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THE EFFECT OF β-HYDROXY-β-METHYLBUTYRATE (HMB) ON SARCOPENIA AND FUNCTIONAL FRAILTY IN OLDER PERSONS: A SYSTEMATIC REVIEW

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Abstract: *Background:* Beta-hydroxy-beta-methylbutyrate (HMB) has been shown to be effective and superior to other types of protein supplements to attenuate loss of muscle mass, strength and function, however, its benefits in sarcopenic and frail older people remain unclear. *Objective:* We seek to determine the effect of HMB on muscle mass, strength and function in older people with sarcopenia or frailty by reviewing results from available randomized controlled trials (RCTs). *Design:* This review was registered at PROSPERO (University of York) with registration number CRD42018088462 and conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analysis (PRISMA) guidelines. Using a pre-determined e-search strategy, we searched PubMed, Medline, EMBASE, CINAHL, LILACS, Web of Science, Cochrane and Scopus databases. Our inclusion criteria were RCTs that assessed the effect of HMB on muscle mass, strength and function in older people with sarcopenia and frailty aged ≥60 years. The main outcomes were lean body mass, handgrip, leg press strength, and Short Physical Performance Battery (SPPB) score. *Results:* Three studies matched our eligibility criteria which enrolled 203 subjects through a variety of definitions of sarcopenia or frailty. Lean body mass increased and muscle strength and function were preserved following HMB supplementation. *Conclusion:* HMB improves lean muscle mass and preserves muscle strength and function in older people with sarcopenia or frailty.

Keywords: Beta-hydroxy-beta-methylbutyrate, HMB, sarcopenia, frailty, muscle.

Introduction

The increase in life expectancy and advances in healthy living and medical care has lead to the development of an aging population. Around 8.5% of world population are aged 65 and above (1). Aging manifests in a progressive decline of muscle mass, strength and function which, when meeting certain clinical criteria, is known as sarcopenia (2, 3). The rate of muscle decline accelerates exponentially from around 8% per decade at 40 years of age to up to 15% per decade after the age of 70 (4). If this loss of muscle mass persists and becomes more severe, it may contribute to the development of frailty where the significant loss of muscle mass and strength confers high risk of falls, dependency, disability, morbidity and mortality rate (5-7). Fried et al. defined frailty according to five components: unintentional weight loss, weakness, self-reported exhaustion, slow walking speed, and low physical activity (5). Loss of muscle mass, strength and function is an important issue in the aging population hence appropriate strategies to mitigate muscle loss are necessary (8).

Muscle protein synthesis (MPS) is dependent on anabolic stimuli such as physical activity and nutrition (9). The rate of MPS decreases by around 44% in older people over 60 years old compared to young individuals aged <60 years old (10). Many strategies have been studied to reverse the age-associated muscle loss, including resistance training (11, 12) and nutritional supplementation (13-15). Supplementation in the form of protein supplement seems to be a promising tool to manage sarcopenia and frailty. Protein has a key role in the stimulation of MPS and the inhibition of muscle catabolism (16). Beta-hydroxy-beta-methylbutyrate (HMB), a leucine metabolite, has been shown in multiple studies to be effective in counteracting sarcopenia by stimulating anabolic signaling pathways and inhibiting muscle proteolysis (15, 17-19). Leucine is known to have the capacity to directly activate the mammalian target of rapamycin (mTOR) pathway and inhibit proteasome to prevent proteolysis (20). Under normal condition, only around 5% of leucine is converted to HMB (21). This means that an individual needs to consume at least 60 g of leucine daily to fulfil the required dose of 3 g of HMB per day to maximally stimulate MPS, an amount that is considerably impractical (18, 22). Consumption of 2 – 3 g of HMB daily is considered safe without any effect on blood or urine parameters of lipid profile, biochemistry, hepatic and renal failure (19). A study using rats showed that a dose equivalent to almost 50 g HMB daily over 3 months has no adverse effects (23).

