Amino Acids (2021) 53:1663–1678
https://doi.org/10.1007/s00726-021-03089-2

ORIGINAL ARTICLE

The use of BCAA to decrease delayed-onset muscle soreness after a single bout of exercise: a systematic review and meta-analysis

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Received: 11 January 2021 / Accepted: 7 October 2021 / Published online: 20 October 2021

Abstract

Branched-chain amino acids (BCAA) are used as a recovery method after exercise-induced muscle damage (EIMD). Although data suggest that BCAA may alleviate the delayed-onset muscle soreness (DOMS) evoked by EIMD, there is no consensus about the most effective supplementation protocol. To investigate the effects of BCAA on DOMS after a single exercise session that caused EIMD, a systematic review and meta-analysis were conducted on the effectiveness of BCAA supplementation to reduce DOMS symptoms in healthy subjects after a single session of EIMD. Randomized clinical trials (RCT) were searched in Medline, Cochrane Library, Science Direct, SciELO, LILACS, SciVerse Scopus, Springer Link journals, Wiley Online Library, and Scholar Google, until May 2021. Ten RCTs were included in the systematic review and nine in the meta-analysis. Seven studies demonstrated that BCAA reduced DOMS after 24 to 72 h. BCAA doses of up to 255 mg/kg/day, or in trained subjects, for mild to moderate EIMD, could blunt DOMS symptoms. However, high variability between studies due to training status, different doses, time of treatment, and severity of EIMD do not allow us to conclude whether BCAA supplementation is efficient in untrained subjects, applied acutely or during a period of pre to post days of EIMD, and at higher doses (> 255 mg/kg/day). The overall effects of BCAA on DOMS after a single session of exercise were considered useful for improving muscle recovery by reducing DOMS in trained subjects, at low doses, in mild to moderate EIMD, and should not be administered only after the EIMD protocol.

Keywords Pain · Physical exercise · Leucine · Skeletal muscle

Abbreviations

1RM	One-repetition maximum
BCAA	Branched-chain amino acids
CK	Creatine kinase
COX-2	Cyclooxygenase-2
DOMS	Delayed-onset muscle soreness
EIMD	Exercise-induced muscle damage
GDNF	Glial cell line-derived neurotrophic factor
GLUT-4	Glucose transporter type 4
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation of scientific evidence
Ile	Isoleucine
iNOS	Inducible nitric oxide synthase
Leu	Leucine
mTORC1	Mechanistic target of rapamycin complex 1
NADPH	Nicotinamide adenine dinucleotide phosphate
NFkB	Nuclear factor kappa B
NGF	Nerve growth factor
PICOS	Patient, Intervention, Comparison/Control, Outcome, and Study strategy
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT	Randomized clinical trials

Handling editor: S. Riechman.

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Treg	T regulatory cell
Val	Valine
$VO2_{max}$	Maximal oxygen consumption
WHO	World health organization

Introduction

Delayed-onset muscle soreness (DOMS) is one of the classical signs and symptoms of exercise-induced muscle damage (EIMD) after unaccustomed, high load, or eccentric exercises (Clarkson and Hubal 2002; Hyldahl and Hubal 2014; Lewis et al. 2012; Mueller-Wohlfahrt et al. 2013; Owens et al. 2019). DOMS is characterized by mechanical hyperalgesia, peaking 24 to 72 h after exercise, with the involvement of the entire muscle or a group of muscles (Clarkson and Newham 1995; Mueller-Wohlfahrt et al. 2013). DOMS symptoms include muscle tenderness, stiffness, limited range of motion (Clarkson and Newham 1995; Mueller-Wohlfahrt et al. 2013), and discomfort during muscle isometric contraction (Cheung et al. 2003; Clarkson and Newham 1995), and these symptoms could impair muscle function for up to 72 h or more (Cheung et al. 2003; Clarkson and Newham 1995; Owens et al. 2019; Silva et al. 2018). Although muscle soreness is not directly associated with the level of muscle damage, the discomfort could cause reductions in muscle power and strength, decreased movement coordination, altered joint kinematics, and an increased risk of joint injury, which may impair physical performance and daily life activities (Cheung et al. 2003).

The DOMS pathogenesis has been attributed to EIMD development, highlighted by myofibrillar damage of skeletal muscle fibers and perimysium (Clarkson and Hubal 2002), vacuolization of t tubules (Cully et al. 2017), and altered intracellular calcium homeostasis (Cully et al. 2017; Owens et al. 2019). This cellular events lead to inflammatory reactions and accumulation of macrophages in perimysium, endomysium, and into necrotic muscle fibers (Hyldahl and Hubal 2014; Paulsen et al. 2012), swelling (Clarkson and Hubal 2002; Nosaka and Clarkson 1996), oxidative stress (Nikolaidis et al. 2007; Retamoso et al. 2016), the release of neurotrophic factors, and nerve injury (Clarkson and Hubal 2002; Hyldahl and Hubal 2014; Mizumura and Taguchi 2016; Owens et al. 2019; Paulsen et al. 2012). However, loss of muscle function and DOMS can be observed after eccentric contractions, even in the absence of myonecrosis or with discrete ultrastructural damage of muscle fibers and a low degree of inflammation (Crameri et al. 2007). In this way, DOMS could not be exclusively attributed to the inflammatory process induced by muscle fiber damage (Mizumura and Taguchi 2016). Therefore, recovery methods targeting inflammatory reactions may not be completely effective for the prevention of DOMS and loss of muscle strength caused by EIMD. Recent theories suggest that during exercises that could cause EIMD, the activation of bradykinin B2 receptors induces upregulation of nerve growth factor (NGF) expression by muscle fibers after 12 to 24 h post-exercise (Mizumura and Taguchi 2016; Murase et al. 2010). NGF sensitizes type C nerve fibers to delayed mechanical hyperalgesia (Mizumura and Taguchi 2016; Murase et al. 2010). Bradykinin also increases cyclooxygenase-2 (COX-2) expression in muscle cells that induces the expression of glial cell line-derived neurotrophic factor (GDNF) after 12 h post-exercise (Mizumura and Taguchi 2016; Murase et al. 2013). Furthermore, GDNF stimulates muscle mechanical hyperalgesia, sensitizing Aδ fibers (Mizumura and Taguchi 2016; Murase et al. 2013).

Although many recovery strategies have been proposed to mitigate DOMS, most of them target the pathogenesis of muscle injury, and the results have been controversial (Cheung et al. 2003; Mizumura and Taguchi 2016; Owens et al. 2019). Recovery methods based on nutritional supplementation can provide chemical elements and essential substances that may decrease EIMD and DOMS symptoms, inducing anti-inflammatory and antioxidant effects as well as accelerating tissue repair (Cruzat et al. 2014; Owens et al. 2019). One of the supplements that have been studied is branched-chain amino acids (BCAA), which is a mixture of three essential amino acids: L-leucine, L-valine, and L-isoleucine. BCAA is abundant in skeletal muscle as the main amino acids of structural proteins and has a role in protein synthesis and energy metabolism during and after physical training (Jackman et al. 2017; Kamei et al. 2020). BCAA has many nutritional and functional roles, such as providing a source of energy during exercise (Kamei et al. 2020; Nicastro et al. 2012), acting as a signaling factor for protein synthesis (Duan et al. 2017; Kamei et al. 2020), inhibiting protein catabolism by the ubiquitin–proteasome pathway (Lysenko et al. 2018), stimulating myotube proliferation (Duan et al. 2017), and decreasing the release of inflammatory cytokines and oxidative stress (Cruzat et al. 2014; Nicastro et al. 2012). Some of the biological effects of BCAA were induced by activation of the mechanistic target of rapamycin complex 1 (mTORC1) and the nuclear factor kappa B (NFkB) signaling pathways in muscle cells (Nicastro et al. 2012), lymphocytes (Ikeda et al. 2017), and macrophages (Ikeda et al. 2017; Nicastro et al. 2012; Zhenyukh et al. 2018). These biological effects on protein synthesis and turnover, as well as modulation of oxidative stress and inflammatory pathways, may contribute to faster muscle recovery and, therefore, may help to blunt the symptoms of DOMS. In addition, BCAA has also been shown to downmodulate NGF release (Scaini et al. 2013; Wisniewski et al. 2016) and expression of COX-2 (Lee et al. 2017) in experimental studies, suggesting it can target upregulation pathways of neurotrophins associated with DOMS.

