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Research Article

Branched-Chain Amino Acid Administration Influences on Ammonia and Lactate post of Eccentric Exercise: A Systematic Review and Meta-analysis

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Abstract

Background: There have been papers on administration of BCAA to diminish fatigue substances such as ammonia and lactate during long periods of severe eccentric exercise have been performed. Although, there are disagreements concerning the results of these investigations. The main claim for the administration usage by the athletes was to diminish or omit fatigue. In previous studies several athletes assert reducing of fatigue after administrating BCAA.

Method: A comprehensive search was performed on electronic databases up to July 2022 for trials evaluating the effects of BCAA on recovery following eccentric exercise. Mean ± standard deviation of follow-up ammonia and lactate levels were extracted to calculate the effect size for meta-analysis.

Results: A total of 201 participants for lactate were found from 12 studies. The findings showed that without considering follow-up times, an overall analysis showed that BCAA was effective in reducing blood lactate in aerobic exercise and the trained status of athletes. Pooled results showed no significant difference in all follow-up times (overall WMD = 0.06 mmol/L; 95% CI, -0.09 to 0.21) in acute BCAA administration, and there was no significant heterogeneity between studies (I2 = 0.0%; p = 0.864). Moreover, a sensitivity analysis indicated that the result was not excessively influenced by any one study. There was no evidence of publication bias among studies after examining the effects of acute BCAA administration on lactate (p = 0.59, Begg's test; p = 0.78, Egger's test).

Conclusions: The benefits of BCAA administration correlate with improved muscle function due to a likely attenuation of fatigue substances instantly after eccentric exercise.

Key Words: branched-chain amino acids; ammonia; lactate; fatigue; eccentric exercise; meta-analysis

Introduction

Eccentric exercise (EE) has many helpful outcomes such as decreasing inflammation, debilitating the process of skeletal muscle protein breakdown, and ameliorating impaired glucose tolerance [1-3]. However, EE can cause fatigue because of adenosine triphosphate (ATP) depletion and exceeding manufacture of fatigue substances such as ammonia and lactate [4]. The inability to preserve a favorable strength output that because of frequent high-intensity activity with short recovery time is known as fatigue [5] that induced by interconnected central and peripheral mechanisms] 6[. Anyway, the indices correlated with central fatigue are less known [7].

In fact, the fundamental physiological responses related to acute peripheral fatigue within the skeletal muscle and nerve are multifaceted and intricate, but the accumulation of plasma lactate, lower blood pH and raised plasma ammonia concentrations are mostly measured beside strength to characterize the amount of fatigue [5]. Eventually, the accumulation of fatigue factors can cause poor efficiency [8]. Indeed, the grade of fatigue related to internal factors (such as energy storage, skeletal muscle mass, and skeletal muscle fiber type), while external factors (such as physical activity severity and period) and reduction in skeletal muscle contraction are closely correlated with the stimulation of fatigue-triggering metabolites, such as ammonia and lactate [9].

Branched-chain amino acids (BCAAs) can participate in the lot of metabolic and cell signaling pathways and are strong modulator of protein turnover all over the activation of several signaling molecules [2, 10] . At rest, in response to functional requirements, branched chain amino acids (BCAAs, i.e., leucine, isoleucine and valine) are used by skeletal muscle for protein synthesis and calory production. BCAAs account for 35-40% of essential amino acids in dietary intake and are usually exist in sports nutrients. BCAAs are presented to diminish fatigue and muscle soreness post EE and can

motivate skeletal muscle protein synthesis to a greater extent than other mixtures of essential amino acids, as well as attenuate exercise-induced protein catabolism [11, 12]. In addition, during heavy EE, BCAA breakdown in the skeletal muscle is much raised and blood BCAA level decrease at the same time [3, 13]. So, when BCAA catabolism is raised, BCAA considerably represses the lactate production [14].

It is clear that BCAAs are firstly catabolized in skeletal muscles, unlike other essential amino acids, which are catabolized largely in the liver [4]. Whereas, BCAA has been presented to be used as an energy source in the skeletal muscle during EE [15]. It has been showed that BCAA catabolism is elevated by EE [4]. In fact, branched-chain amino acids (BCAA) are one of the most beneficial sport nutrients in boosting health and sports performance] 16[and BCAA administration pre or post EE can ameliorate recovery of damaged skeletal muscles [4]. Indeed, during recovery time after EE, BCAA have an anabolic efficacy in human skeletal muscle [17]. Also, these outcomes offer that BCAA administration during EE can impressively repress protein degradation created by EE [18]. Therefore, BCAA might be more significant in supporting the instant recovery time post EE. However, previous investigate results have often been contradictory as to the effect of BCAA on blood fatigue factors post EE. The purpose of our systematic review and meta-analysis (Met-A) is, hence, to evaluate data that considered plasma fatigue factors to intake of BCAA administration post EE.

