

POTENTIAL OF MESOTHERAPY AND BETA-HYDROXY-BETA-METHYLBUTYRATE (HMB) IN MUSCLE HYPERTROPHY

Amanda Figueredo de Oliveira¹; Rodrigo Cé¹

¹Centro Universitário Avantis – UNIAVAN - Av. Marginal Leste, 3600, Estados, Balneário Camboriú – SC – Brazil. CEP: 88339125. E-mail addresses: rodrigoce_@hotmail.com

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Abstract

Introduction: Mesotherapy is a medical technique that administers medications directly to the affected area, using reduced and localized doses to achieve a specific therapeutic effect. **Objective:** To explore the potential of mesotherapy combined with HMB (beta-hydroxy-beta-methylbutyrate) in promoting muscle hypertrophy. **Methodology:** This study consists of a review of the scientific literature, covering articles, meta-analyses, and experimental studies on the synthesis, metabolism, efficacy, dosage, and mechanisms of action of HMB. **Theoretical Framework:** HMB, a metabolite of leucine, is recognized for its anticatabolic effects and is gaining attention for its ability to enhance athletic performance and promote muscle hypertrophy. The role of HMB in preserving and increasing muscle mass underscores its effectiveness in both sports and clinical contexts, particularly in debilitated individuals. However, the efficacy of HMB may vary depending on the context of application, exercise intensity, and the health status of individuals. **Conclusion:** It is concluded that mesotherapy associated with HMB is a promising approach for promoting muscle hypertrophy, especially under specific conditions. However, its efficacy is influenced by various factors, and future research should focus on controlled clinical studies to determine the optimal conditions for HMB use.

Keywords: Mesotherapy; hypertrophy; HMB; muscle mass.

Resumo

Introdução: A mesoterapia é uma técnica médica que administra medicamentos diretamente na área afetada, utilizando doses reduzidas e localizadas

para alcançar um efeito terapêutico específico. **Objetivo:** Explorar o potencial da mesoterapia combinada com o HMB (beta-hidroxi-beta-metilbutirato) na promoção da hipertrofia muscular. **Metodologia:** Este estudo consiste em uma revisão da literatura científica, abrangendo artigos, meta-análises e estudos experimentais sobre a síntese, metabolismo, eficácia, posologia e mecanismos de ação do HMB. **Teórico Referencial:** O HMB, um metabólito da leucina, é reconhecido por seus efeitos anticatabólicos e vem ganhando destaque por sua capacidade de melhorar o desempenho atlético e promover a hipertrofia muscular. O papel do HMB na preservação e aumento de massa muscular ressalta sua eficácia tanto em contextos esportivos quanto clínicos, especialmente em indivíduos debilitados. No entanto, a eficácia do HMB pode variar de acordo com o contexto de aplicação, a intensidade do exercício e o estado de saúde dos indivíduos. **Conclusão:** Conclui-se que a mesoterapia associada ao HMB é uma abordagem promissora para a promoção da hipertrofia muscular, especialmente em legislação específica. Entretanto, sua eficácia é influenciada por diversos fatores, e futuras pesquisas devem se concentrar em estudos clínicos controlados para determinar as condições ideais para o uso do HMB.

Palavras-chave: Mesoterapia; hipertrofia; HMB; massa muscular.

I. INTRODUCTION

Mesotherapy is a medical technique that aims to administer medications directly to the affected area using intradermal or superficial subcutaneous routes. This therapeutic approach, which does not differ from conventional medicine in

terms of the medications used, is characterized by the application of reduced doses near the diseased region [1]. This localized application seeks to achieve a specific pharmacological effect without the need for high doses that affect systemic circulation. It is essential that the technique be performed after a thorough clinical evaluation and a favorable diagnosis [2].

HMB (beta-hydroxy-beta-methylbutyrate) is a natural metabolite derived from the breakdown of leucine, a branched-chain amino acid. In recent years, the popularity of this supplement has grown, motivating various studies to investigate its effects on athletic performance in both trained athletes and untrained individuals [3]. In a meta-analysis conducted by NISSEN and SHARP in 2003 [4], involving 250 supplements for muscle mass gain, only six showed consistent evidence of increased muscle mass, with only two, creatine and HMB, being considered effective for this purpose. Additionally, studies such as that of Holecek in 2017 [5] report the positive effects of HMB on power and endurance exercises, including the reduction of exercise-induced muscle damage, increased hypertrophy and muscle strength, improved performance in aerobic exercises, resistance to fatigue, and regenerative capacity, both in untrained individuals exposed to strenuous exercise and in trained individuals subjected to periods of high physical stress.

Skeletal muscle hypertrophy results from an increase in the cross-sectional area of muscle fibers. This adaptive aspect is common in muscle tissues subjected to physical exercise, especially strength training. The magnitude of hypertrophy is directly related to the type and intensity of exercise, with strength training generally inducing more significant hypertrophy compared to other types of physical exercise [6]. According to Schiaffino et al. (2021) [7], muscle hypertrophy can be triggered by various mechanisms, including the action of hormones and growth factors that act as positive regulators of muscle growth, as well as by neutralizing negative regulators. By stimulating protein synthesis, altering the transcriptional level, and activating ribosomal RNAs and specific

muscle genes, muscle growth can be controlled during the hypertrophy process.

Mesotherapy offers a localized therapeutic approach, aiming to administer medications directly to the affected area, which may have potential in promoting muscle hypertrophy without the adverse effects associated with systemic administration. Meanwhile, HMB (beta-hydroxy-beta-methylbutyrate) has gained prominence as a supplement with the potential to improve athletic performance and promote muscle hypertrophy. Therefore, this study aims to analyze the potential of mesotherapy and HMB in promoting muscle hypertrophy, exploring their theoretical foundations, scientific evidence, and clinical applications. Additionally, it seeks to identify gaps in the literature and suggest directions for future research in this area, aiming to contribute to the development of more effective strategies in the field of bodybuilding and physical conditioning.

II. METHODOLOGY

This literature review manuscript followed a systematic approach to identify, analyze, and synthesize relevant information on the potential of mesotherapy and HMB (beta-hydroxy-beta-methylbutyrate) in promoting muscle hypertrophy. The review focused on analyzing studies that investigate the effects of mesotherapy and HMB on muscle hypertrophy. The main research question was: "What is the scientific evidence on the use of mesotherapy and HMB in promoting muscle hypertrophy?" Included in the review were clinical studies, literature reviews, meta-analyses, randomized clinical trials, observational studies, and systematic reviews published in the last 20 years (2004-2024). Excluded were articles that did not directly address the effects of HMB or mesotherapy on muscle hypertrophy, as well as studies with very small samples or insufficient methodological quality. The search was conducted using scientific databases such as PubMed, Scopus, Web of Science, and Google Scholar. Additionally, references from the selected articles were reviewed to identify further relevant studies. A combination of keywords and MeSH terms was used, including "mesotherapy,"

"HMB," "muscle hypertrophy," "supplementation," "physical exercise," "protein metabolism," and "localized therapy." These terms were combined to broaden and refine the search results.

III. THEORETICAL FRAMEWORK

A. Synthesis and Metabolism of HMB

Leucine, one of the essential amino acids, is a natural precursor of beta-hydroxy-beta-methylbutyrate (HMB), a relevant metabolite. Initially, leucine is converted into alpha-ketoisocaproic acid (alpha-KIC) through a reversible transamination. Alpha-KIC, present at concentrations similar to leucine, seems to have the ability to inhibit the manipulation of muscle proteins. The metabolic pathway of synthesized KIC can diverge depending on cellular location: in the mitochondria, it is converted into isovaleryl-coenzyme A (isovaleryl-CoA) by KIC dehydrogenase, while in the cytoplasm, it is converted into HMB by KIC dioxygenase [8]. Studies indicate that only about 5% of leucine is synthesized and converted into HMB in the cytosol [9].