The effects of BCAA on preventing DOMS caused by EIMD is under debate in the literature since some studies demonstrated that BCAA intake decreased muscle soreness (Howatson et al. 2012; Shimomura et al. 2010; Waldron et al. 2017), while others reported no effects (Ra et al. 2013, 2018), or even increased DOMS symptoms (Kirby et al. 2012; Osmond et al. 2019) after a bout of EIMD. However, different BCAA content and amino acid ratios, dose, time of treatment, type of EIMD protocol, and subject characteristics may account for the controversial results observed in the literature. A systematic review on BCAA for decreasing EIMD (Rahimi et al. 2017) found no effect of the supplement on muscle soreness. However, the authors could not evaluate BCAA effects related to dosage or timing of exposure due to the reduced number of studies. Another systematic review (Foure and Bendahan 2017) addressed the concern that dosage, timing of treatment, and degree of muscle damage need to be taken into account when evaluating BCAA effects on EIMD prevention. Another recent systematic review evaluated the effects of BCAA after a single session of EIMD at different time points of recovery, but the study did not investigate the effects of different levels of muscle damage and BCAA supplementation protocols (Fedewa et al. 2019). In addition, the specific effects on DOMS were not addressed by the authors. Another concern was that the selection criteria did not exclude EIMD protocols performed in successive sessions, which may bias the DOMS evaluation, since DOMS symptoms could impair the performance in the next EIMD due to physical underrecovery.

Considering the evidence that BCAA may have biological properties that could attenuate DOMS symptoms, it is necessary to determine if clinical evidence supports the use of BCAA in the relief of muscle soreness. The objective of this study was to conduct a systematic review and meta-analysis of the literature to elucidate the effects of BCAA supplementation on DOMS caused by EIMD. The study also describes any limitations and biases found in the BCAA clinical trials. The research question of this investigation is "Does BCAA supplementation decrease DOMS symptoms after a session of EIMD when compared to Placebo treatment in healthy subjects?".

Methodology

Search strategy

The preferred reporting items for systematic reviews and meta-analyses (PRISMA; https://www.equator-network.org/reporting-guidelines/prisma) guidelines were followed. No limitations of language, publication status, and year of publication were applied in the literature search. The literature search followed the PICOS (Patient, Intervention, Comparison/Control, Outcome, and Study) strategy and included randomized clinical trials (RCTs), quasi-randomized clinical trials, case–control studies, and crossover trials. Two independent authors (MGW and SSD) searched the databases including the Cochrane Central Register of Controlled Trials (The Cochrane Library), MEDLINE (PubMed), Science Direct, the Scientific Electronic Library Online (SciELO), Latin-American and Caribbean Center on Health Sciences Information (LILACS), SciVerse Scopus, Springer Link journals, Wiley Online Library, and Scholar Google. Searches were performed until May 2021.

The search strategy used for MEDLINE is exemplified below and was adapted to search the other databases: injur*) OR lesion*) OR recover*) OR repair*) OR fatigu*) OR damage*) OR soreness) AND creatine kinase) AND Humans[Mesh])) AND muscle) AND Humans[Mesh])) AND ((((((((((exercis*) OR training) OR power) OR strength) OR aerobic) OR anaerobic) OR effort) OR athlet*) AND Humans[Mesh])) AND Humans[Mesh])) AND (((bcaa OR [branched chain amino acid] OR leucine OR valine OR isoleucine)) AND Humans[Mesh])) AND Humans[Mesh])) AND Humans[Mesh])) AND random* Filters: Humans.

Eligibility criteria

Only studies in which BCAA or the isolated components (L-leucine, Isoleucine, and Valine) were compared to placebo to prevent EIMD after a single session of exercise were eligible for inclusion. The studies needed to be performed in adult healthy subjects (reported by authors as healthy, non-obese, non-pregnant, and with no reported comorbidity), regardless of fitness status (sedentary, trained, athletes). The exercise protocol was required to be one session of physical exercise that caused EIMD with symptoms of DOMS. Considering that increased levels of neurotrophins can induce DOMS even in the absence of significant muscle fiber damage (Crameri et al. 2007; Mizumura and Taguchi 2016), the included articles were required to include other indirect markers of EIMD to ascertain that DOMS was associated with muscle damage.

The EIMD needed to be evaluated by at least two methods to detect indirect markers of muscle damage, including DOMS and a decrement in muscle performance, this latter being considered the more reliable indirect marker of muscle damage (Clarkson and Hubal 2002; Nosaka and Clarkson 1996; Owens et al. 2019). The second EIMD marker could also be increased levels of circulating muscle damage markers (creatine kinase, lactate dehydrogenase, myoglobin), or decreased range of motion, or edema, at least 48 h or more after exercise (Clarkson and Hubal 2002; Hyldahl and Hubal 2014; Paulsen et al. 2012; Warren et al. 1999). The EIMD symptoms were classified as mild, moderate, or severe according to the criteria described by Paulsen et al.

(2012), based on changes in force-generating capacity and circulating levels of creatine kinase.

Studies including successive sessions of EIMD were also excluded to investage DOMS recovery under a standardized condition, i.e., after a singe EIMD stimulus with appropriate physical recovery (24 to 96 h). Sucessive exercise sessions may overestimate DOMS due to mechanical stimulus and underrecovery between EIMD sessions.

Studies needed to describe BCAA composition, the individual dose (total amount or mg/kg), and the duration of administration of BCAA. The control group was required to receive a placebo intervention with an inactive substance or a lower dose (< 0.25 mg/kg/day) of carbohydrates. The main outcome was the decrement in muscle pain, muscle soreness, and/or DOMS reported by participants, evaluated by an algometer, or perceived muscle pain reported on a visual analog scale.

Data extraction and analysis

Information retrieved included age, weight, physical fitness status, EIMD protocol, BCAA treatment protocol, and DOMS. DOMS values were converted to a standardized unit of measure (natural logarithm) to minimize methodological heterogeneity, according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins et al. 2020). Quality of evidence was scored using the Grading of Recommendations, Assessment, Development, and Evaluation—GRADE (https://gradepro.org) (Schünemann et al. 2013).

The risk of bias for included studies was assessed as high, low, or unclear and the potential for bias was screened according to the Cochrane Collaboration's 'seven evidence-based domains' tables. In the meta-analysis, the overall and subgroup analyses for different follow-up time points (24 to 96 h) were plotted with log-transformed mean and standard deviation. The authors were contacted up to three times to retrieve missing data. If no reply was obtained, values were extracted from the graphic data presentation using GetData Graph Digitizer (http://getdata-graph-digitizer.com/). The random-effect model was employed to compute a pooled estimate of mean difference (MD) and respective 95% confidence interval (95%CI). Heterogeneity between studies was detected by I^2 statistics. Risk of bias and meta-analysis was conducted on RevMan 5.1. (The Cochrane Collaboration; V.5.3).

