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Effects of Beta-Alanine Supplementation on Muscle Carnosine Concentration and Physical Performance in Women: A Systematic Review of Literature

Beeta-alaniini toidulisandina manustamise mõju karnosiini kontsentratsioonile skeletilihases ja kehalisele töövõimele naistel: kirjanduse süstemaatiline ülevaade

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TABLE OF CONTENTS

ABBREVIATIONS 3
ABSTRACT 4
LÜHIÜLEVAADE 5
1 INTRODUCTION 6
1.1 Dietary supplements in sport 6
1.2 Acid base balance and physical performance 7
1.3 Dietary supplements influencing the capacity of buffer systems 8
1.4 Beta-alanine as a dietary supplement 8
2 AIM OF SYSTEMATIC REVIEW 10
3 METHODS 11
3.1 Search Strategy 11
3.2 Inclusion/Exclusion Criteria 11
3.3 Study Selection 11
3.4 Data Extraction 12
4 RESULTS 13
4.1 Search strategy 13
4.2 Participants 17
4.3 Study Design and Supplementation Procedures 17
4.4 Impact of BA Supplementation on Muscle 18
4.5 Impact of BA Supplementation on Physical performance and RPE 18
4.6 Impact of BA Supplementation on Body Composition 19
4.7 Impact of BA Supplementation on Physiological and Biochemical Parameters 20
5 DISCUSSION 21
5.1 Impact of BA Supplementation on Muscle Carnosine Concentration 21
5.2 Impact of BA Supplementation on Physical performance and RPE 22
5.3 Impact of BA Supplementation on Body Composition 24
5.4 Impact of BA Supplementation on Physiological and Biochemical Parameters 24
6 CONCLUSIONS 26
7 REFERENCES 27

ABBREVIATIONS

BA – beta alanine

RPE – rating of perceived exertion

TTE – time to exhaustion

ABSTRACT

Aim: The aim of this systematical review was to gather research of BA (beta-alanine) supplementation done on women and compare results with studies done on men and find out, whether there is any difference in effect size of supplementation or sport performance. **Methods:** Search was carried out in EBSCO, PubMed and Google Scholar for identifying suitable studies. PRISMA guidelines were used for reporting data, PICOS model was used to filter studies for inclusion. **Results:** Eleven studies were picked for final examination. Three studies measured TTE. In all of the cases TTE values were longer for the BA group after the supplementation period. RPE values were assessed in 3 studies, one did not see any significant difference and in two studies, RPE values were lower for the supplementation group. Out of 8 studies, where body composition was assessed, none reported any significant difference on body composition as a result of BA consumption. Three studies measured VO_{2peak}, but no significant difference between supplementation group and palcebo group was found for any of the studies. Similar results were found for two studies, which measured VO_{2max} values. Three studies measured lactate levels. One study reported significantly lower lactate levels for BA group after 20-minute rest period of the cycling exercise test. **Conclusions:** Relative rise in carnosine levels is greater for women compared to men.BA supplementation has an effect on TTE values in women, more so than in men. In this work all 3 studies noted significantly longer TTE compared to different results reported in studies conducted on men. BA supplementation seems to lower RPE values for women. VO_{2peak} and VO_{2max} do not seem to be significantly affected in women by BA supplementation, but different results are found in studies done on men. More data on women with different age and training status is needed.

Key Words: beta-alanine, women, systematic review, sports performance

LÜHIÜLEVAADE

Eesmärk: Töö eesmärgiks oli koondada beeta-alaniini toidulisandi efekte uurivad tööd, mis on teostatud naistel, ja võrrelda leitud tööde tulemusi meestel tehtud töödega ning välja tuua erinevused tulemustes ja efekti suuruses, kui neid leidus. **Metoodika:** Otsingu läbiviimiseks kasutatid andmebaase EBSCO, Pubmed ja Google Scholar. Tööde filtreerimiseks ja sobivuse hindamiseks kasutati PICOS mudelit ja tulemuste esitamiseks PRISMA juhiseid. **Tulemused:** Kõigist leitud töödest sobis analüüsimiseks 11 uuringut. Kolmes töös mõõdeti karnosiini kontsentratsiooni lihases, Kolmes töös mõõdeti töö kestvust, mis ka BA manustamise tulemusena igas uuringus pikenes. Kolm tööd hindasid tajutud pingutust, ühel juhul oluline muutus puudus, ühel juhul oli tegemist BA akuutse mõju mõõtmisega, aga sellegipoolest tajutud pingutus oli BA katse puhul oluliselt väiksem, ühel juhul oli tajutud pingutus pärast lisandi manustamise perioodi väiksem. Kaheksas töös mõõdeti kehakoostist. Üheski töös ei märgitud statistiliselt olulisi muutuseid kehakoostises. Kolmes töös mõõdeti VO_{2peak} näitajaid, kuid üheski töös ei toimunud nendes näitajates olulisi muutusi. Sama tulemus oli ka VO_{2max} näitajate puhul, mida mõõdeti kahes töös. Laktaadi taset mõõdeti kolmes töös. Ühe töö puhul oli BA manustajate laktaadi tase pärast 20-minutilist puhkeperioodi katsejärgselt tunduvalt madalam kui platseebo grupil. **Kokkuvõte:** Karnosiini suhteline tõus BA mansutamisel lihastes on naistes suurem kui meestes. BA manustamisel võib olla töö kestvust parandav toime nii meeste kui naiste puhul, kuid kõigis uuringutes, mis antud ülevaateartiklis seda näitajat mõõtsid, paranesid naiste näitajad oluliselt. Meestel tehtud töödes olid tulemused erinevad. Lisaks võib BA vähendada tajutava pingutuse suurust. VO_{2peak} ja VO_{2max} näitajatele naistes ei tundu BA mõju avaldavat, küll aga leidus mitmeid töid meeste kohta, kus vastavad näitajad suurenesid või vähenesid. BA manustamise mõju naistes erinevatele töövõime näitajatele tuleks rohkem uurida, et oleks võimalik teha järeldusi suurema andmehulga põhjal.

Märksõnad: Beeta-alaniin, naised, süstemaatiline kirjanduse ülevaade, sportlik töövõime

1 INTRODUCTION

1.1 Dietary supplements in sport

The term "dietary supplement" has many different definitions (Maughan et al., 2018). According to recently published IOC consensus document (Maughan et al., 2018) dietary supplement is "a food, food component, nutrient, or non-food compound that is purposefully ingested in addition to the habitually-consumed diet with the aim of achieving a specific health and/or performance benefit". The US Food and Drug Administration (FDA) defines supplements as following: "A dietary supplement is a product intended for ingestion that contains a "dietary ingredient" intended to add further nutritional value to (supplement) the diet" (FDA, 2017; quoted in Garthe & Maughan, 2018).