Methods

Searching

Present systematic review and Met-A performed based on the guidelines of PRISMA [19]. A computerized literature search conducted, from inception to July 2022, utilizing the Scopus and Medline databases and Cochrane Library, in combination with a complementary Google Scholar searching. The following phrases and their combinations were used: “branched chain amino acid”, “amino acids, branched-chain”, “BCAA”, “eccentric exercise”, “sport supplements”, “fatigue”, “fatigue substance”, “ammonia”, and “lactate.” References of whole studies checked for identification of more eligible papers (**Figure 1**).

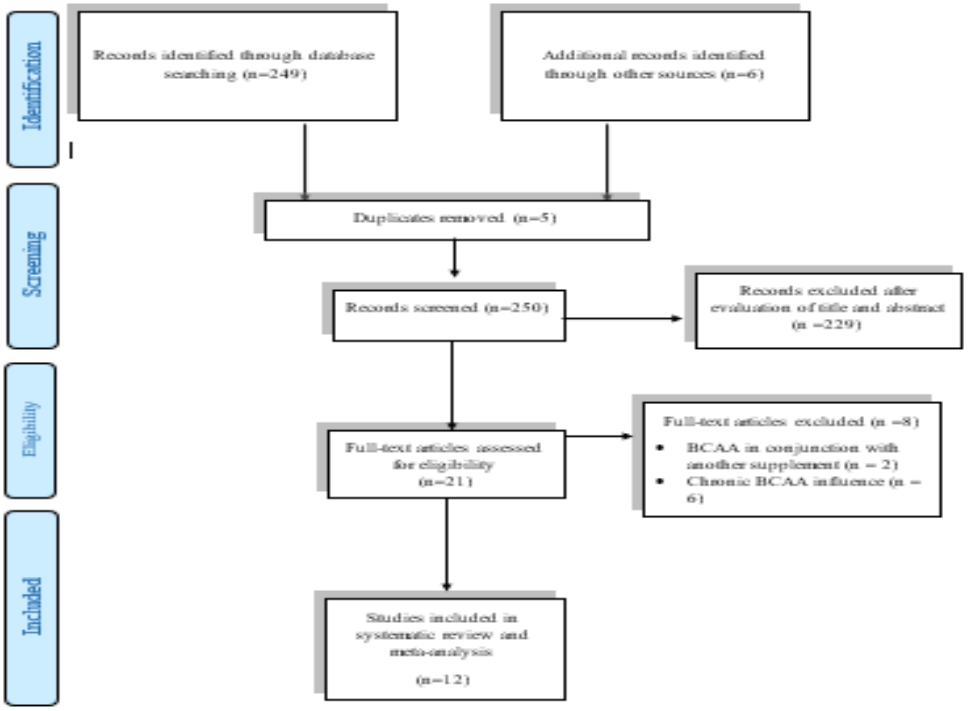

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram of study selection process

Criteria for Eligibility:

Articles selected by applying the following PICOS criteria [19]: (1) healthy participants received standard oral BCAA administration, before and after exercise, as a nutritional strategy; (2) at least one outcome measure of fatigue substance (ammonia and lactate) was reported; and (3) original studies that utilized randomized-controlled trial method. Studies using multiple administrations, including BCAA in combination with another supplement such as carbohydrate [20] and ornithine aspartate (OA) [21], were not considered.

Selection strategy:

After the primary search, titles and abstracts of papers obtained through the search strategy were screened. Two authors selected studies according to the inclusion criteria independently. Articles including eligible criteria in the title/abstract screening were selected to be checked in full-text. Parallel clinical trials using a control group or crossover design studies were selected in the systematic review and Met-A. All categorized trials were retrieved by either of the authors. On the basis of the information thus collated, we used a standardized form to select the trials eligible for inclusion in the review. Conflicting results were solved by consensus, or the third researcher.

