Review article

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β-hydroxy–β-methylbutyrate (HMβ), Physical training and skeletal muscle: a systematic review

GONÇALVES, L.[1,2], MADUREIRA, D.[1], SANTANA, J.[1], FRANÇA, E.[1], MIRANDA, M. L. J.[1], SOUZA, R. R.[1] and CAPERUTO, E.[1,3]*

[1]Grupo de Estudos e Pesquisa Aplicada em Metabolismo do Exercício – GEPAME, Universidade São Judas Tadeu – USJT, Rua Taquarí, 546, Móoca, CEP 03361-000, São Paulo, SP, Brasil

[2]Faculdade Carlos Drummond de Andrade, Rua Professor Pedreira de Freitas, 401, Tatuapé, CEP 03401-001, São Paulo, SP, Brasil

[3]Universidade Presbiteriana Mackenzie, Rua da Consolação, 930, Consolação, CEP 01302-907, São Paulo, SP, Brasil

*E-mail: ericocaperuto@gmail.com

Abstract

Skeletal muscle mass gain is beneficial in several situations. It improves athlete's performance and quality of life in pathological situations. The existence of different methods that are able to increase muscle mass brings up discussions about nutritional supplements use on physically active individuals. β-hydroxy–β-methylbutyrate is a Leucine metabolite and it's believed to have an anticatabolic effect with different results depending on the type of exercise done. **Objective:** The objective of this research was to identify and categorize the methodological features and results of β-hydroxy–β-methylbutyrate (HMβ) studies, physical exercise and its effects on skeletal muscle in the last 20 years. **Materials and Methods:** We carried out a review in the literature using PUBMED and Medline data bases. We analyzed 19 articles from the 4587 initially found, according to the inclusion and exclusion criteria. After the selection we analyzed the date of publishing and country of origin, sample size and type, dosage used, exercise protocol and results on skeletal muscle. **Results:** Most of the studies came from the USA, were published between the years of 2000 and 2005. Most of the papers used only males and the main dosage used was 3.0g/day with resistance exercise, although endurance exercise and untrained individuals showed some interesting results. Data from these studies varied from increase in muscle mass and muscle strength, recovery of isokinetic and isometric muscle function, decrease in lactate dehydrogenase and proteolysis and decrease in creatine kinase. **Conclusion** We can conclude that although HMβ has some positive effects on untrained individuals, its effects on trained individuals still need further confirmation.

Keywords: β-hydroxy–β-methylbutyrate (HMB), physical exercise, skeletal muscle.

1 Introduction

Muscle mass gain is a widely studied topic in order to benefit individuals in various physiological situations such as athletes or patients with diseases associated with muscle wasting syndromes such as AIDS or cancer (MENDES and TIRAPEGUI, 2002).

The existence of different methods and strategies that supposedly accelerate muscle mass increase brings up reflections around pharmacologic agents and nutritional supplements associated with physical activity.

There are many types of nutritional supplements with specific alleged functions. Among these functions, we can find many claims such as energy provision, muscle mass gain, fat loss, etc, although sometimes those claims are not fully met. β-hydroxy-β-methylbutyrate - calcium (HMβ) is one of the supplements that appears to meet its claims (NISSEN and SHARP, 2003).

HMβ is a metabolite of the amino acid leucine. It is known that 5% of the leucine ingested is oxidized to it. HMβ is a branched chain amino acid metabolite so it can be considered a food supplement and it is used to increase performance and muscle mass in athletes and physically active practitioners.

It is believed that HMβ exert anti-catabolic actions, differently from anabolic hormones or other substances that induce muscle hypertrophy by increasing protein synthesis. Its mechanism of action is not fully known, but studies suggest that HMβ minimizes protein breakdown and muscle cells damage that occur with intense physical activity, although this has not been directly assessed (SLATER and JENKINS, 2000; ÁLVARES and MEIRELLES, 2008).

The literature shows mixed results of HMβ supplementation probably due to several factors such as the pathological stress condition, the type of physical activity, morphological and functional changes caused by aging (NISSEN and SHARP, 2003).