Similar to definition, there are several classifications of dietary supplements. For example, Garthe & Maughan, (2018) classify supplements by use into the following categories: sports foods, medical supplements, ergogenic supplements, functional foods and superfoods, and other supplements. However, built up on the same basis, the classification presented in IOC consensus document (Maughan et al., 2018) is more specific and seems more practical. Thus, Maughan et al. (2018) distinguish between supplements that are used to 1) prevent or treat nutrient deficiencies; 2) provide practical form of energy and nutrients; 3) directly improve performance; 4) indirectly improve performance; 5) stimulate gain in lean body mass and loss of body fat mass. Kerksick et al., (2018) classifies food supplements into three categories based on the quality and quantity of available scientific evidence: A) supplements the efficacy and safety of which are supported by strong evidence; B) supplements the efficacy of which is supported by limited or mixed evidence; C) supplements the efficacy and/or safety of which are supported by little to no evidence. Similar categorization of dietary supplements has been previously proposed by Australian Institute of Sport (Burke et al., 2006). Actually the efficacy and/or safety of only a few dietary supplements is supported by adequate amounts and high quality scientific research (Burke et al., 2006; Kerksick et al. 2018; Maughan et al. 2018; Peeling et al., 2019).

In summary, Garthe & Maughan (2018) seem to be right in concluding that although dietary supplements have been defined and categorized in many ways, none of these definitions and classifications are entirely satisfactory. The classifications presented in the IOC consensus document (Maughan et al., 2018) and in the International Sports Nutrition Association position (Kerksick et al., 2018) seem to be the most meaningful.

1.2 Acid base balance and physical performance

One of the fundamental parts of human homeostasis is retaining an optimal acid base balance of extracellular and intracellular fluids (McTavish & Sharma, 2018). Acid base balance is regulated by intracellular buffers, extracellular buffers, dynamic buffering systems and also by respiratory and renal mechanisms (Lancha Junior et al., 2015). In skeletal muscle, the main buffering substances are phosphates, bicarbonate, carnosine and proteins which act in the cytosol of muscle cells (Harris et al. 2006; Lancha Junior et al., 2015). An important dynamic buffering system, especially during exercise, is active and passive transport of hydrogen ions (H^+) out of muscle cells into the surrounding interstitium (Harris et al. 2006; Lancha Junior et al., 2015). The main extracellular buffers acting in blood plasma are bicarbonate, proteins and phosphates (Kenney et al., 2012; Lancha Junior et al., 2015). The oxygen-carrying protein hemoglobin in red blood cells significantly contributes to the overall buffering capacity of the blood (Kenney et al., 2012). While intra- and extracellular chemical buffers only reduce the impact of metabolic acids on acid base balance, the function of respiratory system and kidneys is to expel them from the body (Kenney et al., 2012).

High-intensity exercise results in H^+ accumulation, i.e. acidosis, which is considered one of the major causes of fatigue occurring in this situation. Specifically, intracellular increase in muscle $[H^+]$ has been shown to inhibit myofibrillar ATPase, glycogen phosphorylase and phosphofructokinase, Ca^{2+} binding to troponin C, and sarcoplasmic ATPase, which translates into reduced energy availability for crossbridge function, reduced glycolytic rate, reduced crossbridge activation and reduced Ca^{2+} reuptake and subsequent Ca^{2+} release, respectively (Fitts, 2004; Lancha Junior et al., 2015; Mougios, 2006). In addition to that, severe plasma (extracellular) acidosis may induce fatigue by reducing central nervous system drive to muscle (Cairns, 2006).

High-intensity exercise can lead to a decrease in the intramuscular pH from a resting value of 7.1 to the level of 6.5 (Lancha Junior et al., 2015), or even to as low as 6.0 (Pan et al., 1991). Studies show that phosphofructokinase, one of the key enzymes in the glycolytic pathway, is inhibited at pH 6.9 and further degradation of glycogen is completely blocked at pH 6.4 (Kenney et al., 2012). It has been calculated that without the action of buffers, accumulation of H^+ during high-intensity exercise would lower the pH to about 1.5 which would lethally damage muscle cells (Kenney et al., 2012).

In summary, maintaining an optimal acid-base balance for physiological functions is one of the primary goals of homeostasis achieved by the action of different buffer systems. However, during high-intensity exercise, anaerobic metabolism produces H^+ in excess of the capacity of the buffering systems and causes a significant decrease in both intracellular and extracellular pH, leading to fatigue.

1.3 Dietary supplements influencing the capacity of buffer systems

Research has identified some substances the ingestion of which as dietary supplements may significantly increase the capacity of both extracellular and intracellular buffers, resulting in better control of acid base balance during high-intensity exercise and leading to improved performance. With regards to dietary supplements possessing ability to enhance extracellular buffering capacity, most research has been done on sodium bicarbonate and sodium citrate (Carr et al., 2011; Heibel et al., 2018; McNaughton et al., 2016; Siegler et al., 2016). Intramyocellular buffering capacity has been shown to be increased as a result of beta alanine (BA) supplementation (Culbertson et al., 2010; Sale et al., 2010; Trexler et al., 2015). Sodium phosphate may have impact similar to that of BA, but the available data are incomplete to support this claim (Buck et al., 2013).

1.4 Beta-alanine as a dietary supplement

BA is a non-proteinogenic amino acid (Caruso et al., 2012). BA is a rate-limiting precursor for carnosine, which acts as an important pH buffering agent in skeletal muscle during high-intensity activities (Derave et al. 2010). Carnosine contributes to about 7% of pH buffering capacity in humans, buffering about 2.4 and 10.1 mmol $H+ \cdot kg^{-1}$ dry mass over the physiological pH range 7.1–6.5 (Mannion et al., 1992). Muscle carnosine content is mainly determined by species (thoroughbred horses having more than humans) and by muscle fibre type, with type II fibers having larger amounts of carnosine than type I (Harris et al., 2012). In addition, muscle carnosine concentration seems to be highly dependent on the content and availability of carnosine in the human diet (Harris et al., 2012).

