75.9 (58-92)
5	Dreyer, et al.	2018	EAA	20 g BD for 7 days pre-op and 6 weeks post op	19	-	-	-
6	Kim, et al.	2017	Whey protein	40 g daily for 12 weeks post op	15	15	0	-
7	Laboute, et al.	2013	Leucine supplement	330 mg tablet given BD and 660 mg at night for 3 weeks	22	14	8	23.8 ± 5.6
8	Eraslan, et al.	2015	Glucosamine	1000 mgOD for 8 weeks post op	17	17	0	26.5 ± 5.8
9	Lopez-Videriero, et al.	2019	Progen (hydrolysed collagen peptide and plasma proteins, a hyaluronic acid chondroitin sulfate complex and vitamin C	1 sachet daily for 90 days post op	34	31	3	32.89 ± 9.23

Table 3. Outcomes from studies [12, 15, 17, 18, 20, 21].

Article Number	Author	Year	Outcomes
1	Tyler, et al.	2004	Involved side improvements in knee extension (p<0.0001) and knee flexion (p<0.0001) no change in hip flexion (p=0.15) hip abduction (p=0.54) and hip adduction (p=0.35). Improvements similar between the treatment and control groups. No difference between creatine and placebo (knee extension: creatine: placebo p=0.75; knee flexion creatine: placebo p=0.11)KOS-improvement in KOS not different (p=0.16) between creatine and placebo (pre 70 ± 11 and 76 ± 12 to 89 ± 8 and 89 ± 7 respectively)
2	Roy, et al.	2005	Free fat mass did not change (Placebo group 55.9 ± 13.6 (pre-op) to 56.1 ± 13.2 (post op) Creatine group 60.6 ± 15.3 (pre-op) to 60.3 ± 15.9 (post op)). Dietary supplementation did not influence body mass or FFM. Handgrip strength was maintained with a significant trend (p=0.07) for creatine to enhance hand grip strength (37.6 ± 9.7 to 382 ± 10.4). Both treatment and placebo group took significantly longer to complete timed walk and 4 step climb (p<0.01) with no difference between groups.
3	Holm, et al.	2005	Treatment group 1 and 2 increased quadriceps cross sectional area significantly at all locations (proximal, mid and distal) whereas placebo on at proximal and mid locations (p<0.05). Peak dynamic quadriceps strength increased significantly in treatment arm 1 by 13%± 3% (p<0.001) whereas non-significant changes in treatment arm 2(10%± 5%) and placebo (11%± 7%). Pennation angle increased significantly in both treatment arms (1:pre 10.9 ± 0.5 post 12.7 ± 0.5 p<0.01 and 2: pre 11.0 ± 0.9 post 12.8 ± 0.5 p<0.05), placebo had no change. No significant change was seen in the groups from pre and post training in mean fibre area for slow twitch and fast twitch fibres.
4	Ueyama, et al.	2020	Serum albumin was significantly higher (p=0.009) and VAS significantly lower (p=0.038) at 4 weeks post op in amino acid group. Relative changes in area of Rectus femoris (116% to 97%), quadriceps diameter (123% to 109%) were significantly higher in amino acid group (p<0.05).
5	Dreyer, et al.	2018	Quadricep atrophy was significantly greater in placebo group vs EAA group (13.4% ± 1.9% compared with 28.5% ± 2.5%; p=0.033). Hamstrings also saw atrophy greater in placebo group vs EAA group ((212.2% ± 1.4% compared with 27.4% ± 2.0%; p=0.036). Functional measures and patient reported outcomes demonstrated no significant changes from baseline to 6 weeks post op.
6	Kim, et al.	2017	In PSG, the quadriceps strength deficit reduced 37.4% ± 16.8% to 22.56% ± 5% at 60/sec and 29.2% ± 13.1% to 18.5% ± 7.9% at 180/sec. Whereas NPSG showed reduction by 36.1% ± 15.6% to 28.5% ± 8.8% at 60/sec and 27.8% ± 14.7% to 21.9% ± 9.3% at 180/sec. PSG showed a significantly greater improvement than NSPG at 60/sec and 180/sec (p=0.01 and p=0.03 respectively)
7	Laboute, et al.	2013	Thigh perimeters at 10 and 15 cm from the patella significantly increased (p<0.0001) on the injured side. Isokinetic muscle strength increased according to the speeds being tested (six modes of analysis) with highly significant differences on the injured side
8	Eraslan, et al.	2015	Significant improvements have been noted in VAS, LYS and IKDC scores at the end of the study when compared with pre-study values in both groups (p<0.001). When the mean changes of scores were compared, no statistical significance has been found between GS and P groups. The mean percentage deficits of isokinetic values between the operated and healthy knee were compared. The values revealed no statistically significant difference between the GS and P groups
9	Lopez-Videiro, et al.	2019	Both groups showed significant improvement in pain and function (measured by VAS and IKDC scores) during the 90-day follow-up period (p<0.001 for both), without significant differences between groups. The supplemented group had fewer patients that needed analgesics (8.5% *vs* 50.0%; p<0.05) and attended fewer PT sessions (38.0 *vs* 48.4 sessions; p<0.001) at 90 days and had a higher IKDC score at 60 days (62.5 *vs* 55.5; P . 029) compared with the control group. Patient- and physician-perceived efficacy was considered significantly higher in the supplemented group at 60 and 90 days (p<0.05). Perceived tolerability of the overall intervention was better in the supplemented group at 30, 60, and 90 days (p<0.05). Graft maturation showed more advanced degrees (grades 3 and 4) in the supplemented group at 90 days (61.8% *vs* 38.2%; p<0.01). No intolerance or AEs associated with the nutritional supplement treatment were reported.

