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β-Hydroxy-β-methylbutyrate (HMB) supplementation in prevention and treatment of elderly sarcopenia

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Abstract

β-Hydroxy-β-methylbutyrate (HMB) is a leucine metabolite, naturally appearing in human body. Both leucine and HMB are believed to be potent protein synthesis enhancers in skeletal muscles. The current articles reviews and summarizes findings from original studies on the possible therapeutic role of HMB in elderly sarcopenia. HMB seems to be capable of not only preventing, but also reversing sarcopenia. Five main effects on skeletal muscles have been noted: 1) inhibition of protein breakdown and thus lower muscle degradation, 2) increased endoplasmic reticulum calcium release, 3) lower fat content in skeletal muscle, 4) increased oxygen metabolism, 5) stimulation of satellite cells and thus muscle regeneration. Therefore, HMB emerges as potentially useful agent in treating and preventing sarcopenia.

Keywords: HMB, β-Hydroxy β-methylbutyrate supplementation, sarcopenia, older people, elderly

Introduction

β-Hydroxy-β-methylbutyrate (HMB) is the substance naturally appearing in the human body as it is one of the leucine metabolite (1), and the latter is known to play great role in the muscle as a protein synthesis enhancer (2). Thus, HMB is a very popular supplement among people that are put under increased physical effort, e.g. sportspeople (both professional and amateur) or soldiers, because it can improve not only muscle mass, but also overall endurance, strength, aerobic performance, fat mass loss – in combination with a proper training. Used as a supplement, it helps to reduce some disadvantageous processes that appear during and after periods of intense training or another physical stress, e.g. muscle damage, stress hormone or inflammatory response, and accelerate recovery (2–5). Due to HMB positive impact on skeletal muscle there are many studies describing

various medical uses (solo or in combination with other nutrients), starting from muscle wasting conditions, which will be analyzed partially in this review, through diabetic foot wounds (6) and pressure ulcers (7,8). There are also publications about possible uses of HMB in treatment of head and neck cancer patients for prevention of radiation dermatitis and mucosistis after chemoradiotheraphy (9,10). With potential medical use comes the need of safety evaluation, and here further results come from animal studies. Though there haven't been any adverse effects on internal organs, blood parameters and serum biochemistry pointed out during 90 days administration (11), there have been found disadvantageous impact on peripheral insulin sensitivity, which may cause the concern about later type II diabetes development (12,13).

Every sarcopenia definition emphasizes that this is age related process of muscle mass and function loss (14–19). Primary sarcopenia is diagnosed when there is no other (apart from age) clinical reason for a decrease in muscle mass. Secondary sarcopenia is diagnosed as a condition accompanying other diseases (chronic heart failure, chronic obstructive pulmonary disease, pulmonary fibrosis, rheumatoid arthritis, chronic infections, chronic kidney disease, liver cirrhosis, diabetes mellitus, endocrine diseases, chronic diseases of the gastrointestinal tract, alcoholism, drug abuse, chronic neurological disorder, sedentary lifestyle or dwelling in zero-gravity conditions) (20). In the course of sarcopenia muscle composition changes – type II muscle fiber number and size are decreased and thus, together with accumulation of fat, this may be the reason of muscle strength decline (21). Gradual age related muscle mass and strength loss appears after 50 years of life and comes along with 1-4% loss every year, it appears earlier (22) and is more intense in women than in men (23,24). According to Baumgartner *et al*. sarcopenia affects 13 to 24% of people aged 65 to 70 (25). In another study sarcopenia was diagnosed in 22.6% of women (64-93 years of age) and 26.8% men (64-92 years old) (26). Men and women without chronic diseases in their sixties and seventies lose 20-40% of muscle mass compared to younger people. There is a similar strength reduction for proximal and distal skeletal muscles (15). Possible causes of primary sarcopenia are: decrease in α-motoneuron amount; changes in sex steroids and growth hormone (GH) levels; insufficient calories and protein intake; low physical activity; imbalance between fiber loss and regeneration (15,27,28).

European Working Group on Sarcopenia in Older People indicates dual energy X-ray absorptiometry (DEXA) and bioimpedance analysis (BIA) as the most useful methods for evaluation of muscle mass, handgrip dynamometer for muscle strength measurement, Short Physical Performance Battery test (SPPB) and gait speed test for assessment of physical performance (20). The diagnosis of sarcopenia must be based on documentation of and/or low physical performance (20). There is a negative correlation between C-reactive protein concentration in the blood serum and muscle mass in patients with rheumatoid arthritis and other connective tissue diseases. The proinflammatory cytokines, like TNFα or Il1β, which are involved in pathogenesis of rheumatoid arthritis, play a role in development of sarcopenia (29,30). Aging itself is associated with gradual increase in proinflammatory cytokines: Il-6 and Il-1 (31).

There are studies indicating that, due to β-hydroxy-β-methylbutyrate protein synthesis and breakdown balancing properties, supplementation with HMB or mixtures containing it may improve elderly people physical performance. The main effects of HMB on muscle tissue are shown in Figure 1 (Fig. 1.)

