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Review

Efficacy of β-hydroxy-β-methylbutyrate supplementation in elderly and clinical populations

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ABSTRACT

Muscle loss is common during aging and chronic diseases, such as cancer and acquired immunodeficiency syndrome. Moreover, muscle loss has been correlated with decreased physical function, quality of life, and mortality in these populations. Therefore, interventions to counteract muscle loss in the elderly and clinical populations are needed. Recently, the efficacy of the leucine metabolite, β-hydroxy-β-methylbutyrate (HMB), to maintain muscle mass has been investigated in these populations. Many studies have found increases in lean mass and strength in the elderly and clinical populations when using HMB; however, not all studies have found beneficial effects of HMB supplementation. The present review summarizes published human studies investigating the efficacy of HMB supplementation in the elderly and clinical populations. In addition, the mechanisms by which HMB may exert its effects are summarized and future research directions are suggested.

Introduction

Muscle loss is common throughout the aging process and may begin as young as 30 y of age [1]. Approximately 30% of muscle mass is lost between the fifth and eighth decades of life and rates of muscle loss can reach up to 15% per decade by 70 y of age [2,3]. Moreover, low levels of muscle mass in the elderly have been correlated with decreased physical function [4], decreased quality of life [5], and increased mortality [6]. A similar relation exists in many clinical populations such as patients with cancer or acquired immune deficiency syndrome (AIDS), where muscle wasting is common. Indeed, low levels of lean mass in clinical populations have been correlated with decreased physical function, decreased quality of life, poorer response to treatment, and increased mortality [7–10]. Therefore, interventions to maintain or potentially increase lean mass in elderly and clinical populations are needed. Recently, β-hydroxy-β-methylbutyrate (HMB) has been researched for its muscle-sparing properties in these populations. The present review summarizes the evidence for use of HMB in human elderly and clinical populations.

Methods

Searches were performed using the PubMed database with terms such as *HMB*, *beta-hydroxy-beta-methylbutyrate*, *HMB muscle*, *HMB supplementation*, and *HMB exercise*. Results were thoroughly reviewed for primary research studies on HMB supplementation in clinical and elderly populations, HMB supplementation in animal models of disease, HMB safety and dosage studies, and studies on the potential mechanism of action of HMB. In addition, review articles on HMB supplementation were obtained and the reference sections of all articles were thoroughly examined for appropriate studies. All articles meeting the inclusion criteria are discussed below.

Metabolism and dosage

HMB is a metabolite of the ketogenic amino acid leucine. A small amount (~0.3–0.4 g/d) of HMB is produced endogenously through leucine metabolism. The first step in leucine oxidation is transamination to ketoisocaproate. The majority (approximately 95%) of ketoisocaproate is metabolized to isovaleryl coenzyme A by the mitochondrial enzyme branched-chain α-keto-acid dehydrogenase and ultimately enters the citric acid cycle.

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However, a small amount of ketoisocaproate (approximately 5%) is converted to HMB by α-ketoisocaproate dioxygenase in the cytoplasm and ultimately metabolized into cholesterol [11].

Although HMB can be synthesized endogenously from leucine, approximately 60 g of leucine would need to be consumed daily to reach the HMB dosage of 3 g/d that has been used in most previous studies [12]. High leucine protein sources, such as dairy, eggs, and meats, contain roughly 7% to 10% leucine [13]. Therefore, to obtain 60 g of leucine from the diet, one would have to consume at least 600 g of protein from a high-leucine protein source daily. Clearly, this level of consumption is not practical; therefore, to obtain HMB 3 g/d, supplementation of HMB is necessary.

When supplemental HMB is consumed, HMB peaks in circulation at 1 to 2 h and reaches baseline levels by 9 h after consumption, suggesting that the consumption of HMB in multiple dosages throughout the day may be optimal [14]. In addition, when HMB 1 to 6 g is supplemented, approximately 14% to 29% is excreted in the urine [14,15]. Therefore, it appears that a majority of supplemental HMB remains in the body.