Although there is literature about different HMβ effects, the information is still confusing. Thus, the present systematic review aims to organize and discuss the information published in the last 20 years regarding methodological approaches and studies designs that addressed the role of HMβ combined with physical exercise and its effects on skeletal muscle.

2 Materials and Methods

We reviewed PubMed and Medline for articles with the following key-words: "HMβ", "β-hydroxy–β-methylbutyrate", "exercise", "muscle" with the words being present on the article's title or abstract.

Of all articles obtained through the database search we applied inclusion and exclusion criteria to follow to the next step.

Inclusion criteria were: published articles in indexed journals from the last 20 years (until August 2016), in English, Portuguese and/or Spanish, that had adherence to the review subject.

Exclusion criteria were: other published documents such as thesis, monographs, books or book chapters, studies presented at congresses or conferences, reports, publications of the government and regional international organizations, as well as papers that did not approached HMβ supplementation, physical activities or their effects on skeletal muscle. Also, we excluded papers with HMβ-free acid, not the form of HMβ associated with calcium that is the subject of this paper.

We analyzed the following items: country of origin and date, sample (men or women), dosage used, experimental design and the effects of the substance associated to exercise on skeletal muscle.

3 Results

A great number of studies can be found when the search is conducted only with "β-hydroxy–β-methylbutyrate" and "HMβ". The search we conducted had also "exercise", "training" and "muscle" as key words.

We applied the exclusion criteria previously described through the abstracts and the numbers of this process are presented in Tables 1 and 2.

After the abstracts analysis, 19 non-duplicated articles, from both databases (PUBMED and MEDLINE), were selected. After that, 2 independent reviewers (E.F. and L.G.) further reviewed the papers in order to assure that they had adherence to the subject addressed in the review.

Table 3 shows the selected articles and the type of authorship and year of publishing, country of origin, sample details, HMβ dosage used, study design and results.

4 Discussion

This study is a systematic review of HMβ supplementation associated with exercise training and its effects on skeletal muscle in humans. We found 19 studies that assessed muscle changes following HMB suplementantion.

4.1 Country of origin and year of publishing

All papers were produced by a group of authors, there was no solo production. As to the papers origins, we observed that even with authors from different countries composing the authors group, 10 publications came from the USA, two came from England and Australia, Italy, Israel, New Zealand, Poland, Singapore and Japan had only one publication. This observation is probably linked to the fact that HMβ was created and patented in the USA, by Steven L. Nissen at Iowa State University. Nissen and his colleagues pioneered the HMβ supplementation research in humans with a paper published (NISSEN, SHARP, RAY et al., 1996) with two experiments on muscle parameters.

The temporal distribution of studies conducted on the subject reflects the development of scientific literature about this substance. There is a predominance of publications in 2001, when four papers were published. Then, two articles were published annually in 2000, 2002, 2003, 2004, 2005 and 2009; and only one article was published in the years 1996, 2011, 2013 and 2014.

Until the year 2000, experimental articles with humans were published only in the USA. In 2001, other countries such as Singapore, Australia and Poland also published articles of such type.

In 2001, most researchers were from outside the USA. This finding is probably due to the promising results attributed to HMβ of increasing training performance and muscle mass. This distribution shows the evolution of the substance line of research, whereas the early works showed several positive evidences. Over the years (papers from 2003 to 2005) there were other hypotheses and some of the existing evidences were questioned. In 2009, HMβ again was widely researched after the literature review published by Zanchi, Nicastro, Gualano et al. (2009), putting it in line with a therapeutic approach.

4.2 Sample of participants

Of 19 publications found with humans, eight studies were conducted with both men and women (PANTON, RATHMACHER, BAIER et al., 2000) and only one study was carried out only with women (NISHIZAKI, IKEGAMI, TANAKA et al., 2015). Since most of the studies were made with RT and men as subjects of these studies, the literature shows that HMβ effects are more evident in men. There were two studies that were RCT experiments, they showed that HMβ supplementation may be effective in maximizing

Table 1. Distribution of the number of papers found by keywords in data bases.

