

# EXERCISE-INDUCED HORMONAL RESPONSES TO HMB ADMINISTRATION: A SYSTEMATIC REVIEW AND META-ANALYSIS



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RESPOSTAS HORMONAIIS INDUZIDAS POR EXERCÍCIOS À ADMINISTRAÇÃO DO HMB: UMA REVISÃO SISTEMÁTICA E META-ANÁLISE

RESPUESTAS HORMONALES INDUCIDAS POR EL EJERCICIO A LA ADMINISTRACIÓN DE HMB: REVISIÓN SISTEMÁTICA Y META-ANÁLISIS

Jiang Du<sup>1</sup>   
(Physical Educational Professional)

1. Physical education college of jilin University, Changchun, China.

## Correspondence:

Jiang Du  
Changchun, China, 130000.  
dapao3732@163.com.

## ABSTRACT

**Introduction:** The  $\beta$ -hydroxy  $\beta$ -methyl butyrate (HMB) is an amino acid leucine metabolite with several ergogenic benefits. It is known that it can benefit testosterone and cortisol concentration in athletes. However, no systematic review and meta-analysis has focused on the effects of HMB supplementation on testosterone and cortisol in trained athletes. **Objectives:** The meta-analysis evaluates the effect of HMB supplementation on testosterone and cortisol in trained athletes and verifies conflicting results between studies. **Methods:** A systemic review was performed in Scopus, Medline, and Google scholar databases of articles published until August 2021. The Cochrane Collaboration tool was used to assess the risk of bias and assess the quality of the studies. Random effects model, weighted mean difference (WMD), and 95% confidence interval (CI) were used to estimate the overall effect. **Results:** Although the meta-analysis showed that HMB consumption does not alter cortisol and testosterone concentration, subgroup analysis based on exercise type exhibited a significant decrease in cortisol concentration in resistance training exercises ( $P < 0.05$ ) and a significant increase in testosterone concentration in combined aerobic and anaerobic sports ( $P < 0.05$ ). **Conclusion:** The results indicate that HMB supplementation in athletes can reduce cortisol concentration in endurance exercise and increase testosterone concentration in combined aerobic and anaerobic exercise. **Evidence Level II; Therapeutic Studies – Investigating the results.**

**Keywords:** Hypertrophy; Dietary supplements; Testosterone; Hydrocortisone; Meta-Analysis.

## RESUMO

**Introdução:** o  $\beta$ -hidroxi  $\beta$ -metilbutirato (HMB) é um metabólito de aminoácido leucina e tem vários benefícios ergogênicos. Sabe-se que ela pode beneficiar a concentração de testosterona e cortisol em atletas. Porém, nenhuma revisão sistemática e meta-análise focou-se nos efeitos que a suplementação de HMB provoca sobre testosterona e cortisol em atletas treinados. **Objetivos:** A meta-análise tem como objetivo avaliar o efeito de suplementação de HMB na testosterona e cortisol em atletas treinados, além de verificar resultados contraditórios entre estudos. **Métodos:** Foi feita uma revisão sistêmica nas bases Scopus, Medline e Google scholar dos artigos publicados até agosto de 2021. A ferramenta de colaboração Cochrane foi utilizada para avaliar o risco de viés e também para avaliar a qualidade dos estudos. Modelo de efeitos aleatórios, diferença média ponderada (ADM) e intervalo de confiança de 95% (IC) foram utilizados para estimar o efeito geral. **Resultados:** Embora a meta-análise tenha evidenciado que o consumo de HMB não altere a concentração de cortisol e testosterona, a análise do subgrupo com base no tipo de exercício exibiu uma diminuição significativa na concentração do cortisol nos exercícios de treinamento de resistência ( $P < 0,05$ ) e um aumento significativo na concentração de testosterona em esportes combinados aeróbicos e anaeróbicos ( $P < 0,05$ ). **Conclusão:** Os resultados indicam que a suplementação de HMB em atletas pode reduzir a concentração de cortisol em exercícios de resistência e aumentar a concentração de testosterona em exercícios aeróbicos e anaeróbicos combinados. **Nível de evidência II; Estudos Terapêuticos - Investigação de Resultados.**