As a dietary supplement, BA is classified as a substance that directly improves sports performance (Maughan et al. 2018), the efficacy of which is supported by strong evidence and which is apparently safe (Kerksick et al. 2018). Via BA supplementation, muscle carnosine content can be increased up to 80% (Derave et al. 2010), in some cases even up to 200% (Perim et al., 2019). For increasing muscle carnosine levels significantly, BA supplementation should last at least 28 days (Harris et al., 2006; Harris et al., 2009). Elevated carnosine level leads to increased muscle buffering capacity, delayed onset of muscle fatigue, and enhanced performance during high-intensity exercises (Figure 1) lasting from 0.5-10 minutes according to different sources (Bellinger, 2014; Hobson et al., 2012; Derave et al., 2010). The only known side-effect for supplementing with BA is paraesthesia, which is considered not to be harmful (Dolan et al., 2019). Paraesthesia can be avoided by splitting the amount of supplement to smaller dosages, which should not exceed 800 mg (Artioli et al., 2010).

All in all, the physiological effects of BA supplementation are mapped well by many systematic reviews, but they are giving a generic view and have not taken into account possible differences of the effects of BA supplementation on carnosine content between sexes. These differences might be noticeable due to lower buffering capacity of muscles - up to 20% in some cases - for women, compared to men (Edge et al., 2006). In addition, carnosine content in women is significantly lower than in men, depending on the age and muscle it might be 17–39% lower (Baguet et al., 2012). Muscle buffering capacity can be increased with training, but the increase is more noticeable for subjects with lower baseline values (Edge et al., 2006). These data suggest that BA supplementation may increase carnosine levels in women to a greater extent than in men, since the baseline level is lower in women. In addition, if the increase in muscle carnosine is greater in women than in men, it can be expected that women will benefit relatively more from BA supplementation in terms of physical performance than men.

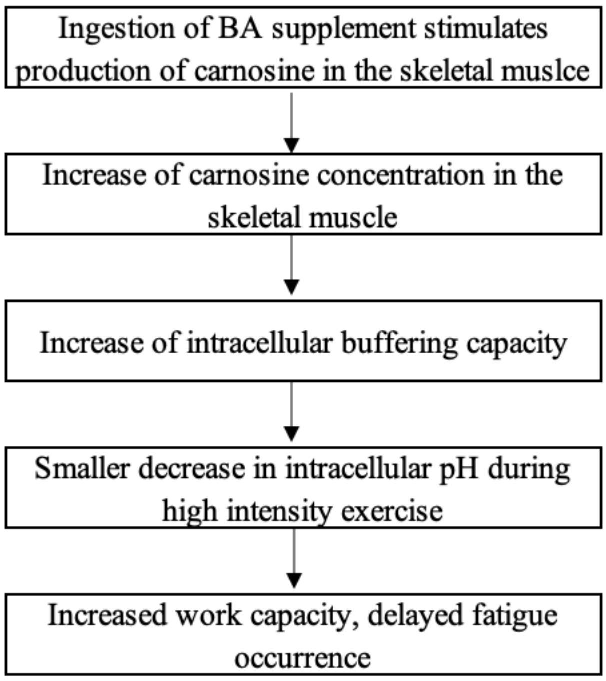

Figure 1. Mechanism of action of beta-alanine supplementation on muscle carnosine levels and physical performance

2 AIM OF SYSTEMATIC REVIEW

The purpose of this systematic review was:

1. To map the effects of BA supplementation concentration of carnosine in skeletal muscle, physical performance and RPE, body composition, maximal oxygen consumption and metabolic responce to exercise from studies conducted on women
2. Compare the results of BA supplementation effects on previously mentioned parameters to studies conducted on men.

3 METHODS

3.1 Search Strategy

This review has taken into account the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines for reporting the results (Liberati et al., 2009). A structured search was carried out in EBSCO (which includes Medline, SPORTdiscus and other sources), Google Scholar and PubMed databases. The dates were picked from 1997-2020. The search terms were specific enough to bring out possibly suitable studies and they were applied to free text or all fields. Same search terms were used in every database, which included: (*beta alanine supplementation* [Title]) AND ((*women* OR *female* OR *woman* OR *females)* [All Fields]). The results of initial search and following inclusion/exclusion are presented in *Figure 2*.

3.2 Inclusion/Exclusion Criteria

The PICOS model was used to determine the inclusion criteria: P (Population): "women", I (Intervention): "beta-alanine supplementation or beta-alanine and something else", C (Comparators): "identical conditions for beta-alanine and placebo experimental trials", O (Outcome): "physical and/or sports performance measurements", and S (study design): "single- or double-blind and randomized design".

As a result, all the studies used in this systematic bibliographic review had to meet the following criteria: (I) population were female in every activity level and any age; (II) participants performed any physical activity, using beta-alanine as an ergogenic aid, which could be taken in as a pill; (III) the effects of beta-alanine supplementation were compared to identical placebo conditions; (IV) effects were examined on physiological performance; (V) study designs were randomized, single- or double-blind, and placebo-controlled.

The exclusion criteria were following: (I) participants were women and men, or only men; (II) intervention did not include beta-alanine supplementation; (III) outcome was not measured with sports performance measurements; (IV) study design was not suitable; (V) article was not accessible as a free full text.

3.3 Study Selection

The search was carried out in different databases and papers identified by the author. The titles of the papers were screened and duplicates removed. Next, the titles and abstracts of the papers were screened to eliminate non subject-related papers. Full accessibility was checked and unsuitable papers removed.

3.4 Data Extraction

Once the suitable studies were set apart, and inlucion/exclusion criteria applied, following data were extracted: study authors and year of publishing, study design, number of participants, age, activity level or sports dicipline, exercise protocol applied (if was), supplementation protocol, tests and measurements used for performance evaluation, and primary outcomes (Table 1).