The efficacy of HMB, when investigated in clinical trials, is inconsistent and unclear (24-27). Some studies show the benefit of HMB (24, 25), while other studies found that HMB has no effect on muscle metabolism (26, 27). A number of systematic reviews and meta-analyses examined on the effectiveness of HMB on muscle mass in various populations including trained individuals, untrained individuals and healthy older adults (8, 17, 18, 28). The outcomes of those reviews may not be reflective of the benefit of HMB in older population with

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sarcopenia or frailty syndrome.

We hypothesized that HMB is more superior to other types of protein supplementation, and has positive effect on muscle mass, strength and function in older individuals with sarcopenia or frailty syndrome. We evaluated available randomised controlled trials (RCTs) which assessed the effect of HMB supplementation on muscle mass, strength and function in sarcopenia or frailty, with or without concomitant exercise intervention.

Methods

Search Strategy

This review was registered at PROSPERO (University of York) with registration number CRD42018088462 and conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) guidelines.

Systematic literature search was conducted in PubMed, MEDLINE, EMBASE, EMCARE, CINAHL, LILACS, Web of Science, the Cochrane Central Registry of Controlled Trials (CENTRAL) and Scopus form inception of the database until May 2018. The following terms were included in the literature search: HMB OR beta-hydroxy-beta-methylbutyrate OR calcium beta-hydroxy-beta-methylbutyrate OR Ca- beta-hydroxy-beta-methylbutyrate OR Ca-HMB OR leucine, frail* OR sarcopeni*. An example of a search strategy developed for MEDLINE (via Ovid) can be found in Table 1. The search was restricted to articles published in or translated to English. Bibliographic search was conducted for inclusion of publications missed in the initial search and for publications containing relevant keywords and topics. Where primary data was not available in full-text, we attempted to contact the authors twice over a two-week period. A study was excluded if there was no response from the authors after being contacted.

Inclusion and Exclusion Criteria

Search results from each database were exported into EndNote X8.0.1. Duplicate publications were removed, and the remaining results were screened based on the following inclusion criteria:

- Randomised controlled trials (RCTs) that compared HMB with placebo in older individuals with sarcopenia or frailty;
- RCTs that compared different amounts of HMB;
- RCTs that compared HMB with other protein supplementation;
- HMB can be in the form of calcium HMB (Ca-HMB) or HMB free acid;
- The population must be ≥60-year-old without any signs of chronic illness (infection, renal failure, cardiovascular or pulmonary diseases, poorly-controlled metabolic diseases, history of recent malignancy (<5 years ago)), and not concurrently taking any dietary supplements;
- The population must meet the criteria of sarcopenia or frailty syndrome according to validated diagnostic tools;
- Studies must be in English or translated in English;
- No restrictions in the year of inclusion;

Exclusion criteria included

- RCTs that combined both exercise program and HMB or that use the combination of HMB and other essential amino acids (EAAs) or other supplements in the experimental group, except where both control and intervention groups received identical additional intervention(s) and HMB was the only variable e.g. identical exercise program or identical additional interventions for both control and intervention group.
- RCTs that included individuals ≥65 year-old with any signs of chronic illness (infection, renal failure, cardiovascular or pulmonary diseases, poorly-controlled metabolic diseases, history of recent malignancy (<5years ago)) and/or currently taking any dietary supplements.
- Healthy older subjects who were not considered sarcopenic or frail.

Data extraction and quality assessment of evidence

The methodological quality of included studies was assessed for risk of bias according the recommendations of the Cochrane Collaboration (29) by two reviewers (JO and JZ) independently, where studies were categorized into having 'low risk', 'high risk', or 'unclear risk' of bias. Any disagreements or discrepancies were resolved through discussion or by a third reviewer (GD).

