

Artículo de Revisión / Review Article

Effects of β -hydroxy- β -methylbutyrate (hmb) and resistance training on body fat and lipid metabolism signaling pathways

Efectos de β -hydroxy- β -methylbutyrate (hmb) y entrenamiento de fuerza en grasa corporal y en las vías de señalización del metabolismo de los lípidos

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ABSTRACT

Excess body fat is a serious problem for increasing the risk of cardiovascular diseases such as obesity, compromising the health and quality of life of the population. In this sense, resistance training (RT) is type of physical exercise which improves body composition by increasing lean mass and reducing fat mass. RT in combination with nutrition (i.e. protein supplementation) is a key intervention to improve body fat metabolism and reducing obesity. Concerning protein supplementation, the β -hydroxy- β -methylbutyrate (HMB) is a metabolite of the branched-chain amino acid leucine that has demonstrated positive effects on body fat reduction. However, the effects of combining HMB supplementation with RT related to adipose tissue metabolic activity are controversial and warrant further investigation. This study analyzed the effects of HMB supplementation associated with RT on body fat concentration and lipid metabolism signaling pathways.

Keywords: Body composition; HMB; Lipid metabolism; Resistance training.

RESUMEN

El exceso de grasa corporal es un problema grave que aumenta tu riesgo de enfermedades y problemas de salud, tales como enfermedad cardíaca, diabetes, presión arterial alta y ciertos tipos de cáncer. En este sentido, y dentro del ejercicio físico, el entrenamiento de resistencia (ER) es un tipo de entrenamiento con pesos que mejora la composición corporal aumentando la masa magra y perdiendo masa grasa. El ER asociado con la nutrición (ej. suplementación proteica) es una excelente

intervención para mejorar el metabolismo de los lípidos al reducir la grasa corporal. En relación con la suplementación proteica el β -hidroxi- β -metilbutirato (HMB) es un metabolito del aminoácido de cadena ramificada esencial leucina que ha demostrado efectos positivos en la reducción de grasa corporal. Sin embargo, los efectos de la suplementación con HMB asociados con TR relacionados con la actividad metabólica del tejido adiposo son controvertidos y necesita la realización de investigaciones adicionales. Este estudio analizó los efectos de la suplementación con HMB asociados con TR en la concentración de grasa corporal y en las vías de señalización que participan en la regulación del metabolismo de los lípidos. Palabras clave: Composición corporal; Entrenamiento de fuerza; HMB; Metabolismo de los lípidos.

INTRODUCTION

The excess of body fat, especially visceral fat, is related to increased risk of several cardiovascular and metabolic diseases such as stroke, atherosclerosis, obesity and diabetes, which compromise health and quality of life of individuals of different ages worldwide^{1,2}. The imbalance between the nutrients intake and the energy expenditure by the body may take the form of either undernutrition or obesity³.

Thus, the reduction of body fat and the enhancement of energy expenditure in white adipose tissue (WAT) metabolism are common goals for both government agencies and the general population that seek strategies to prevent obesity and improve other physiological factors related to high quality of life.

In this context, dietary supplements related to changes of body composition have been currently used by different populations. For instance, β -hydroxy- β -methylbutyrate (HMB) has been used by sedentary individuals, elderly and even athletes^{3,4,5,6,7}. Moreover, epidemiological studies have shown that resistance training (RT) is a suitable type of physical exercise for the prevention of body fat accumulation and for health improvement^{8,9,10}. Therefore, the combination of a balanced diet based on proteins and amino acids with RT has been shown to optimize the reduction of body fat^{11,12}.

In this sense, the molecular signaling pathways of lipid metabolism such as proliferator-activated receptor gamma co-activator 1- α (PGC1- α), irisin and sirtuins (SIRT) which are either activated or inhibited by the combination of HMB supplementation with RT has been investigated, though not fully understood. Thus, in this review we sought to update the signaling pathways (PGC1- α , irisin and SIRT) of lipid metabolism underlying the effects of the combination of HMB supplementation with RT on body composition.

β -hydroxy- β -methylbutyrate

The search for nutritional strategies to increase muscle mass gain and reduce body fat has been a focus of study in the last decades¹³. The increase of muscle strength and improvement of body composition are attributes related to good health for different populations^{14,15}, such as children, adults and the elderly of different physical fitness levels, health or metabolic diseases.

In this context, the HMB is a metabolite resulting from the essential amino acid leucine that has gained notoriety due to its beneficial effects in improving physiological and morphological parameters related to strength gain, muscle

hypertrophy and body fat reduction^{4,5,16}, although there are some conflicting results^{17,18,19}.