**Descritores:** Hipertrofia; Suplementos dietéticos; Testosterona; Hidrocortisona; Metanálise.

## RESUMEN

**Introducción:** El  $\beta$ -hidroxi- $\beta$ -metilbutirato (HMB) es un metabolito del aminoácido leucina y tiene varios beneficios ergogénicos. Está comprobado que puede beneficiar la concentración de testosterona y cortisol en los deportistas. Sin embargo, ninguna revisión sistemática y meta-análisis se ha centrado en los efectos que la suplementación con HMB provoca en la testosterona y el cortisol en atletas entrenados. **Objetivos:** El meta-análisis tiene como objetivo evaluar el efecto de la suplementación con HMB sobre la testosterona y el cortisol en atletas entrenados, y verificar los resultados contradictorios entre los estudios. **Métodos:** Se realizó una revisión sistémica en las bases de datos Scopus, Medline y Google scholar de los artículos publicados hasta agosto de 2021. Se utilizó la herramienta de colaboración Cochrane para evaluar el riesgo de sesgo y también para evaluar la calidad de los estudios. Se utilizó un modelo de efectos aleatorios, una diferencia de medias ponderada (DMP) y un intervalo de confianza (IC) del 95% para estimar el efecto global. **Resultados:** Aunque el meta-análisis mostró que el consumo de HMB no altera la concentración de



cortisol y testosterona, el análisis de subgrupos basado en el tipo de ejercicio mostró una disminución significativa de la concentración de cortisol en los ejercicios de entrenamiento de resistencia ( $P < 0,05$ ) y un aumento significativo de la concentración de testosterona en los deportes aeróbicos y anaeróbicos combinados ( $P < 0,05$ ). Conclusión: Los resultados indican que la suplementación con HMB en los atletas puede reducir la concentración de cortisol en el ejercicio de resistencia y aumentar la concentración de testosterona en el ejercicio aeróbico y anaeróbico combinado.

**Nivel de evidencia II; Estudios terapéuticos - Investigación de resultados.**

**Descriptor:** Hipertrofia; Suplementos dietéticos; Testosterona; Hidrocortisona; Meta-Análisis.

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## INTRODUCTION

In recent years, an enormous growth of interest has been placed on nutritional supplements for enhancing training-induced adaptations. This interest has been motivated by this theory that nutritional supplements may improve performance by increasing anabolic and decreasing catabolic effects, thereby improving body composition and decreasing exercise-induced muscle damage.<sup>1-3</sup>

One potential nutrient is the leucine metabolite  $\beta$ -hydroxy  $\beta$ -methylbutyrate (HMB) supplementation, that it may result in several ergogenic advantages, including anti-catabolic,<sup>4</sup> anabolic<sup>5</sup> (5) and lipolytic impacts.<sup>6</sup> HMB a leucine and 2-ketoisocaproic acid metabolite has been suggested to enhance recovery and improve skeletal muscles during high-volume and high-intensity exercises.<sup>7-10</sup> It has been reported that HMB increased strength,<sup>11</sup> power<sup>12</sup> and lean body mass<sup>5,6</sup> through muscle breakdown inhibition during exercise and protein synthesis increase after exercise. Recent data suggested that the advantages of HMB supplementation may be attributed to the some mechanisms including; 1) upregulation of IGF-1 (Insulin-like growth factor 1) expression in skeletal muscle, 2) stimulating synthesis of protein via the mammalian/mechanistic target of rapamycin complex 1 (mTOR), 3) membrane stabilization of muscle cells, 4) decreasing proteolysis by inhibition of the ubiquitin-proteasome pathway.<sup>8,13</sup>

Previous studies also have found that supplementation with HMB resulted in beneficial effects on performance by increasing anabolic hormones, including IGF-1, growth hormone and testosterone and decreasing catabolic stress hormones such as cortisol.<sup>7,14</sup> HMB also may increase androgen concentration through increasing cholesterol, drawing on this hypothesis that, HMB is metabolized to  $\beta$ -hydroxy  $\beta$ -methylglutaryl CoA (HMG-CoA) which is a main source of cholesterol synthesis and precursor of androgens such as testosterone.<sup>15</sup>

From our point of view, no systematic review and meta-analysis has been conducted over the HMB supplementation effect on testosterone and cortisol in trained athletes. Moreover, due to the contradiction results between studies and common HMB consumption as an ergogenic aid, particularly among athletes, we aimed to conduct this systematic review and meta-analysis to assess the effects of HMB supplementation on testosterone and cortisol in trained athletes.

## METHODS

### Search Strategy

This systematic review and meta-analysis was reported according to the guidelines of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (16). A computerized search was conducted from inception to August 2021 using various databases including PubMed, ISI Web of Science, Scopus, and supplementary Google Scholar search. The following terms and their combinations of MeSH and non-MeSH terms were applied, including: "beta hydroxy beta methylbutyrate", "hydroxy methyl butyrate", "HMB", "exercise", "sport supplements", "endocrine response", "cortisol", and "testosterone". Reference lists of all studies were checked for further eligible articles identification.