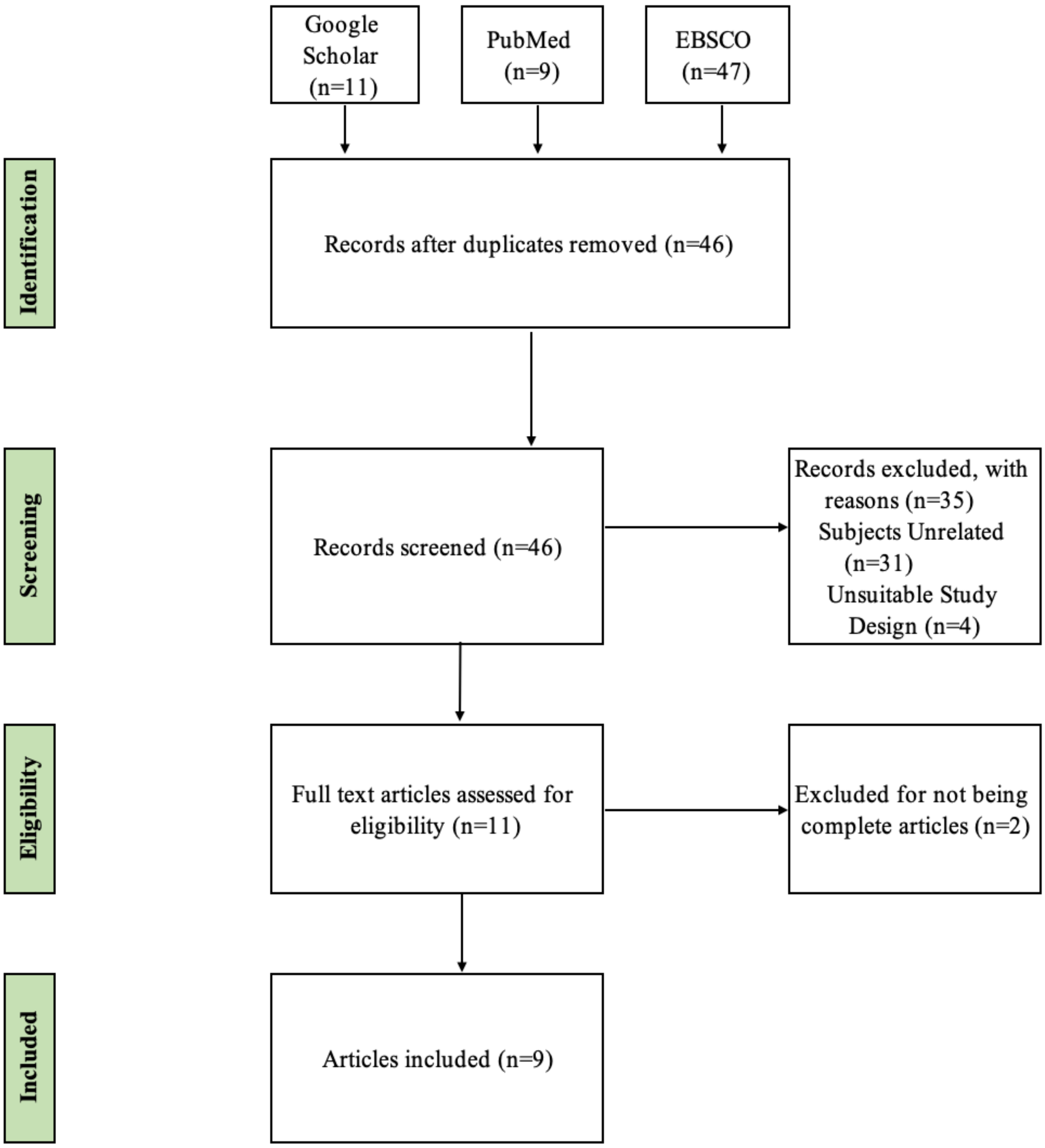

Figure 2. Flow diagram of literature search and selection

4 RESULTS

4.1 Search strategy

After applying search terms to search engines, 11 publications from Google Scholar, 9 publications from PubMed and 47 publications from EBSCO were identified, which makes 67 studies. In total, 9 studies were included in this review from search and in addition 2 studies were identified by browsing the reference section of these 9 studies. Full study selection process is presented in Figure 2. Results from the 11 studies are presented in Table 1.

Table 1.Data extraction and presentation of studies

Authors	Participants & Study Design	Supplementation Protocol	Exercise and Measurements	Outcomes
Glenn et al., 2015a	• 22 female MA(masters) cyclists, age 53.3 ± 1 • BA (n=11); PL(n=11) • Double-blind, randomized study	• BA: 0.8 g BA + 8 g dextrose; 4 x day; 28 days	• GXT-cycling for VO2peak; • TTE at baseline, 7, 14, 21, and 28 days of supplementation; • TWC; LA • DXA; Dietary analysis	BA ↑ TTE compared to PL • TWC was 21% ↑ in BA compared to PL 2%; A significant group x time interaction for LA after the 20-min rest interval; LA was 24 % ↓ for BA compared to PL.
Glenn et al., 2015b	• 12 female cyclists; 26 ±1.3 years; • Double-blind, randomized, crossover study	• All participants completed both conditions in double-blind, randomized order. • All trials were separated by a minimum of 72 h; • 30 min before test - BA: 1.6 g BA + 34 g dextrose	• Wingate cycle test • LA; HR • RPE • Height and BM; BF and lean mass analysis	• A significant interaction was for RPE - BA = ↓ RPE than for the PL trial immediately after the first 2 Wingates, also after each of the 3 rest periods.

Glenn et al., 2016	• 22 female MA cyclists age 53.3 ± 1.0 years; • BA (n=11); PL(n=11) • Double-blind, randomized study	• Supplementation 28 days; PL = 8 g dextrose; BA = 0.8 g + 8 g dextrose) 4 x day.	• Isometric HG strength with hand-held dynamometer • Leg isokinetic strength • Dietary analysis • Body composition with DXA	• At 28-day time point, average peak torque and TWC during the final third of exercise ↑ for BA. • No changes in body composition
Hooshmand et al., 2019	• 34 overweight women; age 20 - 45years; • BA(n=17); PL (n=17) • Double-blind, randomized, placebo-controlled trial	BA: 1.6 g/d (800+800 mg) for 6 weeks	• TTE on a treadmill; ramp protocol; • 1 RM leg press, chest press • BM; fat mass, and fat %; • Waist circumference	• The changes of ramp test parameters, treadmill speed and incline, HRmax and TTE were significant in BA group after 6 weeks. • Significant ↓ in BM; BMI, fat %, waist and hip circumference, abdominal and supra-iliac skinfold in the BA.
Rosas et al., 2017	• 25 female amateur football players; age 23.7 ± 2.4 years; • PL + PLY (n = 8) • BA + PLY(n = 8) • CON (n = 9) • Randomized, double-blind, placebo-controlled trial	• BA: 4.8 g BA day; 6 x 0.8 g every 2 h for 6 weeks; PL+PLY: 4,8 g/day microcrystalline cellulose	• squat jump, countermovement jump, 20 m sprint, RAST, 40 cm drop jump reactive strength index, peak jump power, change-of-direction speed (i.e., Illinois test), 20 m multistage shuttle run, 60 s countermovement jump • Height, BM • Dietary analysis	• BA+ PLY and PL+PLY ↑ the squat and countermovement jump, drop jump reactive strength index and jump power performance; • In 60 s countermovement jump power test, BA+PLY attained a greater training effect compared to PL+PLY; • BA+PLY had ↑ training effects in the RAST and 20 m multistage shuttle run tests compared to CON

