Leucine Metabolite β-hydroxy-β-methylbutyrate (HMB) Supplementation on Muscle Mass during Resistance Training in Older Subjects- A Meta-analysis

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**Running Title:** leucine Metabolite β-hydroxy-β-methylbutyrate (HMB) supplementation during resistance exercise training(RET) and muscle

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**Graphics count:** 3 tables and 7 figures

**Abstract**

***Background****:* Aging accompanied by loss of muscle mass, strength and function, may contribute to the development of frailty and fracture in older people. Inventions such as β-hydroxy-β-methylbutyrate (HMB) treatment and resistance exercise training (RET) have been well established alone in pro-researches to attenuate muscle loss. Nevertheless, there is no consensus whether combination of HMB intervention and RETcould obtain an additional benefit to older population.

***Objective****:* Our aim was to systematically and quantify whether HMB supplementation combined with RET could bring a synergistic effect in muscle mass, strength and function in older adults.

***Methods***：A systematic search was performed using the electronic databases MEDLINE, EMBASE, Cochrane library and Web of Science from inception to Oct 30,2021. The articles were all randomized controlled trials and met the inclusion and exclusion criteria. A fixed or randomized (if data were heterogeneous) effects meta-analysis was performed using the Stata.

***Results***：A total of 256 articles were screened, with 8 studies matched the eligibility criteria which enrolled 333 subjects (≥65 years). Meta-analysis were conducted and the results showed no significant difference between groups in lean mass, fat mass, or physical performance. In the subgroup analysis regarding the differences of muscle strength between appendicular, HMB supplementation combined with RET contributed to improve muscle strength of the lower limbs significantly [n=6 ,SMD 0.55, 95% confidence interval (CI), 0.06 to 1.04].

***Conclusion***: Combination of HMB supplementation and RET in older people has an additional benefit for muscle strength especially in lower limbs, instead of muscle function and physical performance. Further studies are needed to demonstrate the mechanism.

***Key Words:*** β-hydroxy-β-methylbutyrate, HMB, muscle, resistance exercise training

**Introduction**

It is estimated that the number of old people should be 2 billions by 2050. Age-related muscle loss accompanied by decreasing in muscle strength and function which leads to multiple adverse consequences including disability, frailty, morbidity, and mortality has been regarded as an important clinical problem in old people [1]. The prevalence of sarcopenia which charactered of muscle loss and disfunction reported by EWSDOP2 is up to 9.9%~40.4% in old adults [2]. The methods to relieve sarcopenia have been intensively researched, including resistance training, nutritional supplements, hormones and drug treatments, *etc.* For the elderly, especially the disabled elderly, due to the decline in physical function, the interventions mentioned above are greatly restricted in clinical conduction. Therefore, for the high-risk groups of sarcopenia, as well as the elderly, interevent as soon as possible, delay the progress, and explore efficient and multi-target strategies are the key clinical priority.

The atrophy of muscle mass is mainly due to a dynamic imbalance between muscle protein synthesis (MPS) and muscle protein breakdown(MPB).Resistance exercise and nutrition therapy are two promising ways to maintain the protein balance [3][4]. However, it is difficult for some elderly people to implement and persist resistance exercise particular during acute illness and disability. In addition, aiming to reduce the risk of sports injuries and falls, the elderly need professional guidance to carry out resistance training. On the other hand, nutritional supports including protein and amino acid supplements are considered to be safe and convenient, but the efficient depends on the appetite and digestive functions of the elderly. For this reason, investigating novel nutritional supplement programs more available and efficient are wanted.