## Eligibility Criteria

Studies were selected by applying the following Population-Intervention-Comparator-Outcomes-Study design (PICOS) criteria<sup>16</sup>: 1) healthy subjects received oral HMB supplementation, as a nutritional strategy before and after exercise; 2) original randomized-controlled trial researches and 3) reporting at least one outcome measure of hormones (cortisol and testosterone). Studies were not conducted by using multi-supplementations, (HMB in conjunction with other supplement like creatine,<sup>17</sup> arginine, lysine<sup>18</sup> and adenosine monophosphate).<sup>19</sup> There were restrictions on the performed post-exercise and studies that assessed the acute effect of HMB on the hormonal response.<sup>20,21</sup>

## Selection strategy

After computerized search, titles and received papers abstracts were screened by the search strategy. Two authors selected articles based on the inclusion criteria independently. Articles including eligibility criteria in the title and abstract screening were elected to be checked by full manuscript. Parallel clinical trials were elected by applying a control group or crossover design in the systematic review and meta-analysis. All classified trials were retrieved by either of the authors. According to the data within the full information, we used a form to elect the studies eligible for inclusion in the meta-analysis. Contradictions between the authors were solved by consensus or third researcher.

## Data extraction

Two authors extracted following needed information: first author's name, year and publication country, design of studies, gender and age of subjects, HMB dose and sample size, duration of intervention, and training status. Also, we extracted mean and standard deviation (SD) of plasma hormones' status (cortisol and testosterone) at baseline and after the intervention.

## Study quality

Given that trial inclusion with a high risk of bias may distort the outcomes of a meta-analysis,<sup>22,23</sup> the Cochrane Collaboration tool was used for evaluating the risk of bias. The following items were evaluated: randomization sequence generation; allocation concealment; blinding of participants, personnel, investigator, and assessor; attrition rates; and companies financial interest. These items were given high, unclear, or low risk of bias rating. A study was categorized as having low, medium, or high-risk according to the key areas of allocation concealment, reporting of attrition rates, and participants and assessor (high = all 4 factors rated high, medium = 2 or 3 factors rated high or unclear, and low = all key areas rated low).

## Analyses and measures of treatment effect

For each trial, mean differences and standard deviation were calculated for continuous variables. The differences of mean changes in cortisol and testosterone concentration and their correspondence SD were extracted as the effect size. Between-study heterogeneity was assessed using the chi-squared ( $\chi^2$ ) test and quantified applying the

$I^2$  statistic, which shows the total variation percentage across studies that is ascribable to heterogeneity rather than to chance. Significant heterogeneity was defined with a P-value of <0.05.

The random effects model was applied to calculate the weighted mean differences (WMDs) with 95% confidence intervals (CIs) for estimating the overall effect. To evaluate whether the outcomes could have been altered by a single study distinctly, a sensitivity analysis was performed.<sup>24</sup> Publication bias was evaluated by Egger's regression asymmetry test and Begg's rank correlation test. Funnel plots also depicted the effect sizes against their corresponding standard errors. Statistical analyses were conducted applying STATA 11.2 software (StataCorp, College Station, Texas, USA).

## RESULTS

### Search outcomes and overview of included studies

Our initial search led to 184 relevant studies. After removing duplications, a wide range of screening of the titles and abstracts, the careful assessment was performed on 142 related articles. Of these, 11 articles remained after considering the inclusion and exclusion criteria for the eligibility. Eventually, 7 articles, including, 8 effect sizes, which studied

a total of 235 participants aged 16.1 –24.9 years, were identified in the current systematic review and meta-analysis. Figure 1 represents the selection process and reasons for excluding the studies. The data in Table 1 illustrates the main characteristics of the articles in our systematic review and meta-analysis.

In brief, the studies (by 235 participants) were published between 2001 and 2017. The duration of these RCTs ranged between 1.5 to 12 weeks. 2 studies used a randomized crossover design,<sup>25,26</sup> one of them was also single blind<sup>27</sup> and the other studies had the design of double-blind. Two studies were conducted in Poland (25, 26), 1 in the United States,<sup>27</sup> 1 in Iran,<sup>28</sup> 2 in Australia<sup>17,29</sup> and 1 in Israel.<sup>7</sup> The effect of exercise on testosterone and cortisol concentration was examined in 7 studies<sup>7, 17, 25-29</sup>, and 8 effect sizes were extracted from these studies for testosterone and cortisol concentration. The total number of subjects who completed the studies in inclusion criteria was 121 subjects in the intervention and 107 in the placebo groups. The dose of HMB supplementation was 3 g/day in all studies.