Most researchers seem to agree that the optimal dosage of HMB is 3 g/d. This recommendation comes from previous research by Nissen et al. [16] who showed that HMB supplementation at 3 g/d in strength-training healthy subjects increased strength in a dose-dependent manner. Furthermore, Gallagher et al. [15] showed that HMB 3 g/d significantly increased total body strength in healthy strength-training subjects compared with a control group that strength trained but did not receive HMB, whereas the consumption of HMB 6 g/d did not result in any additional increases in total body strength. As a result of these studies, the HMB dosage of 3 g/d is the commonly agreed on dosage of supplemented HMB. Unfortunately, no dose–response studies have been conducted in clinical or aging populations and it is not clear if 3 g/d is ideal under these conditions or if more may be required to optimize the effects of HMB.

Safety of HMB

With consumption of any dietary supplement, safety is a concern. Accordingly, the safety of HMB supplementation has been widely studied [17–20]. Early studies in animals found that the consumption of HMB in dosages as high as 100 g/d in pigs weighing 20 kg (approximately 100 times the HMB dose used in most human studies) for 4 d had no effect on changes in blood cell numbers, organ weights, or histologic lesions [17]. Likewise in humans, the consumption of dosages as high as 6 g/d for 1 mo had no effect on liver enzymes, kidney function, cholesterol, white blood cells, hemoglobin, or blood glucose [18]. Furthermore, two meta-analyses on HMB supplementation have concluded that HMB is safe and does not result in any major side effects [19,20]. In fact, HMB may actually decrease blood pressures and total and low-density lipoprotein cholesterol, especially in hypercholesterolemic individuals [19]. Moreover, two relatively short-term studies in clinical populations showed no major negative side effects [21,22]. However, there is less research on the long-term effects of HMB supplementation in elderly and clinical populations. Recently, Baier et al. [23] examined the effects of HMB 2 to 3 g/d for 1 y in the elderly and found that HMB consumption did not result in any changes in blood or urine markers of hepatic or renal function or blood lipids. Therefore, it appears that up to 1 y of HMB supplementation is safe; however, future studies should investigate the long-term safety of HMB supplementation, especially in clinical populations.

Efficacy of HMB in healthy populations and athletes

Previous studies investigating HMB supplementation in athletes and healthy populations have shown mixed results. A meta-analysis of nine studies found that HMB resulted in significant gains in muscle size and strength [24]. However, a more recent meta-analysis of 11 studies by Rowlands et al. [25] concluded that 3 to 9 wk of HMB supplementation at a dosage of around 3 g/d resulted in only small to trivial increases in muscle strength and only trivial increases in muscle size, regardless of training experience. As pointed out by Wilson et al. [12], the discrepancies in the results of HMB supplementation studies in healthy populations may be due to many factors, including clustering of data in these meta-analyses to include many studies from similar groups, small samples, poorly designed, non-periodized training protocols, and lack of specificity between training and testing conditions. Moreover, thus far, direct measurements of changes in muscle size have been poor and generally indirect, which makes it difficult to truly quantify the effects of HMB in healthy populations. Thus, although the effects of HMB supplementation in athletes and healthy populations can be debated, it is beyond the scope of this review to do so. Interested readers are encouraged to read the article by Wilson et al. [12].

Efficacy of HMB in the elderly

The effects of HMB supplementation in elderly populations have been examined in several studies (Table 1) [23,26–29]. Hsieh et al. [26] investigated the effects of HMB in elderly subjects receiving tube feeding. The subjects were assigned to usual care ($n = 40$) or HMB 2 g/d ($n = 39$) for 28 d. All tube-feeding protocols remained the same throughout the study. After 28 d, HMB supplementation increased weight, body mass index, and waist, hip, and calf circumferences. In addition, HMB supplementation resulted in a decrease in nitrogen excretion, suggesting that HMB decreased protein breakdown and/or increased protein synthesis. The investigators concluded that HMB was beneficial to malnourished elderly receiving tube feeding; however, this study did not measure body composition to determine if the increases in weight were from lean or fat mass.