In a study from the 1990s, it was found that the KIC-dioxygenase enzyme is identical to the tyrosine dioxygenase enzyme, whose stimulating effects include improved performance during training and reduced fatigue [10]. Focusing on the metabolic pathway through KIC dioxygenase, where the description of HMB occurs, it is observed that part of the synthesized HMB can be excreted in the urine, ranging from 10% to 40% of the total, besides the conversion of HMB into HMG-CoA, an essential substrate for the enzyme HMG-CoA reductase, important in cholesterol synthesis [9].

A proposed theory suggests that stressed and injured muscle cells may not be able to produce enough HMG-CoA for cholesterol, impairing their cellular functions, including cell membrane integrity. Thus, HMB supplementation could be an adequate source of HMG-CoA to maintain adequate cellular cholesterol concentrations for various functions. Additionally,

studies indicate that HMB may help reduce muscle damage caused by the release of creatine phosphokinase (CPK) from muscle cells and that the inhibition of cholesterol synthesis in muscle by drugs may, in the worst case, result in muscle cell death [10]. The calcium salt of HMB is the most common form in supplements, with a recommended daily dose of 3g [11].

B. Effects of HMB (Effects on Protein Metabolism in Skeletal Muscle)

HMB demonstrates its efficacy as an anti-catabolic agent, promoting increased strength and muscle mass while reducing the protein breakdown caused by intense physical exercise, contrasting with anabolic agents that focus on protein properties [12]. Through the activation of AMPK kinase and Sirt 1, HMB stimulates mitochondrial biogenesis, resulting in greater oxygen consumption, improved carbohydrate and lipid metabolism, as well as fat breakdown and reduced fat mass [13].

Studies on chronic adaptations indicate positive effects of HMB supplementation on muscle mass, body composition, and strength in both men and women, due to its various mechanisms of action in protein manipulation and synthesis [14]. Research also points to a significant increase in peak and anaerobic power with HMB use, without affecting aerobic influence or anabolic, catabolic, and inflammatory mediators, reinforcing its association with muscle mass and strength gains [15].

Furthermore, HMB can increase intramuscular glycogen and ATP levels [16]. Studies conducted by Pimentel et al. (2011) [17] also demonstrate an increase in mTOR expression and p70s6k phosphorylation, both regulators of protein synthesis in skeletal muscle, supporting HMB's ability to combat muscle atrophy in pathological conditions. HMB reduces muscle damage related to intense exercise and muscle protein breakdown, indicating that its metabolism into HMG-CoA in muscles, mammary tissue, and immune cells, as well as its role in cholesterol synthesis, may be crucial for optimal cell growth and function [18].

C. HMB as a Nutritional Supplement

The inclusion of new dietary supplements is being considered to preserve muscle mass. Examples include vitamin D, creatine, fish oil, and oral nutritional supplements (ONS), administered in isolation with nutritional guidance. HMB is produced in the body in small amounts as a leucine metabolite, representing 0.66% of total leucine turnover. Although HMB can also be found in foods such as cauliflower, avocado, catfish, and grapefruit, it would be impractical to reach the necessary dose solely through diet. Therefore, this nutrient can be supplemented in isolation, often combined with amino acids like arginine and glutamine [19].

From the perspective of muscle mass increase, HMB supplementation shows significant effects, especially in situations where muscle proteolysis is more intense, such as in non-exercising individuals exposed to this stimulation. Additionally, with the benefits brought by supplementation in sports contexts, HMB is also being applied in clinical practice for some pathological conditions [20]. A clinical trial conducted on hospitalized individuals treated with ONS supported evidence that HMB can prevent lean mass loss during bed rest, offering a positive benefit for malnourished and bedridden patients [21].

Muscle functionality, lean mass, and muscle strength show positive increases with HMB supplementation, especially in disease cases that affect physical function and lead to muscle mass loss. However, while many studies relate a significant increase in hypertrophy with HMB supplementation, not all studies achieve the same results. Therefore, it is crucial to consider factors such as underlying disorders, dosage used, and exercise intensity. It is suggested that HMB supplementation is most effective in situations where there is some pathology leading to muscle mass loss, while its effects in trained individuals are minimal [22].

The β -hydroxy- β -methylbutyrate (HMB) supplement has gained prominence for its potential benefits in increasing muscle mass, strength, and hypertrophy. Its mechanisms are associated with

anti-catabolic effects, with studies indicating that its free acid form (HMB-FA) may be even more effective, especially in trained and untrained individuals. Recently, several studies have explored its efficacy in untrained populations, showing an increase in protein synthesis stimulation and a reduction in inflammatory response.

A study involving patients with cirrhosis revealed promising results when comparing HMB supplementation with a control group. There were improvements in liver function scores, increased body mass index, and reduced LDL cholesterol and apolipoprotein B. Surprisingly, HMB-treated patients showed increased liver function, providing an additional beneficial effect of the supplement [23].

Another study, this time focusing on resistance training combined with HMB in an elderly population, did not indicate significant changes in the HMB-supplemented group. However, the placebo group showed a significant decrease in various body measurements, while the HMB group maintained their measurements. Although HMB did not improve outcomes, it appears to preserve body composition. Furthermore, resistance training proved effective in improving body composition and increasing grip strength in elderly patients with sarcopenia after hip arthroplasty. HMB supplementation was also associated with preventing muscle mass and strength loss in these individuals [24].

D. Dosage and Medicinal Forms

Repeatedly employed in isolation in sports contexts, several studies aim to evaluate the effectiveness and potential enhancement of HMB supplementation. This report disagrees on the athletic performance of endurance rowers subjected to a combination of creatine monohydrate and 3g/day of HMB for 10 weeks. During the study, the supplementation showed a positive synergistic effect on aerobic power, although it did not present significant results in terms of muscle mass gain [25]. HMB supplementation during resistance training in debilitated individuals has shown promising results. With the intake of 3g/day for six weeks, there was a significant improvement in muscle mass in younger

individuals, effectively inhibiting protein release. Prolonged HMB supplementation may improve muscle mass and function in conjunction with resistance training in the elderly [26].

A study conducted with a group of healthy elderly women monitored their physical performance, muscle strength, and body composition alterations using oral supplementation of 1.5g of calcium HMB over eight weeks. HMB was chosen due to its muscle-preserving properties, such as improving whole-body protein synthesis, increasing collagen synthesis, and controlling protein release, as well as enhancing cholesterol synthesis in cell membranes. It also reportedly presents beneficial effects in pathologies with severe muscle mass loss [27].

The most common form of HMB supplementation is as calcium salt (Ca-HMB), but the free acid model of HMB (HMB-FA) has also shown excellent results in terms of lean mass, strength, hypertrophy, and biochemical markers, including several hormones. This efficacy can be attributed to the absorption kinetics of HMB-FA, which is superior to Ca-HMB, especially when administered in capsule form. Therefore, it is noteworthy that the HMB-FA form is emerging as a more frequent choice for supplementation [13].