β-Hydroxy-β-methylbutyrate (HMB) is a metabolite of the amino acid leucine. Studies have confirmed its role in relieving and promoting muscle synthesis and relieving muscle atrophy [5][6]. HMB participates cholesterol synthesis by metabolized to β-Hydroxy-β-methylglutaryl -CoA, and then provides material for muscle cell growth [7]. Also, HMB may enhance stability of cell membrane by undergoing polymerization. In clinical studies , the role of HMB combined with RET treatment has not yet reached consensus due to study-specific characteristics. Researchers have found both gains and no change in strength with HMB supplementation. Whether HMB supplementation combined with RET is effective than RET alone which focus on muscle mass, strength and function is unclear in the elderly [8][9]. Hence, we conducted a meta-analysis to assess the influence of HMB supplementation combing with RET in older people on lean mass, body fat mass (FM), muscle strength, and muscle function.

**Methods**

**Study inclusion/exclusion criteria**

Studies that met the following criteria were eligible for inclusion according to the PICOS (Participant, Intervention, Control, Outcome Measures and Study Design) strategy (**Table** [**1**](#Table1)).

**Table 1**. Inclusion and exclusion criteria used to evaluate studies for the meta-analysis

|  |  |
| --- | --- |
| Inclusion criterion | Description |
| Participants | Aged 65 or older. |
| Intervention | HMB oral supplementation in addition to Resistance Training |
| Control | Participants not provided with HMB supplementation (controls or placebo). |
| Outcome | body composition、muscle strength、muscle function |
| Study design | Randomized controlled trial |

**Data sources and searches**

A literature search was conducted by searching relevant databases to investigate the effects of HMB combined with resistance exercise on body composition, muscle strength and function in older adults. Relevant articles from the earliest year to 2000 were searched. Search terms were used including (HMB or beta-hydroxy-beta-methylbutyrate or β-hydroxy-β-methylbutyrate) and (exercise or training or "resistance exercise") and ("older adults" or elderly or elder) and (“muscle mass” or “muscle strength”or sarcopenia). Search electronic libraries included PubMed, Web of Science, Cochrane library, and Embase, with keywords used in various combinations, and maximum search results have been reached (last search date Oct 30, 2021). Trials were conducted in humans.

**Data extraction and Outcome Measures**

The data in the papers were extracted by 2 independent and parallel investigators using a predefined data sheet independently. Firstly, all papers were downloaded by two researchers. Secondly, removing the duplicates ,screening the titles and abstracts to identify the studies which met the eligibility criteria. And after that ,assessment of full text were performed subsequently. Furthermore, we hand-searched the references meeting the inclusion criteria for further analysis. The following data were extracted for each study: authors, years, sample size, gender, mean age, RET intervention, placebo/control information, body composition results, information on muscle strength and muscle function, and any other noteworthy information (e.g., source of bias/conflict of interest).

**Assessment of the methodological quality of include studies and risk of bias**

The methodological quality of the included articles was assessed by two investigators according to the Cochrane Collaboration risk-of-bias tool [10], including seven separate areas: (1) random sequence generation; (2) allocation concealment; (3) blinding of participants and personnel; (4) blinding of outcome assessments; (5) incomplete outcome data; (6) selective reporting; and (7) other sources of bias. When 2 researchers have a disagreement on study eligibility, data extraction, and risk-of-bias assessment, a third investigator was available to arbitrate.

**Data analysis**

The outcome of interest in this paper included the effect on body composition, strength, physical function. If the dependent variable had multiple time points, only pre-intervention and post-intervention values were selected. Meta-analysis was performed on extracted data with Stata-SE. For included studies, given the different ways used to measure muscle mass and strength, effect sizes were expressed as Standardized mean differences (SMDs) with 95% confidence interval (CI). SMD values of 0.2, 0.5, and 0.8 were defined as small, medium, and large effect sizes, respectively [11].The heterogeneity of included studies was determined by I2 (<50% was considered low, 50-74.9% was considered moderate, and 75-100% was considered high heterogeneity). Fixed-effects model were used when I2 was less than 50%, otherwise random-effects model were used.

**Results**

**Study selection**

A total of 256 studies were identified from the search strategy and other searches, and after eliminating duplicates, 215 records were available for title and abstract screening. 37 articles were screened for full text, and after further screening based on our selection criteria, 10 of these articles were reviewed for inclusion. After further exclusion based on our selection criteria, 8 randomized controlled trials met the inclusion criteria and underwent final analysis. **Figure 1** shows the PRISMA flow diagram.