Data base	Key-Words	Key-Words	Key-Words
	β-hydroxy–β-methylbutyrate HMβ	**β-hydroxy–β-methylbutyrate HMβ + Exercise**	**β-hydroxy–β-methylbutyrate HMβ + Exercise + Muscle**
PubMed	237	65	55
MedLine	2295	55	47

Table 2. Distribution of the number of papers found by keywords in data bases following seconds exclusion criteria.

Data base	Key-Words	Key-Words	Key-Words
	β-hydroxy–β-methylbutyrate HMβ	**β-hydroxy–β-methylbutyrate HMβ + Exercise**	**β-hydroxy–β-methylbutyrate HMβ + Exercise + Muscle**
PubMed	45	24	20
MedLine	42	17	14

Table 3. Methods and results summary of the selected articles.

AUTHOR/ YEAR	COUNTRY	PARTICIPANTS (mean age)	DOSAGE	STUDY DESIGN	RESULTS
Nishizaki, Ikegami, Tanaka et al. (2015)	Japan	23 women, ~70.5y, with knee osteoarthritis	2.4 g/day	A RCT study. 5 days of HMβ or placebo supplementation before Knee arthroplasty and for 28 days after surgery. Also, after surgery participants following a RT (rehabilitation) 5 day/wk during 42 days.	HMβ participants has impairment in strength loss after knee arthroplasty and improve strength gain after RT (rehabilitation).
Deutz, Pereira, Hays et al. (2013)	USA	Elderly 60-76 y; Males (n=4) and females (n=20)	3 g/day	A RCT study. Ten days of bed rest followed by 8 wk of RT (rehabilitation). During protocol participants supplemented with HMβ or placebo.	HMβ supplementation prevented decline in LBM over bed rest and improve strength gains in rehabilitation. But not increases LBM.
Portal, Zadik, Rabinowitz et al. (2011)	Israel	Adolescent volleyball players (13.5-18 y, 14 males, 14 females, Tanner stage 4-5)	3 g/day	A RCT study. 7 weeks of placebo or HMβ supplementation together of 18-22 h per week of exercise training equally involving tactical and technical drills emphasizing volleyball skills, power and speed and RT with free weights at 65-75% 1RM.	HMβ supplementation group increased lean body mass, strength and anaerobic properties and no effect on aerobic capacity
Nunan, Howatson and Van Someren (2010)	England	14 healthy males (30 y)	3 g/day of HMβ + 0.3 g/day of KIC	A randomized, controlled, single-blinded, parallel-group design study. 11 days of placebo or HMβ+KIC supplementation before a 40-minute bout of downhill running and continued for 3 days post-exercise.	HMβ+KIC supplementation group had had no significant effect on any of the indices of muscle damage and trend for more rapid rate of recovery of muscular isometric and isokinetic function.
Wilson, Kim, Lee et al. (2009)	USA	16 non-resistance trained healthy males (22 ± 2 y)	3 g/day	A RCT study. Participants were assigned to acute dose of placebo or HMB-Pre or placebo or HMB-Post exercise (in a crossover design). Subjects performed 55 maximal eccentric knee extension/flexion contractions on 2 occasions on either the right or left leg.	HMB-Pre promoted significance in attenuating soreness for the quadriceps and showed no significant increase in Lactate dehydrogenase.
Thomson, Watson and Rowlands (2009)	New Zealand	22 resistance trained men (24 ± 4.0 y)	3 g/day	A RCT study. 9 weeks with RT program with placebo or HMβ supplementation.	HMβ supplementation increase lower body strength but without significance for the body composition.
Kraemer, Hatfield, Volek et al. (2009)	USA	17 healthy men (22.9 ± 3.8 y) recreationally active	1.5 g of HMβ, 7 g of arginine, 7 g of glutamine, 3 g of taurine, and 5.824 g of dextrose	A RCT study. 12-wk (36 sessions). Placebo or HMβ supplementation and nonlinear periodized of RT program: sessions consisted of a three sets of 12- to 14-RM or 8- to 10-RM or 3- to 5-RM .	HMβ supplementation had positive effects on lean body mass, muscular strength energy, hormonal response and markers of muscle damage.