E. Toxicity and Adverse Effects

In a study conducted by Kreider et al. (1999) [28], involving 40 athletes undergoing resistance training, doses of 3 to 6g of Ca-HMB (calcium salt) were administered over 28 days. There was a significant increase in serum and urinary concentrations, with no negative data on general markers, and no signs of toxicity in rinses, liver, muscle enzymes, or body fat. Another study, involving male university students divided into two groups, also received the requested doses of 3g and 6g for eight weeks, without adverse effects on lipid profile, liver enzymes, renal function, or immune system [29].

Animal trials also did not show toxicity or adverse effects with HMB (as calcium salt) supplementation over 90 days in male and female rats. Although there was an increase in inorganic

phosphorus markers in male rats, it was not sufficient to be considered an adverse effect. The estimated doses of CaHMB were 3.49g/kg body weight for males and 4.16g/kg body weight for females, with no adverse effects [30].

Therefore, both human and animal studies have not demonstrated any degree of toxicity or adverse effects of HMB within the range of 3g/day to 6g/day for humans. Furthermore, higher doses in animals also do not exhibit toxicity. Thus, the use of HMB as a nutritional supplement appears increasingly justified due to its ability to reduce proteolysis [11]. HMB has also been tested in the form of free acid gel to enhance its availability in tissues. Studies have shown positive results for both oral administration via gelatin capsule and sublingual administration after ingestion in healthy or sick individuals [31].

F. Possible Mechanisms of Action of HMB

One of the most discussed mechanisms of HMB action is its potential as a precursor to cholesterol. In the cytosol, HMB is converted to HMG-CoA, which is then used in cholesterol synthesis. Cholesterol plays crucial roles in cell function and growth, participating in repairs and the formation of new cell membranes. For muscles, cholesterol is necessary, especially during periods of intense training when the demand for cholesterol exceeds endogenous production. Increasing HMB levels through supplementation can, therefore, boost the concentration of HMG-CoA available for cholesterol synthesis, which is essential for muscle health, considering that endogenous production is the primary source of cholesterol [32].

In studies focused on reversing cachexia in cancer patients, HMB has shown positive results. The loss of skeletal muscle mass is a prominent feature in these individuals, resulting from the manipulation of myofibrillar proteins and suppression of protein synthesis. Supplementation with β -hydroxy- β -methylbutyrate (HMB) becomes necessary due to its ability to inhibit protein manipulation and mitigate the decrease in protein synthesis. When combined with arginine and

glutamine, its efficacy in muscle loss recovery is further enhanced [33].

Additionally, regarding acute endocrine response, free acid HMB (HMB-FA) has demonstrated the ability to increase levels of growth hormones GH and IGF-1. A study conducted with twenty high-performance male athletes showed that the ingestion of 1 g of HMB-FA thirty minutes before an intense exercise protocol resulted in increased GH and IGF-1 responses. This indicates that HMB supplementation may promote a more robust anabolic response [34].

Evidence presented by ELEY, RUSSELL, and TISDALE (2008) [35] highlights the efficacy of β -hydroxy- β -methylbutyrate (HMB) in attenuating muscle atrophy. In catabolic contexts, such as responses to lipopolysaccharides, tumor necrosis factor- α , and angiotensin II, HMB has been shown to reduce muscle atrophy. This occurs, in part, through the attenuation of elongation factor phosphorylation and possibly through increased phosphorylation of mTOR, as well as reduced phosphorylation of eukaryotic initiation factor alpha, which in turn initiates the activation of double-stranded RNA.

In research on cancer cachexia, HMB was investigated as a potential supplement capable of providing beneficial effects and helping to reduce muscle mass loss. One of its mechanisms of action involves reducing protein breakdown and increasing levels of growth hormones (GH) and IGF-1 expression in muscle tissue, through activation of the mTOR pathway. In a study conducted on animals with cachexia (PIF, TNF- α), HMB showed stimulation of protein synthesis through phosphorylation and activation of mTOR, while in animals with MAC 16 tumors, it also showed positive results for the activation of the mTOR/p70s6K pathway. Increased phosphorylation of the mTOR pathway may result in reduced effects of PIF on protein synthesis [36]. Similarly, as HMB has shown to stimulate protein synthesis in rat myotubes, a mechanism of action via the PI3K/Akt and MAPK/ERK pathways has been suggested. The involvement of PI3K/Akt in the effects of leucine and HMB on L6 myotubes

was tested, pre-incubated with PI3K phosphorylation inhibitors before treatment with leucine or HMB. Results did not indicate changes in ERK1/2 signaling effects by leucine or HMB, but blocking PI3K signaling reduced the effects of HMB. Finally, the effects of leucine and HMB on PKB/Akt phosphorylation were investigated, demonstrating that incubation with HMB resulted in a significant increase in PKB/Akt phosphorylation, while leucine had no effect [37].

Moreover, HMB has been shown to have effects on routine, differentiation, fusion, and survival of muscle cell cultures. HMB induced myoblast regulation, with the MAPK/ERK pathway being necessary for this effect. It also prevents apoptosis of muscle cells triggered by cellular deprivation or staurosporine. Additionally, it has been demonstrated that HMB, through PI3K-dependent Akt phosphorylation, stimulates IGF-1 mRNA synthesis. Considering all these data, it is suggested that HMB reduces muscle atrophy and promotes hypertrophy by inhibiting protein breakdown, having a positive impact on skeletal muscle during normal growth or exercise conditions [38].

G. Applications of HMB Mechanisms to Performance Indices and Lean Mass

HMB is often used in the form of Calcium Salt (Ca-HMB), particularly in studies focused on strength and lean mass gains. However, recently, there has been an increase in the use of HMB in its free acid form (HMB-FA). In a three-month study, individuals who combined strength training with HMB-FA supplementation showed significant results compared to the placebo group. They experienced an average increase of 7kg in muscle strength and mass, which was three times greater than the placebo group [39].

Another study involving vertical jump athletes highlighted the benefits of HMB supplementation. Although it did not impact delayed-onset muscle soreness, supplementation with 3g of HMB-FA showed positive effects on recovery of work capacity and vertical jump performance recovery. These effects suggest a

relationship with stimulation of protein synthesis and prevention of proteolysis, indicating the effectiveness of HMB-FA supplementation in post-strength training recovery [40].

A more recent study conducted by SARRIA (2022) [41] with sarcopenic elderly individuals also revealed promising results for HMB. The supplementation was reported to preserve and increase muscle mass, reduce fat mass, prevent weight loss, and improve physical performance and functional recovery. Additionally, some sarcopenic elderly individuals recovered from the condition, and those with pre-frailty experienced an increase in body weight and body mass index. The study also included healthy elderly individuals, confirming improvements in performance and muscle mass due to supplementation, even after a ten-day safety period, with less loss of lean mass compared to the placebo group.

H. The Effect of HMB on the mTOR Kinase Pathway

The mTOR kinase pathway, although unfamiliar to many, is of extreme importance to our body. Also known as mammalian target of rapamycin or mechanistic target of rapamycin, it belongs to the family of kinases associated with phosphoinositide 3-kinase and is a serine/threonine kinase. This highly conserved protein, consisting of 2,549 amino acids, is present in our cells in the form of two complexes: mTORC1 and mTORC2. It plays a crucial role in protein and lipid synthesis, the catabolic process, the ubiquitin-proteasome system, and the regulation of cell growth, survival, and actin cytoskeleton formation. Dysfunction of mTOR may be related to various pathologies, making it an effective pathway for treating these diseases [42].

