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Original Article

The Effects of 8 weeks beta-hydroxy-beta-methylbutyrate (HMB) supplementation on body composition, inflammatory response and muscle damage after eccentric exercise in untrained males

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Summary. Amino acids and their metabolite have shown anti-catabolic properties, through inhibition of muscle proteolysis and enhancement of protein synthesis. Beta-hydroxy-beta-methylbutyrate (HMB) is a derivative of the branched-chain amino acid leucine (LEU). In the context of exercise and recovery, several studies have reported the beneficial effects of HMB, but a limited number of studies have evaluated the efficacy of HMB intake among untrained subjects and also the duration of supplementation in previous studies is relatively short. In the present study, 40 untrained males were supplemented with HMB (3 g/ day) or placebo for 8 weeks and the effects of HMB on body composition and inflammation were investigated. The concentrations of creatine kinase (CK) and lactate dehydrogenase (LDH) were assessed at baseline, and at 1, 24, and 48 hours after exercise. The values of CK and LDH in HMB group were significantly lower ($p=<0.001$) compared to the placebo group. HMB ingestion was also able to decrease inflammatory biomarkers including C-reactive protein (CRP) and interleukin-6 (IL-6). Additionally HMB was associated with a significant improvement in body composition, as it was reflected by decreased percent body fat. In summary, the results of this study showed that HMB supplementation may attenuate the exercise-induced muscle damage and have beneficial effects on post exercise recovery.

Key words: exercise, delayed onset muscle damage, creatine kinase, lactate dehydrogenase, inflammation, HMB, body composition, branched-chain amino acid

Background

Beta-hydroxy-beta-methylbutyrate (HMB) is a derivative of the branched-chain amino acid leucine (LEU) (1), which is an essential amino acid with powerful anti-catabolic effect and regulates protein metabolism (2). Almost two decades ago Nissen et al (3) for the first time demonstrated clinical evidence for anabolic effect of HMB, they found that dietary supplementation with HMB (1.5 or 3.0 g/day) combined with resistance training improved protein balance and augmented gains in lean body mass (LBM) as well as in strength. Since that time the most robust effects of HMB have been demonstrated in untrained individuals, who have experienced increased LBM and strength in as little as 3 weeks following supplementation(4). Beneficial effects of HMB have been reported in several other conditions characterized by loss of muscle mass, including AIDS (5) aging (6) cancer cachexia (7-9), sepsis (10) and endotoxemia (11).

HMB is thought to act via enhanced recovery of damaged skeletal muscle tissue(12). Recently Wilson et al (13) showed that HMB in a free acid form (HMB-FA) given 30 min prior to an acute bout of high-volume resistance training was able to attenuate indices of muscle damage and improve perceived recovery in resistance-trained athletes. Similarly acute ingestion of 3.4 g of HMB-FA has been demonstrated to increase skeletal muscle protein synthesis and decrease protein breakdown by +70 and –56 %, respectively(14).

Empirically, HMB has been classically proposed and is widely used as a nutritional supplement to limit muscle damage during exercise and to increase muscle gain after strenuous exercise or hard training(15). The mechanisms of HMB's effects on muscle damage have not yet been fully elucidated. One study on the effects of HMB supplementation on immune function in humans has indicated decreased inflammatory cytokine production from peripheral mononuclear cells in vitro (16). Interestingly, previous research on resistance training (17) reported that HMB supplementation could decrease inflammatory biomarkers including IL-6. Thus, HMB may exert its effects on muscle via immunomodulation of the damage and repair/remodeling cycle in response to acute and chronic resistance exercise (17). Research is lacking on HMB effects on inflammatory responses to exercise. Therefore, we evaluated the effect of 8 weeks ingestion of HMB on serum indices of muscle damage and inflammatory response to eccentric exercise in untrained males.

Materials and Method

In this clinical trial, 40 untrained male students were selected and randomly divided to two groups. Intervention group (n=21) received HMB and placebo group were given placebo (n=19). The reason for selecting non-athletes men was to observe obvious increments in muscle damage indices and thus possible effects of supplementation (18). The aims of the research were explained for participants and Informed consent was obtained from all participants included in the study.

At the first testing session, aims, details and probable risks of performing the exercise explained to the participants and then they provided with a written consent. Delayed onset muscle soreness (DOMS) and muscle damage in lower body developed using a leg squat machine with a weight equivalent to 75% of 1RM similar to Stock's statement (19). During the first visit, the subjects performed 1RM testing for the barbell squat exercise. The participants were then asked to avoid from vigorous physical activity for the study duration. After eight weeks, the second 1RM test, anthropometric measurements and blood sampling were conducted. Height measured to the nearest 0.1 centimeter using a wall-mounted stadiometer. To measure weight, a precise scale (Camry, model: 9003 EB) was used to the nearest 0.1 kilograms.