Data extraction:

Two authors extracted the following required data: first author’s name, publication year and country, research design, age and gender of participants, sample size, duration of intervention, training status, and BCAA dose. We also extracted mean and standard deviation (SD) of fatigue substance (ammonia and lactate) at baseline and after intervention.

Study quality:

Since it has been accepted that inclusion of trials with a high risk of bias may distort the results of a Met-A [19, 22], the Cochrane Collaboration tool for assessing the risk of bias was used. The following factors were assessed: randomization sequence generation; allocation concealment; blinding of participants, personnel, investigator, and assessor; attrition rates; and financial interest of companies (**Table 1**). These were given a rating of low, unclear, or high risk of bias. An RCT was ranked as having low, medium, or

high risk overall based on the key areas of allocation concealment, reporting of attrition rates, and participant and assessor blinding (high = all four factors rated high, medium = two or three factors rated high or unclear, and low = all key areas rated low).

Study	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall Risk of Bias
Lysenko (2016)	L	L	L	L	L	L	L	Low
Mikulski (2015)	U	L	L	L	L	U	L	Medium
Koo (2014)	L	L	L	L	L	L	L	Low
Kim (2013)	L	L	L	L	L	L	L	Low
Hsu (2011)	U	L	L	L	L	H	L	Medium
Shimomura (2010)	U	L	L	L	L	H	L	Medium
Apro´ (2010)	U	L	L	L	L	H	L	Medium
Matsumoto (2006)	U	L	L	L	L	H	L	Medium
Cheuvront (2004)	U	L	L	L	L	U	U	Medium
Watson (2004)	L	L	L	L	L	L	L	Low
De Palo (1999)	U	L	L	L	L	H	U	Medium
Strüder (1998)	L	L	L	L	L	L	L	Low
Mourier (1997)	L	L	L	L	L	H	H	Medium
Bigard (1996)	H	L	L	U	L	H	U	High
Hall (1995)	U	L	L	L	L	H	L	Medium
McLean (1995)	U	L	U	U	L	U	L	High

L, low risk of bias; H, high risk of bias; M, medium risk of bias; U, unclear risk of bias

Table 1: Cochrane Risk of Bias Assessment

Analysis and measures of treatment effect:

For every study, mean differences and standard deviation were computed for continuous variables. Standardized mean differences were used for variables pooled on the different scales. Between-study heterogeneity was assessed using the chi-squared ($\chi 2$) test and quantified using the I^2 statistic, which represents the percentage of the total variation across studies that is ascribable to heterogeneity rather than to chance. I^2 was calculated using the formula: $I^2 = 100\% \times (Q-df)/Q$, and an I^2 value of 75% or greater was deemed to indicate a high level of inconsistency (Q is the $\chi 2$ statistic and df is the degrees of freedom). Significant heterogeneity was defined with a P-value of <0.05.

Random effect and fixed effect models were applied for assimilating overall effect where evidence of statistical heterogeneity and homogeneity were seen respectively. To determine whether the results could have been affected individually by a single study, an influence analysis was carried out [23].

Publication bias was assessed by Begg's rank correlation test and Egger's regression asymmetry test. Statistical analysis was performed using STATA 11.2 software (StataCorp, College Station, Texas, USA).

Results

Overview of included studies:

We initially identified 255 papers from databases and internet searches and included 12 studies in the present systematic review, studies selected according to the 4-phase flow diagram described in **Figure 1** in the present Met-A. The characteristics of the included studies are summarized in **Table 2**, which provides an overview of the methodological quality of each selected trial. The included studies were trials with numbers of participants ranging from 10 to 28, most of which used a crossover design. Participants tended to be young, with a mean age of 24.9. Most of the studies reported acute administration (1 day). All participants were men (n = 177), except one study in which only women participated (n = 24) [4] and two studies in which both men and women participated (n = 18) [24].