A study conducted by SALTO et al. (2015) [43] in mice investigated the effect of HMB on neurite growth in Neuro2a cells. It was shown that HMB promotes differentiation into neurites independently of cellular dependency. Additionally, it is reported that HMB leads to mTOR phosphorylation, resulting in increased protein

synthesis in Neuro2a cells. The study revealed that HMB acts through the mTORC2 complex, influencing Torin1 activity and the myocyte enhancer factor 2. Activation of the mTOR pathway in neurite growth induced by HMB was confirmed by immunoblotting, showing an increase in mTOR phosphorylation. Thus, the study demonstrated that HMB promotes an increase in neurites in Neuro2a cells, with its neuronal differentiation correlated to glucose transport and activation of mTOR by mTORC2, resulting in increased protein synthesis.

When the body attempts to maintain homeostasis, imbalances may occur, leading to significant muscle mass loss. In such cases, HMB acts directly through the mTOR pathway. mTOR phosphorylation leads to the activation and induction of proteins that, in turn, suppress the manipulation of muscle proteins regulated by the ubiquitin-proteasome system, a crucial system for regulating protein synthesis and manipulation processes over time [44].

Recently, a study on circadian rhythm alterations in myotubes treated with HMB showed activation of the P70S6K and S6 protein effects, independently of mTOR. The goal was to investigate the signaling of the pathway involved in the circadian clock, and it was observed that activation of these proteins occurred when myotubes were treated with HMB in combination with direct and indirect mTOR inhibitors. Therefore, concerning the circadian rhythm, HMB does not activate mTOR but rather the protein effects of P70S6K and S6, resulting in advanced high-amplitude rhythms [45].

I. Ergogenic Effects of HMB Supplementation in Athletes

Ergogenic aids aim to enhance strength and muscle mass gains. β -Hydroxy β -methylbutyrate (HMB) emerges as one of the most promising options currently available for this purpose. A study on its long-term effects on reducing muscle damage in athletes who combined HMB with creatine monohydrate showed positive outcomes. As previously mentioned, HMB can influence glycogen synthesis, delay fatigue, increase testosterone levels, stimulate protein synthesis through insulin-like

growth factor (IGF-1), and enhance mTOR phosphorylation. However, the study demonstrated that supplementation did not result in significant changes in physical damage prevention but showed positive results in faster muscle recovery [25].

Furthermore, HMB has also shown a significant impact on increasing lean mass and reducing immunological markers, such as creatine kinase and lactate dehydrogenase, as well as decreasing LDL cholesterol levels. In double-blind studies involving athletes in canoeing and resistance training, HMB was associated with significant increases in power and muscle thickness compared to the placebo group [46].

HMB continues to be widely used by athletes in endurance and strength-power sports, proving to be a valuable supplement for improving strength and facilitating faster muscle recovery. To help reduce tissue catabolism and promote muscle anabolism, HMB can be applied during periods of intense training and dense competition, allowing for quicker recovery. It can also be useful during injury recovery phases [47]. One of the main advantages of HMB is its anti-catabolic action, which is especially useful when athletes need to manage heavy loads, injuries, or excessive muscle loss, as seen in certain pathological conditions such as sarcopenia, muscular dystrophy, and rheumatoid cachexia [13].

J. Absorption Rate and Bioavailability of Various Chemical Forms of HMB

Studies indicate that the free acid form of HMB (HMB-FA) is absorbed more rapidly compared to the more commonly used calcium salt form (CaHMB). Oral or sublingual administration of HMB-FA results in higher and faster plasma peaks than CaHMB, with minimal urinary excretion, indicating more effective absorption in the body. The faster absorption rate of HMB-FA likely initiates its action in areas closer to the gastrointestinal tract, facilitating the absorption of hydrophilic compounds in the sublingual mucosa and acidic compounds in the stomach [39].

As demonstrated by FULLER et al. in 2015 [48], a comparative study evaluating the

bioavailability of HMB using HMB-FA and CaHMB in capsules administered in water showed that HMB-FA is absorbed more rapidly. However, when administered in water, despite its superior absorption rate, the HMB-FA evaluation rate was lower compared to capsules, suggesting that the capsule formulation improved the determination and availability of HMB. Blood levels confirm the higher bioavailability of HMB-FA in humans.

On the other hand, in a permeability assay conducted on an artificial membrane with CaHMB and HMB-FA, both demonstrated high permeability through the lipid bilayer, similar to other highly permeable molecules such as testosterone and propranolol. This suggests that both forms of HMB move freely across intestinal membranes, achieving plasma concentrations after oral administration. Although the model used in this study was in rats and not humans, the acquisition mechanisms are similar, and it was found that the bioavailability of CaHMB is higher than that of HMB-FA, considering the post-absorptive mechanisms that lead to greater plasma concentration [49].

K. Ideal Doses, Timing, and Duration of HMB

In most studies on HMB supplementation, a common dosage is 3g/day. However, previous research has also demonstrated safety with doses of up to 6g/day in individuals. These doses, both 3g/day and 6g/day, are suitable for individuals weighing around 80kg. The results from these studies have consistently shown positive outcomes, including muscle mass gain, increased strength, and other relevant effects. However, there were no significant differences between the results of individuals receiving 6g/day compared to those receiving 3g/day [50].

BECKER et al. (2016) [46] also noted that the most commonly used dosage in human studies is 3 grams per day of HMB. In terms of endogenous production, this amount is equivalent to 600g of high-quality protein, with only 3 grams of HMB produced. Therefore, external supplementation is crucial, as the amount of protein required to produce HMB internally would be impractical. According to the literature, the dosage and duration of treatment

vary based on several factors, including the form of HMB supplementation and the individuals engaging in physical exercise. HMB effects can be either acute or periodic. For acute effects, administering 3g/day of Ca-HMB at least 60 minutes before intense exercise is suggested, with consumption up to two hours before the workout if combined with glucose. On the other hand, HMB-FA can be consumed 30 to 60 minutes before exercise due to its faster effect. For periodic effects, a daily intake of 3g, divided into three equal portions, is recommended for at least two weeks before engaging in exercises that cause muscle damage [51].

L. The Effectiveness of HMB Supplementation for Untrained Participants

Functional composition indices were used to assess the effects of HMB supplementation combined with vitamin D in elderly individuals, both trained and untrained, over a one-year period, estimating changes in muscle strength. These tests cover daily activities, with notable improvements in a common task like standing up from a chair, which requires muscle strength, power, and balance. The most reported results were in the untrained elderly group that received HMB supplementation, either alone or combined with other amino acids [52].

In contrast, a study conducted by ALVARES and MEIRELLES (2008) [53] found no evidence of changes in muscle mass in untrained individuals with HMB supplementation. Over a four-week supplementation period in untrained individuals, no significant changes in hypertrophy were observed. However, when the same dosage was administered to the same individuals in combination with resistance training, consistent results were obtained in terms of gains in strength, lean mass, and reduction in body fat.

As mentioned earlier, HMB has shown several proven positive effects for increasing muscle mass, including reducing the catabolic effect of prolonged exercise, decreasing muscle soreness and fatigue, lowering muscle injury markers, reducing fat-free mass, and increasing

strength and endurance. These effects have been consistently observed in studies with exercise beginners, indicating greater effectiveness in untrained individuals or those in the early stages of physical activity [54].

M. The Effectiveness of HMB Supplementation for Experienced Athletes

A study conducted with combat sports athletes demonstrated positive results with the inclusion of HMB, particularly in terms of load, peak anaerobic power, speed, and post-exercise lactate concentrations, with no changes in blood markers. This study highlighted the effectiveness of HMB supplementation in combat sports athletes, resulting in reduced body fat and increased peak anaerobic power, among other benefits, with no apparent adverse effects even with long-term supplementation [13].