The efficacy of HMB supplementation on lean mass and physical function in healthy elderly populations has also been investigated. Vukovich et al. [27] compared the effects of 8 wk of HMB supplementation on body composition and strength in 70-y-old men and women. Subjects were assigned to HMB 3 g/d ($n = 14$) or a placebo containing rice flour 3 g/d ($n = 17$) and all subjects participated in 5 d of supervised exercise per week. Strength training was completed twice weekly and consisted of two sets of 10 to 15 repetitions on eight exercises at 70% of one repetition maximum. On the other 3 d of exercise, subjects participated in 60 min of walking and stretching. At the end of 8 wk, upper body strength increased by nearly 15% and lower body strength was increased approximately 20% in the two groups; however, there was no difference in strength changes between the groups. A near significant 0.8-kg increase in lean mass ($P = 0.08$) was observed in the HMB group measured by skinfold calipers, whereas no change was observed in the placebo group. In a subset of subjects, lean body mass was also assessed by dual x-ray absorptiometry (DXA); however, no difference was observed between the groups. The HMB group also had an approximately 8% decrease in fat mass measured by computed tomography; however, no differences in lean mass change were observed between the groups as measured by computed

Table 1
Summary of β-hydroxy-β-methylbutyrate supplementation studies in elderly humans

Study	Dosage (daily)	Length of study	Exercise	Results and comments
Vukovich et al., 2001 [27]	HMB 3 g	8 wk	2 d strength training and 3 d aerobic exercise	HMB ($n = 14$) ↑ LBM by 0.8 kg measured by calipers ($P = 0.08$); no difference in LBM measured by DXA or strength between HMB and placebo groups ($n = 17$)
Flakoll et al., 2004 [28]	HMB 2 g, arginine 5 g, lysine 1.5 g	12 wk	none	HMB ($n = 27$) ↑ LBM by 0.7 kg measured by BIA ($P = 0.08$); HMB ↑ leg extensor strength by 3 kg, ↑ grip strength, and ↓ "timed up-and-go" test time by 2.3 s; no changes in LBM, leg strength, grip strength, or "timed up and go" test time in placebo ($n = 23$) group
Baier et al., 2009 [23]	HMB 2–3, arginine 5–7.5 g, lysine 1.5–2.25	1 y	none	HMB ($n = 40$) ↑ LBM by 0.55 kg measured by DXA; no change in LBM in control group ($n = 37$); no change in bone mineral density, strength, physical function, or quality of life in either group
Hsieh et al., 2010 [26]	HMB 2 g	4 wk	none	subjects receiving tube feeding; HMB ($n = 39$) ↑ bodyweight, BMI, hip, and calf circumference; HMB ↓ nitrogen excretion; no changes in BMI, hip, or calf circumference in control group ($n = 40$)
Fuller et al., 2011[29]	HMB 2–3 g, arginine 5–7.5 g, lysine 1.5–2.25 g	1 y	none	additional analysis of Baier et al. [23]; vitamin D status affected strength gains; HMB + adequate vitamin D status ↑ total body strength by 21%; no change in strength in HMB-supplemented subjects with vitamin D deficiency or in placebo group

↑, increased; ↓, decreased; BIA, bioelectrical impedance analysis; BMI, body mass index; DXA, dual x-ray absorptiometry; HMB, β-hydroxy-β-methylbutyrate; LBM, lean body mass

tomography. Overall, HMB decreased fat mass and may have increased lean mass over a relatively short term in exercising adults; however, this increase in lean mass did not appear to result in additional increases in muscle strength. Moreover, measurements of basic physical function and quality of life were not performed so it cannot be determined if the additional lean mass gained as a result of HMB supplementation resulted in significantly improvements or clinically significant outcomes over strength training alone. In addition, measurement of lean mass with skinfold calipers is not the gold standard method for measuring body composition and skinfold caliper measurements did not show the same results as the subset of subjects who underwent DXA. Although the results in this study provide mild support for the use of HMB in exercising elderly individuals, future studies investigating the effects HMB supplementation in strength-training elderly using a longer intervention and using more precise measurements of body composition are needed to confirm these findings.

The effects of HMB supplementation in the elderly without an exercise intervention have also been examined. Flakoll et al. [28] investigated the effects of 12 wk of HMB supplementation in subjects older than 62 y living in nursing homes. Subjects were randomly assigned to HMB 2 g/d, arginine 5 g/d, and lysine 1.5 g/d ($n = 27$) or a placebo ($n = 23$). A near significant 0.7-kg increase in lean mass was observed ($P = 0.08$) as measured by bioelectrical impedance and Bod Pod (LMI Inc., Concord, CA, USA), whereas no changes in lean mass were observed in the placebo group. Moreover, subjects in the HMB group significantly decreased their "timed up-and-go" test time by 2.3 s, increased leg extensor force by 3.0 kg, and increased handgrip strength compared with the placebo group. These improvements in physical function suggest that HMB supplementation can improve clinically significant outcomes in the elderly. Moreover, all changes were observed without an exercise intervention, suggesting that HMB alone may be able increase lean mass and improve physical function in the elderly.