The waist circumference (WC) and hip circumference were measured was measured according to the National Health and Nutrition Examination Survey (NHANES) guidelines: WC as the abdominal circumference immediately above the iliac crest; the hip circumference was measured in a horizontal plane at maximal extension level of the buttocks. (http://www.cdc.gov/nchs/data/nhanes/nhanes_07_08/manual_an.pdf). Waist to hip ratio (WHR) was calculated by formula: WC divided by hip circumference.

Body composition was determined using a Body Space BF-350E bioelectrical impedance analyzer (BodySpace Corporation, Arlington Heights, South Korea).

Serum CK and LDH activities were measured by commercial kits (Sigma Chemical Co) with automatic analyzers (RA-1000; made by American TECHNICOM Co). The inflammatory biomarkers included CRP and IL-6. To measure the levels of IL-6 and CRP, the ELISA (enzyme-linked immunosorbent assay) method was applied using kits from the French Diaclone Company with sensitivities of less than 7, 2 and 8 pg·mL-1, respectively.

All subjects were university students, used to eat dormitory foods and recommended to refrain high-intensity exercises, use of drugs particularly sedative, supplements and caffeine one week pre-/ and post-testing session. They were told not to alter their usual daily diet and have a comfortable non-stressful 8 hours of sleep, the night before testing. The subjects were asked to eat 3 gram HMB or placebo (maltodextrin)

for 8 weeks. Blood samples were taken at the baseline, 1, 24 and 48 hours after resistant training. HMB and maltodextrin used in the current research prepared from PNC (Karen Pharma & Food Supplement Co., Iran).

Results

Subject characteristics

There were no significant differences between groups for age, and baseline values of anthropometric indices (Table 1). The effect of HMB supplementation compared with placebo on anthropometric measures of the study subjects are shown in Table 1. HMB supplementation resulted in a significant decrease of WC, HC, as well WHR. Additionally a significant decrease was observed in percent body fat. There were significant differences in body weight changes between groups.

The values of serum CK and LDH are presented in Table 2. The trends in changes of LDH and CK levels are compared in Fig1 and Fig2, respectively. The CK values were decreased after the eccentric exercise, however HMB ingestion have shown to be able to decrease the muscle damage and rise in CK values. Additionally the concentrations of LDH in HMB group were significantly lower compare to placebo group.
According to the table 3, IL-6 and CRP responses to exercise was significantly lower in HMB-supplemented group.

Discussion

Findings of the present study reveal that HMB supplementation is able to decrease circulating inflammatory biomarkers including IL-6 and CRP in response to exercise. A few number of studies have investigated the response of IL-6 and CRP to chronic intake of HMB and examining the potential impacts of HMB on inflammation been recommended (20). There is increase in systemic levels of a number of cytokines in response to endurance and resistance exercise with both pro- and anti-inflammatory roles(17). However it has been suggested that an HMB-containing supplement may significantly and positively affect the concentrations of IL-1β, a pro-inflammatory interleukin(17), and have insignificant effect on IL-6 concentration in untrained men(17). Supporting our findings, HMB has been reported to attenuate the circulating IL-6 response to the military training(21). There is evidence that inflammatory biomarkers including TNF-α and IL-1ra are affected by HMB(22).

Table1. Values of anthropometric indices of study participants

Variable	HMB (n=21)	Placebo (n=19)	P[b]
Weight			
Before	74.26 ±4.12	74.63 ± 4.03	0.776
After	74.52 ± 3.92	74.84 ± 4.06	0.802
P[a]	0.024	0.104	
Change	- 0.26 ± 0.49	- 0.21 ± 0.53	0.753
BMI			
Before	24.64 ± 1.60	24.47 ± 1.40	0.718
After	24.81 ± 1.61	24.53 ± 1.39	0.571
P[a]	<0.001	0.093	
Change	- 0.16 ± 0.001	- 0.67 ± 0.16	0.019
WC			
Before	91.00 ± 7.39	90.84 ± 5.30	0.939
After	86.90 ± 6.94	93.68 ± 5.22	0.001
P[a]	<0.001	<0.001	
Change	4.09 ± 1.22	-2.84 ± 0.44	<0.001
Hip circumference			
Before	93.76 ± 6.59	94.74 ± 5.71	0.622
After	91.81 ± 5. 51	94.89 ± 5.22	0.078
P[a]	<0.001	0.454	
Diff	1.95 ± 1.60	-0.16 ± 0.90	<0.001
WHR			
Before	0.97 ± 0.055	0.96 ± .067	0.611
After	0.95 ± 0.054	0.99 ± .061	0.027
P[a]	<0.001	<0.001	
Change	0.0244 ± 0.016	-.0278 ± 0.010	
BODY FAT%			
Before	19.73 ± 1.70	20.00 ± 1.50	0.598
After	18.25 ± 1.69	19.85 ± 1.58	0.004
P[a]	<0.001	0.104	
Change	1.48 ± 0.048	0.16 ± .40	<0.001