Results

Studies

The database search yielded 2238 articles and after the removal of duplicates, 1137 records remained: 15 from Medline, six from SciELO, 10 from LILACS, 12 from Cochrane Library, 266 from Science Direct, 599 from Scopus, 151 from Springer, and 78 from Wiley (Fig. 1). After reading the titles and abstracts, 27 studies remained, of which 18 papers were excluded after review (Armisasan et al. 2015; Asjodi et al. 2018; Atachak and Baturak 2012; Dorrell and Gee 2016; Estoche et al. 2019; Gee and Deniel 2016; Ishikura et al. 2014; Jackman et al. 2010; Kephart et al. 2016; Koo et al. 2014; Leahy and Pintauro 2013; Lysenko et al. 2018; Matsumoto et al. 2009; Mohamad-Panahi et al. 2013; Nosaka et al. 2006; Osmond et al. 2019; Sharp and Pearson 2010; Sheikholeslami-Vatani and Ahmadi 2016) because they did not fit the inclusion criteria. Screening the reference lists of the remaining articles identified one additional paper for inclusion (Kirby et al. 2012). The characteristics of the studies are presented in Table 1.

Participants

A total of 160 participants were investigated (Table 1), 146 (91.3%) male and 14 (8.7%) female. Six (60%) studies investigated untrained or sedentary subjects (Foure et al. 2016; Greer et al. 2007; Kirby et al. 2012; Ra et al. 2013; Ra et al. 2018; Shimomura et al. 2010). Recreationally resistance-trained participants were reported in three (30%) studies (VanDusseldorp et al. 2018; Waldron et al. 2017, 2018) and one (10%) study included athletes (soccer, rugby) (Howatson et al. 2012).

Exercise-induced muscle damage protocol

Six studies induced EIMD with eccentric resistance exercises ($n = 6$, 60%) (Kirby et al. 2012; Ra et al. 2013, 2018; Shimomura et al. 2010; VanDusseldorp et al. 2018; Waldron et al. 2017) (Table 1). Three studies employed eccentric resistance exercises at high intensity and low volume in leg press (120% 1RM) (Kirby et al. 2012) and elbow extension (90% maximal voluntary isometric contraction) (Ra et al. 2013, 2018). Moderate intensity eccentric contractions (70% 1RM) in lower limbs were performed in two (20%) studies (VanDusseldorp et al. 2018; Waldron et al. 2017). Eccentric and concentric contractions at low intensity (body weight) and high volume during squats were applied in one study (Shimomura et al. 2010).

Plyometric exercises, such as drop jumps and split jumps, were performed in four studies (40%) (Howatson et al. 2012; Kirby et al. 2012; VanDusseldorp et al. 2018; Waldron et al. 2018). One study (10%) performed aerobic exercise, cycling (55% $VO2_{max,}$ 90 min)(Greer et al. 2007), and another study used muscle electrical stimulation ($n = 1$, 10%) (Foure et al. 2016) (Table 1).

EIMD symptoms were demonstrated in eight studies (80%), with decreased muscle function and increased serum

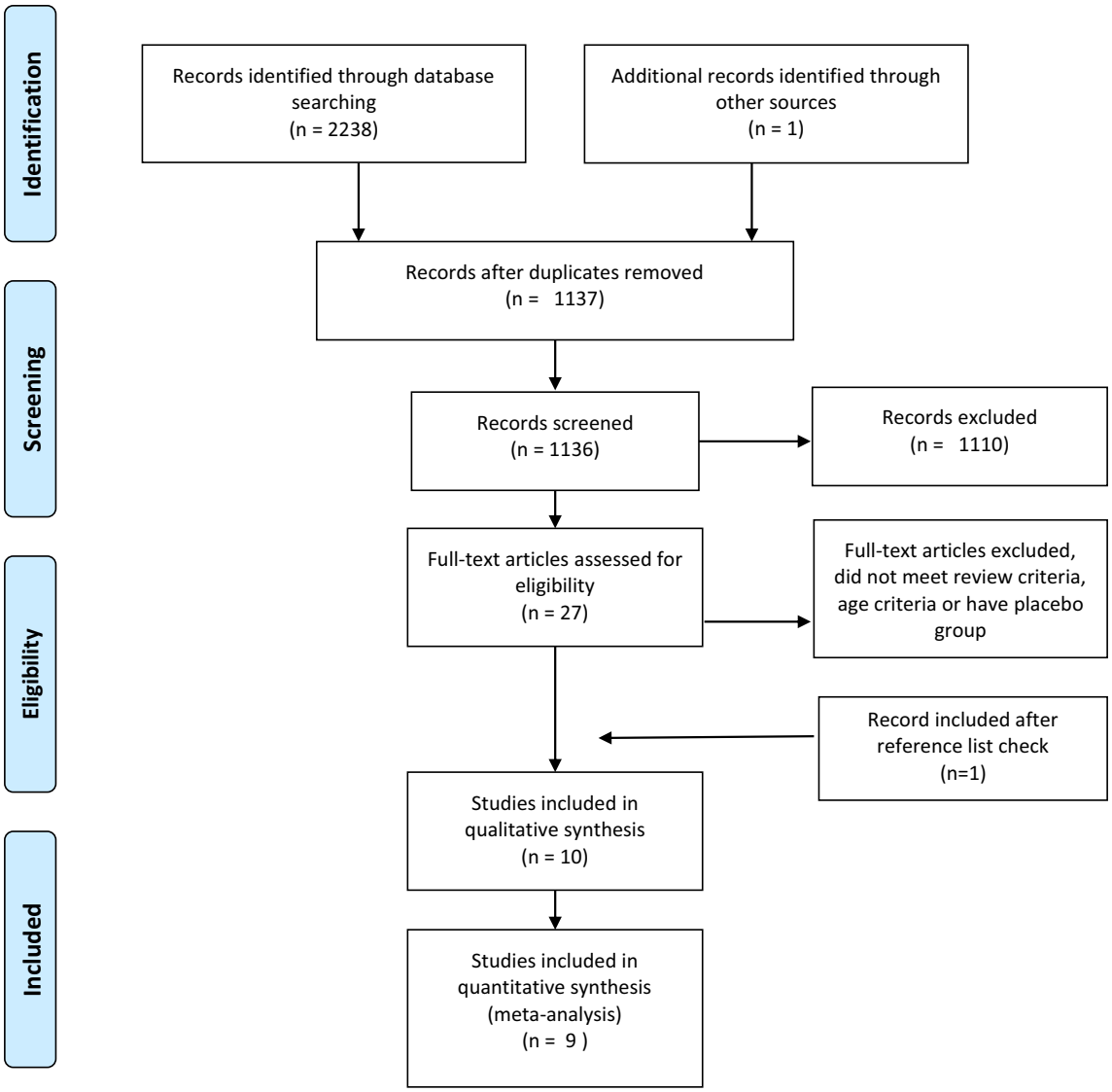

Fig. 1 Study flow chart

levels of creatine kinase (CK) and other indirect blood markers of muscle damage (Foure et al. 2016; Greer et al. 2007; Howatson et al. 2012; Ra et al. 2013, 2018; VanDusseldorp et al. 2018; Waldron et al. 2018, 2017) from 24 to 96 h after the EIMD session. Two (20%) studies demonstrated impaired muscle function after EIMD, but no significant change in CK levels over 72 h of recovery (Kirby et al. 2012; Shimomura et al. 2010). EIMD symptoms were considered mild in two (20%) (Shimomura et al. 2010; Waldron et al. 2018), moderate in five (50%) (Foure et al. 2016; Greer et al. 2007; Howatson et al. 2012; Ra et al. 2013; Waldron et al. 2017) and severe in three studies (30%) (Kirby et al. 2012; Ra et al. 2018; VanDusseldorp et al. 2018).

Delayed-onset muscle soreness

The outcomes for DOMS symptoms are presented in Table 1. Six (60%) studies reported reduced muscle soreness at different times ranging from 24 to 72 h after the exercise session (Greer et al. 2007; Howatson et al. 2012; Shimomura et al. 2010; VanDusseldorp et al. 2018; Waldron et al. 2017, 2018). Two studies (20%) reported no effects of BCAA up to 96 h (Foure et al. 2016; Ra et al. 2013). However, one study demonstrated that muscle soreness was attenuated when BCAA was administered three days before the EIMD protocol, but not when supplemented three days after the protocol (Ra et al. 2018). A single study (10%) demonstrated increased DOMS from 24 to 96 h post an EIMD protocol in subjects supplemented with a high dose of leucine (Kirby et al. 2012).