To further investigate the ability of HMB to increase lean mass and physical function independently of exercise, Baier et al. [23] investigated the effects of 1 y of HMB supplementation in subjects 65 y and older. Subjects were given HMB 2 to 3 g/d, arginine 5 to 7.5 g/d, plus lysine 1.5 to 2.25 g/d ($n = 40$) or an isonitrogenous control made up of non-essential amino acids ($n = 37$). One year of HMB supplementation increased lean mass by 0.88 kg as measured by bioelectrical impedance analysis and 0.55 kg as measured by DXA, whereas no significant changes in lean mass were observed in the control group. However, HMB did not result in any differences in bone density, timed up-and-go test time, chair stand, handgrip strength, leg strength, or quality of life between the groups. Overall, this study indicated that 1 y of HMB supplementation in sedentary older adults could increase lean mass. In addition, HMB supplementation did not improve physical function, which differed from the previous study by Flakoll et al. [28].

Interestingly, additional analysis of the study by Baier et al. [23] by Fuller et al. [29] found that vitamin D status affected strength gains. Subjects with adequate vitamin D status exhibited a nearly 21% net gain in total body strength during the 1-y HMB intervention, whereas those who did not have adequate vitamin D status did not gain strength after HMB supplementation. This suggests that vitamin D deficiency may blunt the increase in strength gains observed with HMB supplementation.

A possible confounder in many previous HMB supplementation studies in elderly populations was that lysine and arginine were supplemented in addition to HMB, so it is not possible to determine which of the supplements was effective or if there was a possible synergistic effect. To isolate the effects of HMB from those of lysine or arginine, our laboratory recently used a Fisher 344 rat model (unpublished data) to investigate the effects of HMB supplementation from young to middle age (44 to 60 wk) and from old to very old age (86 to 102 wk) [30]. HMB was given as 1% of the diet. The supplementation period of 16 wk represented approximately 16% of the rats' life span. Body fat mass increased by nearly 50% from young to middle age as measured by DXA ($P < 0.05$), but HMB supplementation prevented this gain. This is important because research has indicated that the onset of fat gain may increase whole-body inflammation and initiate sarcopenia. Moreover, supplementation with HMB throughout old age prevented any significant loss in muscle fiber dimensions and blunted the increase in the ubiquitin pathway typically seen with

age in the rats' soleus muscles. HMB also decreased fat mass and improved normalized limb strength by 23% as measured by the grip strength test [31] in the old group. Thus, HMB alone supplemented throughout old age may improve strength, maintain muscle size, and create an overall leaner phenotype.

Efficacy of HMB in clinical populations

Patients with a chronic disease such as cancer and AIDS develop significant muscle loss, which leads to decreased physical function, quality of life, and survival [10]. Numerous nutritional interventions have been investigated in an attempt to counteract muscle wasting in these populations; however, many of these interventions have been unsuccessful in attenuating muscle loss (reviewed in Klein et al. [32]). Recently, HMB has been investigated for its anticatabolic effects in clinical populations such as patients with cancer, AIDS, and chronic obstructive pulmonary disease (COPD; Table 2) [21,22,33–36].

Several studies have supported the efficacy of HMB to attenuate muscle loss in cancer cachexia. Numerous animal models of cancer have shown benefits from HMB supplementation, including an attenuation of weight loss [37–39] and tumor growth [38] and prolonged survival [40]. The decrease in tumor growth was thought to occur through a decrease in nuclear factor-κB p65 subunit expression [38]. Likewise, the efficacy of HMB supplementation in patients with cancer has been previously demonstrated. For instance, May et al. [21] recruited patients with solid tumors who had a documented weight loss of greater than 5% and a survival prognosis longer than 3 mo. Patients were assigned to HMB 3 g/d, arginine 14 g/d, and glutamine 14 g/d ($n = 18$) or an isonitrogenous mixture of non-essential amino acids ($n = 14$). HMB supplementation resulted in an approximately 1-kg increase of lean mass in 4 wk as determined by Bod Pod analysis. Despite these promising results, to our knowledge, no additional human trials have been conducted in patients with cancer. Future studies should investigate the long-term effects of HMB supplementation in patients with cancer to determine if the gains in lean mass observed in the first 4 wk are maintained long term and to determine if HMB can increase survival time in humans, as was shown in rats.