Considering that rowing is a high-intensity sport that demands much from its practitioners, a recent study investigated HMB supplementation combined with creatine in rowers, yielding positive results for aerobic power. These results suggest a possible synergy between HMB, which promotes the transformation of muscle fibers from fast-twitch to slow-twitch, along with elevated expression of the coactivator gamma 1-alpha (PGC-1 α). These findings indicate that HMB has significant potential to improve variables related to aerobic capacity, suggesting its use as a supplement for enhancing rowing performance in competitions [55].

In a similar study conducted by DURKALEC and JESZKA (2015) [56] with elite rowers, HMB also proved effective in enhancing aerobic capacity. In addition to the well-known mechanisms of action, such as maintaining cell membrane integrity and improving carbohydrate, glycogen, and fat metabolism efficiency, an increase in aerobic activity under specific training conditions was observed. Therefore, the growth in aerobic adaptation can be attributed to the increased availability of energy substrates, as well as improved physical capacity following intense training, and a shorter post-exercise recovery period with HMB supplementation in rowers.

N. The Effectiveness of HMB Supplementation in the Elderly

A study on interventions for sarcopenia in elderly adults highlighted HMB supplementation. During a 24-week program, community-dwelling, healthy, and bedridden elderly individuals were supplemented with HMB. Although no significant improvement in muscle mass was observed, positive results from HMB supplementation included improvements in muscle strength, physical performance, and the prevention of muscle loss a common issue among elderly individuals with this condition [57].

Physical training and protein supplementation emerge as effective strategies for delaying problems such as frailty and functional impairment in the elderly population. HMB is a promising supplement for this purpose, as it stimulates protein synthesis and mitigates rapid muscle loss. However, a meta-analysis indicated that HMB, on its own, has a low significant impact on delaying muscle loss compared to physical exercise. Nonetheless, when combined with exercise, HMB shows positive results in reducing or delaying muscle loss in the elderly [58]. An analysis of muscle strength in the elderly population demonstrated that HMB and HMB-containing supplements were effective in increasing muscle strength. In a double-blind study, individuals supplemented with HMB showed greater muscle strength compared to the control group. HMB was shown to increase strength in both upper and lower limbs, highlighting its importance as a safe therapeutic supplement for the elderly population [59].

O. Effects of HMB Supplementation on Strength and Body Composition

Muscle loss is believed to be directly related to aging. Therefore, HMB, in combination with arginine and glutamine, has been used as a supplement to combat excessive muscle loss due to its anti-catabolic properties. HMB improves body composition through a synergistic effect of amino

acids, stimulating mTOR signaling pathways involved in muscle protein synthesis. With aging, there is a dysregulation in the activation of these pathways, and HMB appears to address this by activating them more directly [60].

A meta-analysis conducted by ROWLANDS and THOMSON (2009) [61] revealed an increased level of overall strength in untrained weightlifters, but no significant impact on trained lifters. Additionally, untrained individuals showed a greater gain in lower body strength compared to upper body strength. As for body composition, HMB supplementation did not demonstrate significant differences in either trained or untrained individuals. This study suggests that the response to HMB is more pronounced in untrained individuals, possibly due to a lower capacity for adaptation to resistance training.

HMB supplementation, at the recommended dose of 3g/day, is safe and does not cause adverse effects. Therefore, HMB is one of the most recommended supplements for athletes, regardless of gender or age, as it reduces post-exercise physical damage, accelerates injury recovery, increases lean muscle mass, and improves strength and aerobic capacity. When following the recommendations, HMB consumption poses no risks, even over extended periods, such as one year [8].

P. Effects of HMB Supplementation on Protein Homeostasis in Skeletal Muscle

As demonstrated in previous studies, HMB has the ability to inhibit protein turnover in the proteasome and vary protein levels in visceral tissues, promoting changes in body metabolism and increasing muscle mass. This anabolic effect is directly related to skeletal muscle. In addition to benefits in muscle and skeletal systems, recent research is also exploring the effects of HMB on bone tissue, showing that its introduction may induce increased bone mass [62].

A study conducted on rats supplemented with HMB showed a reduction in protein breakdown and protein synthesis throughout the body. There was a significant decrease in proteasome-dependent

proteolysis in skeletal muscle, with no significant changes in other organs. Only a decrease in protein synthesis was observed in the heart, colon, kidney, and spleen, while the liver showed an increase. Thus, the anabolic protein effect of HMB on skeletal muscle is related to the prevention of proteolysis in the proteasome, and changes in protein synthesis in visceral tissues may affect various functions, including overall homeostasis [63].

Skeletal muscle plays a crucial role in maintaining protein and glucose homeostasis, and its dysfunction is directly linked to the development of diabetes. As is known, diabetes can lead to muscle loss, which reduces glucose uptake and worsens the disease. Therefore, nutritional supplementation is increasingly recommended to improve protein turnover and increase glucose uptake. In this study, a combination of HMB with arginine and lysine was proposed. While HMB stimulates protein synthesis, arginine and lysine enhance glucose uptake, preventing muscle loss and progression of diabetes. It is concluded that this combination is effective in controlling glucose levels and preventing muscle atrophy associated with disease advancement [64].

Q. Analysis of HMB Research Trends Over the Past Two Decades

Articles from the past twenty years (2004-2024) were analyzed (Fig. 1 and 2). The color blue (Fig. 1) represents the keyword "HMB (beta-hydroxy-beta-methylbutyrate)," the color orange represents the intersection of "HMB" and "protein metabolism," and the color green represents the intersection of "HMB" and "supplementation." We observed a significant increase in research starting from 2013, primarily focusing on the use of HMB (beta-hydroxy-beta-methylbutyrate). In the second graph (Fig. 2), the color blue represents the intersection of the keywords "HMB" and "muscle hypertrophy," the color orange represents the intersection of "HMB" and "localized therapy," and the color green represents the intersection of "HMB" and "physical exercise." Here, we note that starting from 2015, HMB began to be increasingly associated with physical exercise.

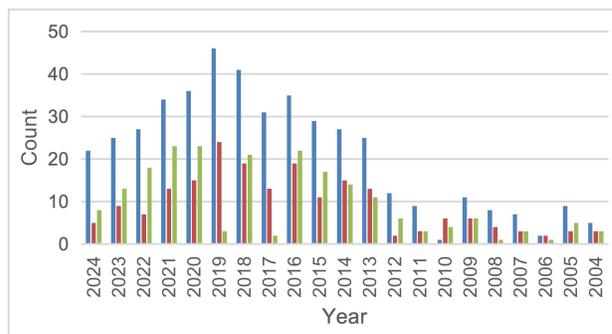


Figure 1: Trend of Publications on HMB (Beta-Hydroxy-Beta-Methylbutyrate) from 2004 to 2024: Focus on Protein Metabolism and Supplementation

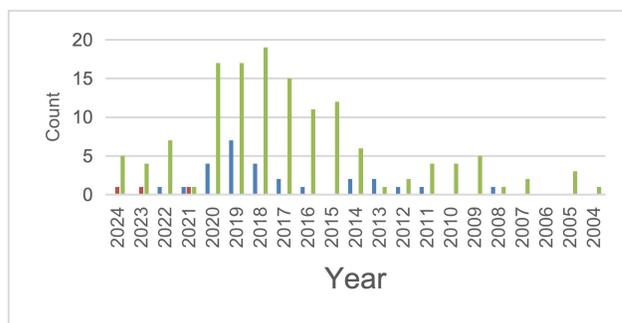


Figure 2. Research Growth on HMB and Muscle Hypertrophy from 2004 to 2024: Associations with Localized Therapy and Physical Exercise

V. CONCLUSION

It is concluded that both oral HMB supplementation and HMB mesotherapy are effective in promoting muscle hypertrophy and increasing strength. However, mesotherapy has proven to be superior, enhancing the effects of HMB and reducing muscle damage. These findings suggest that HMB mesotherapy could be a promising strategy to improve outcomes in resistance training programs, particularly for individuals seeking to optimize muscle growth and recovery. Further studies are needed to fully understand the mechanisms behind this enhancement and to explore the clinical and sports applications of this technique.