Table 1 Authors, study design, participant characteristics (age, sex, and fitness status), exercise-induced muscle damage (EIMD) protocol and outcomes for delayed-onset muscle damage (DOMS)

Author, year	Study design	Participants	EIMD protocol	DOMS outcome
Greer et al. (2007)	RCT, crossover, blinded*	9 males (21.6 ± 3.2 years) Untrained	90 min of cycling at 55% VO_2max	↓ 24 h = 48 h
Shimomura et al. (2010)	RCT, crossover, double-blinded	12 females (20–25 years) Untrained	7 sets of 20 squats (with body weight)	↓ 24 and 48 h = 72 and 96 h
Kirby et al. (2012)	RCT, double-blinded	19 males (21.3 ± 1.6 years) Treated = 10 Placebo = 9 Untrained	100 drop jumps; 10 eccentric leg press contractions at 120% 1RM	↑ 24, 48, 72, and 96 h
Howatson et al. (2012)	RCT, double-blinded	12 males (23 ± 2 years) Treated = 6 Placebo = 6 Football and rugby athletes	100 drop jumps	↓ 24 and 48 h
Ra et al. (2013)	RCT, double-blinded	18 males (22.5 ± 3.8 years) BCAA = 9 Placebo = 9 Sedentary	6 sets of 5 repetitions of eccentric elbow extension at 90% of maximal voluntary isometric force	= 24, 48, 72, and 96 h
Foure et al. (2016)	RCT, double-blinded	26 males BCAA: $n = 13$, 22 ± 1 years; Placebo: $n = 13$, 23 ± 2 years Untrained	Electrical stimulation of contractions in vastus lateralis and vastus medialis muscles	= 24, 48, 72, and 96 h
Waldron et al. (2017)	RCT, double-blinded	14 males (21.8 ± 1.6 years) 2 females (22 ± 1 years) BCAA: $n = 8$ Placebo: $n = 8$ Resistance-trained athletes	6 sets of 10 repetitions of back squats at 70% of 1RM	↓ 24 and 48 h
Ra et al. (2018)	RCT, double-blinded	15 males (21.5 ± 0.4 years) Pre BCAA: $n = 5$ Post BCAA: $n = 5$ Placebo: $n = 5$ Untrained	Six sets of five repetitions of eccentric elbow extension at 90% of maximal voluntary isometric force	Pre group: = 24 h ↓ 48 and 72 h No effects in the POST group
VanDusseldorp et al. (2018)	RCT, double-blinded	20 males (22.3–1.5 year), BCAA: $n = 10$ Placebo: $n = 10$ Resistant-trained	10 sets of 8 repetitions at 70% 1RM squats using a Smith machine; five sets of 20 body-weight split jumps	= 24 h ↓ 48 and 72 h
Waldron et al. (2018)	RCT, double-blinded	15 males (21 ± 1 years) Leucine: $n = 8$ Placebo: $n = 7$ Resistance-trained	100 drop jumps	↓ 24 and 48 h**

RCT randomized clinical trial;

*Authors did not report whether the researchers were blinded or not

**p value was not statistically different from control, but authors reported effect size differences

= No differences in comparison to the control group

↓Decreased DOMS compared to the control group

↑Increased DOMS compared to the control group

BCAA supplementation

The BCAA was supplemented on the day of the EIMD protocol in all studies (Table 2). The Fouré and Bendahan (2017) criteria for treatment duration were adapted and BCAA supplementation was classified as acute (≤ 3 days),

Table 2 BCAA supplementation protocols

Author, publication year	Composition Ile/Leu/Val	Total amount per dose (g)	Individual dose (mg/kg)	Supplementation on days before EIMD protocol	Supplementation in EIMD protocol	Supplementation on days after EIMD protocol	Placebo
Greer et al. (2007)	1: 2.5: 1.5	5	~ 59.4[a]	–	One dose 5 min before and another during (60 min) EIMD protocol	–	Flavored water
Shimomura et al. (2010)	1: 2.3: 1.2	5.5	~ 100[a]	–	1 dose 15 min before EIMD protocol	–	5.5 g of dextrin
Kirby et al. (2012)	0:1:0	Not informed	250	–	1 dose 30 min before + 1 dose immediately before, + 1 dose immediately after EIMD protocol	1 dose/day at 24, 48, 72, and 96 h	3 g artificial sweetener
Howatson et al. (2012)	1:2:1	10	~ 280[a]	2 doses/day, 7 days	One dose 1 h before + One dose immediately after EIMD protocol	2 doses/day, at 24, 48, 72, and 96 h	10 g artificial sweetener
Ra et al., (2013)	1:2:1	3.2	145.7 ± 5.3	3 doses/day, 14 days	3 doses/day after meals	3 doses/day at 24, 48 and 72 h	3.2 g of starch
Foure et al. (2016)	1:2:1	Not informed	100	–	1 dose 30 min before + 1 dose immediately before, + 1 dose immediately after EIMD protocol	1 dose/day at 24, 48, 72, and 96 h	microcrystalline cellulose (amount not described)
Waldron et al. (2017)	1:2:1	Not informed	87	–	1 dose 30 min before + 1 dose immediately after EIMD protocol	2 doses/day at 24, 48 h	0.25 g/kg of dextrose
Ra et al. (2018)	1:2:1	3.2	~ 149[a]	Group PRE: one dose 3 days before EIMD	Group PRE: 3 doses 15 min before EIMD protocol	–	3.2 g of starch
				–	Group POST: 3 doses immediately after EIMD protocol	Group POST: 24, 48, and 72 h	
VanDusseldorp et al. (2018)	1:3:2	Not informed	110	2 doses/day, 4 days before	2 doses before EIMD protocol	2 doses/day, 24, 48, and 72 h	110 mg/kg of maltodextrin
Waldron et al. (2018)	0:1:0	Not informed	87	–	One dose 30 min before + One dose immediately after EIMD protocol	2 doses/day at 24, 48, and 72 h	0.3 g/kg of maltodextrin

EIMD exercise-induced muscle damage

[a]Individual doses were not informed in the article, but estimated by authors based on participants' mean body mass

moderate (4 to 7 days), and long (8 days or more). Acute administration only on the day of exercise was performed in two (20%) studies (Greer et al. 2007; Shimomura et al. 2010) and one study (10%) supplemented for 3 days (Waldron et al. 2017). Moderate duration supplementation of BCAA was performed in four studies (40%) (Foure et al. 2016; Kirby et al. 2012; Ra et al. 2018; Waldron et al. 2018) and long duration in three (30%) studies (Howatson et al. 2012; Ra et al. 2013; VanDusseldorp et al. 2018). The BCAA was also administered 4 days before (Pre EIMD) or 4 days after the EIMD protocol in one study (Ra et al. 2018), for up 72 or 96 h after the EIMD protocol (Post-EIMD) in four (40%) studies (Foure et al. 2016; Kirby et al. 2012; Waldron et al. 2017, 2018), and starting on the days before until after the EIMD protocol (Pre- to Post-EIMD) in three studies (Howatson et al. 2012; Ra et al. 2013; VanDusseldorp et al. 2018) (Table 2).