The efficacy of HMB supplementation to attenuate muscle wasting in AIDS has also been investigated. Clark et al. [22] recruited patients with AIDS and a weight loss greater than 5% over the previous 3 mo. Subjects were assigned to HMB 3 g/d, arginine 14 g/d, and glutamine 14 g/d ($n = 22$) or an isocaloric maltodextrin control ($n = 21$). Similar to the results observed in patients with cancer, 8 wk of HMB supplementation in patients with AIDS increased lean mass by 2.6 kg in 8 wk as determined by the Bod Pod. Moreover, HMB supplementation increased $CD3^+$, $CD4^+$, and $CD8^+$ cell numbers, indicating that HMB may improve the immune system of immunocompromised patients with AIDS. Despite these findings, no additional clinical trials have been performed in patients with AIDS. Therefore, similar to HMB research in patients with cancer, future studies should investigate the long-term effects of HMB supplementation in patients with AIDS and look into possible immune system benefits in patients with AIDS as a result of HMB.

The effects of HMB supplementation in trauma patients have also been investigated. Kuhls et al. [33] recruited trauma patients who were candidates for enteral feeding. Subjects received HMB 3 g/d, arginine 14 g/d, and glutamine 14 g/d ($n = 22$), only HMB 3 g/d ($n = 28$), or an isonitrogenous control ($n = 22$). After 4 wk, the two groups receiving HMB supplementation had decreased nitrogen excretion. The decrease in protein breakdown may have been observed as a result of a decrease in protein breakdown, an increase in protein synthesis, or a combination of these events occurring simultaneously. However, no significant differences were observed in inflammatory markers such as interleukin-6 and C-reactive protein or prealbumin, a marker of nutritional status. This indicates that HMB may decrease muscle protein breakdown in trauma patients; however, this does not appear to happen through a decrease in inflammation. Although these results support the use of HMB in trauma patients, the efficacy of HMB supplementation to maintain lean mass has not been investigated in this population.

Although the previous study did not find a change in inflammation in trauma patients, there is some evidence that HMB may be anti-inflammatory in certain clinical populations. Hsieh et al. [34] assigned patients with COPD to HMB 3 g/d ($n = 18$) or placebo ($n = 16$) for 7 d and found that HMB supplementation decreased C-reactive protein from 111.56 ± 91.47 to 46.19 ± 45.29 mg/L, whereas no change in C-reactive protein was observed in the placebo group. In addition, HMB supplementation lowered white blood cell numbers. However, HMB supplementation also increased total cholesterol, an effect that is different than previous studies, which have primarily shown a decrease in total cholesterol [19]. Although HMB may decrease inflammation in patients with COPD, the mechanism by which this happens is not well understood. Moreover, the effects of HMB supplementation on lean mass and strength have not been investigated in patients with COPD.

All the previously discussed studies have supported the use of HMB in clinical populations; however, not all studies have found

Table 2
Summary of β-hydroxy-β-methylbutyrate supplementation studies in clinical populations

Study	Population	Dosage	Study length	Results
Clark et al., 2000 [22]	AIDS	HMB 3 g, glutamine 14 g, arginine 14 g	8 wk	HMB ($n = 22$) ↑ LBM by 2.6 kg measured by Bod Pod; placebo group ($n = 21$) ↓ LBM by 0.7 kg measured by Bod Pod; HMB ↑ $CD3^+$, $CD4^+$, and $CD8^+$ cell numbers
May et al., 2002 [21]	cancer	HMB 3 g, glutamine 14 g, arginine 14 g	24 wk	HMB ($n = 18$) ↑ LBM by approximately 1 kg measured by Bod Pod; placebo group ($n = 14$) had no change in LBM
Marcora et al., 2005 [35]	rheumatoid arthritis	HMB 3 g, glutamine 14 g, arginine 14 g	12 wk	no effects on LBM, fat mass, bone mineral density, or strength in HMB or placebo group ($n = 18$/group)
Hsieh et al., 2006 [34]	COPD	HMB 3 g	1 wk	HMB ($n = 18$) ↓ CRP and WBC count; no change in CRP in control group ($n = 16$)
Kuhls et al., 2007 [33]	trauma	HMB 3 g, glutamine 14 g, arginine 14 g	4 wk	HMB ($n = 28$) and HMB/arginine/glutamine ($n = 22$) groups but not placebo ($n = 22$), ↓ nitrogen excretion; no change in CRP, IL-6, or prealbumin in any group
Clements et al., 2011 [36]	gastric bypass	HMB 3 g, glutamine 14 g, arginine 14 g	8 wk	no differences in total bodyweight, BMI, fat mass, LBM, or resting metabolic rate between HMB ($n = 14$) and placebo ($n = 16$) groups