Mechanisms of action

The HMB acts through different mechanisms: first, inhibition of the action of the ubiquitin-proteolytic proteasome pathway in extensor digitorum longus of fasting rats²⁰; second, increases the expression of the CoA- β -Hidroxi β -Metilglutaril-CoA (HMG-CoA) reductase enzyme accelerating the cholesterol synthesis of skeletal muscle tissue membrane and liver^{21,22}; third, increases the insulin-like growth factor (IGF-1) in skeletal muscle of rats²³, which stimulates muscle growth via serine/threonine-protein kinases (AKT) phosphorylation and mammalian target of rapamycin (m-TOR) / ribosome protein kinase 1 β (p70S6K) pathway and fourth, increases the proliferation of satellite cells, which stimulates m-TOR/p70S6K in fast muscles of aged rats during recovery from disuse atrophy²⁴, figure 1 illustrates these mechanisms of action.

In general, the mechanisms of action of HMB in the cell could contribute to the maintenance of lean muscle mass (prevention of catabolism) in situations of energy restriction and / or hypocaloric diet for weight loss and increase the basal metabolic rate (ex. activation of IGF-1 and mTOR) optimizing energy expenditure and consequently body fat loss.

Endogenous HMB and supplementation

The liver is the main organ that produces HMB. Skeletal muscle and other tissues also produce HMB in low amounts²². An adult individual of 70 kg weight synthesizes an average of 300/400 mg/day of HMB²⁵. In this sense, to obtain the ergogenic effects of HMB in the human body, it would be necessary to consume it in concentrated amounts in the form of supplements.

In humans, the most used dosage is 38 mg/kg weight/day²⁶. For example, an adult of 70 kg weight should ingest 2.660 mg/day of HMB. In rats, the most found dosage is 320 mg/kg weight/day, dissolved in water²⁶.

HMB is commercialized on the market by capsules and powder and it is found in the form of free acid (FA) or in the form of calcium salt (Ca). In humans, supplementation with HMB-FA showed higher plasma concentrations and greater availability compared to HMB-Ca, without significant differences in the urine metabolite excretion, indicating greater retention of HMB-FA in the body²⁷.

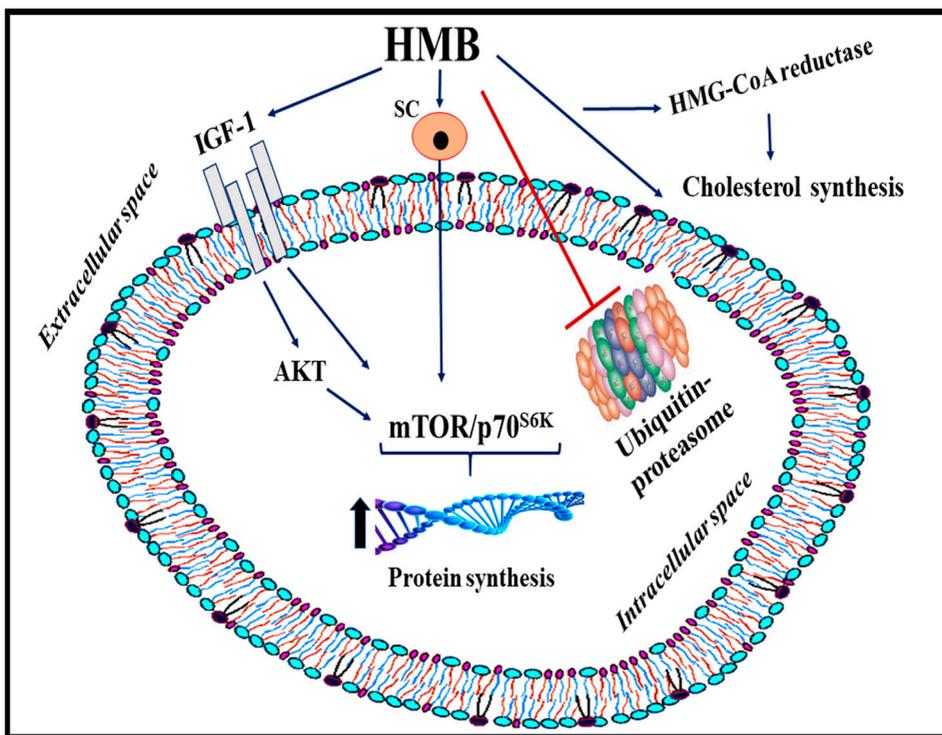


Figure 1: β -hydroxy- β -methylbutyrate mechanisms of action.