HMB supplementation in sarcopenia

Starting from rat experiments – it has been noticed that in aging rats HMB administration prevents from strength loss and muscle fiber size decline. Muscle strength was measured by the grip strength test and, as a result, it has been stated that the limb strength (normalized to body mass) has been retained comparing young and middle aged rats and even increased comparing old and very old rats

(23%) due to HMB supplementation. Using diffusion tensor imaging (DTI) technique it has been shown that cross sectional area of soleus and gastrocnemius muscles has been maintained in old and very old rats comparing to the controls. HMB has also reduced atrogin-1 mRNA level in examined muscles of very old rats, but researchers haven't found any differences in levels of both positive or negative myogenesis factors like IGF or myostatin (32).

In a healthy muscle and without any training HMB hasn't been able to affect lean body mass or body weight in mice (33), which stands in the opposition to human studies, in which HMB in mixtures with arginine and glutamine (34) or arginine and lysine (35) has improved lean body mass without any training. Neither mTOR nor AKT levels have been observed to change in this study, but even though age-related peak force decrease has been attenuated by HMB, and this might be due to reversing unfavorable age-related changes in mMSC (muscle mesenchymal stem/stromal cells), which play a role in satellite cell activation. Additionally, HMB impact on cognitive function has been investigated but no significant changes have been noticed (33). In contrary, in another study HMB has positively influenced working memory performance and learning ability in middle-aged and old rats (36). This is also consistent with the same authors studies with the Morris water maze test performance (37) and examination of pyramidal neurons dendritic tree in rats prefrontal cortex (38). In both experiments, age-related deficits have been reversed by HMB usage, which additionally supports HMB usage among elderly.

12 weeks administration of 2 g of HMB with some arginine and lysine has improved muscle function and strength, protein synthesis level and muscle mass in the group of older women. It has been suggested that HMB has slowed protein breakdown, while protein synthesis has been increased by other mixture components, and triggered lean body mass increase (39). In another study leg muscle strength in older women has been significantly increased due to 1.5 g per day HMB intake, however, there haven't been any advantageous changes in SPPB (Short Physical Performance Battery) score and handgrip strength. In contrary to handgrip, endurance and 6-minute walking test performance have been improved. Authors have proposed that these changes might have appeared due to increased muscle density and decreased fat content in the muscle and thereby better muscle quality (40). The mixture containing HMB and vitamin D has enhanced many anthropometric parameters, e.g. BMI, fat and fat-free mass and weight. Quality of life measured by SF 36 questonnaire has improved and hangrip has been stated to get stronger (41).

In the experiment on the cell culture HMB has augmented C_2C_{12} myoblast proliferation and viability. It has been shown that depolarization-induced and calcium-induced calcium release and total calcium storage in sarcoplasmic reticulum have been increased. This is in line with later observation in another part of this experiment that HMB has shorten the time needed to reach peak contractile force *ex vivo* in muscles from late middle-aged mice. It has been indicated once again that HMB is more effective on fast twitch muscles, like extensor digitorum longus, than slow, like soleus muscle, when it comes to strength and muscle quality maintenance. In co-supplementation with β-alanine HMB has increased contractile force in extensor digitorum longus and resistance to fatigue in soleus muscle (42). The same nutrients combination has been able to decrease MuRF1 level, which suggest restraining effect on muscle protein breakdown, but no effect on muscle mass, cross sectional area and muscle force and fatigue resistance has been stated (43).

Apart from age, lack of physical activity causes additional loss of muscle mass, which promotes further strength loss (44). Strength decrease has been stated as one of the important factors contributing to increased number of falls among older people (45) which leads to hospitalizations and bed rest in the same time with further serious consequences (46). Sarcopenia is an independent risk factor for falls and premature death (47).

In relatively healthy elderly humans it has been noticed that HMB can prevent lean body mass loss after 10 days of bed rest. The supplement administration has restrained lean body mass loss in arms and fat gain, which have appeared in control group. Additionally, in some patients after 8 weeks of recovery, during which resistant training was performed 3 times a week, increase in leg muscle mass and strength in comparison to value from before bed rest has been observed. However, authors haven't found any statistically significant effect on protein synthesis, which they suggest might be due to too low amino acids supply. The values of strength measurements have been slightly higher in HMB group but haven't reached statistical significance (48). In the similar study no difference has been noticed in the cross sectional area of muscle fiber, even though there has been decrease in lean leg mass in the control group. HMB has been stated to protect muscles from inflammatory and ROS degradation during bed rest and increased oxidative phosphorylation processes during resistant training rehabilitation. This suggests that HMB together with training improves muscle fibers oxygen metabolism (49).

