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Review Article

# β-hydroxy-β-methylbutyrate free acid supplementation may improve recovery and muscle adaptations after resistance training: a systematic review

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ARTICLE INFO

*Article history:*
Received 27 March 2017
Revised 20 July 2017
Accepted 24 July 2017

*Keywords:*
HMB free acid
Supplementation
Muscle mass
Calcium HMB
Sports nutrition

ABSTRACT

β-Hydroxy-β-methylbutyrate free acid (HMB-FA) has been suggested to accelerate the regenerative capacity of skeletal muscle after high-intensity exercise and attenuate markers of skeletal muscle damage. Herein a systematic review on the use of HMB-FA supplementation as an ergogenic aid to improve measures of muscle recovery, performance, and hypertrophy after resistance training was conducted. This review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. We included randomized, double-blinded, placebo-controlled trials investigating the effects of HMB-FA supplementation in conjunction with resistance exercise in humans. The search was conducted using Medline and Google Scholar databases for the terms *beta-hydroxy-beta-methylbutyrate, HMB free acid, exercise, resistance exercise, strength training,* and *HMB supplementation.* Only research articles published from 1996 to 2016 in English language were considered for the analysis. Nine studies met the criteria for inclusion in the analyses. Most studies included resistance-trained men, and the primary intervention strategy involved administration of 3 g of HMB-FA per day. In conjunction with resistance training, HMB-FA supplementation may attenuate markers of muscle damage, augment acute immune and endocrine responses, and enhance training-induced muscle mass and strength. HMB-FA supplementation may also improve markers of aerobic fitness when combined with high-intensity interval training. Nevertheless, more studies are needed to determine the overall efficacy of HMB-FA supplementation as an ergogenic aid.



*Abbreviations:* ATP, adenosine triphosphate; CK, creatine kinase; CR3, complement receptor type 3; CRP, C-reactive protein; CWI, cold water immersion; GH, growth hormone; HIIT, high-intensity interval training; HMB, β-hydroxy-β-metylbutyrate; HMB-Ca, β-hydroxy-β-methylbutyrate calcium; HMB-FA, β-hydroxy-β-methylbutyrate free acid; IGF-1, insulin-like growth factor 1; MIP-1β, macrophage inflammatory protein-1β; $PWC_{FT}$, physical working capacity at the onset of neuromuscular fatigue threshold; TNF-α, tumor necrosis factor α; $VO_2$peak, maximal oxygen consumption.

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http://dx.doi.org/10.1016/j.nutres.2017.07.008
0271-5317/

## Article Outline



## 1. Introduction

Nutritional interventions are a commonly used strategy to enhance recovery from exercise, augment body composition, and increase performance. Dietary supplementation with the leucine metabolite, β-hydroxy-β-methylbutyrate (HMB), has been suggested to accelerate the regenerative capacity of skeletal muscle after high-intensity exercise and attenuate markers of skeletal muscle damage [1]. HMB's mechanisms of action are generally considered to relate to its effect on both muscle protein synthesis and muscle protein breakdown (Fig. 1) [2,3]. HMB seems to stimulate muscle protein synthesis through an up-regulation of the mammalian/mechanistic target of rapamycin complex 1, a signaling cascade involved in coordination of translation initiation of muscle protein synthesis [2,4]. In addition, HMB may have antagonistic effects on the ubiquitin-proteasome pathway, a system that degrades intracellular proteins [5,6]. Evidence also suggests that HMB promotes myogenic proliferation, differentiation, and cell fusion [7].