↑, increased; ↓, decreased; AIDS, acquired immunodeficiency syndrome; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CRP, C-reactive protein; HMB, β-hydroxy-β-methylbutyrate; IL-6, interleukin-6; LBM, lean body mass; WBC, white blood cell

beneficial effects of HMB supplementation in clinical populations. Marcora et al. [35] supplemented patients with rheumatoid arthritis with HMB 3 g/d, arginine 14 g/d, and glutamine 14 g/d ($n = 18$) or an isonitrogenous mixture of non-essential amino acids ($n = 18$) for 12 wk. The HMB supplementation did not result in any change in total body mass, lean mass, fat mass, bone mineral density, or strength. Moreover, Clements et al. [36] supplemented the same HMB, arginine, and glutamine cocktail ($n = 14$) or provided usual care ($n = 16$) to patients after gastric bypass surgery for 8 wk and found that HMB supplementation had no effect on body weight, body mass index, fat mass, lean mass, or resting metabolic rate. Discrepancies in the results of these studies should be investigated to determine the potential reasons for differences in HMB efficacy between clinical populations.

A possible confounding factor in the previously discussed studies was that nearly all studies supplemented a cocktail of HMB in addition to arginine and glutamine, which were added to the cocktail for their effects on muscle protein synthesis, immune function, and wound healing [41,42]. Therefore, it is not possible to determine if the effects observed were due to HMB supplementation alone, the addition of the amino acids, or a possible synergistic effect of HMB, arginine, and glutamine. Therefore, future studies are advised to investigate this relation and to determine the effects of HMB alone in human clinical populations.

Efficacy of HMB in animal models of disease

The previously discussed studies are the only published investigations on the efficacy of HMB supplementation in human clinical populations. However, HMB supplementation has also been investigated in animal models of muscular unloading, sepsis, and muscular dystrophy. Hao et al. [43] investigated the effects of HMB using an animal model of unloading and reloading. They found that rats supplemented with HMB had significantly greater force production and increased plantaris and soleus cross-sectional areas after reloading. Moreover, HMB decreased the number of apoptotic nuclei after unloading. Kovarik et al. [44] induced sepsis in mice and injected HMB or saline. HMB decreased protein degradation, leucine oxidation, and proteosome activity, indicating that HMB may attenuate muscle loss during sepsis. In addition, Payne et al. [45] gave a combination therapy of HMB, creatine monohydrate, conjugated linolenic acid, and α-linoleic acid to MDX mice (an animal model of muscular dystrophy) and found that the cocktail increased grip strength, decreased grip strength fatigue, and decreased the amount of internalized myonuclei. These results indicate that HMB may be able to decrease muscle damage in muscular dystrophy and result in an increase in physical function. However, to date, no human studies of HMB supplementation in models of injury rehabilitation and unloading, muscular dystrophy, or sepsis have been performed.

Although HMB supplementation has shown positive results in clinical populations, more work is needed to determine the long-term efficacy and safety of HMB in the clinical populations discussed. Furthermore, research on the efficacy of HMB supplementation should be extended to additional clinical populations, such as patients with congestive heart failure, diabetes mellitus, chronic kidney disease, neurodegenerative diseases, or patients recovering from injuries.