Author	Study Design Characteristics					average age (Y)	Sample Size		Fatigue substance Status
	design	training status	BCAA dose (gr)	Duration (D)	gender		BCAA	Control	
Lysenko (2016)	C-O	t	7	1	M	18–30	9	9	≡ Lactate
Mikulski (2015) *	CO	t	16 (+ OA)	1	M	32.6	11	11	↑ Ammonia
Koo (2014)	CO	t	3.15	6	M	17.2	5	5	≡ Ammonia, ≡ Lactate
Kim (2013)	RCT	u	5.5	1	M	23	13	13	↑ Ammonia, ↓ Lactate
Hsu (2011)	C-O	t	2	1	M	23.4	14	14	≡ Ammonia, ≡ Lactate
Shimomura (2010)	C-O	u	5.5	1	F	22.2	12	12	↑ Ammonia, ≡ Lactate
Apro´ (2010)	C-O	u	6.2	1	M & F	26	9	9	≡ Lactate
Matsumoto (2006)	C-O	u	2	1	M & F	26	8	8	≡ Lactate
Cheuvront (2004)	C-O	t	10	1	M	21	7	7	≡ Lactate
Watson (2004)	CO	t	6	1	M	28.5	8	8	↑ Ammonia, ≡ Lactate
De Palo (1999)	RCT	t	9.64	30	M	32.8	6	5	↓ Lactate
Davis (1998) *	C-O	t	7 + carbohydrate	1	M & F	∧	16	16	≡ Lactate
Strüder (1998)	C-O	t	7	1	M	25.5	10	10	≡ Ammonia, ≡ Lactate
Mourier (1997)	C-O	t	64	19	M	23	6	6	≡ Lactate
Bigard (1996)	RCT	t	7.8	30	M	25-42	12	12	≡ Ammonia, ≡ Lactate

Hall (1995)	CO	t	7.8	1	M	23.3	10	10	↑ Ammonia
Hall (1995)	CO	t	23.4	1	M	23.3	10	10	↑ Ammonia
McLean (1995)	CO	^	5.5	1	M	24.4	5	5	↑ Ammonia, ↓ Lactate

BCAA = branched-chain amino acid; OA = ornithine aspartate; RCT = randomized controlled trial; C-O = cross-over studies; M = men; F = Female; D=days; Y=years; T=trained; U= untrained

*Excluded from meta-analysis; ^Unspecified or unknown.

↑ BCAA group significantly higher compare to control group; ↓ BCAA group significantly lower compare to control group; ≡ No significant difference between trials

Table 2. Summary of relevant sources of data included for meta-analysis

The total participant pool for ammonia and lactate as fatigue substance factors was 101 and 100, respectively. This numbers are inclusive of individuals who were dropouts in some studies.

All studies reported multiple follow-up observations for each outcome. Although most studies reported follow-ups at multiple minutes and hours (e.g., post-exercise for both intervention and placebo at 10, 20, 30, 40, and 50 min, and 1, 2, and 3 h after the start of exercise and administration). This review focused on outcomes undertaken immediately post exercise and the subsequent minutes and hours after the completion of the recovery intervention.

Systematic review:

Among the studies, some of them did not meet the criteria for inclusion in the Met-A. These were therefore explained as a systematic review. Due to the heterogeneity of the study outcomes, designs, and interventions, a Met-A was not undertaken for ammonia concentration.

In addition, the number of studies demonstrating a significant effect on ammonia and lactate was equivalent to the number of studies which showed no effect. Also, a long duration of administration over several days before damaging exercise (at least 6 days prior to damaging exercise in three of the studies [8, 25, 26]) showed no effect of BCAA administration on fatigue substances. Mikulski et al. (31) suggested that ingestion of combined BCAA and ornithine aspartate played a role in increasing ammonia 90 min after exercise, in comparison with placebo. Although Hall et al. demonstrated the effect of a low and a high dose of BCAA (7.8 and 23.4 g/day) on increasing ammonia exactly after exercise [27]. Three studies [4, 28, 29] used 5.5 g/day BCAA and showed a positive role of BCAA in increasing ammonia and decreasing lactate after exercise, with the exception of Shimomura et al. who did not see this effect on lactate [4], an observation consistent with that of Watson et al. [30], who used 6 g/day BCAA.

Meta-Analysis:

Amongst the 12 studies that recorded lactate concentration (201 participants), four studies applied more than 1 day BCAA administration [8, 25, 26, 31]. We therefore separated the analysis of acute BCAA administration (1 day) and more than 1 day BCAA administration (from 6 to 30 days). We detected the heterogeneity source for lactate that was follow-ups times which a subgroup analyses performed based on follow-ups times (<60, ≥60 and ≥120 minutes). We conducted subgroup analysis based on follow-ups times in acute BCAA administration in <60 and 60≤ min after exercise and in more than 1day BCAA administration, immediately post exercise (0 min) and 30 or 60 min post exercise.