**Figure 1.** Flow through of articles through the search and review process.

**Study characteristics**

The 8 eligible randomized controlled trials involved a total of 333 older adults: 159 received the experience group and 174 were assigned to the control group. Due to the unavailable data of 2 studies [16][19], the authors were contacted to provide additional data and did not receive any response. The characteristics of these studies, as shown in **Table 2** . The studies were conducted in healthy older adults which average age over 65 years. No studies mentioned the race of the subjects. The duration of the intervention varied widely, from 6 weeks to 12 months, and the frequency was 2 to 3 times per week. the HMB dose varied between 1.5 g/d (n = 2) and 3.0 g/d (n = 6). **Table 3** provides main outcomes on the included trials.

**Table 2**. Study characteristics of included trials

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Author, Year | Subjects | No.(C;T) | Age.（C; T） | Training Regimen | | | | HMB Supplementation | | | | |
| Length | Frequency | Intensity (Reps） | Sets | | Loading | Daily dose | Control | |
| Stout, 2013 | Man,woman; healthy | NC=20; NT =16 | 73.0±1.0; 73.0±1.0 | 21(wk) | 3/wk | 8-12 at 80% 1-RM | 3 | | mixture | 3 g HMB/d | Placebo | |
| Stout, 2015 | Man; healthy | NC =12; NT =12 | 72.1±5.7; 72.1±5.7 | 12(wk) | 3/wk | N.R | N.R | | mixture | 3 g HMB/d | Placebo | |
| Din, 2019 | Man; healthy, | NC =8; NT =8 | 68.5±1.0; 67.8±1.15 | 6(wk) | 3/wk | 6-8 at 75% 1-RM | N.R | | mixture | 3 g HMB/d | Placebo | |
| Vukovich, 2000 | Man, woman; healthy | NC =17; NT =14 | 70.0±1.0; 70.0±1.0 | 8(wk) | 2/wk | 10-12 at 70% 1-RM | 2 | | capsules | 3 g HMB/d | Placebo | |
| Berton L, 2016 | Women; healthy | NC =33; NT =32 | 69.5±5.3; 69.5±5.3 | 8(wk) | 2/wk | mild fitness | N.R | | drink | 1.5 g ca-HMB/d | Standard diet | |
| Deutz, 2013 | men, women;  healthy | NC =11; NT =8 | 67.1±1.7; 67.4±1.4 | 8(wk) | 3/wk | 8-10 at 80% 1-RM | 3 | | sachet | 3 g HMB/d | Placebo | |
| Rathmacher, 2020 | men, women;  healthy | NC =34; NT =30 | 67.7±0.7; 67.2±0.7 | 12(mon) | 3/wk | 60 minutes of supervised resistance | 3 | | capsules | 3 g ca-HMB/d  plus vitamin D3 (2,000 IU/day) | Placebo | |
| Osuka, 2021 | Woman | NC =39; NT =39 | 71.8±4.1; 73.5±4.2 | 12(wk) | 2/wk | 50 min resistance training | N.R | | powder | 1.5g ca-HMB/d | Placebo | |
| C: control; T: treatment; No: number; NC :number of control; NT :number of treatment; PL: Placebo , ca-HMB: calcium beta-hydroxy-beta-methylbutyrate; N.R.: not reported.; 1-RM：one repetition maximum | | | | | | | | | | | |