Most of published research has administered HMB in the form of calcium HMB (HMB-Ca). Some studies have shown HMB-Ca supplementation to be associated with greater increases in lean body mass, strength, and power in conjunction with a resistance training program [1], whereas others have shown no effect from HMB-Ca supplementation [8,9]. Recently, HMB in free acid form (HMB-FA) has emerged as a novel alternative purported to exert a greater ergogenic effect. Calcium HMB has generally been shown to have a slow rate of appearance taking approximately 60 to 120 minutes to reach peak plasma concentrations [10]. In contrast, when HMB is provided in its free acid form, the absorption rate seems to be accelerated demonstrating peak plasma concentrations approximately 30 minutes after ingestion [2,10,11]. Furthermore, compared with HMB-Ca, HMB-FA increased peak plasma HMB concentration along with an increased plasma clearance rate [12]. The greater absorption rate, peak plasma concentration, and clearance rate are purported to result in greater intramuscular HMB bioavailability and thus provide a superior, more practical stimulus for exercise recovery [2,10].

Exogenous HMB-FA administration has shown to increase intramuscular anabolic signaling, stimulate muscle protein synthesis, and attenuate muscle protein breakdown in humans [2]. Therefore, the anabolic and anticatabolic properties of HMB-FA offer an appealing nutritional supplement for athletes participating in high-intensity, muscle-damaging exercise. Recently, several studies investigated the efficacy of HMB-FA supplementation in conjunction with resistance training. The purpose of this review was to perform a systematic analysis on the effects of HMB-FA supplementation with regard to actions on muscle recovery, performance, and hypertrophy in humans after resistance training.

## 2. Approach

This systematic review was performed using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses. This review was registered in PROSPERO on June 28, 2016, and

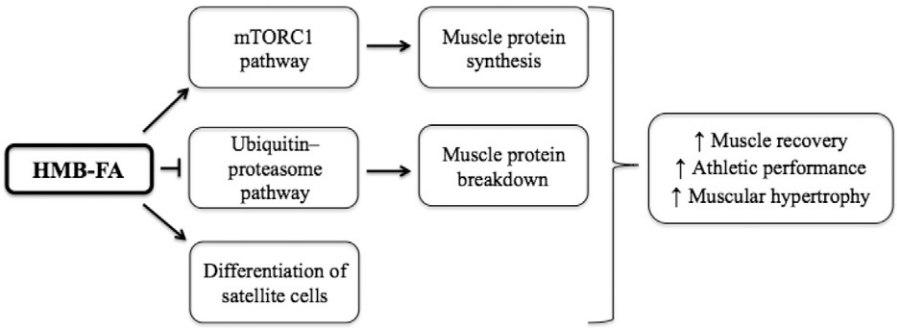


**Fig. 1 – Simplistic overview of HMB-FA's proposed mechanisms of actions on biochemical pathways and muscle cells and tissues. HMB-FA indicates β-hydroxy-β-methylbutyrate free acid; mTORC1, mammalian/mechanistic target of rapamycin complex 1.**

can be accessed in PROSPERO by the code CRD42016038761. We included only randomized, double-blinded, placebo-controlled trials investigating the effects of HMB-FA supplementation in conjunction with resistance exercise in humans. The search was conducted using Medline and Google Scholar databases to identify all relevant articles. Search terms included *beta-hydroxy-beta-methylbutyrate, HMB free acid, exercise, resistance exercise, strength training,* and *HMB supplementation.* Studies included were English-language, peer-reviewed, randomized controlled trials assessing the effects of HMB-FA supplementation on measures of muscle recovery, performance, and hypertrophy after resistance training in healthy men and women. Research articles published from 1996 through 2016 was considered for analysis. The search strategies, along with inclusion and exclusion criteria, are depicted in Fig. 2.

## 3. Findings

In the initial search for the selected terms, 128 articles were identified. Twenty-nine were excluded because they were restricted to animals or not written in English. Of the remaining 99 published studies, 9 studies met the criteria for inclusion in the analyses. Five studies investigated the acute effects of HMB-FA supplementation on the resistance exercise–induced response and/or muscle recovery in resistance-trained men (Table 1). Two studies investigated the effects of HMB-FA supplementation on resistance training-induced muscular adaptation in resistance-trained men (Table 2). Two studies investigated the effects of HMB-FA supplementation on high-intensity interval training (HIIT) in recreationally active men and women (Table 3). The primary intervention strategy involved administration of 3 g of HMB-FA per day. These studies are compiled with details in Tables 1-3 and discussed in this review.