Pooled outcomes showed no significant difference in all follow-ups times (overall WMD = 0.06 mmol/L; 95% CI, -0.09 to 0.21) in acute BCAA administration, and there was no significant heterogeneity between studies (I^2 = 0.0%; p = 0.864) (**Figure 2**). Moreover, a sensitivity analysis indicated that the result was not excessively influenced by any one study. There was no evidence of publication bias among studies after examining the effects of acute BCAA administration on lactate (p = 0.59, Begg's test; p = 0.78, Egger's test).

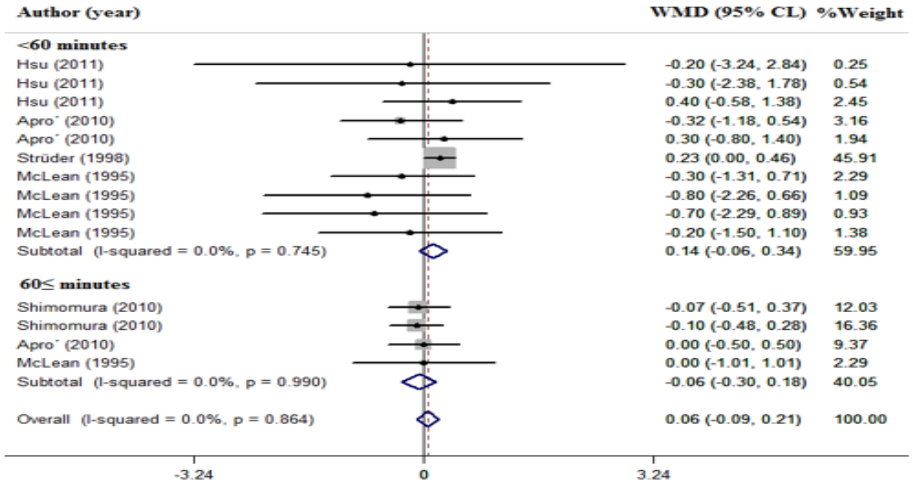

Figure 2. Forest plot of the effect of acute BCAA administration on lactate level sub grouped by study follow ups, WMD = weighted mean difference; CI = confidence interval.

In addition, **Figure 3** shows that intake of BCAA for more than 1 day had no significant effect on lowering lactate concentration in the follow-up times post exercise, compared to a placebo (overall WMD = -0.09 mmol/L; 95% CI, -0.33 to 0.14). There was no evidence of significant heterogeneity between the effect sizes of the included studies (I^2 = 0.0%; p = 0.381). The sensitivity analysis indicated that the result was not excessively influenced by any one study. There was no evidence of publication bias among studies examining the effects of more than 1-day BCAA administration on lactate (p = 0.47, Begg's test; p = 0.61, Egger's test).