RT: Resistance training; USA: Unites States of America; CK: Creatine Kinase; LDH: Lactate dehydrogenase; RCT: Randomized double-blind placebo-controlled study.

Table 3. Continued...

AUTHOR/ YEAR	COUNTRY	PARTICIPANTS (mean age)	DOSAGE	STUDY DESIGN	RESULTS
Van Someren, Edwards and Howatson (2005)	England	8 healthy men (23 ± 4 y)	3 g/day of HMβ + 0.3 g/day of KIC	A RCT counterbalanced crossover design study. Following the 14 d of placebo or HMβ supplementation, subjects performed an exercise protocol designed to induce muscle damage: exercise protocol consisted of 3 sets of 10 reps of single arm biceps curls at 70% of a previously determined 1 RM for the involved arm	HMβ supplementation attenuated CK response, decreased symptoms of muscle damage and the percentage decrement in 1RM, and the percentage increase in limb girth due exercise induce muscle damage.
Panton, Rathmacher, Baier et al. (2000)	USA	Either a trained or untrained healthy 39 men and 36 women between the ages of 20-40 y.	3 g/day	A RCT study. Participants follow a RT program3x per week during 6 months with placebo or HMβ supplementation.	HMβ supplementation increased upper body strength and minimized muscle damage.
Hoffman, Cooper, Wendell et al. (2004)	USA	26 men football players (20.7 ± 1.2 y)	1 g/ three times/ day (3 g/day)	A randomized, controlled, single-blinded, parallel-group design study. 10 days of football practices and 3 sessions of RT program with placebo or HMβ supplementation.	Short duration HMβ supplementation does not provide any ergogenic benefit (on anaerobic power, testosterone, cortisol, CK or myoglobin analysis) in collegiate football players during preseason training camp.
O'Connor and Crowe (2003)	Italy	30 males rugby athletes (24.9 ± 1.5 y)	3 g/day of HMβ or; 3 g/day HMβ + 3 g/day of creatine (Cr)	A randomized, controlled, single-blinded, parallel-group design study. Subjects were tested prior to and following the 6-week of placebo or HMβ + Cr supplementation period. All subjects underwent an aerobic, plyometric, skill training and RT program throughout the 6-week supplementation period.	HMβ and HMβ + Cr were concluded to have no ergogenic effect on muscular strength and endurance, leg power, or anthropometry when taken orally by highly trained male athletes over 6 weeks.
Ransone, Neighbors, Lefavi et al. (2003)	USA	35 males, collegiate football players (21 y)	3 g/day	A randomized double-blind crossover study. 4 weeks of strenuous exercise program.	HMβ supplementation had no significant effect in muscle strength and body composition.
Paddon-Jones, Keech and Jenkins (2001)	Australia	17 untrained healthy males (21 y)	3.4 g/day (divided three times/day)	A RCT study. 6 days of placebo or HMβ (TRH or SH) supplementation before an acute session of RT to induce muscle damage: 6 reps X 4 sets of maximal voluntary eccentric contractions.	HMβ supplementation had no effect on swelling, muscle soreness, torque following 10 days from exercise induce muscle damage.

RT: Resistance training; USA: Unites States of America; CK: Creatine Kinase; LDH: Lactate dehydrogenase; RCT: Randomized double-blind placebo-controlled study.

Table 3. Continued...