Two review authors worked independently and in parallel to assess the full-text of included studies. The following data were extracted from each study using an EXCEL spreadsheet (Microsoft, Redmond, WA, USA): author, year, design, country, sample size, sex, mean age, control, intervention, amount of HMB supplementation (g/day) and duration (weeks), muscle mass outcomes, muscle strength outcomes and physical performance outcomes.

Each outcome extracted was assessed as either 'very low', 'low', 'moderate' or 'high' quality of evidence according to GRADE criteria (30) The assessment of quality was based on eight criteria: risk of bias, inconsistency, indirectness, imprecision, publication bias, large magnitude of effect, dose response and effect of all plausible confounding factors.

Results

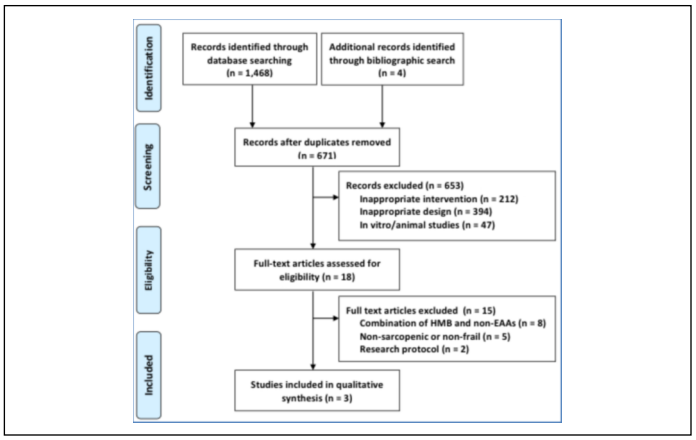
Studies Characteristics

A total of 1,472 articles were identified through the literature search. After removing duplicates (n=801), 671 articles were identified of which 653 were excluded during title and abstract screening (Figure 1). Following full-text review of 18 articles, three studies comprising 203 participants were included for the qualitative analysis.

The included studies were conducted in the United States of America and Spain, covering mainly Caucasian population both

community-dwelling and patients in rehabilitation facilities. All three studies were RCTs (Table 2). The average age ± standard deviation (SD) of the participants in the included studies ranged from 67.1 ± 1.7 to 85.4 ± 6.3, where 63.6% (n = 129) of the participants were female. Study sizes ranged from 19 to 107 participants and follow-up duration ranged from around 42.3 ± 20.9 days in a study conducted on patients in rehabilitation facilities (31) to 12 months (19). All participants were classified as either frail or sarcopenia according to a variety of measures such as the definition of sarcopenia proposed by the European Working Group on Sarcopenia in Older People (EWGSOP) (n = 107) (31) and having score between 10 to 20 seconds in Get-up-and-Go test (n = 77) (19). One study recruited healthy individuals who were then confined to complete 10-day bed rest period to allow significant decline in MPS, and hence resulting in muscle atrophy (15).

Figure 1
PRISMA Flowchart of the review process



One study combined HMB with other essential amino acids such as L-arginine (Arg) and L-lysine (Lys) (19). That study adjusted the dosage of HMB according to body weight, where subjects were provided with either 2 g or 3 g of HMB per day if their weights were ≤68 kg or >68 kg respectively (19). The other two studies provided 3 g of Ca-HMB supplements per day in the form of commercially-available drink (Ensure® Plus Advance, Abbot Laboratorios S.A.) (31), and in powder form (15). The control treatments were normal diet and placebo supplement containing no HMB.

Deutz et al (15) enrolled the participants in resistance training rehabilitation program following the 10-day bed rest period, where both control and intervention received the same set of training program.

Quality of included studies and risk of bias

One of three studies was at a high risk of detection bias, as participants were not blinded to their allocations. Two studies were at high risk of attrition bias due to intention-to-treat analysis was not performed or not specified (Supplemental Figure 1). None of the studies showed clear evidence of small study effect bias.

