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Review

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Effects of β-hydroxy-β-methylbutyrate supplementation on recovery from exercise-induced muscle damage: a mini-review

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[Purpose] Several studies have reported that β-hydroxy-β-methylbutyrate (HMB) has beneficial effects on exercise-induced muscle damage (EIMD). Here, we examine the effects and mechanisms of HMB supplementation on exercise-induced muscle damage EIMD and provide guidelines for the application of supplementary HMB.

[Methods] For this review, we performed web searches using PubMed, Web of Science, and Wiley Online Library. Keywords used were 'HMB,' 'HMB and EIMD,' 'HMB and recovery,' 'HMB and resistance exercise,' and 'HMB and eccentric muscle contraction.'

[Results] Several previous studies have shown that HMB supplementation can reduce EIMD and promote recovery. In particular, reductions were detected in certain markers of muscle membrane damage, including creatine kinase and lactate dehydrogenase. There may be multiple mechanisms in which HMB supplementation reduces EIMD, including reducing muscle-damage-induced inflammation and oxidative stress and promoting cellular cholesterol synthesis by increasing the production of β-hydroxy-β-methylglutaryl-Co-A, a product of HMB metabolism. In general, the suggested daily intake of HMB is 3 g. In addition, the timing and duration of HMB intake can be classified as chronic [≥ 2 weeks, in which a total of 3 g is consumed daily (3 × 1 g taken at breakfast, lunch, and dinner)] or acute (taken 30–60 min before exercise). The timing of intake during exercise may vary depending upon whether the formulation is calcium HMB (60–120 min before exercise) or the free-acid form of HMB (30–60 min before exercise). Notably, the co-administration of HMB and creatine does not appear to be effective in reducing EIMD.

[Conclusion] HMB supplementation can be considered as an effective nutritional strategy to minimize EIMD.

[Keywords] β-hydroxy-β-methylbutyrate, muscle damage, nutritional supplement, recovery, resistance exercise

INTRODUCTION

Exercise-induced muscle damage (EIMD) has been extensively studied in the field of exercise science[1]. In general, EIMD is induced when performing unaccustomed exercises or repetitive eccentric muscle contractions and is accompanied by multiple physiological and biochemical phenomena that contribute to a general decline in condition[2]. Consequently, numerous studies have investigated different strategies designed to reduce EMID and promote recovery, among which, the consumption of nutritional supplements has in particular attracted public attention, owing to its convenience of intake and affordability. Moreover, by improving health, exercise adaptation, and recovery from injury, nutritional supplements can enable athletes to train and compete more effectively[3].

β-Hydroxy-β-methylbutyrate (HMB) is a well-established metabolite of the essential amino acid leucine[4], which is used by athletes and bodybuilders as a nutritional supplement to enhance strength, muscle mass, and exercise performance[5]. Leucine acts as a signaling molecule to induce protein synthesis and can thereby promote increases in several anabolic responses of the muscles[6]. In skeletal muscles, leucine is converted to α-ketoisocaproic acid (KIC) by BCAA aminotransferase, and approximately 5% to 10% of this KIC is metabolized to HMB via the activity of KIC dioxygenase[7]. The produced HMB promotes protein synthesis and an up-regulation of the mechanistic target of rapamycin pathway. It also plays an essential role in reducing protein breakdown by attenuating the ubiquitin-proteasome pathway and caspase activity[8].

The findings of several studies have indicated that HMB also has beneficial effects with respect to the reduction of EMID[9,10]. For example, Van Someren et al.[10] reported that when untrained men were given HMB supplementation prior to performing eccentric exercises, significant reductions in the levels of creatine kinase (CK) and delayed onset muscle soreness (DOMS) were observed post-exercise. Tsuchiya et al.[9] found that in untrained men provided with HMB supplementation for ≥ 2 weeks, there was a decline in the reduction in maximal strength and range of motion (ROM) after exercise. However, despite these findings, indicating that HMB benefits the recovery from EIMD, most of the studies on HMB supplementation have focused solely on the changes in strength and

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muscle mass following supplementation, whereas the effects of HMB on EIMD and the underlying mechanisms have received comparatively little attention. Hence, in this review, we sought to investigate the roles and potential mechanisms of HMB supplementation with respect to EIMD and its reduction, based on previous research, and provide multiple guidelines for supplementation with HMB.