The total BCAA per dose ranged from 5 to 10 g (Greer et al. 2007; Howatson et al. 2012), with total amounts ranging from 5.5 to 20 g on the day of the EIMD protocol (Howatson et al. 2012; Shimomura et al. 2010). The average amount per kg of body mass ranged from approximately 59.4 to ~ 560 mg/kg/day (Greer et al. 2007; Howatson et al. 2012), with a mean value of 218.5 ± 160.5 mg/kg/day between studies (Table 2). According to a previous review, a cut-off amount of > 200 mg/kg/day was considered as a high dose and may have some beneficial effects on EIMD recovery (Foure and Bendahan 2017; Howatson et al. 2012). In the present study, a BCAA dose limit of 255 mg/kg/day was defined as a posteriori of study selection, based on mean values of doses employed in selected studies and reaching a standard value corresponding to three times the recommendation of daily intake (WHO 2007). Based on this criterion, studies were analyzed in subgroups divided according to low doses (< 255 mg/kg/day) (Greer et al. 2007; Shimomura et al. 2010; VanDusseldorp et al. 2018; Waldron et al. 2017, 2018) and high doses (> 255 mg/kg/day).

The BCAA formulations and placebo were powder diluted in water (Howatson et al. 2012; VanDusseldorp et al. 2018; Waldron et al. 2017, 2018), flavored beverages (Greer et al. 2007; Kirby et al. 2012; Shimomura et al. 2010), or an InOrpha® aromatized vehicle solution (Foure et al. 2016). Two studies administered the supplements orally to the participants with sachets containing placebo or BCAA but did not inform the vehicle (Ra et al. 2013, 2018). Two studies investigated the combinations of the association of BCAA + taurine (Ra et al. 2013) and leucine + glutamine (Waldron et al. 2018), but only data from groups ingesting isolated BCAA, leucine, and placebo were extracted from these studies.

Bias risk

The absence of sample size or statistical power calculation was observed in four (40%) studies (Ra et al. 2013, 2018; Waldron et al. 2017, 2018). Dietary intake was not monitored in only one study (Ra et al. 2018), and no studies reported estimates of daily BCAA intake. Random sequence generation and allocation concealment were not presented in three (30%) studies (Greer et al. 2007; Shimomura et al. 2010; VanDusseldorp et al. 2018). In one study, the blinding of researchers was not performed (Greer et al. 2007). Although all studies reported masking taste and/or color of supplements and placebo, no studies investigated the allocation guess of participants.

Meta-analysis

Visual analog scales were employed to evaluate muscle soreness in all studies. All values were converted to natural logarithms, using mean and standard deviation, for entry in the meta-analysis. The meta-analysis was performed with subgroup analysis according to follow-up time from 24- to 96-h post-EIMD (peak symptoms of EIMD) (Fig. 2). One article was not included in the meta-analysis because the DOMS score was presented as a percentage change from baseline (Waldron et al. 2017).

Overall, pooled data revealed a random effect for treatment ($z = 4.84$, $p < 0.0001$) on DOMS decrements of − 0.29 (95% CI of − 0.41 to − 0.17) with low heterogeneity for log-transformed values in the overall analysis ($Chi^2 = 30.8$, $I^2 = 0\%$, $p = 0.53$). No significant differences ($Chi^2 = 7.19$, $I^2 = 45.9\%$, $p = 0.14$) were detected between subgroups (follow-up 24 to 96 h) (Fig. 2). Significant effects on DOMS decrease were found in 24 h and 72 h, but a moderate degree of heterogeneity for 96 h (Fig. 2). GRADE criteria indicated high certainty for 24, 48, and 72 h analysis, and moderate for 96 h. However, due the potential source of heterogeneity arising from subject training status (untrained or trained), treatment schedule (pre-, during, and post-EIMD protocol), total amount of BCAA ingestion, and severity of EIMD, a second subgroup analysis by heterogeneity sources is presented in Table 3.

Trained subjects presented a beneficial effect for BCAA at 24 h and 72 h, but with a moderate level of heterogeneity and quality of evidence at 72 h (Table 3). Supplementation of BCAA only on the day of EIMD (acute supplementation) presented random effects favoring BCAA treatment, but with lower quality of evidence. Post-EIMD protocols (up to 72 h) presented no effects favoring BCAA treatment. A large effect for DOMS decrements was observed in studies that supplemented BCAA chronically (pre to post) (Table 3).

Lower doses presented a random effect favoring BCAA treatment, but with a moderate degree of heterogeneity and

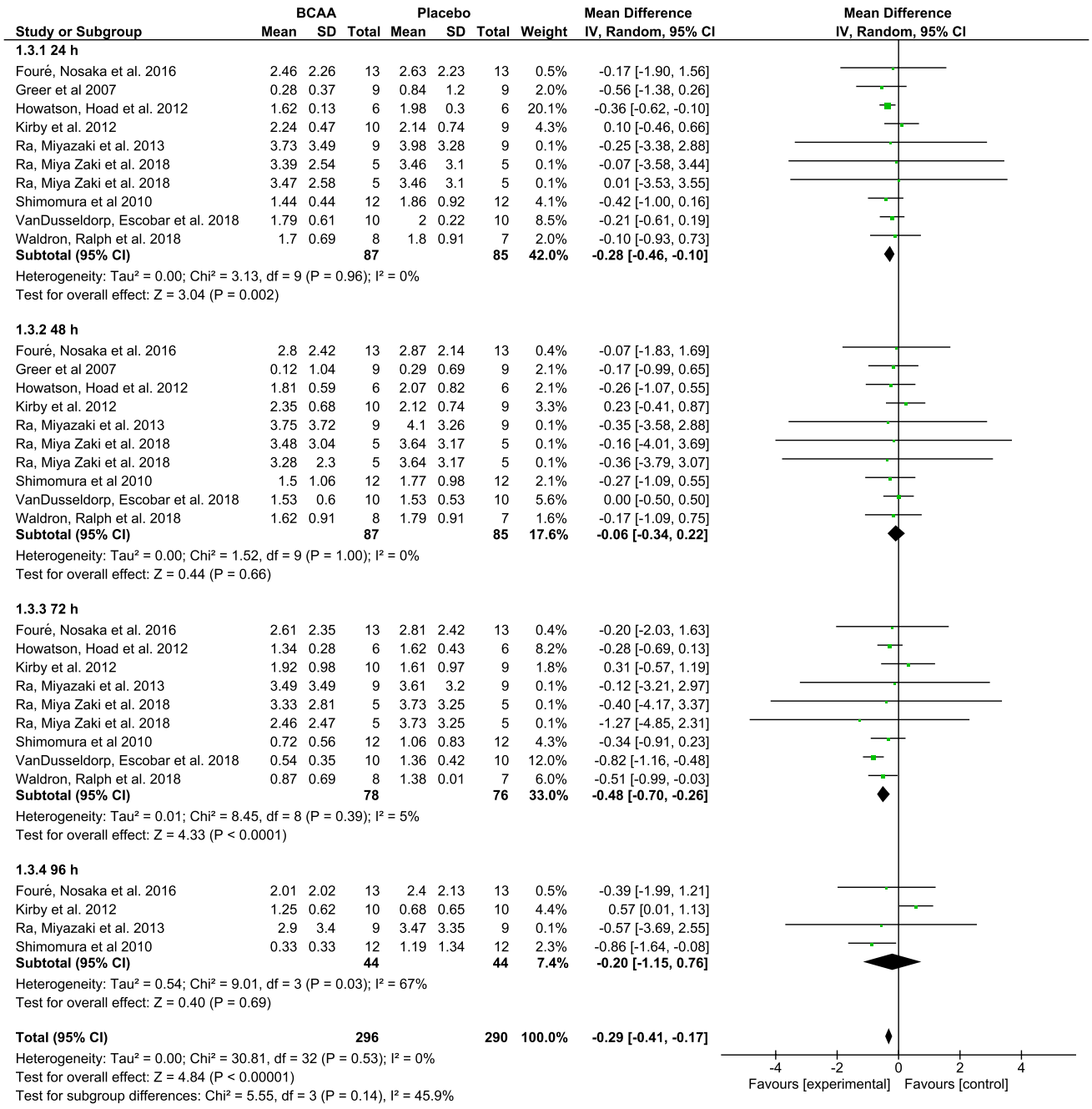

Fig. 2 Meta-analysis of log-transformed values of selected studies

quality of evidence (Table 3). Higher doses presented no effects in DOMS relief (Table 3). Regarding EIMD severity, an effect favoring BCAA was observed for moderate levels of injury (Table 3).