AUTHOR/ YEAR	COUNTRY	PARTICIPANTS (mean age)	DOSAGE	STUDY DESIGN	RESULTS
Slater, Jenkins, Logan et al. (2001)	Singapore	17 males water polo and 10 rowers, national-level athletes. They had ≥2 y of RT	3 g/day (1 g/ three times/day) in a time release capsule (TRH) or standard encapsulation (SH)	A RCT study. 6-wk of placebo or HMβ (TRH or SH) supplementation, during a RT program: 2-3 whole body sessions weekly (3-5 sets per exercise with 4-6 reps- total of 24-32 sets per session)	HMβ supplementation di not promote significant effect on lean mass or strength gain or LDH, testosterone, cortisol, creatinine and serum urea. A trend toward decrease in plasma CK were found in HMβ supplementation.
Jówko, Ostaszewski, Jank et al. (2001)	Poland	40 untrained healthy males (19-23 y)	20.0 g of Cr/d for 7 d followed by 10.0 g of Cr/d for 14 d; or 3.0 g of HMβ/d: or Cr plus HMβ (Cr/ HMβ)	A RCT study.3-wk of RT with placebo or HMβ or CR/HMB supplementation. The RT sessions were nonconsecutive 3x wk whole body training (3-4 sets per exercise at 5-15 reps at 59-75% 1 RM).	HMβ supplementation decrease plasma CK. Cr, HMβ or Cr/ HMβ increased lean body mass and strength over the placebo group;
Vukovich, Stubbs and Bohlken (2001)	USA	Both untrained 15 healthy men and 16 healthy women, (70 ± 1 y)	1 g/ three times/ day (3 g/day)	A RCT study. 8 wk of aerobic and RT. RT: two nonconsecutive days per week (session with two sets of 10-12 reps at 70% 1RM); aerobic training: three days per week (6 laps/ mile; 3.7 laps/km).	HMβ supplementation tended to increase lean body mass and decreased body fat loss.
Gallagher, Carrithers, Godard et al. (2000)	USA	37 untrained healthy males (18-29 y)	3 g/day or 6 g/day	A RCT study. Subject attended to 8wk of RT with placebo or HMβ (3 g/day or 6g/day) supplementation.	Both HMβ dosages supplementation increased lean body mass, isometric and isokinetic torque, besides decreased plasma CK.
Knitter, Panton, Rathmacher et al. (2000)	USA	8 males and 8 females healthy runners (20-50 y)	3 g/day	A matched, controlled, double-blinded, parallel-group design study. After 6 wk of placebo or HMβ supplementation, subjects participated in a prolonged (20-km) run.	HMβ supplementation decreased lactate dehydrogenase, decreased CK.
Nissen, Sharp, Ray et al. (1996)	USA	41 untrained healthy males (19-29 y)	0, 1.5 or 3.0 g HMB/day	A RCT study. 3 and 7 wk of RT with placebo or HMβ supplementation.	HMβ supplementation with either 1.5 or 3 g/ day decreased proteolysis and plasma CK after 3 wk of intervention and increased lean body mass after at 2 4-6 wk of intervention.

RT: Resistance training; USA: Unites States of America; CK: Creatine Kinase; LDH: Lactate dehydrogenase; RCT: Randomized double-blind placebo-controlled study.

the beneficial changes (increase upper body strength and minimize muscle damage) associated with exercise during the early adaptation period of RT, regardless of training status. However, studies with athletes HMβ (HOFFMAN, COOPER, WENDELL et al., 2004; O'CONNOR and CROWE, 2003; RANSONE, NEIGHBORS, LEFAVI et al., 2003; SLATER, JENKINS, LOGAN et al., 2001), supplementation had no ergogenic effect.

4.3 Dosage used

Most of the 19 selected studies used doses of 3 g/day^{-1}, one study (GALLAGHER, CARRITHERS, GODARD et al., 2000) used both 3 g/day^{-1} and 6g/day doses. The studies that combined RT with HMβ supplementation used 3 g/ day^{-1}, based on the evidence that this dose produces greater results than 1.5 g/ day-1 and equivalent results compared to 6 g/ day-1 (GALLAGHER, CARRITHERS, GODARD et al., 2000; NISSEN, SHARP, RAY et al., 1996). However, several researchers believe that the dose response of this supplement might be affected by the degree of muscle catabolism and not by the amount of HMβ administered (GALLAGHER, CARRITHERS, GODARD et al., 2000; NISSEN, SHARP, RAY et al., 1996). For instance, Nissen and colleagues found that 7-wk of supplementation with 1.5 and 3.0 g/HMβ·day^{-1} with concomitant RT performed 3x a week caused a significant reduction in muscle protein degradation (indicated by the decrease in the urinary excretion of 3-methyl-histidine) and also at muscle damage (indicated by reduced plasma CK), in a dose dependent manner. In the same study, the authors concluded that 7-wk of HMβ supplementation, with 3 g/day^{-1}, associated with RT (3x a week) provided significant increases in lean body mass.