EFFECTS OF HMB SUPPLEMENTATION ON EIMD

EIMD is accompanied by symptoms such as reductions in maximal strength and ROM, DOMS, and leakage of intramuscular proteins (e.g., CK) into the bloodstream. Given the practical difficulties in directly monitoring muscle damage, these symptoms are used as indirect indicators to measure the changes in and recovery from EIMD. Several studies have shown that HMB supplementation can reduce the symptoms of EIMD and promote recovery[11-13]. Among these symptoms, reductions in indicators of muscle fiber disruption, such as CK and lactate dehydrogenase (LDH), have been reported in response to HMB supplementation. For example, Nissen et al.[11] gave daily supplementation of 1.5 or 3 g of HMB to untrained male university students for 3 weeks, during which they performed free-weight exercise, and reductions in elevated levels of urine 3-methylhistidine and CK were detected. Similarly, in a study conducted by Panton et al.[12], males and females aged between 20 and 40 years were provided 3 g of HMB supplementation daily over a 4-week period, during which they performed resistance training, and the HMB group was found to show significantly lower increases in CK compared with the subjects in the placebo group, indicating that an exercise program coupled with HMB supplementation can minimize muscle damage. Accordingly, in a study conducted by Jówko et al.[14], active male university students were given daily supplementation with 3 g of HMB over a 3-week period, during which they performed free-weight exercise, and significant suppression of increases in CK levels was detected. Furthermore, in the study performed by Wilson et al.[13], subjects were given 3 g of supplementary HMB before or after resistance exercise involving repeated eccentric muscle contraction, and in subjects consuming HMB prior to exercise, an inhibition was observed in the increase of LDH, which is one of the markers of muscular damage.

The findings of more recent studies have confirmed that HMB supplementation is effective in reducing muscle damage induced by repeated eccentric muscle contraction. For example, Tsuchiya et al.[15] gave a daily supplementation of 3 g of HMB to untrained males for periods of 2 or 4 weeks, during which they used dumbbells to practice repeated eccentric muscle contractions; they found that the HMB supplementation group had smaller reductions in ROM and maximal strength compared with that of the placebo group. Furthermore, upper arm circumference (an indirect indicator of inflammation after muscle damage) and muscle stiffness were found to be significantly lower in the HMB supplementation group. The fact that no significant differences were detected between the 2- and 4-week HMB supplementation groups with respect to any of the assessed indicators suggests that ≥ 2 weeks of HMB supplementation can have beneficial effects in preventing muscle damage. Tsuchiya et al.[9] also demonstrated that at a lower HMB dosage (1.5 g/day), the observed changes in maximal strength and ROM after repeated eccentric muscle contraction were comparable to those recorded at a dosage of 3 g/day, thereby indicating that even low-dose HMB supplementation can be effective in reducing muscle damage.

HMB supplementation has also been found to be effective in endurance exercise[16,17]. For example, Knitter et al.[16] found that compared with the placebo group, increases in the levels of CK and LDH after a 20 km run following an initial 6 weeks of exercise were significantly lower in the HMB supplementation group (6 weeks of exercise coupled with 3 g/day of HMB supplementation) and suggested that long-term HMB supplementation is necessary to reduce muscle damage. Nunan et al.[17] have also reported that a daily intake of 3 g of HMB starting from 11 days prior to performing downhill running and continuing to 3 days post-running hastened the recovery of isometric and isokinetic muscle function, thereby indicating that HMB supplementation can contribute to muscle recovery in untrained individuals or in those who have performed unaccustomed exercise. Consistent with these findings, those reported in a recent meta-analysis study indicated that HMB has positive effects on reducing post-EIMD levels of blood proteins such as CK and LDH. Hence, it can be considered as a primary intervention for promoting post-EIMD recovery[18]. In contrast, a number of studies have reported findings indicating that HMB supplementation is ineffective in reducing EIMD[19,20]. Such disparities in the conclusions of different studies appear to be attributable to a number of different factors, such as the differences in target subject characteristics, exercise methods, and duration of HMB intake.