Legend: HMG, CoA- β -Hidroxi β -Metilglutaril-CoA; IGF-1, insulin-like growth factor; SC, satellite cells; AKT/m-TOR/p70S6K, serine/threonine-protein kinases / mammalian target of rapamycin / ribosome protein kinase 1 β . Source: Author elaboration.

Resistance Training

RT enhances sports performance by increasing the strength, hypertrophy and oxidation of energetic substrates in skeletal muscle²⁸, as well as promoting health benefits by reducing body fat, plasma triglycerides, blood pressure and risk of type 2 diabetes^{8,29,30}, which contributes positively to quality of life³¹. In addition, chronic RT improves the immune system, through modulation of pro-inflammatory and anti-inflammatory cytokines^{32,33}, thus contributing to the prevention of diseases caused by various types of microorganisms.

HMB and Resistance Training

Athletes from different sports and people who exercise regularly use HMB as a supplement to gain lean body mass, muscle strength, and reduce fat mass^{26,34,35,36}, although there are some conflicting results^{17,18,19}.

In fact, several studies have shown that HMB supplementation along with RT for a period of time more than 3 weeks improves physical performance, strength^{36, 37,38} and body composition (gain of lean mass and lose of fat mass) of adults^{3,38} and elderly persons^{4,5,39}. Table 1 summarizes the main effect of HMB supplementation associated with RT on body composition among humans.

In relation to individuals with high physical fitness level or elite athletes, there are different results from the effectiveness of HMB supplementation along with RT in reducing body fat^{17,18,19}. It is possible that the HMB does not alter the metabolic activity of adipose tissue due to the suppression of the proteolysis induced by the adaptation to RT, which may mitigate the effects of HMB.

It's important to highlight that carbohydrates are the main energy (ATP hydrolysis) substrate during RT for skeletal muscle contraction and RT is mostly associated with hypertrophy instead of increases in oxidative metabolism⁴⁰. However, several studies with different human populations (young/elderly/trained/untrained)^{3,4,5,38,39} showed that HMB supplementation optimize the effects of RT on the body fat loss than RT only.

These results suggested that HMB could be used as a nutritional ergogenic supplement to improve hydrolysis of triglycerides in WAT and consumption of fatty acids by muscle fibers during RT.

Although this intervention may be effective for reduction of body fat, the cellular signaling pathways of lipid metabolism activated by HMB associated with RT in humans are still very limited. Most studies analyzed on this topic are with animal models.

Table 1. Effects of β -hydroxy- β -methylbutyrate supplementation associated with resistance training on body composition.

Study design	Exercise program	Type of HMB and doses	Method for body composition	Results	Reference
65 elderly individuals: 33 control (only exercise program) and 32 intervention (exercise program + Ca-HMB), mean age 69.5±5.3.	Mild fitness program (aerobic + RT), 2 times a week for 8 weeks.	Ensure Plus Advance of Abbott Nutrition. 1.5 g of Ca-HMB/day.	DXA.	No difference: Body composition. Increased: Muscle strength and physical performance parameters for Ca-HMB group.	Berton et al. ³⁷
41 young individuals divided into 5 groups: control (only RT program); Ca-HMB/1 (1.5 g/day); Ca-HMB/2 (3.0 g/day); protein supplement 1 (117 g/day) and protein supplement 2 (175 g/day), age 19-29.	RT program: 3 times a week (1.5 h/day) for 3 weeks.	Metabolic technologies Inc. (Mtl, Ames, IA, USA). Ca-HMB: 0, 1.5 or 3.0 g/day or protein supplement: normal-117 g/day or high-175 g/day.	TOBEC	Increased: Body composition (gain of lean mass and fat mass loss for all groups). Superior gains of strength for Ca-HMB groups than control. No difference: Among Ca-HMB and protein supplement groups.	Nissen et al. ⁶
54 elderly individuals- Phase 1: 27 control (placebo) and 27 Ca-HMB. Phase 2: 27 RT and 27 RT+Ca-HMB, age ≥ 65.	Phase 1: 24 weeks of supplementation. Phase 2: RT program: 3 times a week for 24 weeks.	Abbott Nutrition, Columbus, OH. 3.0 g/day of Ca-HMB.	DXA	Phase 1 - Increased: Body composition (gain of lean mass for Ca-HMB group). Phase 2 - Increased: Body composition (gain of lean mass for 2 groups and reduction of fat mass only for RT+CaHMB group).	Stout et al. ³⁹
48 elderly individuals divided into 4 groups: Control; Ca-HMB; RT and RT+CaHMB, age: 72.1 ± 5.7.	RT program: 3 times a week for 12 weeks.	Abbott Nutrition, Columbus, OH. 3.0 g/day of Ca-HMB.	DXA	Increased: Body composition (reduction of abdominal fat only for RT+CaHMB group).	Stout et al. ⁵
20 young, trained individuals: 9 control (only RT); 11 intervention (RT+ HMB-FA), age: 21.6 ± 0.5.	RT program: 12 weeks of global RT 3 times a week.	Metabolic technologies Inc. (Mtl, Ames, IA, USA). 3.0 g/day of HMB-FA.	DXA	Increased: Body composition (gain of lean mass and lose of fat mass) and strength for 2 groups. Intervention group (RT+HMB-FA): superior improvement for body composition and strength than control (RT).	Wilson et al. ³