### 3.1. HMB-FA supplementation on muscle

#### 3.1.1. Acute effects of HMB-FA supplementation on the resistance exercise–induced response and/or muscle recovery

Several studies have investigated the acute effects of HMB-FA supplementation on the resistance exercise–induced response and/or muscle recovery [11,13-16]. Two studies have evaluated the effect of acute HMB-FA supplementation on markers of muscle damage and subsequent recovery [11,13]. Wilson et al [13] reported that short-term supplementation (2 days; 3 $g \cdot d^{-1}$) decreased indices of muscle damage after a high-volume resistance training session. Twenty resistance-trained men were randomly assigned to receive either 3 $g \cdot d^{-1}$ of HMB-FA or placebo. A 1-g serving was provided 30 minutes before the high-volume resistance training session, and the remaining 2 servings were provided with lunch and evening meals. Creatine kinase (CK) increased to a significantly greater extent in the placebo group (329%) compared with the HMB-FA group (104%). Muscle protein breakdown, measured by urinary 3-methylhistidine/creatinine ratio, remained constant in the placebo group, while approaching a statistically lower ratio ($P = .08$) in the

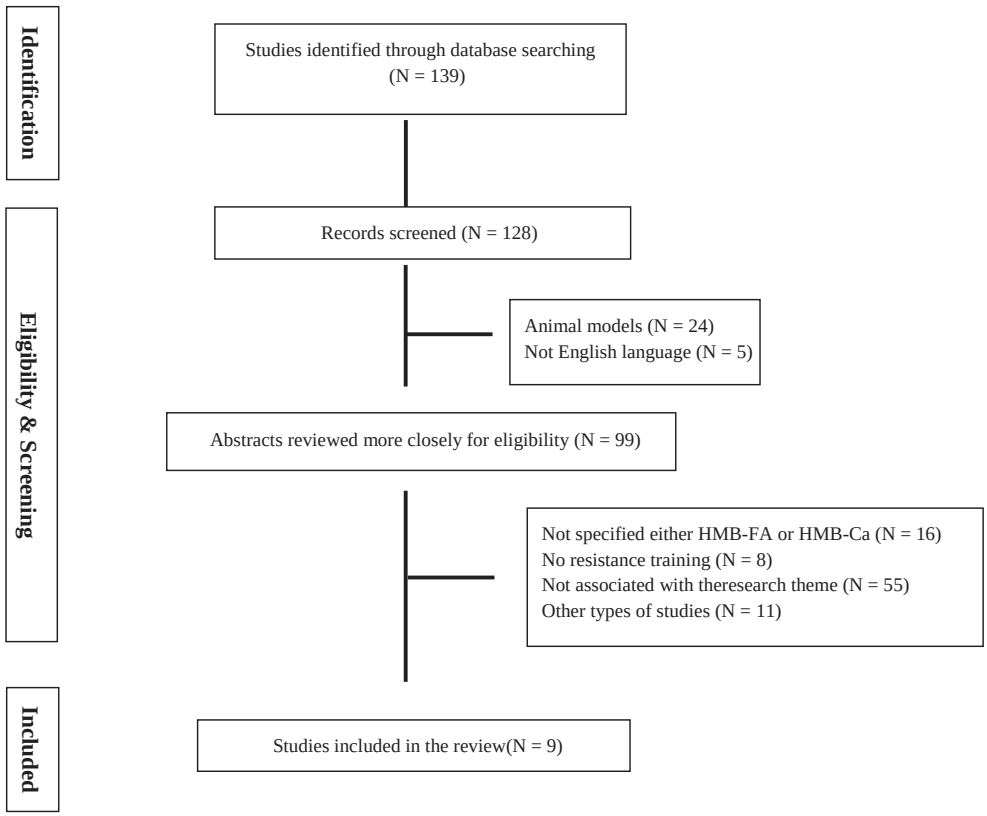


**Fig. 2 – PRISMA diagram for the search and selection process of articles considered in this review. PRISMA indicates Preferred Reporting Items for Systematic Reviews and Meta-Analyses.**