Kresta et al., 2014	• 32 recreationally active women; age 21.5 ± 2.8 years • BA (n = 8), CRE(n=8) BA+ CRE (n = 9) PL (n = 7) • randomized double-blind, placebo-controlled study	• BA –0.1 g/kg /d for 28 days with 0.3 g/kg/day of dextrose for week 1 and 0.1 g/kg/day of dextrose for weeks 2–4 • CRE - 0.3 g/kg/d for week 1 and 0.1 g/kg/day for weeks 2–4, with 0.1 g/kg/day maltodextrin • BA+CRE –0.1 g/kg/d of BA for 28 days (ca 6.1 ± 0.7 g/day) + 0.3 g/kg/ day of CRE week 1 (about 18 ± 1.8 g/day) and 0.1 g/kg/day of CRE for weeks 2–4 (ca 6.1 ± 0.7 g/ day)	• GXT-cycling for VO2peak with LA threshold determination; Wingate tests • Muscle biopsy analyzed for PCr, Cr and carnosine • Body composition	• Mean muscle carnosine levels in the PL were ↓; BA and BA+CRE - greatest ↑ in muscle carnosine levels. Differences not significant. • BA ↑ baseline peak LA response; peak LA levels ↓ after 4-weeks of BA supplementation. Differences not significant. • No significant differences in body composition
Smith et al., 2012	• 24 recreationally active women; age 21.7 ± 2.1 years; • BA (n=13); PL (n=11) • randomized, placebo controlled, mixed factorial design	• BA: 800 mg x 2 tbl;3 x a day; 28 days	• GXT on a treadmill for VO2max • 40-min treadmill run at 70% PV • RPE • Blood collection • Antioxidant markers - superoxide dismutase, 8-ISO; GSH • Dietary analysis	• ↓ RPE at 40 min for BA • Slight ↓ in 8-ISO levels
Stegen et al., 2014	• 34 physically active men (n=16) age 19.4 ± 1.1 and women (n=18) age 19.3 ± 0.9; 3 sex-balanced groups; randomized	• BA: 4 x 800 mg/day (3.2 g) for 6 weeks for all 3 groups	• Body composition • Carnosine content	• Relative carnosine levels ↑ for women +50.8% ± 30.7%, compared to men +31.6% ± 17.5% for gastrocnemius m.

Stout et al., 2007	• 22 women; age 27.4 ± 6.1 years • BA (n=11); PL (n=11) • double-blind, randomized, placebo-controlled, parallel design	• BA: days 1–7 3.2g/d, and days 8-28 6.4g/d; 4 x a day; 28 days total • Exercise and diet to remain the same during trial.	• GXT - cycling • VO2max, VT, PWCFT, TTE	• 13.9% ↑ in VT for the BA • 12.6% ↑ in PWCFT for the BA
Varnoske et al., 2017	• 26 men (n=13) and women (n=13); • BA (n=6 men; n=8 women); PL (n=7men; n=5 women) • Randomized study	• BA: 3 x 2g a day (total 168 g) or PL 28 days	• BM • Body composition • Muscle biopsy for carnosine and L-histidine • Isokinetic endurance	• Men had ↑ carnosine at baseline than women; • Carnosine ↑ likely greater in women compared to women than in men compared to men • Similar increase in carnosine content for both sexes • Attenuated decline in peak torque in BA group for men and women
Walter et al., 2010	• 44 recreationally active women; age 21.8 ± 3.7 years; BA (n=14); PL (n=19) CON (n=11) • randomized, double-blind, placebo-controlled, parallel design	• For 21 days: BA:1.5 g BA + 15 g dextrose in 4–8 oz of water; 4 x a day; • Next 21 days: BA:1.5 g BA + 15 g dextrose 2 x a day	• GXT – cycling; VO2peak and VT • BM, fat%, FFM • Dietary analysis • Training on 3 nonconsecutive days per week for 3 weeks of HIIT; retested (week 4) for body composition, VO2peak, and VT, then 3 weeks of HIIT increased volume and intensity	• VO2peak ↑ for the BA and PL from weeks 0 - 8; • BM ↑ for the BA weeks 0 to 8; • Fat % ↓ from weeks 0 - 4 and weeks 0 - 8 for BA, PL, and CON • FFM ↑ from weeks 0 – 8 for BA, PL, and CON.

(↑ - increased/higher; ↓ - decreased/lower; BA – beta-alanine/beta-alanine supplementation group ; GXT – graded exercise test; PL – placebo group; CON – control group; TWC – total work completed; TTE -time to exhaustion; LA – lactate; HR- heart rate; RPE – rating of perceived exertion; BM – body mass; BF- body fat; HG – hand grip; PWC_{FT} - physical working capacity at fatigue threshold; PLY – plyometric training; CRE – creatine; VT- ventilatory threshold; FFM – fat free mass; HIIT – high intensity intermittent training; RAST – running anaerobic sprint test)

4.2 Participants

In total, 268 women took part in the studies included in this review, aged between 18,4 - 54 years. In 3 studies, participants were cyclists, with training load of cycling on 3 days a week minimum and at least 2 years of competitive experience in 2 of the studies (J. M. Glenn et al., 2015a a; Jordan M. Glenn et al., 2016), and in the third study, cyclists with training experience an average of 3.92 ± 0.64 years were used (Jordan M. Glenn et al., 2015 b). In 3 studies recreationally active women were used with exercise status at least 30 minutes per day for 3 days per week for at least 3 months in one study (Kresta et al., 2014), 1–5 hours of exercise per week in other (Walter et al., 2010), engaging in 3–7 days per week of aerobic, resistance or recreational activities in third (A. E. Smith et al., 2012). No information on exercise level was found in one study, which only advised for activity level to remain the same during trial (Stout et al., 2007a). In 1 study participants were amateur football players (Rosas et al., 2017), and in 1 study, participants were overweight sedentary women (Hooshmand et al., 2019).

4.3 Study Design and Supplementation Procedures

Eight studies were randomized, double-blind, placebo-controlled trials, with 2 of them 2 group parallel design (Stout et al., 2007a; Walter et al., 2010), 1 mixed factorial (A. E. Smith et al., 2012), and 1 was a double-blind, randomized crossover design (Glenn et al., 2015b). In two studies, only randomization was mentioned (Stegen et al., 2014;Varanoske et al., 2017).