### Risk of bias

The quality of the studies is presented in Table 2. Briefly, random sequencing generation was unclear in 3 studies.<sup>17,27</sup> Participants and

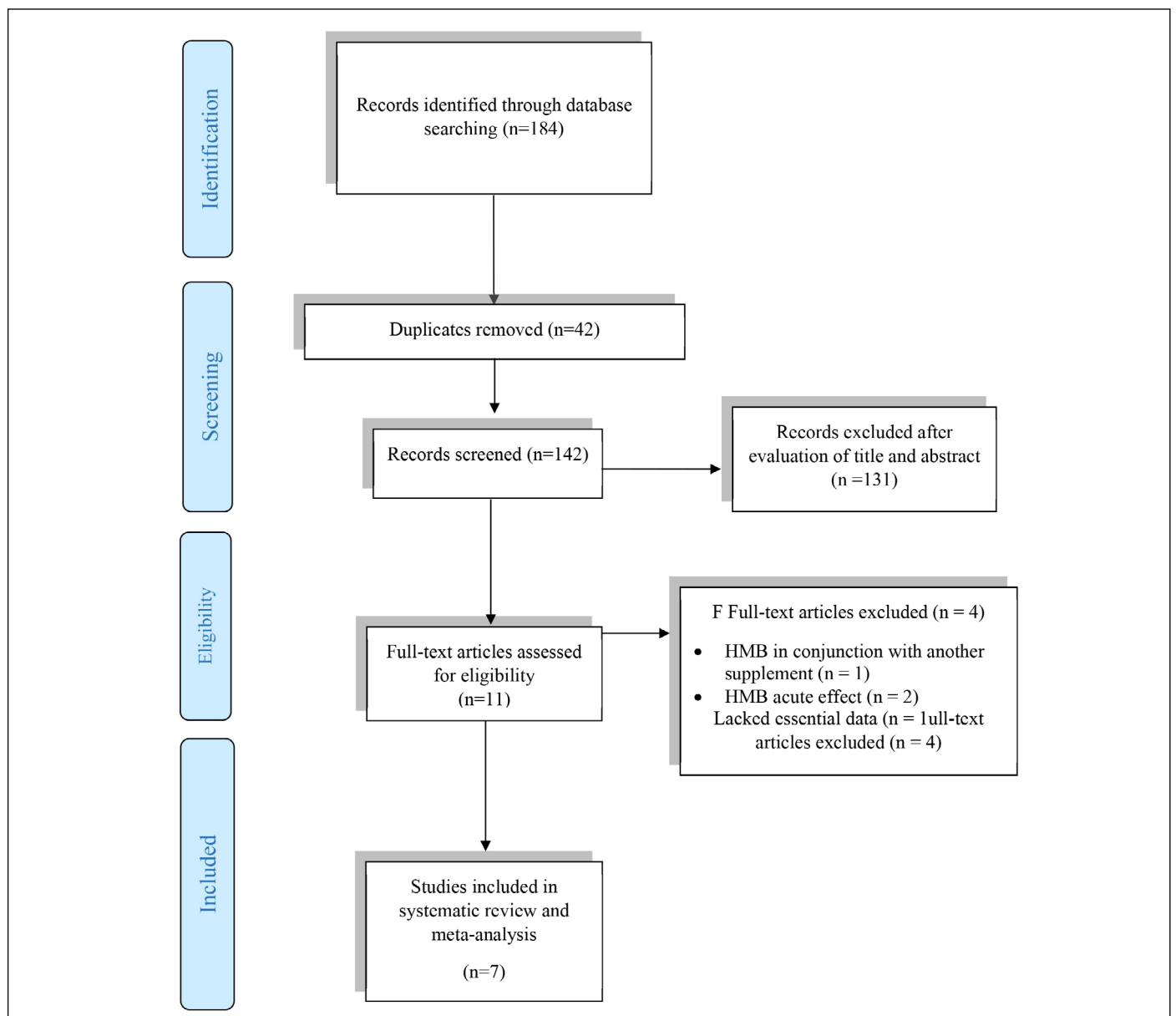


Figure 1. Flow diagram of the study selection process.