Discussion

The results of the present systematic review and meta-analysis suggest that BCAA presented effects on DOMS relief at low doses (< 255 mg/kg/day), when BCAA was supplemented before exercise protocols, for low to moderate EIMD symptoms, and in trained subjects. Although the majority of the studies demonstrated a beneficial effect (Greer et al. 2007; Howatson et al. 2012; Shimomura et al. 2010; VanDusseldorp et al. 2018; Waldron et al. 2017,

Table 3 Subgroup meta-analysis of participants stratified by fitness level, days of BCAA supplementation, mean daily intake

Subgroup (n = number of studies; participants)	z score	p	Random mean	95% CI	I^2	Certainty (GRADE)
Fitness levels						
Untrained						
24 h (n = 6; 113)	1.28	0.20	−0.23	−0.58 to 0.12	0%	+ + +
48 h (n = 6; 113)	0.16	0.87	−0.03	−0.44 to 0.37	0%	+ + +
72 h (n = 5; 107)	0.75	0.45	−0.17	−0.62 to 0.28	0%	+ + +
92 h (n = 4; 88)	0.40	0.69	−0.20	−1.15 to 0.6	67%	+ +
Trained						
24 h (n = 3; 45)	2.76	0.006	−0.21	−0.37 to −0.06	0%	+ + + +
48 h (n = 3; 45)	0.42	0.68	−0.08	−0.47 to 0.31	0%	+ + + +
72 h (n = 3; 45)	3.27	0.001	−0.56	−0.89 to −0.22	51%	+ + +
Period of intervention (duration)						
Acute						
24 h (n = 2; 42)	1.94	0.05	−0.47	−0.73 to 0.00	0%	+ +
48 h (n = 2; 42)	0.75	0.46	−0.22	−0.80 to 0.36	0%	+ +
Post-EIMD (moderate)						
24 h (n = 4; 70)	0.10	0.92	0.02	−0.42 to 0.47	0%	+ + + +
48 h (n = 4; 70)	0.24	0.81	0.06	−0.42 to 0.54	0%	+ + + +
72 h (n = 4; 70)	1.58	0.11	−0.33	−0.74 to 0.08	0%	+ + + +
96 h (n = 3; 46)	1.06	0.29	0.39	−0.34 to 1.12	19%	+ + + +
Pre- and post-EIMD (long)						
24 h (n = 3; 50)	2.97	0.003	−0.18	−0.30 to −0.06	0%	+ + + +
48 h (n = 3; 50)	1.78	0.08	−0.39	−0.81 to 0.04	0%	+ + + +
72 h (n = 3; 50)	2.40	0.02	−0.56	−1.01 to 0.10	52%	+ + +
BCAA dose (mg/kg/day)						
Lower (< 255)						
24 h (n = 4; 77)	1.99	0.05	−0.29	− 0.56 to −0.01	0%	+ + +
48 h (n = 4; 77)	1.78	0.07	−0.31	− 0.61 to 0.03	0%	+ + +
72 h (n = 3, 59)	4.36	< 0.001	−0.63	−0.91 to −0.34	18%	+ + +
Higher (> 255)						
24 h (n = 5;95)	2.65	0.008	−0.17	−0.29 to −0.04	0%	+ + + +
48 h (n = 5;95)	0.11	0.91	0.03	−0.45 to 0.51	0%	+ + + +
72 h (n = 5;95)	1.02	0.31	−0.19	−0.55 to 0.17	0%	+ + + +
96 h (n = 3;64)	1.65	0.10	0.44	−0.08 to 0.96	0%	+ + + +
EIMD severity						
Mild						
24 h (n = 2; 39)	1.31	0.19	−0.32	−0.79 to 0.16	0%	+ + + +
48 h (n = 2; 39)	0.74	0.46	−0.22	−0.80 to 0.36	0%	+ + + +
72 h (n = 2; 39)	2.36	0.02	−0.44	−0.80 to −0.07	0%	+ + + +
Moderate						
24 h (n = 4; 74)	2.98	0.003	−0.19	−0.31 to −0.06	0%	+ + + +
48 h (n = 4; 74)	0.71	0.48	−0.20	−0.76 to 0.35	0%	+ + + +
72 h (n = 3;56)	1.35	0.18	−0.27	−0.67 to 0.12	0%	+ + + +
96 h (n = 2;44)	0.59	0.56	−9.43	−1.81 to 0.99	0%	+ + + +
Severe						
24 h (n = 3; 59)	0.63	0.53	−0.10	−0.43 to 0.22	0%	+ + +
48 h (n = 3; 59)	0.93	0.35	−0.18	−0.57 to 0.20	0%	+ + +
72 h (n = 3; 59)	1.02	0.31	−0.42	−1.23 to 0.39	47%	+ + +

GRADE score for evidence consistency and quality of evidence: + + + + high, + + + moderate, + + low

BCAA branched-chain amino acids, *EIMD* exercise-induced muscle damage

2018), the different supplementation doses, time of intervention, subjects characteristics, physical fitness, EIMD protocols (eccentric/isometric vs. concentric contractions, aerobic exercise, electrical stimulation, intensity), and level of EIMD may have accounted for the high variability in DOMS outcomes between studies. Although the low degree of heterogeneity suggested no significant variability between standardized results of studies, we sought to consider these factors as a potential influence on DOMS outcomes. Considering the magnitude of DOMS symptoms and time to relapse of symptoms, as well as the overall meta-analysis, a subgroup analysis was also performed for each variable of interest from 24 to 96 h. The analysis of quality of evidence suggested that most of the evidence for different variables and time presented high quality, based on GRADE criteria. However, the quality of evidence for treatments in untrained subjects, acute administration, lower doses, and severe EIMD was considered low to moderate, due to the low number of studies, risk of bias, and moderate heterogeneity at some time points of analysis.

The most widely used clinical evaluation of signs and symptoms of EIMD are indirect markers, including loss of muscle strength, DOMS, and circulating biomarkers (especially CK) (Cheung et al. 2003; Clarkson and Hubal 2002; Hyldahl and Hubal 2014; Owens et al. 2019; Paulsen et al. 2012). However, these indirect biomarkers of muscle damage do not peak at same moments and are poorly correlated (Clarkson and Newham 1995; Paulsen et al. 2012). Moreover, evidence suggests that different biological mechanisms may be involved in the increase in different biomarkers (Crameri et al. 2007; Cully et al. 2017; Hyldahl and Hubal 2014; Murase et al. 2010). For example, whereas mechanical stretching of the cell membrane (activation of stress-activated channels) (Hyldahl and Hubal 2014), disturbance in calcium homeostasis and inflammation (Hyldahl and Hubal 2014; Paulsen et al. 2012), and cytoskeleton disorganization are associated with loss of muscle strength (Clarkson and Hubal 2002; Hyldahl and Hubal 2014), the release of neurotrophins (Mizumura and Taguchi 2016; Murase et al. 2013) and calcium disturbance in vacuolized t tubules may be associated with DOMS (Cully et al. 2017). Thus, some recovery methods may be more efficient in blunting an EIMD marker than others, depending on their biological effect. Different from previous systematic reviews (Foure and Bendahan 2017; Rahimi et al. 2017) that investigated an overall effect of BCAA on the three indirect markers of EIMD, we proposed to first study the effects on DOMS, since BCAA biological effects may be useful in relieving DOMS symptoms, but may have different effects on muscle function and cell damage. We believe that it is necessary to clarify the BCAA effect on DOMS, and its ideal prescription, to instigate its use solely or in combination with other recovery methods. Nevertheless, for other biomarkers, different prescriptions may be necessary, and this issue will be addressed in other reviews that our research group is concluding.