In 1 study, BA was administered only once, 30 minutes before the trial (Jordan M. Glenn et al., 2015 b), in 4 studies the supplementation period was for 6 weeks and in 5 studies BA was taken for 28 days, which makes overall supplementation period lasting from 1 - 42 days. Daily supplementation doses ranged from 1.6 g one time dosage for the acute effects (Jordan M. Glenn et al., 2015), to 1.6 g – 6.8 g daily for longer period studies. BA was provided in tablet, capsule or powdered form. Dosage varied from 0.8 g - 2 g taken in at one turn and they were equally spreaded throughout the day, ranging from supplementing 2-4 times a day. In one study, supplementdosage was being personalized to 0.1g per kg of bodyweight daily, with average of 6.1 ± 0.7 g/day (Kresta et al., 2014).

4.4 Impact of BA Supplementation on Muscle

Three studies (Kresta et al. 2014; Varanoske et al. 2017) directly measured muscle carnosine content before and after the BA supplementation. Muscle samples were collected from 31 participants and 27 were suitable for measuring carnosine content (Kresta et al., 2014). The administered dosage in the study for BA was 0.1 g per kg of bodyweight, which makes about 6.1 ± 0.7 g daily (Kresta et al., 2014). This supplementation protocol increased carnosine levels in BA and BA+creatine group from 19.74 ± 8.69 (µmol/g) and 20.81 ± 7.66 (µmol/g) at baseline, to 23.68 ± 1.56 (µmol/g) and 24.23 ± 4.09 (µmol/g) after the supplementation period, respectively (Kresta et al., 2014). Howerver, the results did not show statistically significant difference when compared to creatine only and placebo group (Kresta et al., 2014). Varanoske et al. (2017) reported the results using magnitude-based inferences and noted, that changes in carnosine content were likely greater for men and very likely greater for women, but when comparing the results between sexes, the difference was unclear. Stegen et al., (2014) were interested in maintanance levels. They reported that after supplementing BA 3.2g/day for 6 weeks, the absolute rise in carnosine level was 1.5-2 mM and this was not dependent on sex or muscle type (Stegen et al., 2014). Since women had lower baseline levels, relative increase in carnosine levels was greater for women, reaching up to +50.8% ± 30.7%, compared to men +31.6% ± 17.5% (Stegen et al., 2014). This increase was reported for gastrocnemius muscle, but not for soleus muscle (Stegen et al., 2014).

4.5 Impact of BA Supplementation on Physical performance and RPE

Out of 10 studies, 3 (Glenn et al., 2015a ; Hooshmand et al., 2019; Stout et al., 2007) evaluated TTE (time to exhaustion). There were significant changes reported in TTE values for sedentary women in the BA group compared to placebo group, resulting in a change from 8.06 ± 2.24 min to 8.85 ± 2.04 min after the supplementation (Hooshmand et al., 2019). Siginificantly longer TTE (23% change) values as well as increased total work completed values (23% change) in BA group, compared to 1% change in TTE and 2% change in total work done in placebo group were noticed from pre to post supplementation period by Glenn et al. (2015a). Stout et al. (2007) noted 2.5 % increase in TTE values in the BA group and 12.6% increase in physical working capacity at fatigue threshold.

Out of 10 studies, 3 (Glenn et al. 2015 b; Kresta et al. 2014; Smith et al. 2012) measured RPE. Kresta et al., (2014) did not report any significant differences among BA, BA in addition to creatine, creatine only and placebo group RPE values. Smith et al. (2012) indicated significantly lower RPE values between the BA and placebo groups after a 40-minute running test. For trained cyclists, RPE was lower for BA trial than for the placebo trial immediately after completing two Wingates tests and also after every rest period (Glenn et al., 2015 b). In this study, BA was administered as one time dosage only, meaning, there was no supplementation period (Glenn et al., 2015 b).

Ventilatory threshold was assessed in 2 studies. No significant difference in ventilatory threshold during a 40-minute treadmill run was seen by Smith et al., (2012). Stout et al., (2007), who used a graded exercise cycling test to assess ventilatory threshold and other measurements, saw a 13.9% increase in ventilatory threshold for BA group, but no changes were seen in placebo group from pre to post supplementation period. In both of the studies (A. E. Smith et al., 2012; Stout et al., 2007b), participants were not athletes.

One study (Glenn et al., 2016) measured isometric strength with hand-held dynamometer and isokinetic strength with isokinetic dynamometer, with results indicating BA increased average peak torque by 8% from baseline and total work completed values by 24% during final third of isokinetic lower-body exercise compared to placebo group.

One study evaluated the impact of plyometric training with BA supplementation on maximal – intensity exercise and endurance in female football players (Rosas et al., 2017). In 60 s countermovement jump power test, BA + plyometric group attained a greater training effect compared to placebo + plyometric group or control group. In addition, BA + plyometric group had greater effects in the running anaerobic sprint test and 20 m multistage shuttle run tests compared to control group (Rosas et al., 2017).

One study (Varanoske et al., 2017a) measured maximal voluntary isometric contractions as a muscle fatiguing protocol and reported that for both, men BA group and women BA group, BA supplementation very likely attenuated peak torque decline.

4.6 Impact of BA Supplementation on Body Composition

Eight studies out of 11 measured body composition or measured bodyweight, 3 did not include body composition data in results. None of the 5 studies, which measured fat percentage or fat mass noted any significant differences in the values after the supplementation when compared to the placebo group. Hooshmand et al., (2019), who investigated the effects of BA supplementation in sedentary overweight women reported that BA supplementation group lowered fat percentage from 35.86 ± 2.4 to 34.9 ± 2.9 %, but this difference was not significant compared to the placebo group. None of 4 the studies, which measured fat free mass reported any significant changes from baseline to post supplementation values compared to placebo groups. Only 1 of 7 studies which measured body mass reported significant changes - Walter et al., (2010) noted increased body mass in BA group from weeks 0 to 4, 4 to 8 and 0 to 8, compared to no changes in placebo or control group after 6-week supplementation and high intensity interval training program.

4.7 Impact of BA Supplementation on Physiological and Biochemical Parameters

Three studies (Glenn et al. 2015 a; Kresta et al. 2014; Walter et al. 2010) measured VO_{2peak}. Glenn et al., (2015 a) used a graded exercise test for evaluating masters cyclists' performance, but no significant effect was seen in VO_{2peak} values. Kresta et al., (2014) also did not mark any significant difference in VO_{2peak} values in recreationally trained women. In addition, no significant changes in VO_{2peak} values as an effect of BA supplementation were found by Walter et al., (2010), who had participants doing a high intensity interval training protocol with BA supplementation.