**Table 1.** Characteristics of the Included Studies.

Author	Study Design Characteristics					average age (y)	Sample Size		Evaluated hormones
	design	country	HMB dose (gr)	Duration (w)	gender		HMB	Control	
Durkalec-Michalski et al. (2017)	C-O	Poland	3	12	M	22.8	42	42	C, T
Asadi et al. (2017)	P	Iran	3	6	M	21.4	8	8	C, T
Durkalec-Michalski et al. (2015)	C-O	Poland	3	12	M	19.5	16	16	C, T
Portal et al. (2011)	P	Israel	3	7	M & F	16.1	14	14	C, T
Hoffman et al. (2004)	P	USA	3	1.5	M	20.7	15	15	C, T
Crowe et al. (2003)	P	Australia	3	6	M	24.9	11	5	C, T
Slater et al. (2001)	P	Australia	3 (Standard)	6	M	24.6	7	7	C, T
Slater et al. (2001)	P	Australia	3 (Time Releasing)	6	M	24.6	8	7	C, T

C, Cortisol; T, Testosterone; HMB,  $\beta$ -hydroxy- $\beta$ -methylbutyrate; P, Parallel; C-O, cross-over studies; M, men; F, Female; W, weeks; Y, years; t, trained; U, untrained.

**Table 2.** Cochrane Risk of Bias Assessment.

Study	Random Sequence Generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective outcome reporting	Other sources of bias	Overall Risk of Bias
Durkalec-Michalski et al.(2017)	L	L	L	L	L	L	L	L
Asadi et al. (2017)	L	H	L	L	L	L	L	L
Durkalec-Michalski et al. (2015)	H	L	L	L	L	L	L	L
Portal et al. (2011)	L	L	L	L	L	L	U	L
Hoffman et al. (2004)	U	U	L	L	L	L	L	L
Crowe et al. (2003)	U	H	H	H	H	L	L	H
Slater et al. (2001)	U	L	U	U	U	L	L	M

L, low risk of bias; H, high risk of bias; M, medium risk of bias; U, unclear risk of bias.

outcome blinding and incomplete outcome data were high and unclear risk of bias in only two studies, respectively.<sup>17,29</sup> And then ranked as low risk of bias for 5 studies,<sup>7,25-28</sup> medium risk of bias for 1 study,<sup>29</sup> and high risk of bias for 1 study.<sup>17</sup> Most of studies had a low risk of bias for selective reporting and other sources of bias except for one study.<sup>17</sup>

## Findings from the meta-analysis

### Effects of HMB supplementation on serum cortisol concentration

Overall, HMB consumption had no significant effect on cortisol concentration: WMD= -1.35  $\mu$ g/dl; 95% CI: -2.70, 0.002; P= 0.050. There was no significant heterogeneity among the studies (Cochran's Q test = 14.05, P= 0.050, I<sup>2</sup>=50.2%). Subgroup analyses of different types of exercise showed that cortisol concentration significantly reduced after resistance exercises (WMD= -3.30  $\mu$ g/dl; 95% CI: -5.50, -1.10; P= 0.003), whereas it had not significant effect on cortisol concentration in aerobic and anaerobic combined activities (WMD= -0.16; 95% CI: -1.16, 0.84; P= 0.753). The forest plot is shown in Figure 2.

### Effects of HMB supplementation on testosterone concentration

Our preliminary analysis indicated that HMB consumption did not significantly improve serum testosterone concentration (WMD= 0.75 nmol/L; 95% CI: -0.09, 1.58; P= 0.079). Also, no significant heterogeneity was observed among studies (Cochran's Q test = 3.33, P= 0.853, I<sup>2</sup> = 0.00%). Subgroup analysis was conducted to check as to how the effect of HMB supplementation on serum testosterone is different according to type of exercise activities (Figure 3) or duration of the interventions (Figure 4). This analysis revealed that the pooled effect of HMB supplementation on testosterone concentration was influenced by the duration of the supplementation (<6 weeks versus  $\geq$ 6 weeks), in which a significant increase in testosterone concentration was found in studies that lasted longer than 6 weeks (WMD= 1.60 nmol/L; 95% CI: 0.08, 3.12; P= 0.039). Also, subgroup analysis based on the type of exercise training indicated that the increasing effect of HMB supplementation on serum testosterone is significant in aerobic and anaerobic combined activities (WMD= 1.60 nmol/L; 95% CI: 0.08, 3.12; P= 0.039). Subgroup analysis didn't show any

significant effect of HMB supplementation on testosterone concentration in studies lasting lower than six weeks (WMD= 0.38; 95% CI: -0.62, 1.38; P= 0.455) or on resistance training exercise (WMD= 0.38 nmol/L; 95% CI: -0.63, 1.38; P= 0.464).