A previous systematic review also found an overall effect of BCAA on DOMS relief from 24 to 96 h (Rahimi et al. 2017), presented from pooled data of four articles, including three included in our meta-analysis (Foure et al. 2016; Howatson et al. 2012; Ra et al. 2013). One study was not included in our review due to the absence of information regarding the age of participants and because the methodology of DOMS assessment included two different outcomes for the same BCAA treatment (Jackman et al. 2017). Rahimi et al. (2017) found no effect in subgroup analysis at 24, 48, 72, and 96 h. In the present meta-analysis, the addition of more studies demonstrated effects favoring BCAA at 24 and 72 h, besides a pooled effect of BCAA in attenuating DOMS symptoms. Another systematic review (Foure and Bendahan 2017) investigated the literature regarding BCAA supplementation on EIMD, but with no direct discussion of DOMS findings. The authors pointed out that controversial results regarding BCAA effectiveness in attenuating EIMD may be attributed to different supplementation protocols and quality of studies (Foure and Bendahan 2017). Aditionally, Foure and Bendahan (2017) suggested that positive effects of BCAA in EIMD were found in poor-quality studies. However, in our analysis, we found both negative or no effects (Kirby et al. 2012; Ra et al. 2013, 2018) and positive effects (Foure et al. 2016; Howatson et al. 2012; Ra et al. 2013) in studies with a lower risk of bias.

A positive effect of BCAA on decreasing DOMS symptoms was observed in three studies with trained individuals or athletes (Howatson et al. 2012; VanDusseldorp et al. 2018; Waldron et al. 2018), with a high quality of evidence. However, a limitation of one study is the unclear definition of "resistance-trained" subjects (Waldron et al. 2018) since the authors only mention that the participants had 1 year of experience in resistance training. We included resistance-trained individuals and athletes in the same subgroup analysis considering that these participants present adaptations in skeletal muscle due to training and cannot be compared to untrained subjects. This result was previously suggested by another systematic review (Fedewa et al. 2019), but the authors included a single study with trained subjects (Howatson et al. 2012). There is no clear mechanism by which BCAA could be more efficient in attenuating DOMS symptoms in trained subjects. However, we can speculate that some protective effects of BCAA in trained participants may be associated with better adaptation of skeletal muscle, including increased mobilization and activation of anti-inflammatory T regulatory cells (Tregs) (Dorneles et al. 2020; Ikeda et al. 2017). Treg cell proliferation and activation are upregulated by BCAA (Ikeda et al. 2017). Indeed, muscle damage was considered low to moderate in

two studies (Howatson et al. 2012; Waldron et al. 2018) with effects at 24 and 48 h favoring BCAA. But it is not clear in these studies if the low level of damage was the effect of previous anti-inflammatory training adaptation or the type of EIMD protocol. Whether BCAA could help to decrease muscle soreness in trained subjects due to muscle adaptations or whether trainability has any synergic influence on BCAA biological effects should be investigated in future studies.

Protective effects were not detected by metanalysis at 24, 48, 72, and 96 h in untrained subjects. However, there was a low to moderate level of quality of evidence, in addition to which, an increased risk of bias in some studies (Greer et al. 2007; Shimomura et al. 2010), different levels of muscle damage ranging from mild (Shimomura et al. 2010), to moderate and severe (Kirby et al. 2012; Ra et al. 2018), supplementation protocols, and EIMD protocols might have contributed to our inconclusive data. This supports the need for standardization in damage and supplementation protocols to make rigorously evidence-based recommendations of BCAA supplementation to improve recovery in untrained subjects.

Analysis of the time of administration demonstrated a high level of quality of evidence that post-EIMD supplementation had no clinically important effect on DOMS symptoms. However, acute and previous supplementation decreased DOMS symptoms. This is in agreement with Foure and Bendahan (2017) who reported that studies employing BCAA intake before the exercise, for longer periods, could alleviate EIMD symptoms (Coombes and McNaughton 2000; Howatson et al. 2012). One of the included studies in our review investigated the effects of timing of BCAA administration and concluded that supplementation before the EIMD protocol rather than after exercise was efficient in attenuating DOMS, loss of range of motion, and circulating biomarkers CK, LDH, and aldolase (Ra et al. 2018). Of concern, other studies with chronic BCAA applied supplementation for days before and after EIMD protocols (Howatson et al. 2012; Ra et al. 2013; VanDusseldorp et al. 2018) and not exclusively before. In these studies, we cannot ascertain whether the beneficial effects were due to administration prior to the EIMD protocol, or are the result of a long administration time, as argued by Foure and Bendahan (2017). For instance, the studies using acute doses (administration only on the day of the EIMD protocol) included in our review (Greer et al. 2007; Shimomura et al. 2010) demonstrated reduced DOMS at 24 h. However, these studies induced low to moderate EIMD, and presented a high risk of bias (Greer et al. 2007) and a moderate degree of quality of evidence.

The positive effects of BCAA intake before EIMD may be related to inhibition of DOMS mediators. It has been suggested that key mediators released during exercise (bradykinin and COX-2) account for increased secretion of neurotrophins (NGF and GDNF) during the peak of muscle soreness (12 to 24 h) (Mizumura and Taguchi 2016; Murase et al. 2010; Murase et al. 2013). BCAA has been shown to inhibit NGF secretion in experimental (Scaini et al. 2013; Wisniewski et al. 2016) and clinical studies (Woo et al. 2019). Experimental data also demonstrated that BCAA can inhibit COX-2 (Lee et al. 2017), which could decrease GDNF secretion. Whether BCAA could reduce the bradikynin, COX-2, NGF and GDNF expression in muscle cells needs further investigation.

Foure and Bendahan (2017) suggested that a longer duration (> 10 days) of BCAA supplementation may be necessary to decrease EIMD. However, the present review demonstrated that protocols with acute administration (Greer et al. 2007; Shimomura et al. 2010), moderate duration (3 to 8 days) (Ra et al. 2018; VanDusseldorp et al. 2018; Waldron et al. 2017, 2018), and long duration (12 days) presented decreased DOMS symptoms. On the other hand, one study presenting long-duration treatment (18 days), high-frequency intake per day, and a high dose, failed to demonstrate a preventive effect of DOMS (Ra et al. 2013). A more recent work from the same research group (Ra et al. 2018), with a 5 day supplementation protocol, demonstrated that timing (Pre- or Post-EIMD protocol) of administration may be an important aspect of the treatment since only BCAA administered prior to the EIMD protocol presented beneficial effects on DOMS relief.

One study that reported increased muscle soreness supplemented participants exclusively with leucine (Kirby et al. 2012). Failure to blunt DOMS with leucine may demonstrate a possible relationship between the other two amino acids in this process. Indeed, another study also found that the use of isolated leucine in place of BCAA increased muscle soreness after EIMD (Osmond et al. 2019), so the combination of these amino acids (Leucine, Valine, and Isoleucine) seems to play an important role in reducing DOMS. On the other hand, Waldron et al (2018) observed no statistical difference but a large effect size for DOMS decrements after 24 and 48 h in subjects supplemented with isolated leucine. Caution should be taken when comparing studies since Kirby and coworkers (2012) supplemented with a high dose (750 mg/kg/day) and induced severe muscle damage, whereas Waldron and coworkers (2018) employed a lower dose (150 mg/kg/day) and mild EIMD. Moreover, the small number of participants ($n = 5$) and missing information about sample size calculations and statistical power may be a limitation of the study (Waldron et al. 2018). Further investigations on the effects of isolated amino acids on EIMD are necessary to clarify the effects of each amino acid on DOMS relief.