CONFLICT OF INTEREST

The authors affirm that they have no conflicts of interest.

REFERENCES

- 1- BARRI, Ana López. ¿ Para qué sirve la mesoterapia?. Más dermatología, n. 3, p. 20-23, 2007.
- 2- MAMMUCARI, Massimo et al. Role of mesotherapy in musculoskeletal pain: opinions from the Italian Society of Mesotherapy. Evidence-based Complementary and Alternative Medicine, v. 2012, 2012.
- 3- CARVAJAL, Eliana Patricia Cuellar et al. Posibles efectos en la hipertrofia muscular con suplementación de HMB: revisión narrativa. Perspectivas en Nutrición Humana, v. 25, n. 1, 2023.
- 4-NISSEN, Steven L.; SHARP, Rick L. Effect of dietary supplements on lean mass and strength gains with resistance exercise: a meta-analysis. Journal of applied physiology, 2003.
- 5- Holeček M. Beta-hydroxy-beta-methylbutyrate supplementation and skeletal muscle in healthy and muscle-wasting conditions. J Cachexia Sarcopenia Muscle. 2017 Aug;8(4):529-541. doi: 10.1002/jcsm.12208. Epub 2017 May 10. PMID: 28493406; PMCID: PMC5566641.
- 6- MELONI, Victor Hugo Maciel. O papel da hiperplasia na hipertrofia do músculo esquelético. Rev. Bras. Cine. Des. Hum. ISSN, v. 1415, p. 8426, 2005.
- 7- Schiaffino S, Reggiani C, Akimoto T, Blaauw B. Molecular Mechanisms of Skeletal Muscle Hypertrophy. J Neuromuscul Dis. 2021;8(2):169-183. doi: 10.3233/JND-200568. PMID: 33216041; PMCID: PMC8075408. (pubmed)
- 8 - Kaczka P, Michalczyk MM, Jastrzab R, Gawelczyk M, Kubicka K. Mechanism of Action and the Effect of Beta-Hydroxy-Beta-Methylbutyrate (HMB) Supplementation on Different Types of Physical Performance - A Systematic Review. J Hum Kinet. 2019 Aug 21;68:211-222. doi: 10.2478/hukin-2019-0070. PMID: 31531146; PMCID: PMC6724588.
- 9- MENDES, Renata Rebello. EFEITOS DA SUPLEMENTAÇÃO DE β -HIDROXI β -METILBUTIRATO (HMB) SOBRE O GANHO DE MASSA.
- 10 -NISSEN S., R.L. Sharp, L. Panton, M. Vukovich, S. Trappe, J.C. Fuller, et al. β -Hydroxy- β -methylbutyrate (HMB) supplementation in humans is safe and may decrease cardiovascular risk factors. The Journal of nutrition, v. 130, n. 8, p. 1937-1945, 2000.
- 11- DE OCA, Rafael Manjarrez-Montes et al. El β -hidroxi- β -metilbutirato (HMB) como suplemento nutricional (I): metabolismo y toxicidad. Nutrición hospitalaria: Organo oficial de la Sociedad española de nutrición parenteral y enteral, v. 31, n. 2, p. 590-596, 2015.
- 12- SLATER, Gary J.; JENKINS, David. Suplementação de β -hidroxi- β -metilbutirato (HMB) e promoção do crescimento e força muscular. Medicina Esportiva, v. 30, pág. 105-116, 2000.
- 13- DURKALEC-MICHALSKI, Krzysztof; JESZKA, Jan; PODGÓRSKI, Tomasz. 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, v. 9, n. 7, p. 753, 2017.
- 14- KRAEMER, William J. et al. Effects of amino acids supplement on physiological adaptations to resistance training. Medicine & Science in Sports & Exercise, v. 41, n. 5, p. 1111-1121, 2009.
- 15- Portal S, Zadik Z, Rabinowitz J, Pilz-Burstein R, Adler-Portal D, Meckel Y, Cooper DM, Eliakim A, Nemet D. The effect of HMB supplementation on body composition, fitness, hormonal and

inflammatory mediators in elite adolescent volleyball players: a prospective randomized, double-blind, placebo-controlled study. *Eur J Appl Physiol.* 2011 Sep;111(9):2261-9. doi: 10.1007/s00421-011-1855-x. Epub 2011 Feb 16. PMID: 21327797.

16- Pinheiro CH, Gerlinger-Romero F, Guimarães-Ferreira L, de Souza AL Jr, Vitzel KF, Nachbar RT, Nunes MT, Curi R. Metabolic and functional effects of beta-hydroxy-beta-methylbutyrate (HMB) supplementation in skeletal muscle. *Eur J Appl Physiol.* 2012 Jul;112(7):2531-7. doi: 10.1007/s00421-011-2224-5. Epub 2011 Nov 11. PMID: 22075640.

17- Pimentel GD, Rosa JC, Lira FS, Zanchi NE, Ropelle ER, Oyama LM, Oller do Nascimento CM, de Mello MT, Tufik S, Santos RV. β -Hydroxy- β -methylbutyrate (HMB) supplementation stimulates skeletal muscle hypertrophy in rats via the mTOR pathway. *Nutr Metab (Lond).* 2011 Feb 23;8(1):11. doi: 10.1186/1743-7075-8-11. PMID: 21345206; PMCID: PMC3048483.

18- NISSEN, Steven L.; ABUMRAD, Naji N. Nutritional role of the leucine metabolite β -hydroxy β -methylbutyrate (HMB). *The Journal of Nutritional Biochemistry*, v. 8, n. 6, p. 300-311, 1997.

19- Prado CM, Orsso CE, Pereira SL, Atherton PJ, Deutz NEP. Effects of β -hydroxy β -methylbutyrate (HMB) supplementation on muscle mass, function, and other outcomes in patients with cancer: a systematic review. *J Cachexia Sarcopenia Muscle.* 2022 Jun;13(3):1623-1641. doi: 10.1002/jcsm.12952. Epub 2022 Mar 17. PMID: 35301826; PMCID: PMC9178154.

20- ZANCHI, Nelo Eidy et al. Suplementação de HMB: relevância clínica e mecanismos de ação. *Revista Mackenzie de Educação Física e Esporte*, v. 8, n. 1, 2009.

21- Deutz NE, Matheson EM, Matarese LE, Luo M, Baggs GE, Nelson JL, Hegazi RA, Tappenden KA,

Ziegler TR; Grupo de Estudos NOURISH. Readmissão e mortalidade em adultos desnutridos, idosos e hospitalizados tratados com um suplemento nutricional oral especializado: um ensaio clínico randomizado. *Clin Nutr.* Fevereiro de 2016;35(1):18-26. doi: 10.1016/j.clnu.2015.12.010. Epub 2016, 18 de janeiro. PMID: 26797412.