75 individuals: 36 control (only RT) and 39 intervention (RT+ HMB), age: 20 - 40.	RT program: 4 weeks of RT 3 times a week.	Metabolic technologies Inc. (Mtl, Ames, IA, USA). 3.0 g/day of Ca-HMB.	Skinfold thicknesses (Pollock and Wilmore protocol).	Increased: Body composition (gain of lean mass and fat mass loss) and strength for 2 groups. Intervention group (Ca-HMB): superior improvement for body composition and strength than control (RT).	Panton et al. ³⁸
32 elderly individuals: 16 control (only RT); 16 intervention (RT+ Ca-HMB), age: 70 ± 1	RT program: 8 weeks of RT 3 times a week.	Metabolic technologies Inc. (Mtl, Ames, IA, USA). 3.0 g/day of Ca-HMB.	DXA	Increased: Body composition (gain of lean mass) for 2 groups. Intervention group (RT+CaHMB) superior improvement for fat loss than control (RT).	Vukovich et al. ⁴

Legend: RT (resistance training), Ca-HMB (calcium salt of β -hydroxy- β -methylbutyrate), HMB-FA (free acid of β -hydroxy- β -methylbutyrate); DXA (dual-energy X-ray absorptiometry); TOBEC (total body electrical conductivity).

Bostrom et al.⁴¹ reported for the first time the signaling pathways of FNDC-5/irisin related to thermogenesis of adipose tissue. In this study, the authors showed that aerobic exercise promotes, in the skeletal muscle, an increase of PGC-1- α , which, in turn, stimulates the production of the FNDC-5 in which is cleaved forming irisin. Once produced, irisin is transported through the blood to the adipose tissue stimulating UCP-1 activity. This action increases the browning of WAT, converting it to brown adipose tissue and, consequently, increasing the WAT thermogenesis and oxidation of fatty acids. Similar results to activation of adipose tissue pathways of Bostrom et al.⁴¹ study has been demonstrated with animal model submitted to RT^{42,43}.

In rats, RT alter irisin levels and gene expression of fibronectin type III domain-containing protein 5 (FNDC-5) in the muscle and UCP-1 in the WAT^{42,43}, and HMB has been suggested to increase lipid oxidation in adipose tissue via increase in the gene and protein expression of hormone-sensitive lipase⁴⁴, mitochondrial biogenesis in myocytes⁴⁵ and activation of the PGC-1 α ⁴⁶. Shirvani et al.⁴⁷ demonstrated that supplementation with HMB-FA associated with RT for 8 weeks increased muscle strength, gene expression of the PGC1- α in skeletal muscle and plasma irisin concentration.

Additionally, a recent study produced by our group⁴⁸ evaluated the effects of CaHMB supplementation associated with RT in the body composition and gene expression of cytokines related to skeletal muscle hypertrophy and WAT of rats after 8 weeks. Compared to RT alone, the association of CaHMB with RT further reduced abdominal circumference (5.3%), Lee index (2.4%), fat percentage (24.4%), plasma VLDL-cholesterol (16.8%) and triglycerides (17%) and increased the gene expression of FNDC-5 (78.9%) and IL-6 (47.4%) in skeletal muscle and irisin concentration (26.9%) in WAT. In conclusion,

CaHMB supplementation increased the beneficial effects of RT on body fat reduction and was associated with muscular gene expression of FNDC-5 and irisin concentration in WAT, despite no change in gene expression of UCP-1, protein mass and maximal strength.