According to the World Health Organization, the daily requirement for BCAA in adults is 85 mg/kg/day (WHO 2007), balanced in ~ 19, 40, and 20 mg/kg/day of

isoleucine, leucine, and valine, respectively (Kurpad et al. 2006). In the present study, we set the cut-off for high and low daily doses of BCAA based on the mean value observed between the studies included in this review and standardized to three times that recommended by the WHO (2007). Epidemiologic data demonstrated mean daily consumption of BCAA of 203.1 mg/kg/day in the diet of the adult population (Pallottini et al. 2017). Safe limits of total BCAA daily intake for healthy adults were estimated in a range from 144 to 210 mg/kg/day based on amino acid oxidation (Riazi et al. 2003). A leucine dose above 150 mg/kg/day was enough to significantly decrease circulating levels of valine and isoleucine, whereas leucine increased (Elango et al. 2012). The mean BCAA dose used in the included studies was 218.5 ± 160.5 mg/kg/day, including some studies that potentially reached daily leucine intake that may have had effects on decreasing valine and isoleucine circulation or increasing blood ammonia (Foure et al. 2016; Howatson et al. 2012; Kirby et al. 2012; Ra et al. 2013, 2018). Ra et al. 2013, demonstrated that daily doses of ~ 149 mg/kg/day did not change circulating levels of leucine, valine, and isoleucine, whereas the intake of ~ 449 mg/kg/day evoked a transient circulating peak in the three amino acids. On the other hand, Shimomura et al. (2010) reported increased levels of the three amino acids using a lower and single dose of approximately 100 mg/kg. Only Ra et al. (2013) and Ra et al. (2018) gave a rationale for the choice of BCAA dose, based on circulating levels. Only two studies performed a planned diet intake during the study to control levels of BCAA (Waldron et al. 2017, 2018). In the other studies, it is not possible to state that the subjects ingested adequate levels of BCAA in their normal diets, how much circulating BCAA was achieved during the studies and whether circulating levels were under safe limits.

In the present review, BCAA doses up to 255 mg/kg/day (low) seemed to have better results than studies with high doses. However, this should be interpreted with caution since two of the studies (Greer et al. 2007; Waldron et al. 2018) induced mild EIMD. These studies also presented a risk of bias (Greer et al. 2007; Shimomura et al. 2010; VanDusseldorp et al. 2018) which decreased the quality of evidence to moderate. In this review, higher doses did not demonstrate a beneficial effect on the BCAA group, with a high degree of quality of evidence. Experimental studies showed that high doses of BCAA have harmfull effects due to oxidative stress (Piscopo et al. 2011; Zhenyukh et al. 2017; Zhenyukh et al. 2018), and expression of inflammatory mediators (Wessler et al. 2019; Zhenyukh et al. 2017; Zhenyukh et al. 2018), and endothelial dysfunction (Wessler et al. 2019; Zhenyukh et al. 2018). A high intake of leucine in BCAA formulations may have decreased valine and isoleucine bioavailability, and other essential amino acids, through a phenomenon called BCAA antagonism (Block and Harper 1984; Elango et al. 2012; Wolfe 2017). Importantly, isoleucine is necessary to maintain anti-inflammatory Treg cells (Ikeda et al. 2017). BCAA antagonism should be evaluated in future studies to guarantee this effect was not associated with reduced circulation of other essential amino acids, decreasing BCAA efficacy on muscle recovery.

Our results regarding the effectiveness of low to high BCAA doses were different from the results of a previous systematic review (Foure and Bendahan 2017). Other authors found positive effects for EIMD prevention in studies that employed > 200 mg/kg/day (Coombes and McNaughton 2000; Gee and Deniel 2016; Howatson et al. 2012; Matsumoto et al. 2009). Of note, we excluded the study of Matsumoto et al (2009) from our review because the authors employed a 3-day high-intensity training program and volunteers run different distances (Matsumoto et al. 2009). In the present study, a protective effect was observed in one study with a lower dose and severe EIMD (VanDusseldorp et al. 2018). Two studies with high doses and moderate (Howatson et al. 2012) and severe EIMD (Ra et al. 2018) also found protective effects, but these studies had a low number of participants per group (5 to 6) and accounted with little effect in metanalysis. Given this, it is possible that higher doses of BCAA have no effect or could impair muscle recovery, whereas lower doses may demonstrate better effects.

Another important fact was that BCAA appeared more efficient in mild and moderate muscle damage than in severe EIMD, with high-quality evidence. This is in agreement with a previous systematic review, concerning blunting of EIMD symptoms (not specifically DOMS) (Foure and Bendahan 2017). However, two studies evaluated mild EIMD (Shimomura et al. 2010; Waldron et al. 2018), and differences at 72 h are not representative of a clinically significant effect, since subjects are expected to be physically recovered 72 h after the EIMD protocol (Paulsen et al. 2012). In moderate EIMD studies, a high quality of evidence was observed, but DOMS was significantly blunted only at the 24 h analysis. Otherwise, moderate EIMD studies included three studies with high BCAA doses (Foure et al. 2016; Howatson et al. 2012; Ra et al. 2013) and one study with a high risk of bias which analyzed only 24 and 48 h (Greer et al. 2007). No significant protective effects could be attributed to BCAA supplementation in severe EIMD. However, a moderate quality level of evidence was observed in severe EIMD analysis. This was attributed to the risk of bias and moderate heterogeneity in the included studies.

A limitation of the included studies is the monitoring of circulating BCAA and daily intake in the diet, which did not allow estimation of the total amount (diet + supplementation) of daily intake of BCAA ingested by the study participants. Another concern was that only two studies

(Shimomura et al. 2010; Waldron et al. 2017) evaluated females and none investigated older participants. An additional limitation to comparisons between studies was the diversity of exercise protocols used. Although eccentric and plyometric exercises are more suitable to cause moderate to severe EIMD, studies vary in intensity, volume, interval between series, and muscles involved in exercises and may contribute to the variability in DOMS outcomes. Moreover, some studies used non-conventional EIMD protocols (cycling, free-weight squats) or electrical stimulation (Foure et al. 2016; Greer et al. 2007; Shimomura et al. 2010) which may not be appropriate since DOMS is manly developed by lengthening contractions (Murase et al. 2010). The difference in BCAA effectiveness may arise from differences in mechanical damage and inflammatory reactions elicited by exercise load, muscle groups, or voluntary contraction vs. electrical stimulation (Crameri et al. 2007; Paulsen et al. 2012). A limitation of this review is the use of a single session of EIMD, instead of repeated days of physical efforts during competitions. From a practical point of view, our results may be helpful in situations such as a one-day competition, after an unaccostumated effort, or the adjustment of resistance or plyometric loads during training periodization. In these situations, it is expected the subjects will have time to physically recover before the next high load effort is applied in the same muscle groups. This is necessary as EIMD causes underperformance, DOMS, and an increased risk of injuries (Clarkson and Hubal 2002; Soligard et al. 2016; Walters et al. 2018). If BCAA has an effect on DOMS relief, subjects could return to train the damaged muscles after a shorter recovery interval.

The results suggest that BCAA supplementation could decrease DOMS symptoms in some clinical contexts, depending on the training status, supplementation protocol, and degree of muscle damage. The results of the present study apply in the context of BCAA supplementation before a single exercise session where EIMD and DOMS are expected to occur due to the application of a new exercise or load to which the individual is not yet accustomed. Based on the present findings, practical recommendations include BCAA supplementation for trained subjects. Modest evidence suggests BCAA could decrease DOMS at low doses, but study limitations should be addressed in future studies to draw a definitive conclusion. Evidence still does not support BCAA supplementation for untrained subjects or severe EIMD. BCAA supplementation improved DOMS symptoms when administered days before and/or on the day of the EIMD protocol.

Acknowledgements The authors would like to thank the Coordenação de Aperfeiçoamento de Pessoa de Nível Superior (CAPES) and Conselho Nacional de Pesquisa e Desenvolvimento tecnológico (CNPq) for the grant to TRA (grant n. 146644/2018-2).

Funding Conselho Nacional de Pesquisa e Desenvolvimento tecnológico (CNPq) for the grant to TRA (grant n. 146644/2018-2).

Declarations

Conflict of interest Not applicable.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

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