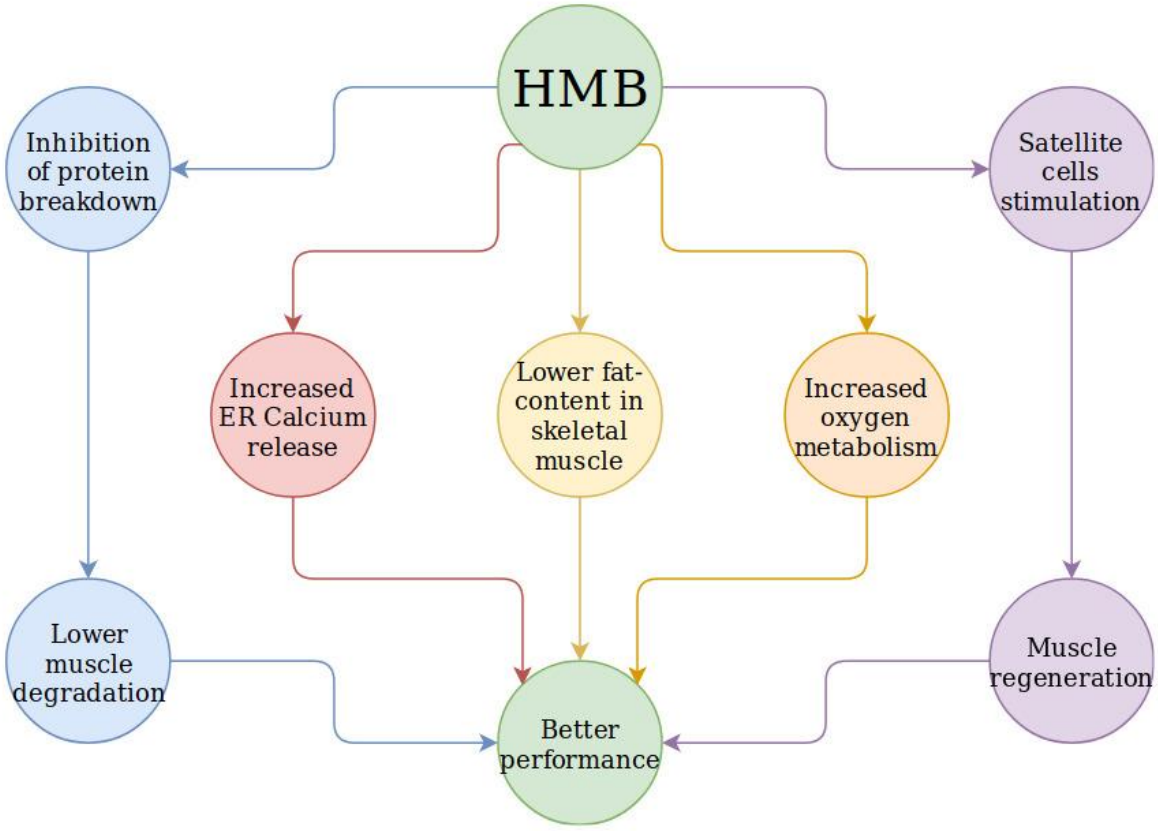

Fig. 1. Five main effects of HMB supplementation on skeletal muscles. ER – endoplasmic reticulum, HMB – β-hydroxy-β-methylbutyrate.

Another experiment examined HMB influence on muscle regeneration process after limbs immoblization in old rats – to test the supplement usefulness in sarcopenia resulting form muscle disuse. It has been shown earlier that muscle regeneration in such states is effective in young animals, but not so much in old ones. In this study HMB has demonstrated positive effect on muscle satellite cells proliferation and differentiation. Thereby, amount of cells in the muscle fiber has increased which positively influences muscle protein synthesis. These effects have been marked mostly in fast twitch muscle fibers. No significant differences have been observed in the levels of mTOR signaling pathway proteins (50). Though HMB cannot restrain muscle mass loss during

hindlimb suspension, it can partially prevent fiber cross sectional area decrease and improve regeneration process after unloading due to, among other possible mechanisms, suppression of mitochondrial-caspase signaling pathway. Nuclei apoptosis is decreased during unloading, so after that protein synthesis ability is better and muscle can regenerate (51).

However, in comparison with leucine HMB seems to have weaker protecting effect on muscles while immobilized or during dexamethasone treatment. While leucine is able to retain muscle mass in immobilized rats, HMB haven't done that both in case of immobilization and dexamethasone treatment (44). Though, the experiment was conducted on soleus muscle, in which majority of fibers are slow ones, and HMB is known to affect fast twitch fibers more (50), in this study cross sectional area of any type of fibers hasn't been maintained due to HMB administration. But when it comes to atrogenes, HMB has been able to decrease upregulated level of Mafbx/Atrogin only in dexamethasone group, while leucine has done that in both immobilized and dexamethasone treatments (44).

Summary

The results of numerous studies show that HMB can be recommended as a useful supplement in preventing or even reversing muscle loss in elderly. It acts in several ways: enhancing satellite cells proliferation and differentiation, suppressing inflammatory response and nuclei apoptosis, lowering protein breakdown level and increasing calcium releasing from sarcoplasmatic reticulum.

The authors declare no conflict of interest.

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