### Sensitivity analysis and publication bias

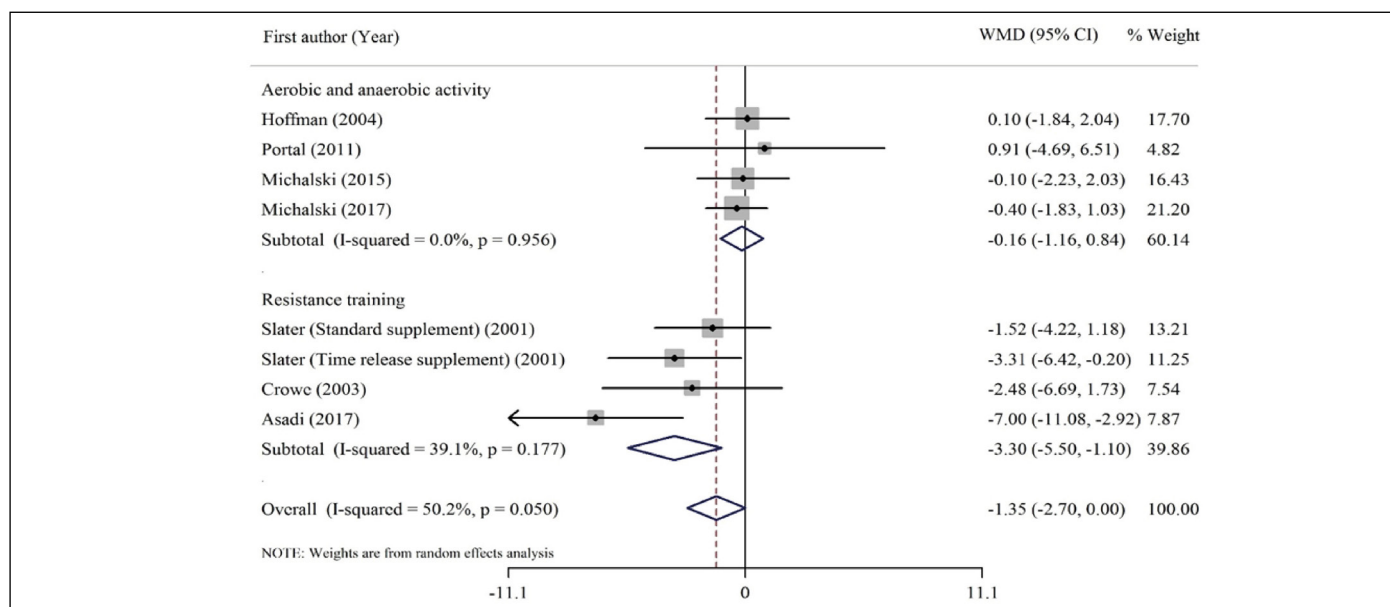
Sensitivity analysis showed that the omission of any of the studies from the meta-analysis, create no change in the outcomes of the meta-analysis on testosterone concentration whereas, the results on cortisol concentration were sensitive to omitting 3 studies.<sup>7,25,27</sup> Funnel plots for cortisol and testosterone were visually symmetrical, and the results of Egger's test did not determine any evidence of publication bias in studies that examine the effect of HMB consumption on cortisol (Egger's test, P = 0.337) and on testosterone (Egger's test, P = 0.140).