**Table 1 – Acute effects of HMB-FA supplementation on the resistance exercise–induced response and/or muscle recovery**

| Reference | Type of study | Sample | Supplementation protocol | Exercise protocol | Main findings |
|---|---|---|---|---|---|
| Wilson et al [13] | Randomized placebo-controlled | 20 resistance-trained men (21.6 y) | 3 g · $d^{-1}$ HMB-FA divided equally into 3 servings | Full-body resistance training session | ↓ CK<br>↑ perceived recovery status<br>= cortisol, CRP, and free and total testosterone |
| Townsend et al [14] | Placebo-controlled, double-blind, randomized | 40 resistance-trained men (22.3 y) | 3 g · $d^{-1}$ HMB-FA divided equally into 3 servings<br>Supplementation was associated with or without CWI (10–12 °C) immediately after exercise protocol | Lower-body resistance training session | ↓ TNF-α concentrations<br>↓ TNFR1 expression |
| Gonzalez et al [15] | Randomized, double-blind, placebo-controlled | 39 resistance-trained men (22.2 y) | 3 g · $d^{-1}$ HMB-FA divided equally into 3 servings<br>Supplementation was associated with or without CWI (10-12 °C) immediately after exercise protocol | Lower-body resistance training session | ↑ % of monocytes expressing CR3<br>= MIP-1β |
| Gonzalez et al [11] | Randomized, double-blind, placebo-controlled study | 40 resistance-trained men (22.3 y) | 3 g · $d^{-1}$ HMB-FA divided equally into 3 servings<br>Supplementation was associated with or without CWI (10-12 °C) immediately after exercise protocol | Lower-body resistance training session | = CK, myoglobin, CRP, IL-6, and IL-10<br>= performance recovery<br>= perceived recovery status<br>↑ average power per repetition (HMB-FA + CWI only) |
| Townsend et al [16] | Placebo-controlled, double-blind, randomized | 20 resistance trained men (22.3 y) | 1 g HMB-FA consumed 30 min before the exercise protocol | Lower-body resistance training session | ↑ GH response at IP<br>↑ AUC for GH and IGF-1 |

Abbreviations: 3MH/Cr, ratio of urinary 3-methylhistidine to creatinine; AUC, area under the curve; CK, creatine kinase; CR3, complement receptor type 3; CWI, cold water immersion (findings not shown); GH, growth hormone; HMB-FA, β-hydroxy-β-methylbutyrate free acid; IGF-1, insulin-like growth factor 1; IL-6, interleukin 6; IL-10, interleukin 10; MIP-1β, macrophage inflammatory protein-1β; RT, resistance training; TNF-α, tumor necrosis factor α; TNFR1, monocyte TNF-α receptor 1. ↑, significantly greater (HMB-FA vs placebo); ↓, significantly lower (HMB-FA vs placebo); =, no significant differences (HMB-FA vs placebo).