Four outcomes were assessed for quality of evidence through GRADEpro (30), of which all outcomes were low in certainty of evidence (Supplemental Figure 2).

Main outcomes

Baier et al (19) demonstrated a significant increase of lean body mass in the intervention group compared to control group measured by BIA ($p = 0.002$) and a significant maintenance of lean body mass as measured by DXA scan ($p = 0.05$). This study also showed that muscle strength and function remained unchanged over 12-month supplementation period as assessed by handgrip strength, leg strength, "Get-up-and-Go" and 'Get-up' functionality tests compared to gradual loss experienced by the control group (19).

In an RCT conducted in healthy older people after completing 10 days of complete bed rest (15), the intervention group experienced reduced loss of muscle mass, strength and function compared to the control group during the bed rest period. Moreover, the intervention group subsequently experienced greater improvement in muscle strength and function following the training program that was conducted post bed rest (15).

A multi-centered study conducted in Spain (31) showed that HMB supplementation preserved muscle mass on sarcopenic patients with hip fracture compared to the reduction in muscle mass observed in the control group.

Discussion

The purpose of this review was to assess the effect of HMB on sarcopenia and frailty in older persons. The included studies showed positive benefits of HMB to either improve or preserve muscle mass, strength and function in older people with loss of muscle.

Our findings were similar with the results from a similar systematic review conducted by Wu et al. (8) where HMB was found to be useful to prevent lean body mass loss in older adults. However, our study has contradicting results with this systematic review regarding the effect of HMB on muscle strength and function, where we found that HMB preserved muscle function and strength in the intervention group compared to the gradual loss experienced by the control group (8). This discrepancy is due to differences in inclusion and exclusion criteria. Unlike Wu et al. (8) that recruited any RCTs assessing the effect of HMB on any older population, our study only included RCTs that recruited older individuals who were diagnosed as either sarcopenic or frail.

There are many factors that could contribute to the findings of this review, in particular the definitions of sarcopenia and frailty applied to the participants in each included study. All included studies recruited older individuals with a degree of muscle loss, with only one study specifically recruited participants who met the criteria of sarcopenia according to

Table 1
Example of search strategy

Medline search			
#	**Searches**	**Results**	**Search type**
1	HMB.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2580	Advanced
2	3-hydroxy-3-methylbutyrate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7	Advanced
3	3-hydroxy-3-methylbutanoate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	0	Advanced
4	beta-hydroxyisovalerate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	12	Advanced
5	3-hydroxyisovalerate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	38	Advanced
6	3-hydroxy-3-methyl-butanoate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	0	Advanced
7	beta-hydroxy-beta-methylbutyrate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	262	Advanced
8	calcium beta-hydroxy-beta-methylbutyrate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7	Advanced
9	Ca-beta-hydroxy-beta-methylbutyrate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2	Advanced
10	Ca beta-hydroxy-beta-methylbutyrate.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	2	Advanced
11	Ca-HMB.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	14	Advanced
12	HMB calcium.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	7	Advanced
13	leucine.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	75765	Advanced
14	frail*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	19948	Advanced
15	sarcopeni*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	5714	Advanced
16	sarcopaeni*.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms]	41	Advanced
17	(1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11or 12 or 13) and 14	42	Advanced
18	(1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11or 12 or 13) and 15	208	Advanced
19	(1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11or 12 or 13) and 16	1	Advanced