**Table 3**. Individual study outcome included in the meta-analysis

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Author,Year | Measuring methods | Measurement of body composition | Measurement of muscle strength | Measurement of physical function | |
| Stout,2013 | DXA | Total lean mass, kg | Extensor 180°·s−1 | Get up and go, s | |
| Leg lean mass, kg | Flexor 180°·s−1 |  | |
| Total fat mass , kg | Extensor 60°·s−11 |  | |
|  |  |  | Flexor 60°·s−1 |  | |
|  |  |  | Hand grip strength, kg |  | |
| Stout,2015 | DXA | abdominal fat mass ,kg |  |  | |
| Din, 2019 | DXA | Thigh lean muscle mass, g | MVC，Nm |  |
|  |  | Thigh fat free mass, g | 1-RM：Nm |  |
| Vukovich,2000 | DXA | Body fat,% | upper body strength, % |  | |
| Fat-free mass, kg | lower body strength，% |  | |
| Berton L,2016 | DXA | ASMMI | PT isokinetic Nm: | Chair stand times, s | |
|  | Abdominal fat mass, kg | PT isokinetic ext, Nm: | 6MWT, m | |
| pQCT | Fat-free mass ,kg | PT isokinetic flex, Nm: | Walking time, s | |
| Radial pQCT | Muscle area,mm2 | handgrip strength，kg | Balance test,score | |
| Fat area,mm2 | Handgrip endurance, s | SPPB | |
| Tibial pQCT | Muscle area, mm2 |  |  | |
| Fat area,mm2 |  |  | |
| Deutz,2013 | DXA | Leg Lean ,Kg | knee extensor (60°) strength, Nm |  | |
| Total body fat mass, kg | knee extensor (180°) strength, Nm |  | |
| Total lean Mass ,Kg |  |  | |
| Rathmacher,2020 | DXA | Lean Mass ,kg | Hand grip strength, kg | Get up and go, s | |
|  |  | Body fat（%） |  | Get up（reps） | |
| Osuka，2021 | DXA | Appendicular lean mass, kg | Knee extensor strength, N | Usual gait speed, m/s | |
|  |  | Fat-free mass, kg | Hip adductor strength, N | Maximal gait speed，m/s | |
|  |  | Skeletal muscle index, kg/m2 | Handgrip strength ,kg | Timed up-and-go，s | |
|  |  | Fat mass, kg |  | Five-repetition sit-to-stand，s | |
|  |  | Upper-extremity lean mass, kg |  |  | |
|  |  | Lower-extremity lean mass,kg |  |  | |

DXA: dual X-ray absorptiometry; SPPB: short physical performance battery. MVC：maximal voluntary contraction。1-RM：one repetition maximum.

**Quality of included studies and risk of bias**

No study was considered low risk of bias in all categories. Scout’ research showed the high risk in selective reporting because of the difference with the pre-registered trial [16]. The smallest biases were found in allocation concealment and blinding of outcome assessments. **Figure 2** contained the risk of bias assessment.



**Figure 2.** Risk-of-bias summary for all studies and outcomes.

**Main outcomes**

All studies included reported measurements of body composition, including fat mass, fat-free mass, which based on DXA or computed tomography (CT), with measurement cycle ranging from 6 weeks to 12 months. Five studies reported the effects of HMB on lower-body strength, including knee flexion/extension by isokinetic, isometric, one maximum repetition (1RM), maximal voluntary contraction (MVC), peak torque (PT) isometric and isokinetic strength of the lower limbs, and Hip adductor strength, *etc.* Four studies reported the effects on upper-body strength muscle strength, including handgrip strength and handgrip endurance [12][13][18][19], 1 study reported percentage change in upper and lower body strength [14]. Four studies reported the effects on muscle function, including SPPB, get-up and go, and 4-meter walk time and 6-second walk distance, usual gait speed, five-repetition sit-to-stand [12][13][18][19]. Mean standard difference (MSD) at the end of the intervention period between HMB groups and placebo combined with resistance exercise was used for analysis.