With the advance of knowledge, HMβ supplementation was proposed to be used as a therapeutic agent. To this end, the therapeutic effects of HMβ supplementation also seem to be dose-dependent (SMITH, MUKERJI and TISDALE, 2005). In a mice study with cancer-induced muscle loss (MAC16 tumor), HMβ supplementation was effective in reducing the weight loss induced by cancer in doses higher than 0.125 g/Kg^{-1} (8.75 g/day^{-1} for an adult human). Although this dose is considered high, HMβ supplementation is safe because it does not produce any adverse physical or psychological effect and keeps organic and tissue function indicators unchanged (KREIDER, 1999; NISSEN and ABUMRAD, 1997; NISSEN, SHARP, RAY et al., 1996). However, the metabolic pathway of this supplement need to be further explored. In vitro experiments and animal model have provided a major breakthrough in this field, but human studies are still scarce. Further studies are required to validate these information, varying the dose of the supplement and with different degrees of cancer catabolism.

4.4 Exercise type and effects on skeletal muscle

Regarding the type of exercised used in the study design, fourteen used RT, three studies performed both aerobic and RT (PORTAL, ZADIK, RABINOWITZ et al., 2011; O'CONNOR and CROWE, 2003; VUKOVICH, STUBBS, BOHLKEN, 2001) and two studies used the aerobic training (downhill) (NUNAN, HOWATSON and VAN SOMEREN, 2010; KNITTER, PANTON, RATHMACHER et al., 2000). There were three studies using aerobic training plus HMβ supplementation (presented in this review): two studies suggested that HMβ supplementation might prevent muscle damage in strenuous aerobic exercise (KNITTER, PANTON, RATHMACHER et al., 2000) and improve lean mass and strength gains (PORTAL, ZADIK, RABINOWITZ et al., 2011), however, these effects does not seem to occur in elite athletes (O'CONNOR and CROWE, 2003).

4.5 Concluding remarks

One interesting point of this review is that the dosages used in training protocols for muscle mass gain differ from those used in studies for therapeutic approach. The vast majority of studies in which there is concurrent supplementation with exercise used 3 g/day^{-1} of HMβ. Researchers believe that the dose response relationship for this supplement might be affected by the degree of muscle catabolism and not by the amount of HMβ administered. Smith, Mukerji and Tisdale (2005) claim that the therapeutic effects of HMβ supplementation are dose-dependent. In their study of a mice cancer model, they only achieved positive results with doses greater than 8 g/day^{-1}.

Concomitant resistance training with HMβ supplementation provides the best results compared to other training types. That seems to be an agreement when we looked to all the studies. Both aerobic (O'CONNOR and CROWE, 2003) or RT (THOMSON, WATSON and ROWLANDS, 2009; HOFFMAN, COOPER, WENDELL et al., 2004; RANSONE, NEIGHBORS, LEFAVI et al., 2003; SLATER, JENKINS, LOGAN et al., 2001) protocols show little or no significant changes in skeletal muscle in elite athletes or trained men. The reasons for this lack of results of HMβ in trained individuals is not yet explained. Other studies with different doses, training protocols and molecular variables still need to be explored in order to verify if HMβ supplementation had any result in the skeletal muscle of trained individuals.

Most of the papers presented in this systematic review show good results from the use of HMβ in skeletal muscle. The effects range from increased lean body mass and muscle strength, recovery of isometric and isokinetic muscle function, decreased lactate dehydrogenase and creatine kinase concentrations (implicating in less muscle damage) and decreased proteolysis in untrained individuals. However, the current data do not support the HMβ as a dietary supplement for trained individuals.

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