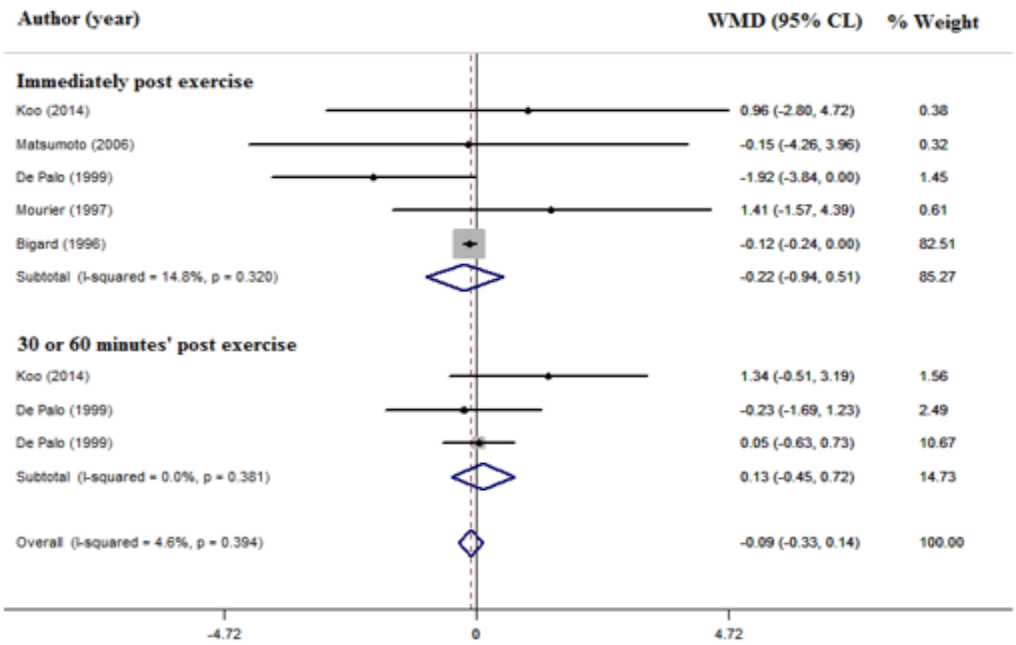

Figure 3. Forest plot of the effect of more than 1-day BCAA administration on lactate level sub grouped by study follow ups, WMD = weighted mean difference; CI = confidence interval.

Further subgroup analysis based on the dose of BCAA administration, exercise type, and training status is presented in **Table 3**. We divided the dose of BCAA into low and high based on a 5 gr/day cut-off point. In addition, exercise was sub grouped based on aerobic vs. anaerobic and trained and vs. untrained status. There was a significant decrease in ammonia by ≥ 5 g/day BCAA administration, aerobic exercise, and untrained status. However, due to high heterogeneity (p for heterogeneity = 0.00), these results should not be considered reliable. Moreover, there was a significant decrease in lactate in aerobic exercise (WMD = -0.22 mmol/L; 95% CI, -0.39 to -0.06) and trained status (WMD = -0.25 mmol/L; 95% CI, -0.42 to -0.08). There was no evidence of significant heterogeneity between the effect sizes of the included studies (I^2 = 0.0%; p = 0.87) and (I^2 = 0.0%; p = 0.93), respectively.

Sub grouped by	No. of trials	Effect size[1]	95% CI	I^2 (%)	p for heterogeneity
Ammonia					
Dosage					
≥ 5 g/day	16	**-8.90**	**-14.12 to -3.68**	0.76	0.00
< 5 g/day	4	-4.21	-10.03 to 1.61	0.00	0.90
Exercise type					
Aerobic	10	**-14.84**	**-1.42 to -28.25**	83.9	0.00
Anaerobic	10	2.07	-0.29 to 4.43	12.3	0.32
Training status					
Trained	9	-8.49	-19.94 to 2.96	70.9	0.00
Untrained	11	**-6.14**	**-11.22 to -1.06**	77.2	0.00
Lactate					
Dosage					
≥ 5 g/day	16	0.09	-0.04 to 0.22	0.00	0.74
< 5 g/day g	4	0.16	-0.67 to 0.98	0.00	0.77
Exercise type					
Aerobic	8	**-0.22**	**-0.39 to -0.06**	0.00	0.87
Anaerobic	12	-0.12	-0.33 to 0.09	0.00	0.99
Training status					
Trained	6	**-0.25**	**-0.42 to -0.08**	0.00	0.93
Untrained	14	-0.11	-0.31 to 0.08	0.00	0.99

Table 3. Subgroup Analysis to Assess the Effect of BCAA Administration on Ammonia and Lactate.

[1]Calculated by random effects model.

CI = confidence interval; BCAA = branched chain amino acid

Discussion

To our knowledge, the influence of BCAA has not been firmly established for fatigue. Branched chain amino acids (leucine, isoleucine, and valine) are the most oxidized types of amino acids that are catabolized in the muscle and enhance skeletal muscle regeneration by repressing endogenous post-EE skeletal muscle protein breakdown [28, 32]. So, insufficient essential post-EE amino acids can postpone motivating muscle protein synthesis. The popularity of protein and amino acid administration for athletes is growing [33].

Therefore, this systematic review and Met-A has sought to prepare insight into the potential benefits conferred by such administration to enable athletes to make informed decisions as to their effectiveness and use. The results of our Met-A, performed in 20 randomized controlled trials, disclosed no significant effects of BCAA administration in reducing fatigue substances during training procedures of various durations.