leg. Although no other parameters showed any statistical significance López-VE, Laboute E, et al. conducted a study using Progen (a *nutrition* supplement that contained hydrolysed collagen peptides and plasma proteins, a hyaluronic acid-chondroitin sulfate complex, and vitamin C). The authors found taking the supplement improved pain, clinical outcomes and graft maturation [19, 22].

It should also be noted that all nine studies utilised an exercise programme either led by a physiotherapist or via a home-based exercise prescription. In all studies, with favourable outcomes, it was observed that this combination of supplementation and exercise was beneficial to the assessed outcomes, however interestingly no study combined both protein and creatine within one treatment group.

Discussion

The aim of this review was to analyse the literature and theorise whether protein and creatine supplementation or their combination can be used successfully within the peri-operative period of MSK surgery and whether such supplements have a meaningful effect on clinical outcomes and rehabilitation. The review's finding suggests that only protein supplementation may play a role in the pre-and post-operative periods of orthopaedic surgery.

It is apparent that preserving function of muscles and joints is crucial in orthopaedic surgery when considering positive outcomes. Muyskens JB, et al. assessed how EAA supplementation can help to reduce muscle atrophy. Through stimulation of Mammalian Target of Rapamycin (mTOR) and inhibiting autophagy, EAA's may help to alter cytokines and lead to reduced macrophage activity. Further to this EAA's have been shown to stimulate myogenesis *via* the action of satellite cells, when given pre and post operatively, helping to reduce muscle atrophy and facilitate quicker recovery [24]. Likewise, in rats it has been shown that creatine supplementation with resistance training has led to increased satellite cell mitotic activity, however this is yet to be evidenced in human studies [25].

The studies analysed in this review focused more on elective MSK procedures, but there have been studies in orthopaedics investigating protein supplementation in emergency procedures-in particular hip fractures Ekinci, O., et al. provided a multi-*nutrien*t supplement containing 36 g/day of protein, Calcium β-Hydroxy-β-Methylbutyrate and Vitamin D in comparison to a placebo condition, showing a decrease in wound healing time, reduced immobilisation time and increased strength [26]. Subsequently, certain EAA's-such as arginine and the conditionally essential amino acid glutamine-have been shown to have positive effects on human collagen stores which has assisted with wound healing [27].

It has also been suggested that pre-operative levels of serum albumin and pre-albumin have been indicators of mortality and morbidity [3]. A significant increase in serum albumin was observed by which highlights the possibility that this may account for the enhanced recovery seen by the featured treatment arm [21]. However, it is noteworthy that Botella-CJ, et al. saw an increase in serum albumin and pre-albumin which wasn't significant ($p=0.251$ and $p=0.582$ respectively) when a dose of 36 g/day protein was given 48 hrs post operatively for 6 days [28]. Likewise, Neumann M, et al. also showed no significant changes in serum prealbumin; although when given the protein brand Booth drink was provided a significant difference was seen in pre and post-operative serum albumin levels ($p<0.019$) [4].

Whilst protein/EAA supplementation showed a beneficial effect when provided post-operatively within the studies discussed, creatine supplementation showed no benefit from the two studies analysed. Kreider, RB et al. have discussed that for rapid saturation of creatine stores, creatine supplementation requires 5 g four times a day for 5-7 days, followed by a maintenance of 5 g daily [16]. Although interestingly, the creatine supplementation loading protocol by (10 g a day for 10 days) did show a significant increase in serum creatine ($p<0.05$), and a similar concentration pre and post-operatively of urinary creatine. Despite this there was no benefit to strength recovery Roy BD, et al. did hypothesise that this was due to impairment in the transport or uptake of creatine into skeletal muscle; however this was very much a theoretical perspective [17]. Furthermore this may also be due to creatine being an energy producing substrate for muscle. Without the necessary amount of protein required to permit hypertrophy of an already atrophied muscle, increasing the energy stored may have limited effect on muscle strength and size.