HMB mechanism of action

Muscle tissue mass represents the net balance between muscle protein synthesis and degradation. The continuous process of building and replacing muscle protein allows muscle to repair and adapt to environmental conditions. Net protein balance is positive during growth when protein synthesis exceeds degradation, whereas the net balance is negative during weight loss, aging, and in clinical populations when degradation exceeds synthesis. Accordingly, numerous studies have investigated the effects on HMB on muscle protein balance. A summary of the potential mechanisms by which this occurs is found in Figure 1. Results of studies using cultured muscle cells have found that HMB decreases muscle protein degradation [37,46]. Moreover, HMB has been shown to decrease whole-body proteolysis in vivo [47]. However, the effects of HMB on muscle protein synthesis have shown mixed results, with studies finding that HMB supplementation results in increases [37] or no change [48] in muscle protein synthesis. Despite the discrepancies in the results of turnover studies, HMB supplementation has been shown to result in increases in phosphorylation of the mammalian target of rapamycin and its downstream signaling targets, indicating an increase in skeletal muscle protein translation [39,46]. In addition, increased muscle insulin-like growth factor-1 expression has been observed after the culture of myoblasts with HMB, which may contribute to an increase in protein synthesis [49]. Overall, it appears that HMB inhibits protein degradation and may stimulate protein synthesis, which may be due at least in part to an upregulation of muscle insulin-like growth factor-1 and increased mammalian target of rapamycin activation.

HMB may attenuate protein degradation through the inhibition of multiple catabolic pathways. The ubiquitin–proteosome pathway is upregulated in catabolic states [50] and results in an increased degradation of proteins. However, HMB has been shown to decrease ubiquitin–proteosome expression [37] and activity [37,44,47,51] during catabolic states, thereby attenuating ubiquitin–proteosome-induced protein degradation.

Caspases are commonly upregulated in catabolic states and induce muscle proteolysis by the apoptosis of myonuclei and are involved in the initial cleavage of the actomyosin complex [52]. However, HMB has been shown to attenuate increases in activated caspases in catabolic states such as skeletal muscle unloading [43] and in skeletal muscle cells cultured with large concentrations of tumor necrosis factor-α and angiotensin II [53]. In these studies, the decrease in caspase activation was correlated with decreased myonuclear apoptosis [43,53]. Thus, it appears that HMB attenuates apoptosis in catabolic states through an attenuation of caspase activation.

Muscle regenerative capacity is impaired in the elderly and cachexic states, which may further contribute to muscle protein catabolism [54]. Recently, HMB has been investigated for its effects on muscle regenerative capacity. Kornasio et al. [49] cultured myoblasts in a serum-starved state to induce apoptosis. When myoblasts were incubated with HMB, expressions of myogenic regulatory factor D (Myo D) and myogenin were increased, which suggests that HMB may increase satellite cell activation and increase muscle regenerative capacity. This may have occurred through an observed increased in Akt phosphorylation, which may have decreased FOX-O translocation and resulted in a decrease in atrogin-1, which may have resulted in a decreased degradation of Myo D [30]. Moreover, research from our laboratory has indicated that old resistance-trained rats supplemented with HMB were able to increase insulin-like growth factor-1 mRNA expression, whereas those not provided with HMB did not (unpublished data). In addition, HMB decreased the apoptosis of myoblasts, which suggests that HMB may be able to attenuate the decreases in the satellite cell numbers observed in the elderly and in cachexic states [55,56].