POTENTIAL MECHANISMS UNDERLYING THE EFFECTS OF HMB SUPPLEMENTATION IN REDUCING EIMD

High-intensity exercise, particularly that involving repetitive eccentric muscle contractions, can promote acute oxidative stress and inflammation, which are known to exacerbate muscle damage[21]; HMB has been reported to reduce such inflammation and oxidative stress (Figure 1)[22-24]. In this regard, Hoffman et al.[23] detected reductions in several indicators, including tumor necrosis factor-alpha (TNF-α), granulocyte colony-stimulating factor, interleukin 10, interferon-γ, interleukin 8, and C-X3-C motif chemokine ligand 1, in combat soldiers who were given HMB supplementations for 23 days before performing high-intensity military training. Similarly, supplementary HMB was given to resistance-trained men before and after high-intensity acute resistance exercise, involving squats, dead lifts, and split squats, and Townsend et al.[24] found that the HMB group

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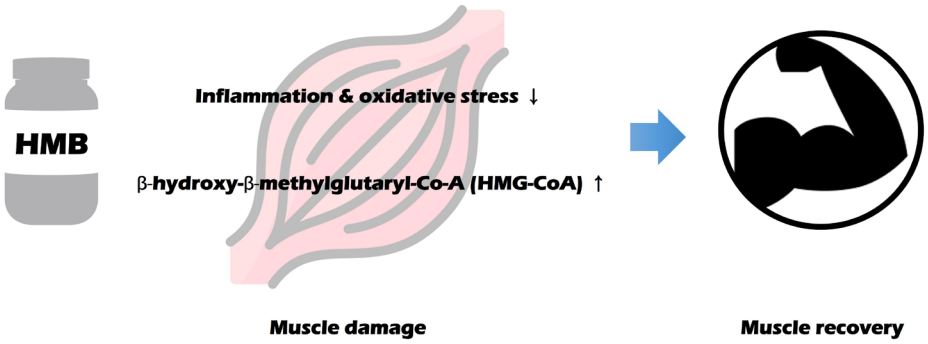

Figure 1. Potential mechanisms underlying the effects of β-hydroxy-β-methylbutyrate supplementation in reducing exercise-induced muscle damage.

subjects had lower expression levels TNF-α and TNF-α receptor 1, which are markers of inflammatory responses that occur during the recovery period. These authors accordingly concluded that HMB supplementation can reduce the early immune responses to intense exercise and shorten the time to recovery. Recently, Arazi et al.[22] found that in subjects administered HMB supplementation 30 min before and 1 h after performing plyometric exercise, there were reductions in the levels of oxidative stress markers, such as 8-hydroxy-2-deoxyguanosine, malondialdehyde, and protein carbonyl, compared with those in the placebo group. The findings of other studies have, nevertheless, indicated that HMB supplementation has little-to-no effect on exercise-induced inflammation or oxidative stress[25,26]. Consequently, further studies are required to clarify the associated mechanisms.