Data are shown as means ± SD. BMI: body mass index; WC: waist circumference; WHR: waist to hip ratio.

Table2. The values of CK and LDH at baseline, 1, 24 and 48 hours after eccentric training in participants.

Variable/ time of measurement	Pre-intervention	1h after	24 h after	48h after	P[b]
LDH					
HMB (n=21)	247.52 ± 66.17	361.43± 37.42	317.52±39.87	282.14 ±58.61	<0.001
Placebo (=19)	239.68 ± 37.71	427.47± 38.52	397.47 ± 38.51	348.74 ± 54.09	<0.001
P[a]	0.645	<0.001	<0.001		0.001
CK					
HMB (=19)	138.41 ± 8.55	312.29 ± 27.15	292.21 ± 27.16	254.80 ± 30.34	<0.001
Placebo (=19)	136.48 ± 7.17	369.50 ± 23.42	349.49 ± 23.41	295.87 ± 35.81	<0.001
P[a]	0.448	<0.001	<0.001	<0.001	

Data are shown as means ± SD.

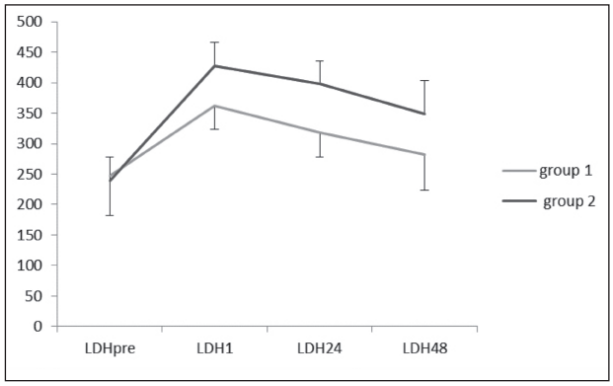

Figure 1. Mean serum concentrations of LDH in both groups at base line, 1 hour, 24 hours and 48 hours after exercise, group 1: HMB and group 2: placebo

Table 3. The Comparison of serum concentrations of IL-6 and CRP in participants

Variable	HMB (n=21)	Placebo (n=19)	Pb
IL-6			
Before	1.29 ± 0.57	1.25 ± 0.46	0.822
After	0.9524 ± 0.42	1.23 ± 0.43	0.045
Pa	0.007	0.62	
Change	0.34 ± 0.52	0.0247 ± 0.213	<0.001
CRP			
Before	2.10 ± 0.70	1.83 ± 0.69	0.238
After	1.42 ± 0.42	1.82 ±0.60	0.017
Pa	<0.001	0.898	0.017
Change	0.68 ± 0.56	0.26 ± 0.008	

Data are shown as means ± SD.

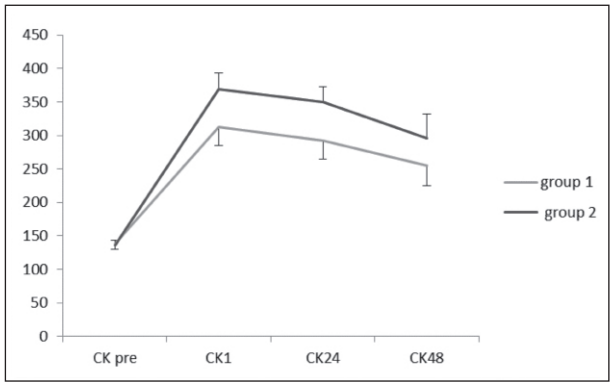

Figure 2. Mean serum concentrations of CK in both groups at base line, 1 hour, 24 hours and 48 hours after exercise,, group 1: HMB and group 2: placebo