22- DEXHEIMER, Georgia Muccillo et al. Efetividade clínica da suplementação de BCAA, L-Carnitina, Creatina, Glutamina e HMB: Um mapa de evidências. *RBNE-Revista Brasileira de Nutrição Esportiva*, v. 18, n. 108, p. 111-134, 2024.

23-Espina S, Sanz-Paris A, Gonzalez-Irazabal Y, Pérez-Matute P, Andrade F, Garcia-Rodriguez B, Carpéné C, Zakaroff A, Bernal-Monterde V, Fuentes-Olmo J, Arbones-Mainar JM. Randomized Clinical Trial: Effects of β -Hydroxy- β -Methylbutyrate (HMB)-Enriched vs. HMB-Free Oral Nutritional Supplementation in Malnourished Cirrhotic Patients. *Nutrients.* 2022 Jun 3;14(11):2344. doi: 10.3390/nu14112344. PMID: 35684144; PMCID: PMC9183090.

24- Han Z, Ji NN, Ma JX, Dong Q, Ma XL. Effect of Resistance Training Combined with Beta-Hydroxy-Beta-Methylbutyric Acid Supplements in Elderly Patients with Sarcopenia after Hip Replacement. *Orthop Surg.* 2022 Apr;14(4):704-713. doi: 10.1111/os.13208. Epub 2022 Feb 23. PMID: 35195339; PMCID: PMC9002065.

25 - Fernández-Landa J, Fernández-Lázaro D, Calleja-González J, Caballero-García A, Córdova Martínez A, León-Guereño P, Mielgo-Ayuso J. Effect of Ten Weeks of Creatine Monohydrate Plus HMB Supplementation on Athletic Performance Tests in Elite Male Endurance Athletes. *Nutrients.* 2020 Jan 10;12(1):193. doi: 10.3390/nu12010193. PMID: 31936727; PMCID: PMC7019716.

26- 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. doi: 10.1016/j.clnu.2018.09.025. Epub 2018 Sep 27. PMID: 30360984; PMCID: PMC6876270.

27- 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. doi: 10.1371/journal.pone.0141757. PMID: 26529601; PMCID: PMC4631374.

28- Kreider RB, Ferreira M, Wilson M, Almada AL. Effects of calcium beta-hydroxy-beta-methylbutyrate (HMB) supplementation during resistance-training on markers of catabolism, body composition and strength. *Int J Sports Med.* 1999 Nov;20(8):503-9. doi: 10.1055/s-1999-8835. PMID: 10606212.

29- Gallagher PM, Carrithers JA, Godard MP, Schulze KE, Trappe SW. Beta-hydroxy-beta-methylbutyrate ingestion, part II: effects on hematology, hepatic and renal function. *Med Sci Sports Exerc.* 2000 Dec;32(12):2116-9. doi: 10.1097/00005768-200012000-00023. PMID: 11128860.

30- Baxter JH, Carlos JL, Thurmond J, Rehani RN, Bultman J, Frost D. Dietary toxicity of calcium beta-hydroxy-beta-methyl butyrate (CaHMB). *Food Chem Toxicol.* 2005 Dec;43(12):1731-41. doi: 10.1016/j.fct.2005.05.016. PMID: 16006030.

31- Fuller JC Jr, Sharp RL, Angus HF, Baier SM, Rathmacher JA. Free acid gel form of β -hydroxy- β -methylbutyrate (HMB) improves HMB clearance from plasma in human subjects compared with the calcium HMB salt. *Br J Nutr.* 2011 Feb;105(3):367-72. doi: 10.1017/S0007114510003582. Epub 2010 Dec 7. PMID: 21134325.

32- Manjarrez-Montes-de-Oca R, Torres-Vaca M, González-Gallego J, Alvear-Ordenes I. El β -hidroxi- β -metilbutirato (HMB) como suplemento nutricional (II): mecanismos de acción moleculares y celulares [β -hydroxy- β -methylbutyrate as a dietary supplement (II): cell and molecular mechanism of action]. *Nutr Hosp.* 2014 Nov 27;31(2):597-605. Spanish. doi: 10.3305/nh.2015.31.2.8437. PMID: 25617540.

33- MIRZA, Kamran A. et al. Comparison of the anticatabolic effects of leucine and Ca- β -hydroxy- β -methylbutyrate in experimental models of cancer cachexia. *Nutrition*, v. 30, n. 7-8, p. 807-813, 2014.

34- Townsend JR, Hoffman JR, Gonzalez AM, Jajtner AR, Boone CH, Robinson EH, Mangine GT, Wells AJ, Fragala MS, Fukuda DH, Stout JR. Effects of β -Hydroxy- β -methylbutyrate Free Acid Ingestion and Resistance Exercise on the Acute Endocrine Response. *Int J Endocrinol.* 2015;2015:856708. doi: 10.1155/2015/856708. Epub 2015 Feb 22. PMID: 25792982; PMCID: PMC4352513.

35- Eley HL, Russell ST, Tisdale MJ. Attenuation of depression of muscle protein synthesis induced by lipopolysaccharide, tumor necrosis factor, and angiotensin II by beta-hydroxy-beta-methylbutyrate. *Am J Physiol Endocrinol Metab.* 2008 Dec;295(6):E1409-16. doi: 10.1152/ajpendo.90530.2008. Epub 2008 Oct 14. PMID: 18854427.

36 - GOMES, Tiago Manuel Rufino. Caquexia oncológica: como modular a sua progressão. 2018. Trabalho de Conclusão de Curso. [sn].

37- Girón MD, Vilchez JD, Salto R, Manzano M, Sevillano N, Campos N, Argilés JM, Rueda R, López-Pedrosa JM. Conversion of leucine to β -hydroxy- β -methylbutyrate by α -keto isocaproate dioxygenase is required for a potent stimulation of protein synthesis in L6 rat myotubes. *J Cachexia Sarcopenia Muscle.* 2016 Mar;7(1):68-78. doi: 10.1002/jcsm.12032. Epub 2015 May 14. PMID: 27065075; PMCID: PMC4799859