**Table 2 – Effects of HMB-FA supplementation on resistance training-induced muscular adaptation**

| References | Type of study | Sample | Supplementation protocol | Exercise protocol | Main findings |
|---|---|---|---|---|---|
| Wilson et al [23] | A 3-phase double-blind, placebo- and diet-controlled | 24 resistance-trained men (21.6 y) | 3 g · $d^{-1}$ HMB-FA divided equally into 3 servings | 8-wk periodized RT program followed by a 2-wk overreaching cycle and a 2-wk taper | ↑ lean body mass (7.4 ± 4.2 vs 2.1 ± 6.1 kg)<br>↓ fat percentage (–5.4% ± 1.6% vs –1.7% ± 2.7%)<br>↑ quad thickness (7.2 vs 2.4 mm)<br>↑ total strength (77.1 ± 18.4 vs 25.3 ± 22.0 kg)<br>↑ vertical jump power (991 ± 168 vs 630 ± 167 W)<br>↑ Wingate power (158.9 vs 103.4 W)<br>↑ perceived recovery status<br>↓ CK and cortisol<br>= CRP, 3MH/Cr and free and total testosterone |
| Lowery et al [17] | A 3-phase double-blind, placebo- and diet-controlled | 17 resistance-trained men (21.7 y) | 3 g · $d^{-1}$ HMB-FA divided equally into 3 servings 400 mg · $d^{-1}$ATP provided as a single daily bolus serving | 8-wk periodized RT program followed by a 2-wk overreaching cycle and a 2-wk taper | ↑ lean body mass (8.5 ± 0.8 vs 2.1 ± 0.5 kg)<br>↓ fat percentage (–8.5% ± 0.9% vs –2.4% ± 1.1%)<br>↑ quad thickness (7.8 ± 0.4 vs 2.4 ± 0.7 mm)<br>↑ total strength (96.0 ± 8.2 vs 25.3 ± 7.3 kg)<br>↑ vertical jump power (1076 ± 40 vs 630 ± 56 W)<br>↑ Wingate power (210 ± 20 vs 103 ± 21 W)<br>↑ perceived recovery status<br>↑ 3MH/Cr<br>↓ CK and cortisol<br>= CRP and free and total testosterone |

Abbreviations: 3MH/Cr, ratio of urinary 3-methylhistidine to creatinine; ATP, adenosine triphosphate; CK, creatine kinase; CRP, C-reactive protein; HMB-FA, β-hydroxy-β-methylbutyrate free acid; RT, resistance training; Total strength, 1-repetition maximum for bench press, squat, and deadlift. ↑, significantly greater (HMB-FA vs placebo); ↓, significantly lower (HMB-FA vs placebo); =, no significant differences (HMB-FA vs placebo).

**Table 3 – Effects of HMB-FA supplementation on high-intensity interval training**

| References | Type of study | Sample | Intervention protocol | Exercise protocol | Main findings |
|---|---|---|---|---|---|
| Robinson et al [18] | Double-blind, placebo-controlled | 26 recreationally active men and women (22.7 y) | 3 g · $d^{-1}$ HMB-FA divided equally into 3 servings | 4-wk cycle ergometry HIIT program | ↑ $VO_2$peak<br>↑ ventilatory threshold<br>= time to exhaustion<br>= respiratory compensation point<br>= body composition<br>= training volume |
| Miramonti et al [19] | Double-blind, placebo-controlled | 28 recreationally active men and women (22.8 y) | 3 g · $d^{-1}$ HMB-FA divided equally into 3 servings | 4-wk cycle ergometry HIIT program | ↑ physical working capacity at the onset of neuromuscular fatigue threshold |

Abbreviations: HMB-FA, β-hydroxy-β-methylbutyrate free acid; HIIT, high-intensity interval training $VO_2$peak, peak oxygen consumption. ↑, significantly greater (HMB-FA vs placebo); =, no significant differences (HMB-FA vs placebo).