## DISCUSSION

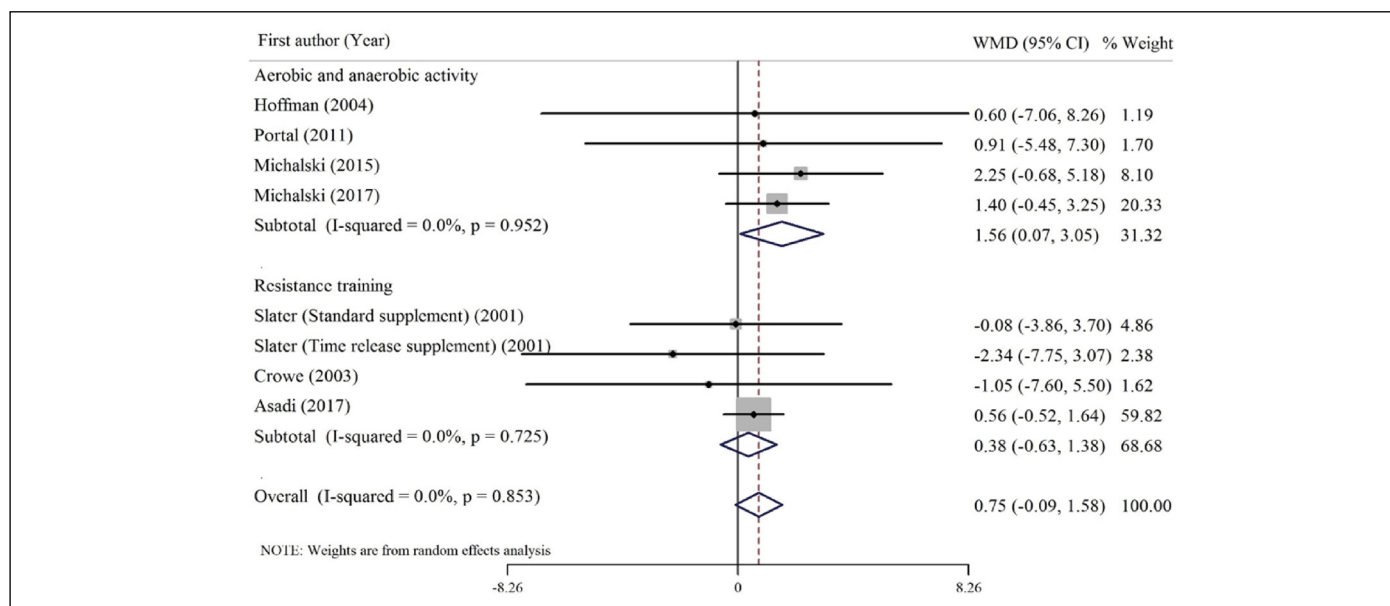
In this systematic review and meta-analysis of 7 studies (235 participants), we found that HMB consumption led to a significant decrease in cortisol and increase in testosterone concentrations after resistance exercises and aerobic and anaerobic combined activities, respectively. Several probable mechanisms have been suggested for the beneficial effects of HMB supplementation on testosterone and cortisol concentration in athletes.

Cortisol, is a catabolic hormone and basic glucocorticoid form in humans, secreted from the adrenal cortex in response to psychological and physical stress.<sup>30</sup> During cortisol elevates in exercise, impacts of this hormone happen after exercise within the early recovery. Elevation in plasma cortisol concentration, within the physiological range in short-term, motivates proteolysis and augments plasma leucine utilization and concentration.<sup>31</sup> The study of Knitt<sup>32</sup> showed that HMB operated as an anti-catabolic agent rather than an anabolic agent. The mechanism for this reaction is not exactly obvious. Some studies support the anti-catabolic hypothesis of HMB expressed by reductions in the muscle damage indices such as creatine phosphokinase and lactate dehydrogenase<sup>15,33</sup> and subsequent lower cortisol levels.

Moreover, cortisol shows an anticipatory reaction to exercise and physical activity (34), and Kraemer et al. previously suggested that this



**Figure 2.** Forest plot representing the effect of HMB supplementation on the cortisol concentration. The analysis was done using a random-effects model, subgroup analysis performed based on the type of exercise activities.



**Figure 3.** Forest plot representing the effect of HMB supplementation on the testosterone concentration. The analysis was done using a random-effects model, subgroup analysis performed based on the type of exercise activities.

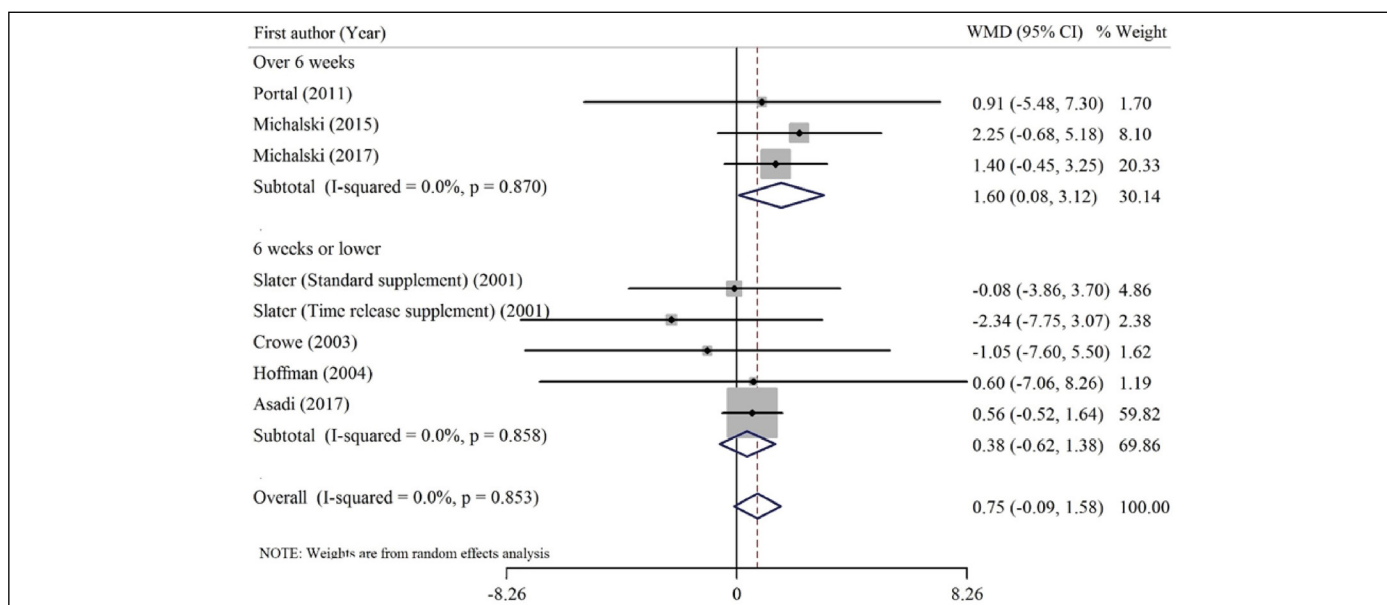
reaction was reduced using a herbal supplement with specifically designed.<sup>35</sup> Because amino acids supplementation increases the circulating amino acid concentrations,<sup>36</sup> possibly less cortisol was needed for gluconeogenesis before exercise to break down proteins into amino acids.