- 38- Kornasio R, Riederer I, Butler-Browne G, Mouly V, Uni Z, Halevy O. Beta-hydroxy-beta-methylbutyrate (HMB) stimulates myogenic cell proliferation, differentiation and survival via the MAPK/ERK and PI3K/Akt pathways. *Biochim Biophys Acta*. 2009 May;1793(5):755-63. doi: 10.1016/j.bbamcr.2008.12.017. Epub 2009 Jan 3. PMID: 19211028.
- 39- TRITTO, Aline Cristina Capparelli. Efeitos da suplementação de HMB-AL e HMB-Ca sobre as respostas de força e hipertrofia musculares em indivíduos treinados submetidos a treinamento de força. 2018. Tese de Doutorado. Universidade de São Paulo.
- 40 - CORREIA, Ana Luiza Matias. Efeito da suplementação de β -hidroxi- β -metilbutirato ácido livre (hmb-fa) na recuperação do dano muscular induzido pelo exercício em homens fisicamente ativos. 2017.
- 41- SÁRRIA, Joana Lima. O efeito do β -hidroxi β -metilbutirato na sarcopenia e fragilidade em pessoas idosas: uma revisão de literatura. 2022. Trabalho de Conclusão de Curso. [sn].
- 42- Mao B, Zhang Q, Ma L, Zhao DS, Zhao P, Yan P. Overview of Research into mTOR Inhibitors. *Molecules*. 2022 Aug 19;27(16):5295. doi: 10.3390/molecules27165295. PMID: 36014530; PMCID: PMC9413691.
- 43- Salto R, Vilchez JD, Girón MD, Cabrera E, Campos N, Manzano M, Rueda R, López-Pedrosa JM. β -Hydroxy- β -Methylbutyrate (HMB) Promotes Neurite Outgrowth in Neuro2a Cells. *PLoS One*. 2015 Aug 12;10(8):e0135614. doi: 10.1371/journal.pone.0135614. PMID: 26267903; PMCID: PMC4534402.
- 44- LATY, Bianca Cristina et al. Propriedades funcionais e terapêuticas do beta-hidroxi beta-metilbutirato (HMB): uma revisão integrativa. *Research, Society and Development*, v. 9, n. 3, p. e69932422-e69932422, 2020.
- 45- COHEN-OR, Meytal; CHAPNIK, Nava; FROY, Oren. O β -hidroxi- β -metilbutirato (HMB) leva à ativação da fosfolipase D2 (PLD2) e altera os ritmos circadianos nos miotubos. *Alimentação e Função*, 2024.
- 46- BECKER, Lenice Kappes et al. Efeitos da suplementação nutricional sobre a composição corporal e o desempenho de atletas: uma revisão. *Revista Brasileira de Nutrição Esportiva*, v. 10, n. 55, p. 93-111, 2016.
- 47- Albert FJ, Morente-Sánchez J, Ortega FB, Castillo MJ, Gutiérrez Á. USEFULNESS OF B-HYDROXY-B-METHYLBUTYRATE (HMB) SUPPLEMENTATION IN DIFFERENT SPORTS: AN UPDATE AND PRACTICAL IMPLICATIONS. *Nutr Hosp*. 2015 Jul 1;32(1):20-33. doi: 10.3305/nh.2015.32.1.9101. PMID: 26262692.
- 48- Fuller JC, Sharp RL, Angus HF, Khoo PY, Rathmacher JA. Comparação da disponibilidade e taxas de depuração plasmática da entrega de β -hidroxi- β -metilbutirato nas formas de ácido livre e sal de cálcio. *Jornal Britânico de Nutrição*. 2015;114(9):1403-1409. doi:10.1017/S0007114515003050
- 49- Shreeram S, Johns PW, Subramaniam S, Ramesh S, Vaidyanathan V, Puthan JK, Mandal S, Mamidi VK, Gelling RW. The relative bioavailability of the calcium salt of β -hydroxy- β -methylbutyrate is greater than that of the free fatty acid form in rats. *J Nutr*. 2014 Oct;144(10):1549-55. doi: 10.3945/jn.114.196527. Epub 2014 Aug 20. PMID: 25143371.
- 50- NUNES, Everson Araújo; FERNANDES, Luiz Cláudio. Atualizações sobre beta-hidroxi-beta-metilbutirato: suplementação e efeitos sobre o catabolismo de proteínas. *Revista de Nutrição*, v. 21, p. 243-251, 2008.
- 51- Wilson JM, Fitschen PJ, Campbell B, Wilson GJ, Zanchi N, Taylor L, Wilborn C, Kalman DS, Stout JR, Hoffman JR, Ziegenfuss TN, Lopez HL, Kreider

- RB, Smith-Ryan AE, Antonio J. International Society of Sports Nutrition Position Stand: beta-hydroxy-beta-methylbutyrate (HMB). *J Int Soc Sports Nutr.* 2013 Feb 2;10(1):6. doi: 10.1186/1550-2783-10-6. PMID: 23374455; PMCID: PMC3568064.
- 52- 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. doi: 10.1093/gerona/glaa218. PMID: 32857128; PMCID: PMC7566440.
- 53- ALVARES, Thiago da Silveira; MEIRELLES, Cláudia de Mello. Efeitos da suplementação de b-hidroxi-b-metilbutirato sobre a força e a hipertrofia. *Revista de Nutrição*, v. 21, p. 49-61, 2008.
- 54- BALINHA, João Ricardo Marques. Suplementos nutricionais no desporto: monografia: nutritional supplements in sports. 2008.
- 55- Kim J, Kim EK. Nutritional Strategies to Optimize Performance and Recovery in Rowing Athletes. *Nutrients.* 2020 Jun 5;12(6):1685. doi: 10.3390/nu12061685. PMID: 32516908; PMCID: PMC7352678.
- 56- Durkalec-Michalski K, Jeszka J. The efficacy of a β -hydroxy- β -methylbutyrate supplementation on physical capacity, body composition and biochemical markers in elite rowers: a randomised, double-blind, placebo-controlled crossover study. *J Int Soc Sports Nutr.* 2015 Jul 30;12:31. doi: 10.1186/s12970-015-0092-9. PMID: 26225130; PMCID: PMC4518594.
- 57- Cruz-Jentoft AJ, Landi F, Schneider SM, Zúñiga C, Arai H, Boirie Y, Chen LK, Fielding RA, Martin FC, Michel JP, Sieber C, Stout JR, Studenski SA, Vellas B, Woo J, Zamboni M, Cederholm T. Prevalence of and interventions for sarcopenia in ageing adults: a systematic review. Report of the International Sarcopenia Initiative (EWGSOP and IWGS). *Age Ageing.* 2014 Nov;43(6):748-59. doi: 10.1093/ageing/afu115. Epub 2014 Sep 21. PMID: 25241753; PMCID: PMC4204661.
- 58- 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. doi: 10.3390/nu11092082. PMID: 31484462; PMCID: PMC6769498.
- 59- Lin Z, Zhao A, He J. Effect of β -hydroxy- β -methylbutyrate (HMB) on the Muscle Strength in the Elderly Population: A Meta-Analysis. *Front Nutr.* 2022 Jul 13;9:914866. doi: 10.3389/fnut.2022.914866. PMID: 35911112; PMCID: PMC9326439.
- 60- Ellis AC, Hunter GR, Goss AM, Gower BA. Oral Supplementation with Beta-Hydroxy-Beta-Methylbutyrate, Arginine, and Glutamine Improves Lean Body Mass in Healthy Older Adults. *J Diet Suppl.* 2019;16(3):281-293. doi: 10.1080/19390211.2018.1454568. Epub 2018 Apr 19. PMID: 29672184; PMCID: PMC6314919.
- 61- Rowlands, David S; Thomson, Jasmine S .Efeitos da suplementação de β -hidroxi- β -metilbutirato durante o treinamento de resistência na força, composição corporal e danos musculares em homens jovens treinados e não treinados: uma meta-análise. *Journal of Strength and Conditioning Research* 23(3):p 836-846, maio de 2009. | DOI: 10.1519/JSC.0b013e3181a00c80
- 62- ANDREO, Camile Bermejo et al. Efeitos da suplementação com Beta-Hidroxi-Beta-Metilbutirato (HMB) sobre o tecido ósseo de ratos submetidos ao tratamento com dexametasona em curto prazo. 2015.
- 63- M. Holecek, T. Muthny, M. Kovarik, L. Sispera, Effect of beta-hydroxy-beta-methylbutyrate (HMB) on protein metabolism in whole body and in selected

tissues, Food and Chemical Toxicology, Volume 47, Issue 1, 2009, Pages 255-259, ISSN 0278-6915,

64- Manzano M, Girón MD, Salto R, Burgio C, Reinoso A, Cabrera E, Rueda R, López-Pedrosa JM. Arginine and Lysine Supplementation

Potentiates the Beneficial β -Hydroxy β -Methyl Butyrate (HMB) Effects on Skeletal Muscle in a Rat Model of Diabetes. Nutrients. 2023 Nov 7;15(22):4706. doi: 10.3390/nu15224706. PMID: 38004100; PMCID: PMC10674618.