All included studies were tested for heterogeneity: fat mass, fat free mass, lower-body strength, upper-body strength and muscle function, which were high heterogeneous. Therefore, random effects models were applied to the meta-analysis. Eight studies were included in the meta-analysis, revealing evidence that HMB or supplements containing HMB improved lower-body strength compared with controls, but with a moderate to large effect size (SMD = 0.55; 95% CI: 0.06, 1.04; P = 0.000; I2= 86.9%, **Figure 3**). The effect of HMB was not significantly effect to upper-body strength (SMD = 0.27; 95% CI: -0.55, 1.09; P = 0.000; I2= 92.0%, **Figure 4**). Almost no effect was found in fat mass (SMD = 0.25; 95% CI: -0.18, 0.75; P = 0.001; I2= 82.1%, **Figure 5**), and fat-free mass (SMD = 0.04; 95% CI: -0.26, 0.33; P = 0.000; I2= 76.3%, **Figure 6**), and muscle function (SMD = 0.15; 95% CI: -0.21, 0.51; P = 0.000; I2= 83.7%, **Figure 7**).



**Figure 3.** Forest plot of the results of a random-effects meta-analysis of HMB shown as pooled standard mean differences with 95% CIs on lower-body strength.



**Figure 4.** Forest plot of the results of a random-effects meta-analysis of HMB shown as pooled standard mean differences with 95% CIs on upper-body strength.



**Figure 5.** Forest plot of the results of a random-effects meta-analysis of HMB shown as pooled standard mean differences with 95% CIs on fat mass.



**Figure 6.** Forest plot of the results of a random-effects meta-analysis of HMB shown as pooled standard mean differences with 95% CIs on fat-free mass.



**Figure 7.** Forest plot of the results of a random-effects meta-analysis of HMB shown as pooled standard mean differences with 95% CIs on muscle function.

**Sensitivity analyses and publication bias**

Recording to recommendations of the Cochrane Handbook for Systematic Reviews of Interventions, statistical tests to build funnel plot asymmetry were not undertaken owing to the use of standard mean difference (SMD) in the meta-analysis.

**Discussion**

This study was conducted to compare the effects on the muscle mass, strength and function intervened by HMB supplementation in addition to RET and RET alone in healthy community-dwelling elder adults. HMB supplementation and RET are well recognized effective treatments for sarcopenia and the synergy effects of the intervention methods mentioned above had been evaluated before [20][21]. However, there was no consensus reached. Josephine S. Jakubowski concluded that HMB and RET treatment had a small effect on total body mass (TBM) gain, but this effect did not seen in free fat mass (FFM), muscle strength or decreases in fat mass (FM) [22]. David S. Rowlands and Jasmine S. Thomson determined that there was a synergistic effect in leg strength gains in previously untrained men by supplementing with HMB during resistance training, but this effects in trained lifters were trivial [23]. These different results may relate to the heterogeneity of the participants included and the interventions used. Although weather HMB combined with RET brought additional effects in muscle gains is unclear, it was too early to draw a final conclusion and more updated researches should be included for evaluation. Our analysis including the latest clinical RCT studies showed that HMB supplementation combined with RET significantly enhanced muscle strength of lower limbs in the elderly, but no positive effect was noted for muscle strength of upper limbs, lean mass, fat mass and muscle function during the entire study. We here found that in the elderly population, supplementing HMB on the basis of resistance training could achieve additional positive effects on muscle strength of lower limbs. This conclusion was similar to the previous study conducted among untrained lifters.

With the aging of the population intensifying, we conducted this study mainly for the elderly, who often suffered multiple chronic diseases. The synergy of HMB supplementation and RET in the elderly is not surprising. It is well known that physical inactivity and malnutrition which interacts each other are common conditions in older adults. Nutritional interventions are important to promote physical activity. Exercise, in turn, also helps to improve appetite and promote nutrient absorption. Although a recent meta-analysis suggested that HMB supplementation in addition to physical exercise had low impact in improving muscle strength in adults aged 50 to 80 years [24], we found preserved muscle strength in the intervention group compared to the gradual loss experienced in the control group, might due to the findings of our meta-analysis were mainly based on older adults who were untrained or lightly exercised.