HMB-FA group 48 hours after exercise. HMB-FA also significantly improved participants' subjective perceived recovery score. However, HMB-FA did not augment acute changes in plasma total testosterone, free testosterone, cortisol, or C-reactive protein (CRP). Therefore, HMB-FA supplementation seemed to mitigate resistance exercise–induced muscle damage and speed recovery in trained men. However, Gonzalez and colleagues [11] also examined the effects of HMB-FA with and without cold water immersion (CWI) on resistance exercise–induced markers of muscle damage and subsequent resistance exercise performance. Forty resistance-trained men performed a high-intensity lower-body resistance exercise routine and were randomly assigned to 1 of 4 treatment groups: (1) placebo, (2) HMB-FA, (3) HMB-FA and CWI, and (4) Placebo and CWI. The HMB-FA groups ingested 3 g · $d^{-1}$ following the same dosing strategy as Wilson et al [13], whereas the CWI groups submersed their lower body into 10 °C to 12 °C water for 10 minutes after exercise. Contrary to Wilson et al [13], no differences between groups were observed for CK. Furthermore, HMB-FA did not seem to provide benefit over placebo for performance recovery, perceived recovery status, or changes in myoglobin, CRP, interleukin 6, and interleukin 10. HMB-FA may have attenuated the increase in CRP when combined with CWI, and only the HMB-FA and CWI combination group showed significantly greater improvements in performance recovery (ie, average power output).

In subsequent analyses, Gonzalez et al [15] and Townsend et al [14] also analyzed the effects of HMB-FA and CWI on the inflammatory response to resistance exercise. Similarly, resistance-trained men performed a high-intensity lower-body resistance exercise routine and were randomly assigned to 1 of the 4 aforementioned groups. Gonzalez et al [15] measured complement receptor type 3 (CR3) expression on $CD14^+$ monocytes along with circulating macrophage inflammatory protein (MIP)-1β, while Townsend et al [14] measured circulating concentrations of tumor necrosis factor α (TNF-α) and monocyte TNF-α receptor 1 expression via flow cytometry. CR3 and MIP-1β facilitate monocyte recruitment, adhesion, and subsequent infiltration into damaged muscle tissue [15], and TNF-α is involved in signaling the migration of neutrophils and macrophages to the site of muscle damage to initiate the breakdown of tissue [20]. All treatment groups attenuated the rise in CR3 expression at 30 minutes after exercise, whereas only HMB-FA supplementation significantly elevated the percentage of monocytes expressing CR3 during recovery. No effects were observed for MIP-1β concentrations [15]. Compared with placebo and CWI groups, HMB-FA supplementation also seemed to attenuate elevations in circulating TNF-α and TNF-α receptor 1 expression after an acute bout of resistance exercise [14]. Although HMB-FA may alter inflammatory responses to resistance exercise, supplementation did not contribute to a more rapid recovery or improve subsequent performance. Therefore, the significance of these findings remains unknown because the time course that inflammatory responses are most beneficial has yet to be determined.

Lastly, Townsend et al [16] examined the acute effect of HMB-FA on the endocrine response (ie, testosterone, growth hormone [GH], insulin-like growth factor 1 [IGF-1], and insulin) after a bout of high-intensity lower-body resistance exercise. Twenty resistance-trained men were randomly assigned to consume either HMB-FA (1 g) or placebo 30 minutes before a bout of lower-body resistance exercise. Both groups elicited significant elevations in plasma testosterone, GH, and insulin immediately after resistance exercise; GH and insulin also remained elevated 30 minutes after resistance exercise. However, the HMB-FA group demonstrated significantly greater elevations in GH immediately after resistance exercise, and area under the curve analysis revealed a significantly greater GH and IGF-1 response in the HMB-FA group compared with the placebo group. Hence, HMB-FA supplementation before resistance exercise may enhance the transient response of anabolic hormones including GH and IGF-1. In agreement with Wilson et al [13], HMB-FA did not affect the testosterone response to resistance exercise. Although these findings provide support for the potential anabolic benefits associated with HMB-FA supplementation, transient elevations in the hormonal milieu after resistance exercise may not be related to exercise-induced muscle hypertrophy; thus, whether the observed increases in anabolic hormones would translate into greater muscle hypertrophy remains questionable [21,22].