The observed reduction in CRP in our study suggests that HMB may moderate inflammatory response to exercise induced muscle damage which is repeated Vulcan, Paul Raymond study(22). Moreover, there is evidence (21) that HMB supplementation may attenuate the inflammatory response to high intense military training and it has been suggested (23) that during times of intense conditioning, the addition of HMB would enhance the recovery benefits of whey protein. In contrast, there is evidence of no change in the IL-6 levels following HMB supplementation in elite athletes (24). In addition, IL-6 is considered to play protective and restorative roles that improve muscle recovery(25). Since HMB could help to attenuate tissue

catabolism and initiate muscle anabolism particularly in untrained individuals exposed to strenuous exercise(15); part of these discrepancies can be explained by differences in the differences in the participants' level of training(12). There is no solid date regarding the effects of HMB on inflammatory biomarkers response to exercise, the potential impacts of HMB on inflammatory biomarkers deserve more research.

In contrast to WC and WHR, we observed no statistically significant alteration in body weight following HMB ingestion. These findings support the hypothesis that HMB increases lipolysis and decreases the content of adipose tissue with no change in body mass(26).

Our findings show that HMB supplementation could assist in decreasing body fat in untrained healthy individuals. These results are consistent with previous review study which concluded similar results in similar untrained subjects as well as in elderly individuals (15). However, the mentioned study reported no evidence of significant changes in body composition among those subjects who were already on a physical training regimen(15). The precise mechanism underlying the effects of HMB supplementation on fat loss is poorly understood. The potential mechanisms are improvement in fatty acid oxidation(27), as well as the stimulation of the mTOR signaling pathway that enhance the biochemical mechanisms necessary for protein synthesis, leading to increases in fat free mass(28). Additionally, increased mitochondrial content and size may also contribute to increasing fat loss(29).

Of main findings of this study is that chronic supplementation with HMB, was able to attenuate muscle damage following exercise. We found an increase in serum levels of CK of 1, 24 and 48 h post-exercise, however; HMB supplementation decreased the rise in CK efficiently. In athletic context, a number of studies during the last 15 years have indicated that HMB supplementation may elicit several ergogenic benefits, including better recovery (13, 30).

This study supports the previous findings that demonstrated supplementation with HMB for 12 weeks was able to attenuate the rise in CK following training in resistance-trained individuals(13). Additionally it has been shown that HMB consumption 3 gr/day for 14 days prior to a single bout of eccentric resistance exercise could improve the CK response(31). A review study(32) suggested that HMB may attenuate symptoms of exercise-induced muscle damage in relatively untrained individuals who are unaccustomed to eccentric exercise, similar to our study participants. Similarly, HMB supplementation has been reported to positively affect the inhibition of protein degradation (10, 33, 34) and to entirely attenuate total protein degradation induced by angiotensin II and tumor necrosis factor-α/ interferon-γin murine myotubes. It also decreases the formation of reactive oxygen species (ROS) via activation of p38 MAPK and the activity of both caspase-3 and eight. These results suggest that HMB plays a critical role in protein degradation and muscle damage(35). Creatine kinase is an intracellular enzyme which thought to increase with cell membrane permeability as a result of skeletal muscle damage, however; by the ability of to stabilize membranes, HMB has been reported to reduce circulating CK (36). Also HMB supplementation may stabilize cellular membranes, allowing for maximal cell growth(37). The ability of HMB to aid the recovery process following resistance training could thus play an important role, because it has been suggested that CK should return to normal in order to avoid overtraining or muscular pathology(38). These results were duplicated in more recent work, which showed that HMB supplementation is accompanied by significant reductions in CK with one session or 12 weeks of resistance training (13, 39).

In conclusion, from the results of this study it can be concluded that HMB supplementation may attenuate the exercise-induced muscle damage, and may have offered some benefit for exercise recovery. Additional research is needed to substantiate the potential benefits of HMB supplementation on exercise with different intensity or its effects on well trained athletes.

Our study has some strength and limitations. Investigations on effects of chronic ingestion of HMB on untrained subjects has been recommended(40). The findings of present study show that HMB could have beneficial effects on post exercise recovery, such as attenuation of the rise in CK, LDH and decrease inflammation following exercise in untrained males.

In this study, we did not measure the plasma concentrations of HMB, which is one of study limitation. To better understanding of the mechanisms of HMB

effects, the measurement of blood levels of HMB in order to find the potential changes is suggested for future research.

Conclusions

We concluded that the ingestion of HMB could decrease body fat percent, inhibit inflammation and increment of muscle damage markers after eccentric exercise, compare to ingestion of placebo. HMB supplementation could be considered as a signalling molecule that may play a critical role in recovery. Future researches are needed to elucidate the underlying mechanisms by which HMB improves adaptations.

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