Co-supplementation of protein and creatine has been studied in the wider literature but there are limited data Collins J, et al. investigated supplementation of 20 g whey protein with 5 g creatine combined with resistance training in an elderly population, this was compared to 20 g of whey protein supplementation [29]. No significant changes in body composition were recorded pre to post intervention in either group. However, all participants experienced an significant increase in muscle function across a variety of assessments, although the addition of creatine did not enhance these effects. Collins J, et al. also failed to show any effect on body composition of co-supplementation (5 g creatine and 35 g protein per day alongside resistance training) in middle aged men [29].

The results of the studies discussed above are somewhat unexpected as many studies have showed that creatine supplementation combined with resistance training has led to improvements in body composition [15, 24-26]. In addition conducted a meta-analysis where they found that creatine supplementation was shown to increase muscle strength in a younger male populations. The majority of the creatine supplementation research has been carried out in young individuals who are fit and mobile without complications such as arthritis or other pathologies which induce functional limitations. These such pathologies may hamper the effects of creatine which regards to muscular strength adaptation, however creatine supplementation pre and post-operatively may be better suited to investigate regarding time to recovery as an outcome variable.

It is notable that despite this lack of significant effect in improving body composition and additional effects on muscular strength, both studies do not consider potential benefits to muscle recovery and the time course at which this occurs after exercise [24, 25]. Regarding speed of recovery, which is perhaps more beneficial to patients undergoing elective surgeries, Cooke MB, et al. have shown that creatine supplementation provides a faster recovery of muscular strength after eccentric exercise [30]. They also showed that plasma creatine kinase levels were significantly lower in treatment groups from 48 hrs post exercise through to seven days post exercise, highlighting a potential reduction in muscle damage with creatine supplementation [30]. Similarly, have also demonstrated that creatine supplementation prior to running a 30 km race reduces biochemical markers involved in cell death, muscle soreness and proteolysis (lactate dehydrogenase, prostaglandin E2 and tumor necrosis factor α) theoretically aiding and priming the recovery process. These findings suggest that potentially the assessment parameters used by Roy BD, Tyler TF, et al. were perhaps limited and required further scope and that post-operative recovery is a better criteria to investigate when using creatine as part of an ERAS pathway [17, 18].

Within the wider literature creatine has been shown to have generally positive outcomes in regard to improving strength, muscle mass and acute exercise recovery within healthy individuals. Potentially enhanced intramuscular phosphocreatine stores can aid healing and recovery from surgery and also promote greater work tolerance during rehabilitation physiotherapy treatment/exercise prescription. Whilst protein/EAA supplementation can assist with to repair and remodelling of muscle and provide the essential building block *nutrients* required for growth. Safety considerations are important when choosing to provide a *nutrition*al supplement. Creatine has been widely reported as being a safe supplement with no/little impact on hepatic and renal function in healthy young adults. Translating this to the elderly population creatine has also been used safely in Parkinson's patients with little impact on renal function when taking 4 g daily for two years Bender A, et al. This has been further detailed in a review by Kreider RB, et al. where dosages of 0.3 kg/day-0.8 kg/day for up to five years have shown no adverse health risks, leading for it to be deemed safe for use in adults by the International Society of Sports *Nutrition* [16, 31].

The evidence behind the use of creatine has yet to be translated into clinical practice when it comes to speed and time course of recovery, with studies opting more for assessment protocols to determine effects on muscular strength and power. This highlights the scope for further research into the combined use of protein/EAA and creatine for recovery after MSK surgery. Specifically of interest, would be research investigating the combination of protein/EAA's alongside creatine in patients undergoing elective orthopaedic procedures.

Limitations

This study isn't without limitations. The first being the small sample number of studies and that no featured study investigated combining both protein and creatinine available in the literature, which is a primary focus of the article.

Further to this is the limitations in the design of some of the featured studies. This in itself hinders the authors from making a recommendation without the presence of bias. Within the studies there was frequent heterogeneity in: the type of supplement, how supplementation was given, the amount of supplementation and the outcomes looked at.

Conclusion

Supplementation with protein/EAA's is beneficial for those in the post-operative period in helping to reduce muscle atrophy and wound healing. There is limited evidence investigating the clinical effects of creatine supplementation. Despite this, there is a very good safety profile for both protein/EAA and creatine, highlighting that supplementation is safe and can be experimented with in clinical settings. Outcomes on muscle strength and body composition have been highlighted in this review as being the main outcomes within current research in regards to these supplements. However, in relation to post-operative care more concern in placed upon speed of recovery and subsequent outcome benefits on patient care. This review highlights the need for research investigating the provision of a combination of both creatine and protein/EAA's given pre and post-operatively.

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