### 3.2. *HMB-FA supplementation effects on resistance training-induced muscular adaptation*

Few studies have investigated the effects of chronic HMB-FA supplementation in conjunction with a resistance training program [17,23]. Wilson and colleagues [23] investigated the effects of 12 weeks of HMB-FA supplementation on skeletal muscle hypertrophy, body composition, strength, and power in trained individuals. Twenty resistance-trained men were

randomly assigned to receive either 3 g · $d^{-1}$ of HMB-FA or a placebo. On training days, a 1-g serving was provided 30 minutes before exercise and the remaining 2 servings were ingested along with mid-day and evening meals. On non–training days, participants were instructed to consume 1-g servings with each of 3 separate meals throughout the day. All participants performed an 8-week periodized resistance training program followed by a 2-week overreaching cycle and a 2-week taper. Supplementation with HMB-FA diminished the rise in CK and cortisol over the 12-week study; however, CRP, free testosterone, total testosterone, and urinary 3-methylhistidine/creatinine ratio were unaltered by supplementation. HMB-FA also enhanced hypertrophy, strength, and power outcomes after the 12-week resistance training program while preventing decrements in performance observed in the placebo group after the overreaching phase of training.

Lowery et al [17] investigated the effects of the combination of HMB-FA (3 g · $d^{-1}$) and adenosine triphosphate (ATP; 400 mg · $d^{-1}$) supplementation in trained men. All participants performed a similar 12-week resistance training program and followed the same HMB-FA dosing protocol described by Wilson et al [23]. ATP supplementation was provided as a single daily bolus serving. Supplementation with HMB-FA/ATP attenuated the rise in CK and cortisol over the 12-week study, whereas no effects were observed for CRP, free testosterone, or total testosterone levels during the training program. HMB-FA/ATP supplementation resulted in a significant increase in urinary 3-methylhistidine/creatinine ratio when compared with the placebo group during the first week of training; however, no significant difference was observed between groups during the overreaching phase of training. The HMB-FA/ATP supplement also enhanced hypertrophy, strength, and power outcomes after the 12-week resistance training program in addition to blunting the typical performance decrements associated with overreaching. However, in this study, HMB-FA was administered in combination with ATP, which makes it difficult to discern to what degree the results were attributable to HMB-FA.

Collectively, these 2 studies suggest that, in conjunction with a resistance training program, supplementation with HMB-FA (3 g · $d^{-1}$) results in increases in lean body mass, muscle hypertrophy, strength, and power in resistance-trained men. However, although speculative, it is noteworthy to acknowledge that the sizeable increases in lean body mass have raised skepticism and debate [24-26]. The reported increases in lean body mass associated with HMB-FA supplementation (7.4 ± 4.2 kg [23] and 8.5 ± 0.8 kg [17], respectively) is rather extreme, especially among trained participants who would have had less propensity to gain lean body mass. Regardless, future research is warranted to replicate these findings and determine the efficacy of chronic HMB-FA supplementation in various populations.

### 3.3. *HMB-FA supplementation effects on HIIT*

High-intensity interval training is an alternative form of resistance training that comprised intermittent bouts of resistive exercise such as cycling. Few studies have investigated the effects of chronic HMB-FA supplementation in conjunction with HIIT [18,19]. Robinson et al [18] examined the effect of HMB-FA on maximal oxygen consumption ($VO_2$peak), ventilatory threshold, respiratory compensation point, and time-to-exhaustion after a 4-week cycle ergometry HIIT program. Twenty-six recreationally active college-aged men and women were randomly assigned to receive either HMB-FA (3 g · $d^{-1}$) or a placebo, whereas 8 participants served as controls. On training days, 1-g servings of HMB-FA were provided 30 minutes before exercise, 1 hour later, and 3 hours after exercise. On non–training days, participants consumed 1 g with 3 separate meals throughout the day. Interestingly, HMB-FA supplementation significantly improved $VO_2$peak and ventilatory threshold compared with placebo, whereas no differences were observed for time-to-exhaustion, respiratory compensation point, training volumes, or body composition between groups. Thus, when combined with HIIT, HMB-FA supplementation may further improve markers of aerobic fitness. The authors speculate that HMB-FA supplementation may have enhanced the effects of HIIT by improving mitochondrial biogenesis, fat oxidation, and/or metabolism; however, more research is needed to support these proposed mechanisms in humans.