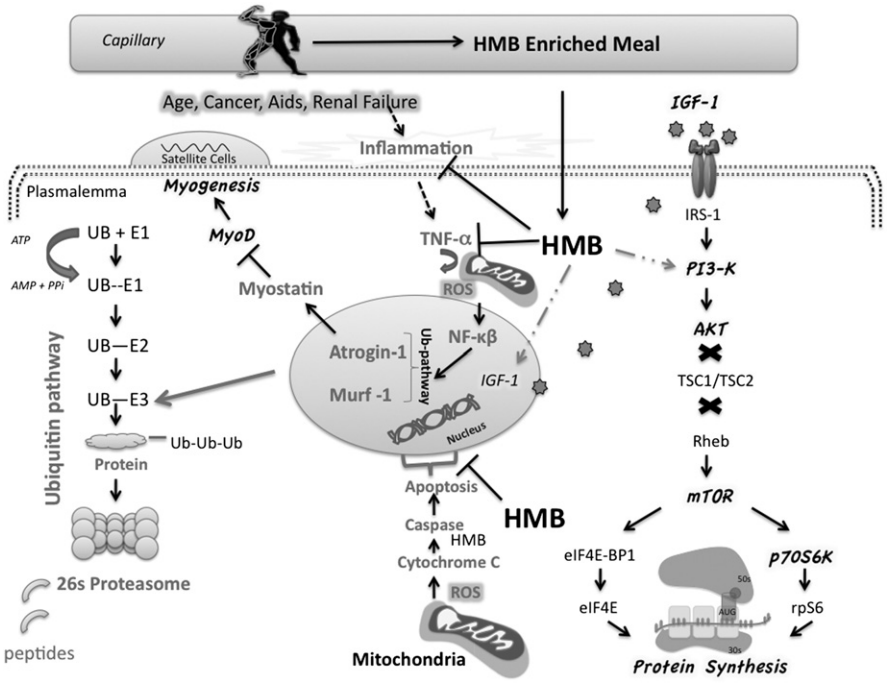

Fig. 1. Potential Mechanisms by which HMB increases anabolic and decreases catabolic pathways in skeletal muscle. Italicized text refers to signaling pathways that are decreased in the skeletal muscle cells of elderly and clinical populations as compared to healthy populations, while bold text refers to signaling pathways that are increased. HMB may increase protein synthesis by decreasing inflammation, increasing IGF-1, and increasing protein translation through activation of mTOR. Additionally, HMB may decrease protein catabolism through down regulation of the ubiquitin proteasome pathway and reductions in caspase activity. AMP, adenosine monophosphate; ATP, adenosine triphosphate; eIF4e-BP1, eukaryote initiation factor 4e binding protein 1; HMB, β-hydroxy-β-methylbutyrate; IGF-1, insulin-like growth factor-1; IRS-1, insulin receptor substrate-1; mTOR, mammalian target of rapamycin; MyoD, myogenic regulatory factor D; NF-κB, nuclear factor-κB; PI3-K, Phosphatidylinositol 3- and 4-kinase; PPi, Pyrophosphate; Rheb, Ras homolog enriched in brain; rpS6, ribosomal protein S6; ROS, reactive oxygen species; TNF-α, tumor necrosis factor-α; TSC, tuberous sclerosis complex; UB, ubiquitin.

Increased inflammation is common in aging and chronic disease and may lead to an increase in muscle protein degradation through the upregulation of the ubiquitin–proteasome pathway [57]. As mentioned previously, HMB may be able to decrease systemic inflammation in clinical populations [34]; however, not all studies have found decreases in inflammatory markers in human clinical populations after HMB supplementation [33]. Recently, Nunes et al. [58] investigated the mechanism by which HMB affects inflammation by culturing human peripheral blood mononuclear cells from healthy subjects in the presence of concanavalin A to stimulate an inflammatory response and increase concentrations of HMB. Peripheral blood mononuclear cells cultured with HMB and concanavalin A showed a significantly decreased production of inflammatory cytokines, including tumor necrosis factor-α and interferon-γ, compared with peripheral blood mononuclear cells cultured with concanavalin A alone. These results suggest that the decrease in muscle protein catabolism by HMB may be due in part to the effect of HMB on inflammatory cells; however, future studies are needed to confirm this potential mechanism.

Overall, HMB appears to exert its effects on skeletal muscle protein metabolism through numerous mechanisms, including improved muscle protein balance. HMB may increase skeletal muscle protein synthesis through an activation of the mammalian target of rapamycin pathway and by increasing skeletal muscle insulin-like growth factor-1 expression. In addition, HMB may decrease protein degradation by decreasing the activity and expression of the ubiquitin–proteosome pathway and caspases. Moreover, HMB may decrease inflammation and have beneficial effects on muscle regeneration. However, it should be noted that many of the mechanistic studies were performed in animal or cell culture models, where dosages of HMB were much larger than the dosages commonly used in human studies. Thus, future studies are needed to investigate the mechanisms of HMB action using more physiologic doses.

Conclusions

Muscle loss is common during aging and in chronic diseases, leading to decreased physical function, a decreased quality of life, and increased mortality. Recently, HMB has been shown to attenuate muscle loss in the elderly and in clinical populations such as patients with AIDS and those with cancer; however, a limited number of studies have investigated this question, with relatively small samples. In addition, the effects of HMB in clinical populations appear to differ depending on the population investigated. Accordingly, future studies should investigate the effects of HMB in other catabolic clinical populations. Overall, several studies have supported the efficacy of HMB supplementation in the elderly and clinical populations as a means to increase lean mass and strength; however, the data are not entirely consistent. Larger long-term studies are needed to clarify these promising preliminary results.

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