Although studies have shown that RET alone is an effectively way to prevent weakness and sarcopenia, nutritional supplementation compared to RET is still a safer, simpler and more feasible intervention in older people. HMB has been widely recognized as a nutrient ingredient for the treatment of sarcopenia by activating the major signaling pathways leading to protein synthesis [25][26]. In several preclinical models, HMB has been shown to improve muscle protein synthesis by activating the mammalian target of rapamycin (mTOR). To explore the exact role of HMB intervention during RET treatment, subgroup analysis were conducted and we found that HMB combined with RET mainly improved lower limbs muscle strength rather than upper limbs. What needs to be pointed out is the strength of the lower limb muscles is more important to improve the self-care ability and stability of the elderly. This novel result may provide optimized strategies to prevent frailty and sarcopenia. The findings of our analysis showed blunted effects of HMB supplement additionally in muscle mass. This result may due to four reasons. Firstly, the analysis included studies of healthy older adults who might not suffered by malnutrition. The effects of HMB interventions might be blunted among older adults who habitually consume sufficient nutrients. Second, compared with the young , the elderly, due to the degradation of digestion and absorption function, the conventional dose of HMB may not achieve the expected effects. In addition, due to the imbalance of muscle protein metabolism in older adults, long-term nutritional supplementation is needed, while short-term supplementation may not show obvious effects. Moreover, inflammation, immobilization and chronic comorbidities could further lead to muscle loss. Thus, the different results may indicate that different populations respond differently to HMB supplementation combined with RET.

Through the results of this study, we once again confirmed that HMB supplementation combined with RET had a positive effect on the muscle improvement of the elderly living in the community, although this positive effect was limited to the muscle strength of the lower limbs. Of course, among the elderly in the community, the molecular mechanism of HMB supplementation on the basis of RET to improve the muscle strength of the lower limbs needs to be further studied. At the same time, more researches are needed to explore the appropriate timing, intensity and prognosis of intervention.

**Limitations**

Because the high heterogeneity in this meta-analysis was the result of including trials of different genders, it is unclear whether older men and women respond similarly to HMB supplementation during RET because the main limitation of this meta-analysis was the small number of included studies and the exclusion of subgroup analyses. Also the sample size was relatively small and Different RET protocols (training length, training volume and number of exercises performed), different intervention doses, measurement modalities and choice of outcome indicators can influence the final conclusions.

**Conclusion**

Combination of HMB supplementation and RET in older people has an additional benefit for muscle strength especially in lower limbs, instead of muscle function and physical performance. Further studies are needed to demonstrate the mechanism.

**Declarations**

**Authors’ contributions**

Made substantial contributions to conception and design of the study and performed data analysis and interpretation: Guang-Qin Zou, Quan Wang, Xiang Lu, Wei Gao

Performed data acquisition, as well as provided administrative, technical, and material support: Guang-Qin Zou, Hua Wang, Wei Gao

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**Conflicts of interest**

All authors declared that there are no conflicts of interest.