Reduced cortisol at rest enhances the anabolic-to-catabolic hormone ratio, that in theory, would increase testosterone chronically and muscle tissue protein balance.<sup>12</sup> Also, the primitive destination of HMB is a conversion to HMG-CoA in the cytosol of liver and muscle, thus HMB is a precursor of cholesterol,<sup>37,38</sup> and HMB supplementation leads to an increase in synthesis of cholesterol and may act as a structural component of cell membranes.<sup>39</sup> Given that damaged muscle cells after exercise<sup>40</sup> may lose their ability to make sufficient HMG-CoA for the synthesis of cholesterol, HMB supplement for more than 6 weeks may be a suitable source of HMG-CoA to synthesize testosterone.<sup>15,41</sup> The increment in testosterone concentration seems to be linked with an increase in the endogenous cholesterol that is a substrate in the steroidogenesis process. Additionally, our results

in regard to the HMB and aerobic and anaerobic exercise effects on changes in the testosterone response propose that acute ingestion does not increase the testosterone response to exercise. Townsend et al. study carried out 3 exercise protocols throughout the 12 weeks to assay the supplementation acute response. At supplementation of weeks 6 and 9, the response of testosterone was increased in the intervention group.<sup>20</sup> Therefore, chronic supplementation of HMB may lead to a more pronounced response of testosterone. The increase of testosterone concentration could be considered as a beneficial result and demonstrate a better anabolic status in athletes, which plays a key roles in training adaptation and recovery in well-trained athletes.<sup>42</sup>

To the best of our knowledge, this study is the first systematic review and meta-analysis that attempt to summarize the role of HMB supplementation on hormonal changes (cortisol and testosterone) in athletes. All included studies administered the same doses of HMB for intervention and all participants were male (except in one study)<sup>43</sup> that resulted in a decrement in heterogeneity. Moreover, the absence





**Figure 4.** Forest plot representing the effect of HMB supplementation on the testosterone concentration. The analysis was done using a random-effects model, subgroup analysis performed based on the duration of the interventions.

of heterogeneity among the included studies enhanced the power of our outcomes. However, some limitations should be mentioned. Considering the above items, it is not possible to evaluate the effect of the HMB consumption in female athletes and dose-response relationship between HMB supplementation and hormonal changes. Lack of information about data on frequency and intensity of exercise, genetic background, lifestyle factors and lack of complete baseline cortisol and testosterone data for subgroup analysis make overall interpretation of the results difficult. Eventually, the type of exercise was varied among the included studies, which could affect the reported outcomes.

## CONCLUSION

The current systematic review and meta-analysis outcomes revealed that HMB supplementation may be linked with a decrease in cortisol concentration after resistance exercise. In contrast to cortisol, testosterone concentration significantly increased in aerobic and anaerobic combined training. More investigations are recommended with a variety of doses and exercises, longer time in periods and in both sexes of athletes.

The author declare no potential conflict of interest related to this article

**AUTHORS' CONTRIBUTIONS:** The author has completed the writing of the article and the critical review of its knowledge content. This paper can be used as the final draft of the manuscript. JD: writing and execution.

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