Alternatively, several authors have proposed that the efficacy of HMB supplementation in reducing muscle damage is associated with the production β-hydroxy-β-methylglutaryl-Co-A (HMG-CoA)[9], which is derived from the conversion of a compound formed from the coupling of HMB with a coenzyme A molecule (HMB-CoA)[8]. HMG-CoA subsequently undergoes conversion to mevalonic acid via reductase activity, and this metabolite serves as a precursor for cholesterol synthesis[27]. Muscle damage has been reported to be associated with reductions in sarcolemma integrity and the capacity of cells to produce sufficient amounts of cholesterol required for different cellular functions[28]. Hence, it is assumed that HMB supplementation promotes an increase in the synthesis of HMG-CoA, which can be used for cholesterol synthesis in the cytosol of muscle cells, in turn contributing to the restoration of sarcolemmal integrity[9,27]. The involvement of this mechanism is supported by the findings of several studies that have confirmed significant reductions in markers of cell membrane damage, such as CK and LDH, after EIMD[12-14]. However, this mechanism still requires further verification.

SUPPLEMENTATION GUIDELINES FOR FIELD APPLICATION OF HMB

The efficacy of HMB supplementation is dependent on several different factors, notably intake amount, timing, duration, and HMB form. With respect to dosage, the preponderance of research suggests 3 g to be an appropriate daily dose for supplemental HMB. Although supplementation with HMB at a dosage of 1.5 g has been shown to be effective in reducing EIMD, the effects were more pronounced upon 3 g administration of HMB[29]. A daily HMB dose of 3 g has been confirmed to be safe with no apparent adverse side effects[28].

The timing and duration of HMB intake can be classified as either chronic or acute, and the findings of previous studies have indicated that HMB can have both chronic and acute effects in reducing EIMD[9,12,13]. For chronic effects, HMB supplementation of at least 2 weeks is necessary[12,14,15], as has been demonstrated by Wilson et al.[29], who found that HMB administered over a course of ≥ 2 weeks can reduce the levels of muscle damage markers, and that to achieve such effects, the supplementation should commence at least 2 weeks prior to the start of training. HMB supplements can be consumed during breakfast, lunch, or dinner. Upon review of the previous research, we found no specific recommendations regarding the timing of HMB supplementation in terms of exercise, although in several studies, a regimen in which a total of 3 g/day of HMB was consumed over three time points, namely, 1 g consumed at breakfast, lunch, and dinner, respectively, has been reported[10,12,14].

With respect to acute effects, HMB supplementation can be taken 30 to 60 min prior to commencing high-intensity exercise[13,24]. However, there is a need for further studies on the protocols that should be used to determine the effective dosage for acute intake of HMB. For example, it has yet to be sufficiently established as to whether HMB should be consumed both before and after exercise or only before exercise. In a study conducted by Townsend et al.[24], 1 g of HMB was administered 30 min before and at 2 and 6 h after exercise, whereas in a study conducted by Wilson et al.[13], HMB (3 g) was only given 60 min before exercise, as these authors reported that taking HMB only after exercise is ineffective in reducing EIMD. In this context, the findings of several studies have indicated that the timing of HMB intake is dependent on which of the two forms of HMB [calcium HMB (HMB-Ca) and free-acid form of HMB (HMB-FA)] is administered[29]. These two forms differ in terms of the magnitude and rate of appearance in blood circulation

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and in the subsequent rate of clearance[22,29]. Wilson et al.[29] proposed that HMB-FA should be taken 30 to 60 min before exercise, whereas HMB-Ca should be taken 60 to 120 min before exercise. However, further research is required to establish which of these two forms is more effective in reducing EIMD.

Studies have also assessed the effects of the co-administration of HMB and creatine on EIMD. However, the findings tend to indicate that this combination does not offer any beneficial effects with respect to EIMD reduction[14], which has been confirmed by recent studies that have concluded that HMB combined with creatine does not have any significant effects on EIMD-associated markers[30].

In conclusion, HMB supplementation can be considered as an effective nutritional strategy to minimize EIMD. Individuals participating in high-intensity exercise would be able to use HMB supplementation for recovery. Nevertheless, further research is needed to address some of the limitations of previous studies.

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