**References**

1. Cruz-Jentoft AJ, Sayer AA. Sarcopenia. Lancet. 2019 Jun 29;393(10191):2636-2646.
2. Mayhew AJ, Amog K, Phillips S, Parise G, McNicholas PD, de Souza RJ, Thabane L, Raina P. The prevalence of sarcopenia in community-dwelling older adults, an exploration of differences between studies and within definitions: a systematic review and meta-analyses. Age Ageing. 2019 Jan 1;48(1):48-56.
3. Bischoff-Ferrari HA, Vellas B, Rizzoli R, Kressig RW, da Silva JAP, Blauth M, Felson DT, McCloskey EV, Watzl B, Hofbauer LC, Felsenberg D, Willett WC, Dawson-Hughes B, Manson JE, Siebert U, Theiler R, Staehelin HB, de Godoi Rezende Costa Molino C, Chocano-Bedoya PO, Abderhalden LA, Egli A, Kanis JA, Orav EJ; DO-HEALTH Research Group. Effect of Vitamin D Supplementation, Omega-3 Fatty Acid Supplementation, or a Strength-Training Exercise Program on Clinical Outcomes in Older Adults: The DO-HEALTH Randomized Clinical Trial. JAMA. 2020 Nov 10;324(18):1855-1868.
4. Nilsson MI, Mikhail A, Lan L, Di Carlo A, Hamilton B, Barnard K, Hettinga BP, Hatcher E, Tarnopolsky MG, Nederveen JP, Bujak AL, May L, Tarnopolsky MA. A Five-Ingredient Nutritional Supplement and Home-Based Resistance Exercise Improve Lean Mass and Strength in Free-Living Elderly. Nutrients. 2020 Aug 10;12(8):2391.
5. Gepner Y, Varanoske AN, Boffey D, Hoffman JR. Benefits of β-hydroxy-β-methylbutyrate supplementation in trained and untrained individuals. Res Sports Med. 2019 Apr-Jun;27(2):204-218.
6. He X, Duan Y, Yao K, Li F, Hou Y, Wu G, Yin Y. β-Hydroxy-β-methylbutyrate, mitochondrial biogenesis, and skeletal muscle health. Amino Acids. 2016 Mar;48(3):653-664.
7. Duan Y, Li F, Li Y, Tang Y, Kong X, Feng Z, Anthony TG, Watford M, Hou Y, Wu G, Yin Y. The role of leucine and its metabolites in protein and energy metabolism. Amino Acids. 2016 Jan;48(1):41-51.
8. Weihrauch M, Handschin C. Pharmacological targeting of exercise adaptations in skeletal muscle: Benefits and pitfalls. Biochem Pharmacol. 2018 Jan;147:211-220. Durkalec-Michalski K, Jeszka J, Podgórski T. The Effect of a 12-Week Beta-hydroxy-beta-methylbutyrate (HMB) Supplementation on Highly-Trained Combat Sports Athletes: A Randomised, Double-Blind, Placebo-Controlled Crossover Study. Nutrients. 2017 Jul 14;9(7):753.
9. Teixeira FJ, Matias CN, Monteiro CP, Valamatos MJ, Reis JF, Tavares F, Batista A, Domingos C, Alves F, Sardinha LB, Phillips SM. Leucine Metabolites Do Not Enhance Training-induced Performance or Muscle Thickness. Med Sci Sports Exerc. 2019 Jan;51(1):56-64.
10. Cochrane Handbook for Systematic Reviews of Interventions, V ersion5.1.0 [updated March 2011]. The Cochrane Collaboration; 2011.
11. Cohen J. Statistical Power Analysis for the Behavioural Sciences. Hillsdale, NJ: Lawrence Erlbaum; 1988
12. Berton L, Bano G, Carraro S, Veronese N, Pizzato S, Bolzetta F, De Rui M, Valmorbida E, De Ronch I, Perissinotto E, Coin A, Manzato E, Sergi G. Effect of Oral Beta-Hydroxy-Beta-Methylbutyrate (HMB) Supplementation on Physical Performance in Healthy Old Women Over 65 Years: An Open Label Randomized Controlled Trial. PLoS One. 2015 Nov 3;10(11):e0141757.
13. Stout JR, Smith-Ryan AE, Fukuda DH, Kendall KL, Moon JR, Hoffman JR, Wilson JM, Oliver JS, Mustad VA. Effect of calcium β-hydroxy-β-methylbutyrate (CaHMB) with and without resistance training in men and women 65+yrs: a randomized, double-blind pilot trial. Exp Gerontol. 2013 Nov;48(11):1303-10.
14. Vukovich MD, Stubbs NB, Bohlken RM. Body composition in 70-year-old adults responds to dietary beta-hydroxy-beta-methylbutyrate similarly to that of young adults. J Nutr. 2001 Jul;131(7):2049-52.