Miramonti et al [19] investigated the effects of HIIT, with and without HMB-FA supplementation, on physical working capacity at the onset of neuromuscular fatigue threshold ($PWC_{FT}$), which is defined as the onset of neuromuscular fatigue measured as a significant increase in electromyography amplitude during exercise. Twenty-eight recreationally active college-aged men and women were randomly assigned to receive either HMB-FA (3 g · $d^{-1}$) or a placebo, whereas 9 participants served as controls. All participants performed a similar 4-week cycle ergometry HIIT program and followed the same HMB-FA dosing protocol described by Robinson et al [18]. HMB-FA supplementation significantly improved $PWC_{FT}$ compared with placebo and control groups. HIIT has shown to be an effective training modality to improve aerobic fitness and neuromuscular fatigue thresholds in young men and women; however, it seems that adding HMB-FA supplementation with HIIT may further improve endurance performance measures. The authors suggest that HMB-FA may act to enhance the effects of HIIT on $PWC_{FT}$ by improving recovery between HIIT sessions, thereby allowing for greater training adaptations in $VO_2$peak and lactate metabolism. More research is warranted to investigate these mechanisms along with the efficacy of chronic HMB-FA supplementation in conjunction with HIIT.

## 4. Future directions

More studies are needed to determine the overall efficacy of HMB-FA supplementation as an ergogenic aid. Given the controversy surrounding the studies investigating the effect of HMB-FA supplementation on resistance training–induced muscular adaptation [24-26], future research is needed to evaluate the effects of HMB-FA on resistance training outcomes. Similarly, more research is warranted to verify the effects of HMB-FA on markers of aerobic fitness including investigations into the potential mechanisms by which these improvements may manifest. HMB-FA may also potentially

serve as a therapeutic strategy for the prevention of muscle mass loss in several myopathies; therefore, along with resistance-trained individuals, future research should also be conducted in nonathletic populations including sedentary, elderly, and sarcopenic individuals. There also remains a need for future research investigating optimal dosing and timing strategies of HMB-FA supplementation, along with studies investigating the potential synergistic effect of HMB-FA with other anabolic supplements such as whey and leucine. Lastly, there has yet to be a study directly comparing the chronic effects of HMB-FA with HMB-Ca, which makes it difficult to discern if HMB-FA is indeed the superior supplement strategy.

## 5. Conclusions

HMB-FA seems to be a safe dietary supplement in otherwise healthy populations. No differences in blood chemistry, hematology, or urinalysis values have been reported after chronic HMB-FA supplementation compared with placebo [23]. In addition, no adverse effects have been associated with HMB-FA supplementation in any of the aforementioned studies.

HMB-FA supplementation has shown to increase intramuscular anabolic signaling, stimulate muscle protein synthesis, and attenuate muscle protein breakdown in humans [2]. The effect of HMB-FA supplementation on markers of muscle damage and perceived recovery after resistance exercise have yielded mixed results; however, supplementation may attenuate markers of muscle damage and augment acute immune and endocrine responses. In conjunction with a 12-week resistance training program, HMB-FA supplementation has demonstrated to augment hypertrophy, strength, and power outcomes in resistance-trained men. In addition, HMB-FA supplementation has shown to improve markers of aerobic fitness including $VO_2$peak and $PWC_{FT}$ when combined with HIIT in recreationally trained individuals.

## Acknowledgment

There was no external funding, and the authors have no conflicts of interest to declare. The contribution of the authors is as follows: GDP and VRS designed the search strategy. All authors carried out the literature searches, screened initial results, extracted data, analyzed the findings, and drafted tables. AMG and VRS drafted the manuscript. All authors contributed to synthesizing the results and critical revisions of the manuscript, and all authors approved the final version. The authors also wish to thank Ana C. Marini and João F. Mota for their assistance in the design of this research.

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