In humans, the effects of RT on the activation of FNDC-5/irisin and WAT thermogenesis are still very limited. In this context, Norheim et al.⁴⁹ demonstrated that UCP-1 mRNA did not correlate with gene expression of FNDC-5 in skeletal muscle, adipose tissue and serum irisin levels in response to 12 weeks intervention of combined endurance and RT.

So, as shown by our group⁴⁸ and Norheim et al.⁴⁹ it is conceivable that irisin may act on WAT by increasing energy expenditure, fatty acids oxidation and thermogenesis through other mechanisms beyond UCP-1 activity.

Therefore, our results suggest that HMB supplementation associated with RT amplifies the effect of RT on body fat reduction by activating FNDC-5/irisin pathway related thermogenesis in WAT. However, others signaling pathways of WAT activated by RT and HMB should be investigated, figure 2.

Beyond the activation of FNDC-5/irisin pathway in muscle cell, as a transcription factor, in cultured cells and in mouse tissues, PGC-1 α can bind to targets such as the peroxisome proliferator-activated receptors (PPARs), nuclear respiratory factors (NRFs) 1 and 2 and estrogen-related α receptors (ERR- α)^{50,51}. In WAT, these factors improve β -oxidation and mitochondrial biogenesis through increased activity of fatty acid transport proteins into the mitochondria and activation the nuclear transcription of oxidative enzymes^{50,51}. Thus, it is possible that all these factors (PPARs, NRFs and ERR- α) activated by PGC1- α could be affected by RT associated with HMB supplementation. However, this theory should be tested (Figure 2).

Another important signaling pathway of WAT is the SIRT6. This pathway is activated by elevated NAD⁺ levels induced during states of high energy demand, such as fasting, calorie restriction and exercise. In response to metabolic alterations of muscle cells, SIRT6 activate several gene transcription factors such as signal transducer and activator of transcription 3 (STAT3), forkhead box protein 1 (FOXO1), PPARs and PGC1- α ⁵². These classes of proteins increase mitochondrial biogenesis, fatty acid oxidation and gluconeogenesis⁵² (Figure 2).

Recent studies of Lamb et al.⁵³ showed that RT increases muscle NAD⁺ and NADH concentrations as well as global SIRT6 activity in middle-aged, overweight, untrained individuals. Similar results of Hooshmand et al.⁵⁴ reported that 12 weeks of RT with sedentary elderly

men was a useful strategy for increasing of SIRT6 and PGC-1 α .

In relation to HMB supplement, Baggett et al.⁴⁶ showed that 6 weeks of HMB supplementation associated with resveratrol resulted in an 86% increase in plasma irisin (p= 0.03), a two-fold increase in PGC1- α in WAT (p= 0.04) and a 344% increase in UCP1 expression (p<0.05). The results of this study demonstrate that HMB combined with polyphenol optimizes browning of WAT. In this context, it is relevant to investigate the effect of RT associated with HMB supplementation on activity of SIRT6 and gene transcription factors related to fatty acid oxidation of WAT.

Figure 2 summarizes the effect of HMB supplementation associated with RT on body fat and the possible signaling pathways of lipid metabolism.