15. Din USU, Brook MS, Selby A, Quinlan J, Boereboom C, Abdulla H, Franchi M, Narici MV, Phillips BE, Williams JW, Rathmacher JA, Wilkinson DJ, Atherton PJ, Smith K. A double-blind placebo controlled trial into the impacts of HMB supplementation and exercise on free-living muscle protein synthesis, muscle mass and function, in older adults. Clin Nutr. 2019 Oct;38(5):2071-2078.
16. Stout JR, Fukuda DH, Kendall KL, Smith-Ryan AE, Moon JR, Hoffman JR. β-Hydroxy-β-methylbutyrate (HMB) supplementation and resistance exercise significantly reduce abdominal adiposity in healthy elderly men. Exp Gerontol. 2015 Apr;64:33-4.
17. Deutz NE, Pereira SL, Hays NP, Oliver JS, Edens NK, Evans CM, Wolfe RR. Effect of β-hydroxy-β-methylbutyrate (HMB) on lean body mass during 10 days of bed rest in older adults. Clin Nutr. 2013 Oct;32(5):704-12.
18. Rathmacher JA, Pitchford LM, Khoo P, Angus H, Lang J, Lowry K, Ruby C, Krajek AC, Fuller JC, Sharp RL. Long-term Effects of Calcium β-Hydroxy-β-Methylbutyrate and Vitamin D3 Supplementation on Muscular Function in Older Adults With and Without Resistance Training: A Randomized, Double-blind, Controlled Study. J Gerontol A Biol Sci Med Sci. 2020 Oct 15;75(11):2089-2097.
19. Osuka Y, Kojima N, Sasai H, Wakaba K, Miyauchi D, Tanaka K, Kim H. Effects of exercise and/or β-hydroxy-β-methylbutyrate supplementation on muscle mass, muscle strength, and physical performance in older women with low muscle mass: a randomized, double-blind, placebo-controlled trial. Am J Clin Nutr. 2021 Oct 4;114(4):1371-1385.
20. Rowlands DS, Thomson JS. Effects of beta-hydroxy-beta-methylbutyrate supplementation during resistance training on strength, body composition, and muscle damage in trained and untrained young men: a meta-analysis. J Strength Cond Res. 2009 May;23(3):836-46.
21. Bear DE, Langan A, Dimidi E, Wandrag L, Harridge SDR, Hart N, Connolly B, Whelan K. β-Hydroxy-β-methylbutyrate and its impact on skeletal muscle mass and physical function in clinical practice: a systematic review and meta-analysis. Am J Clin Nutr. 2019 Apr 1;109(4):1119-1132.
22. Jakubowski JS, Nunes EA, Teixeira FJ, Vescio V, Morton RW, Banfield L, Phillips SM. Supplementation with the Leucine Metabolite β-hydroxy-β-methylbutyrate (HMB) does not Improve Resistance Exercise-Induced Changes in Body Composition or Strength in Young Subjects: A Systematic Review and Meta-Analysis. Nutrients. 2020 May 23;12(5):1523.
23. Rowlands DS, Thomson JS. Effects of beta-hydroxy-beta-methylbutyrate supplementation during resistance training on strength, body composition, and muscle damage in trained and untrained young men: a meta-analysis. J Strength Cond Res. 2009 May;23(3):836-46.
24. Courel-Ibáñez J, Vetrovsky T, Dadova K, Pallarés JG, Steffl M. Health Benefits of β-Hydroxy-β-Methylbutyrate (HMB) Supplementation in Addition to Physical Exercise in Older Adults: A Systematic Review with Meta-Analysis. Nutrients. 2019 Sep 3;11(9):2082.
25. Duncan, N.; Fuller, J.C.;Baier, S.M.; Naimo, M.A.; et al. The effects of 12 weeks of beta-hydroxy-beta-methylbutyrate free acid supplementation on muscle mass, strength, and power in resistance-trained individuals: A randomized, double-blind, placebo-controlled study . Eur. J. Appl. Physiol. 2014, 114, 1217–1227.
26. Kraemer, W.J.; Hatfield, D.L.; Volek, J.S.; Fragala, M.S.; Vingren, J.L.; Anderson, J.M.; Spiering, B.A.; Thomas, G.A.; Ho, J.Y .; Quann, E.E.; et al. Effects of amino acids supplement on physiological adaptations to resistance training. Med. Sci. Sports Exerc. 2009, 41, 1111–1121.