Two studies (Smith et al., 2012; Stout et al., 2007) measured VO_{2max}. There were no significant changes in VO_{2max} values found in recreationally trained women in study done by Stout et al., (2007) nor by Smith et al., (2012), who did not note activity level of the participants.

Out of 11 studies, 3 (Glenn et al. 2015 a; Glenn et al. 2015 b; Kresta et al. 2014) measured blood lactate levels. Glenn et al. (2015 b) did not reveal any significant effect of BA supplementation on lactate levels in their work on acute effects of BA supplementation. Twelve subjects were included in the study and they all completed 2 trials consisting of 3 Wingate tests, one with supplementing BA pre trial and one trial, where placebo was taken (Glenn et al., 2015 b). Significant effects on female masters cyclists' lactate levels measured after 20-minute rest of the graded exercise test were found in a study by Glenn et al. (2015 a), where supplementation period lasted for 28 days. Lactate levels were 24% lower for the BA group when compared to the placebo group (Glenn et al., 2015a). Kresta et al. (2014) noted time x group effecs in peak lactate for BA group, who had higher baseline peak lactate response than other groups and peak lactate levels decreased after 4 weeks of BA supplementation. BA group also experienced less change in resting to maximal lactate levels, though the amount of work done was similar for week 1 and week 4 of BA supplementation (Kresta et al., 2014). Despite noticable differences, these results were not presented in the conclusion part (Kresta et al., 2014).

5 DISCUSSION

Work about the effects of BA supplementation that has been done on women, varies by sports field specific tests, measurements taken and also by participants, from overweight women to athletes and from young to senior women. In this systematic review, 11 studies done on female participants were investigated for the effects of BA on carnosine content, physical performance, RPE and metabolic responses to exercise.

5.1 Impact of BA Supplementation on Muscle Carnosine Concentration

Varanoske et al. (2017) measured muscle carnosine content in men and women, and found men to have significantly higher baseline carnosine concentration than women. Similar results were reported by Mannion et al., (1992). These results can be explained by higher concentrations of carnosine in people with higher concentration of fast-twitch muscle fibers (Derave et al. 2010), and according to Staron et al., (2016), space occupied by different muscle fiber types is fast-twich over slow-twich muscle fibers for men and vice versa for women. In addition, the cross-sectional area of each type of muscle fiber is larger for men (Staron et al., 2016).

When adding supplementation, Bex et al., (2013) found carnosine loading to be more noticeable in trained muscles compared to untrained muscles. Difference in carnosine loading between sexes seems not to be that noticable, for example, Varanoske, et al., (2017) reported that after BA supplementation, absolute rise in carnosine levels was similar for men and women. On the other hand, Stegen et al., (2014) reported absolute rise in carnosine levels to be similar for men and women, about 1.5 – 2 mM, but relative rise in gastrocnemius muscle was greater for women reaching from +50.8% ± 30.7%, compared to men +31.6% ± 17.5%. However, these results did not apply to soleus muscle. This can be explained by difference in fiber type ratio in these muscles as mentioned earlier. Kresta et al., (2014), who measured carnosine levels for BA and creatine supplementation independently and together in women, noted incresase in carnosine levels in BA group, and also BA + creatine group, but those results were not significant compared to creatine only and placebo groups. They noted that statistically unsignificant difference might have been due to small sample size or large variability in muscle carnosine levels observed in response to BA supplementation or array variability (Kresta et al., 2014). This is interesting, since there seems to be reliable information on the amount of BA needed to increase carnosine content significantly. For example, Baguet et al., (2010) had male paritcipants ingest BA 5 g a day for 7 weeks and measured a rise of 45% and 28% in soleus and gastrocnemius muscle, respectively. For pariticipants in Kresta et al., (2014) study, the daily ingestion of BA was on average 6.1 ± 0.7 g, and supplementation period lasted for 28 days, which should have been enough for noticable increase.

It can be concluded that increase in carnosine levels will take place for both, men and women, but relative increase is greater for women.

5.2 Impact of BA Supplementation on Physical performance and RPE

Glenn et al. (2015a) measured high-intensity cycling performance in female masters athletes and their results indicated that by the 28th day of supplementation the BA group had increased time to exhaustion (TTE) from ca 85 s to 110 s, which makes about 23% increase. Changes for the placebo group were only 1% (Glenn et al. 2015a). Significant changes in TTE values were also seen by Hooshmand et al. (2019), whose study participants were overweight sedentary women. However, the methods used by Hooshmand et al., (2019) do not seem to evaluate the effect of time x group before t-tests are executed (Leppink et al., 2017), so there is a chance that the interpretation of the data might not be accurate. Stout et al., (2007) also noted 2.5 % longer cycling capacity at the end of 28-day supplementation period for young women. For all of these studies, the participants differed greately by their activity level and age. This means that BA supplementation could prolong time to exhaustion for people with different training status, as is also reported by Saunders et al., (2017). Many studies done on men have reported prolonged time to exhaustion as a result of BA supplementation (Bassinello et al., 2019; P. M. Bellinger & Minahan, 2016a, 2016b; Furst et al., 2018), but still the effects of BA supplementation for prolonged TTE in men are not that clear. For example, Derave et al. (2007) showed carnosine loading to slightly attenuate fatigue in repeated bouts of exhaustive dynamic contractions, but not isometric endurance nor 400 - m sprint results in male athletes. No significant effect on TTE was noted by Jagim et al., (2013), who investigated BA supplementation effects on sprint endurance at supramaximal intensities for recreationally trained male subjects. On the other hand, significant increase in TTE values were seen for male physical education students by Ghiasvand et al., (2012). Furst et al., (2018) reported middle-aged individuals, who were in BA group, to cycle significantly longer than placebo group. It should be mentioned that there were only 12 participants all together divided into 2 groups, which might not be big enough of a sample size. There are also other studies that have reported no effect on TTE (Outlaw et al., 2016; Smith et al., 2008; Smith-Ryan et al., 2012).

Taking into account that all three studies (Glenn et al. 2015a; Hooshmand et al., 2019 ;Stout et al., 2007), where participants were female, reported increased TTE values, it could be that BA supplementation has a positive effect on attenuating fatigue occurrence in women. As mentioned earlier, results for men are not that straight-forward.

Some studies also measured the amount of work, which subjects could do. For example, total work completed at 120% VO_{2max} increased by 21% in BA group, compared to 2% increase in placebo group for female masters cyclists (Glenn et al. 2015 a). In comparison, in a 10 week supplementation period study, Hill et al. (2007) reported a 13.2% increase after 4 weeks of supplementation and a further 3.2% increase after 10 weeks of supplementation for total work completed at 110% VO_{2max} for physically active male subjects. The supplementation period was longer for the latter study, but great increase in both studies was noted none of the less.