Table 2
Characteristics of the studies included

Author, Year	Study design	Eligibility criteria	Sample size	Intervention	Control	Amount of HMB (g/d)	Duration
Baier et al., 2009 (19)	RCT	≥65, TUG between 10-20 seconds without any liver or kidney disease or uncontrolled hypertension or diabetes or morbidly obese (body fat >30% for male or 35% for women)	77	HMB, 5 g L-arginine and 1.5 g L-lysine. If weight >68 kg, 3 g HMB, 7.5 g L-arginine, 2.25 g L-lysine per day	Placebo drink	2-3	12 months
Deutz et al., 2013 (15)	RCT	60-79yo, healthy SPPB ≥9, not taking any protein supplements. After recruitment, participants were confined to complete bed rest for 10 days	19	2 x 1.5 g Ca-HMB, 4 g maltodextrin and 200mg calcium with additional sweetener and flavoring agents	Placebo	3	8 weeks
Malafarina et al., 2017 (31)	RCT	≥65, diagnosed with hip fracture (Barthel Index <40 prior to fracture, and pathological fracture were excluded), diagnosed with sarcopenia according to EWGSOP	107	Standard diet, 2 x 220mL HMB (Ensure Plus), 0.7 g HMB/100mL	Standard diet	3.08	Unspecified (from admission to rehabilitation centre until discharge – average length of stay was 42.3 ± 20.9 days)

EWGSOP (31). The use of specific criteria to define sarcopenia or frailty may be crucial in recruiting participants who had experienced significant muscle loss to receive the expected benefit of supplementation. Further RCTs which use clear operational criteria for sarcopenia or frailty are required to confirm this finding.

All included studies provided 3 g of HMB supplementation (15, 19, 31), an amount that has been shown to attenuate protein breakdown (18, 32). Baier et al. (19) adjusted the dosage of HMB supplementation according to the weight of subjects, where subjects weighing ≤68 kg were assigned to 2 g of HMB/day, while those weighing over 68 kg were provided with 3 g of HMB/day. In a human study comparing different daily dosage of HMB (32), 3 g of HMB/day resulted in dose-response attenuation of muscle breakdown as indicated by decreased levels of muscle enzymes creatine kinase (CK) and lactate dehydrogenase (LDH).

One study combined HMB with L-arginine (Arg) and L-lysine), two essential amino acids that are also known to have the capacity to stimulate protein synthesis (33-35). L-lysine is considered as the most limiting amino acid in MPS and having additional L-lysine with HMB supplementation could further stimulate MPS (34, 35). Therefore, a combination of HMB/Arg/Lys supplement could synergistically improve muscle mass, strength and function.

HMB supplementation is also considered safe as shown by studies done in animals and humans. In an animal study, a dose equivalent to almost 50 g HMB daily for 81 kg human male showed no adverse effects in rats over 3 months (23). Furthermore, consumption of 2 – 3 g HMB daily had no adverse effects on blood or urine parameters of blood lipid profile, biochemistry, hepatic and renal function (19). Similarly, administration of 6 g HMB did not result in changes in those urine and blood parameters (36). However, there have been contradicting reports regarding the effect of HMB on insulin sensitivity. One study reported that HMB could potentially ameliorate insulin resistance via the inhibition of GLUT-2 in liver (37). Another study on rats reported hyperinsulinemia following HMB supplementation that could indicate a degree of insulin resistance (38). This hyperinsulinemic state could be due to the increase in the activity of growth hormone/insulin-like growth factor axis following HMB supplementation (38). On the other hand, Yonamine et al (39) reported impairment of insulin sensitivity upon consumption of HMB in healthy sedentary rats. However, no similar findings have been demonstrated in humans (18). To date, the consumption of HMB has been deemed as safe for both young and old populations. Further research is still required to further assess possible adverse outcomes of HMB, including on insulin sensitivity.

The main limitations of this study are the small number of studies and sample size. The variation in subject recruitment and methodology could also have influenced the outcome of this study. Hence, the effect of HMB supplementation on muscle mass, strength and function in older people with sarcopenia or frailty could be underestimated.

Conclusion

This systematic review shows that HMB can improve lean body mass and preserve muscle strength and function in older people with sarcopenia and frailty. Further well-designed RCTs in this area of research are necessary to better identify the role of HMB in this population.

Conflict of interest: The authors have no conflict of interest to declare.

Ethics standard: The authors declare that the review comply with the current laws of the country in which it was performed.

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