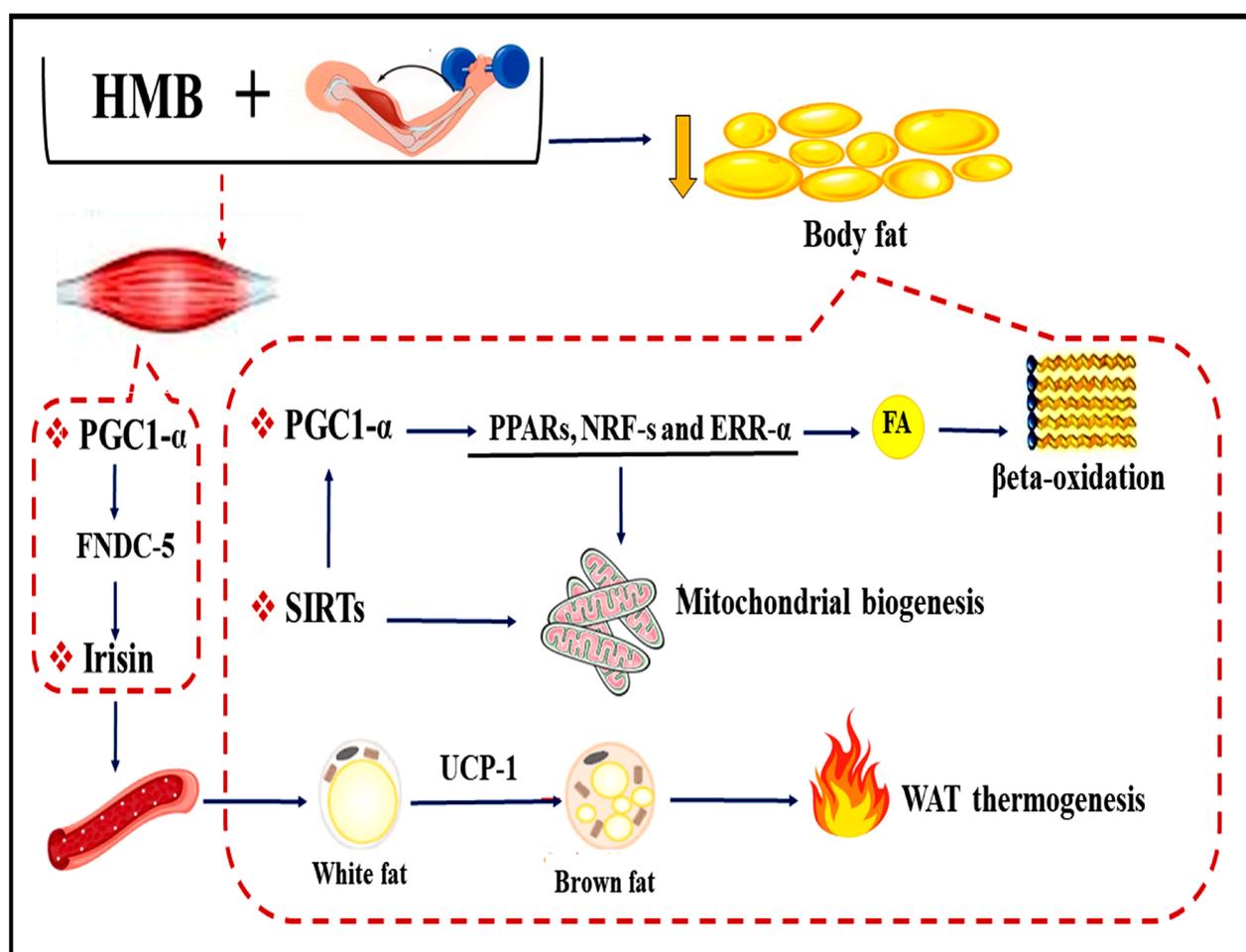


Figure 2: Effects of β -hydroxy- β -methylbutyrate supplementation associated with resistance training on body fat and the possible signaling pathways of lipid metabolism.

Legend: PGC1- α , proliferator-activated receptor gamma co-activator 1 α ; SIRT6, sirtuins; FNDC-5, fibronectin type III domain-containing protein 5; UCP-1, type 1 mitochondrial uncoupling protein; PPARs, peroxisome proliferator-activated receptors, NRFs, nuclear respiratory factors 1 and 2; ERR- α , estrogen-related α receptors; FA, fatty acids; WAT, white adipose tissue. Source: Author elaboration.

It is important to highlight that the reduction of body fat is important for several reasons: protection against cardiovascular and metabolic diseases caused by excess adipose tissue 1; improvement of body composition and sports performance in several modalities^{55,56}; and reduction of psycho-social problems⁵⁷. In this context, HMB supplementation associated with RT emerges as an interesting intervention for the reduction of body fat, which, in turn, is an important factor for improving health and sports performance.

The results of studies on the effectiveness of HMB associated with RT in the metabolic activity of adipose tissue should be analyzed carefully since there are variations among studies' methodologies, dosage supplement (HMB-AL or HMB-Ca), duration of intervention and populations. Thus, it is essential that other studies are carried out to address this question.

CONCLUSION

In this review we updated the effects of HMB supplementation associated with RT on body fat concentration and lipid metabolism signaling pathways. We concluded that HMB supplementation associated with RT optimize body fat loss.

However, the framework of lipid metabolism signaling pathways is not completely known which warrants further investigation, especially on PGC1- α , FNDC-5/irisin, and SIRT6.

Specifically, HMB associated with RT amplifies the effect of RT on body fat reduction by activating FNDC-5/irisin pathway related thermogenesis in WAT. However, we cannot conclude the same of PGC1- α and SIRT6. In this context, it is relevant that other studies investigate the effects of this intervention on signaling pathways of WAT metabolism.

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