Stout et al., (2007) found in his study on women a 12.6% increase in peak power output. Van Thienen et al., (2009) were interested in BA supplementing effects on cycling sprint performance for men at the end of a simulated race and found that supplementing improved peak power output by 11.4 % and mean power output by 5%, compared to placebo group. When comparing the results of these two studies, the effect seems to be similar for both, men and women.

Many studies have also evaluated the rating of perceived exertion (RPE) of the subjects. Interestingly, Kresta et al. (2014) reported non-significantly higher RPE values for BA group after the supplementation period compared to before supplementation period. On the other hand, Glenn et al. (2015 b), who measured acute effects of BA supplementation, observed RPE values to be significantly lower for BA group immediatley after Wingate test and also after the recovery time. While previous results were reported for tests which lasted for a short period of time, Smith et al. (2012) saw significantly lower RPE values after 40 minutes of running in BA group compared to control group. It should be noted that exercise and supplementation protocols, age and training level of the participants vary greatly for many of the studies in comparison, so it would be inadequate to draw any clear conclusions. For example, although Kresta et al., (2014) and Glenn et al., (2015 b) both used a graded exercise cycling test for evaluating the performance, the supplementation period lasted 28 days for Kresta et al., (2014) but Glenn et al., (2015 b) measured acute effects, so the supplement was given 30 minutes prior testing.

For men, lower subjective feelings of fatigue after Wingate test were reported after 21 days of BA supplementation by Hoffman et al., (2008), who did various tests on male collegiate football players. In addition, lower RPE values were reported immediately after the muscle fatiguing protocol in physically active male participants (Invernizzi et al., 2016).

All in all, it can be said, that some effects for rating of perceived exertion are seen for both, men and women, but no clear conclusions can be made.

5.3 Impact of BA Supplementation on Body Composition

None of the studies included in this review reported any significant changes in body composition when supplementing with BA. When comparing these results with work done on men, improvement from pre- to mid-testing in lean body mass for recreationally trained men was noted by Smith et al. (2009). Kern and Robinson (2009) mention a significant increase in lean mass in BA group, while loss in lean mass in placebo group in collegiate wrestlers and fooball players, who were previously trained. This study (Kern and Robinson 2009) also involved HIIT training, so it can be said, that BA supplementation contributed to changes in body composition for this study. Freitas et al. (2019) saw a non-significant trend for greater increase in fat free mass in BA versus placebo group with resistance training and BA supplementation combined versus resistance training only, and Jordan et al. (2010) noted an increase in body mass in BA group along with decrease in BMI in recreationally trained men. Many other studies have not reported significant effects of BA supplementation on body composition (Black et al., 2018; Gross et al., 2014; McCormack et al., 2013; C. R. Smith et al., 2019).

These data suggest that BA supplementation alone may not significantly contribute to body composition changes in men or women, but for men, potential increase in lean mass can be seen in some of the previously reported studies.

5.4 Impact of BA Supplementation on Physiological and Biochemical Parameters

Walter et al. (2010), who evaluated the effects of HIIT (high intensity interval training) and BA supplementation in recreationally trained women, reported increased VO_{2peak} values in the BA and placebo group, but not in the control group. These increases VO_{2peak} values from previously mentioned study (Walter et al. 2010) could have been more likely attributed to HIIT regiment, rather than BA supplementation. Other studies done on women, which were included in this review, where VO_{2peak} or VO_{2max} were measured, did not see any significant difference in the results. When looking at research done on men, Black et al. (2018) did not notice any significant changes in VO_{2peak} measures, but they also did not see a significant rise in carnosine content in recreationally trained men. Smith et al. (2008) noted increase in VO_{2max} from 3.28 ± 0.57 to 3.67 ± 0.58 (l·min-1*kg) in BA group with male participants. Similar trend was noticed by Milioni et al. (2019) and Ghiasvand et al. (2012) for male physical education students. Also, significant changes in VO_{2max} values were observed in recreationally trained men in a study by Jordan et al. (2010), however, VO_{2max} results in their work decreased for BA group from 4.57 ± 0.8 l·min-1*kg pre-supplementing to 4.31 ± 0.8 l·min-1*kg post-supplementing. Overall, BA supplementation seems to have little to no effect on VO_{2max} or VO_{2peak} values in women, but some effects are seen in men.

Twenty four percent lower lactate level in female masters athletes reported by Glenn et al., (2015a) may indicate to some effect of BA supplementation on lactate accumulation. Other studies included in this review (Glenn et al., 2015b; Kresta et al., 2014) did not find signifant difference in lactate levels. Results on lactate levels definitely need further investigation, because all three studies done on women (Glenn et al., 2015a; Glenn et al., 2015b; Kresta et al., 2014), which measured lactate levels, had different supplementation protocol, supplementation period and age of the participants. As for studies conducted on men, results are mixed, but so are the exercise test protocols used for evaluating the impact of the supplementation. Bellinger and Minahan (2016 b) did not see any significant difference in blood lactate in work on supramaximal cycling and 4000 m cycling time-trial performance in trained male cyclists. Also, no differences in blood lactate were noted in male alpine skiers supplementing with BA nor in recreational male club runners (Ducker et al. 2013; Gross et al. 2014). Jordan et al., (2010) on the other hand reported improved endurance at submaximal load for BA group by delaying the onset of blood lactate accumulation for recreationally trained men. A study done on healthy men on a 10 km running time trial observed significantly lower blood lactate measures for BA group, and also, the BA group ended the run faster than the placebo group (Santana et al., 2018). It might be that the effect of BA supplementation on lactate levels is greater for older and recreationally trained people, not dependent on sex.

As possible limitations for this study, the author has reported the shortage of studies on this topic for inclusion in the review. Since not all of the studies measured every variable presented in this review, the amount of data for every variable might not have been adequate to make any clear conclusions.

6 CONCLUSIONS

The aim of this systematic review was to look at the effects of BA supplementation on physical performance and physiological parameters in women and compare the results with studies done on men.

1. BA supplementation contributes to absolute rise in carnosine levels similarly both, in men and women, but relative rise is greater for women.
2. BA supplementation contributes to prolonged time to exhaustion in both, female and male subjects, but fairly clear effects are seen for women.
3. BA supplementation does not have an effect on VO_{2peak} and VO_{2max} values in women, but mixed results are found for men.
4. BA supplementation does not have an effect on body composition in women, but increased lean mass can be seen for men.
5. More research is needed on sport-specific tests/activities and women with different training status and age.

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