A review study by Hormoznejad et al. [34] reported that, in order to evaluate fatigue, blood ammonia activity and blood lactate level are extensively used as factors. Anyway, the above Met-A was accomplished based on ammonia and lactate. These factors are not only the most used consequences: they are the best factors of skeletal muscle fatigue [28, 30, 35]. Data for ammonia was heterogenic and a Met-A was not undertaken. Despite the high heterogeneity of the data, a Met-A was conducted before without any subgroup for follow-up time [34], and in our opinion, these results should not be considered trustworthy. In addition, administrate of BCAA for any duration had no considerable effect on lowering lactate level in the follow-up times after EE, compared to a placebo. However, without considering follow-up times, with an overall analysis BCAA was effective in lactate diminution for subgroups of aerobic exercise and trained status of athletes **(Table 3)**.

Lactate is considered to reflect the anaerobic glucose metabolism during physical activity. Lactate is the most significant barometer known to affect the restriction items of skeletal muscle activity and skeletal muscle fatigue [14]. The rate of lactate manufacture exceeds the rate of removal during high-intensive EE. The overplus lactate comforts acidosis and represses the enzymatic activation correlated with glycolysis, which prevents ATP synthesis and eventually leads to fatigue. It is not physiologically possible for lactic acid to be within human cells and hence lactate, not lactic acid is organized during high-intensity EE [5] . McLean et al. [29] offered that a 77 mg/kg dose of BCAA does not considerably change the overall distribution of pyruvate into lactate and alanine, compared with placebo. Matsumoto et al. [18] reported an raise in circulatory BCAA concentrations and offered that BCAA administration induced an elevate in BCAA oxidation during the EE. It was thus speculated that an elevate in acetyl-CoA and succinyl-CoA supply to the TCA cycle via the BCAA catabolic pathway repressed lactate production during the EE. In a study by Kim et al. [28], lactate levels of the two groups of BCAA and controls, respectively, demonstrated a statistically considerable elevate at 30 min into EE. Lactate levels in the BCAA intake group showed a statistically significant reduction instantly post EE and returned to a stable level at 30 min post EE. Although in the present Met-A, we could not analyze instantly post EE follow-up due to the high heterogeneity of the data.

Ammonia is often brought up as a waste product of the catabolism of amino acids and other nitrogenous combination. So, for normal function of body it has to be eliminate as soon as possible [36]. On the other hand, ammonia production following high-intensity EE, which happens owing to the deamination of adenosine monophosphate (AMP) to , inosine monophosphate (IMP) along with BCAA deamination [36], motivates phosphofructokinase (PFK) [37] and AMP deaminase itself is motivated by low pH, raised adenosine diphosphate (ADP), and raised AMP level [38]. In fact, Ammonia is alkaline, and is low in level (~2 mmol·kg-1 wet weight) [39] relative to lactate (several hundred mmol ·kg-1 wet weight) [40] and as a result, does not contribute to acidosis. Thus, the rate of muscular level, which forms ADP, AMP, Pi, and H+, dictates the production of lactate and ammonia through overlapping negative feedback loops begun by fast adenosine monophosphate (ATP) hydrolysis [5].

In recent years, many studies have shown the beneficial effects of BCAAs on physical activity efficiency. BCAA as a nutritional administrate can better blood level of fatigue substances such as lactate and ammonia [32]. Previous data showed that the ammonia produced from BCAAs leads to reaction that preserves the energy source of the cells. So, BCAA administration during EE is the key factor that alters the arterial NH3 production [29, 41]. The results of one investigation offer that BCAA administration had a useful effect on lactate and ammonia, although, they did not observe helpful effects of BCAAs on central fatigue. Generally, BCAAs as an useful nutritional administrate for exercise fatigue [32].

Several items can affect the high heterogeneity and the result less findings that have been reported. Some of these are: the percentage of leucine, isoleucine, and valine; different manufacturers of BCAA; and variations in BCAA classifications between countries. All these items can contribute to the inconsistencies in results. Furthermore, the studies included in this review reported different dosages, ranging from 1.5 g/day [42] to 64 g/day [25].

Conclusion

To our knowledge, this is the first systematic review and Met-A to investigate the effects of BCAA on fatigue post EE. The current evidence-based data shows that administration with BCAA is better than passive recovery or rest after various forms of damaging and exhausting EE. as well as, in aerobic exercise and trained status of participants, the effect of BCAA was considerable in achieving lactate reduction. It seems that BCAA is more effective for trained athletes who do aerobic exercise. more research is essential to quantify BCAA influence in a homogenous administration method and the same exercise strategy over a longer timeframe and to illuminate possible interactions with diet and environment.

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