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Konstantinos D Tambalis
Department of Nutrition and Dietetics, School of Health Science & Education, Harokopio, Greece

Giannis Arnaoutis
Department of Nutrition and Dietetics, School of Health Science & Education, Harokopio, Greece

Corresponding Author:
Department of Nutrition and Dietetics, School of Health Science & Education, Harokopio, Greece

Nutritional ergogenic aids favorably affect protein metabolism, athletic performance and health: An update

Konstantinos D Tambalis and Giannis Arnaoutis

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Abstract
Athletes take nutritional supplements because they believe it will provide them with a convenient and effective source of nutrients. Creatine and ß-hydroxy-ß-methyl-butyrate (HMB) are two of the most popular and legal ergogenic dietary supplements. These two compounds may have a comparable ergogenic effect since they favor muscle protein synthesis and proteolysis during exercise. This narrative review seeks to offer the most recent scientific literature on these two ergogenic aids in detail. HMB has been found to improve strength and lean muscle mass by acting as an anti-catabolic agent, reducing muscle breakdown and protein degradation following exercise. In terms of muscle absorption and the ability to boost high-intensity exercise capacity, creatine monohydrate (CM) is the most clinically effective nutritional supplement. Athletes utilize creatine pills to boost their exercise performance. The combination of CM and HMB has the potential to increase fat-free mass while lowering fat mass.

Keywords: Creatine, HMB, exercise training, nutrition supplements

1. Introduction

Athletes primarily consume nutritional supplements and sports foods in the belief that they will provide them with benefits such as (a) an increase in energy reserves; (b) the promotion of training adjustments and competitive performance; (c) the maintenance of more efficient and rigorous training by promoting recovery between sessions; (d) the protection of health and the reduction of "lost" training sessions due to chronic fatigue, illness, or injury; and (e) the consumption of a convenient, effective source of nutrients [1]. The last is the most common reason given by athletes for taking nutritional supplements before, during, or after an exercise [1]. Creatine and ß-hydroxy-ß-methyl-butyrate (HMB) are two of the most popular and legal ergogenic dietary supplements [2]. These two compounds may have a comparable ergogenic effect since they favorably affect muscle protein synthesis and proteolysis during exercise [3].

HMB is a metabolite of leucine, an amino acid (essential for the human body). HMB is produced in the human body in around 2-10% of the typical oxidation of leucine [4]. Leucine is an amino acid that regulates protein synthesis and catabolism in human muscle groups [5]. Supplementing the diet with the amino acid leucine and doing resistance training together enhances muscle mass, strength, and lowers body fat [6]. Leucine is thought to alleviate skeletal muscle soreness after eccentric exercise and to prevent testosterone circulation and skeletal muscle strength declines following severe exercise [7]. Leucine promotes strength-training adaptations by functioning as the primary signal for protein synthesis activation. It has anti-proteolytic properties as well [7, 8]. Ten to 20 times (5-10 mM/L) of the concentration required to maximally stimulate muscle protein synthesis maximizes the effects of leucine on muscle proteolysis [9]. As a result, these effects could be caused by the conversion of leucine to a specific metabolite [2]. HMB, a leucine-derived metabolite, is a strong candidate.

Creatine (Cr) is a nitrogenous organic acid that aids in the energy production of all body cells, particularly those in the muscles [2]. This is accomplished by boosting adenosine triphosphate production (ATP). It is generated in the body at a rate of around 1 g/day, primarily in the liver and kidneys, and it is also consumed at a rate of about 1 g/day by food [4]. Creatine can enter the muscle and attach straight to a phosphate radical, forming phosphocreatine (PCr), a high-energy molecule in the ATP-PCr energy system [1]. Creatine concentration in muscular tissue is normally 120-140 mmol/kg dry muscle (60-65 % as PCr, 35-40 % as Cr).

Creatine reserves can be increased or decreased depending on dietary creatine availability [10]. Supplementing with creatine can boost creatine reserves by up to 160 mmol/kg dry muscle. However, under some circumstances, the normal human can store up to 60 grams of creatine [11]. Creatine reserves can be restored through dietary creatine or endogenous glycine, arginine, and methionine production [2]. The debate over the use of legally consumed ergogenic aids to improve athletic performance in anaerobic exercise and, in particular, strength training has centered on their common role in protein synthesis and proteolysis, as the above-mentioned substances are thought to positively affect this process [12].

This narrative review aims to present the most recent scientific literature on two main ergogenic aids, namely HMB and creatine, in terms of (a) their potential beneficial effect on athletic performance through the moderation of protein metabolism in exercised muscle; (b) their effect on health in both exercised and non-exercised individuals; and (c) current recommendations for safe administration.

2. Materials and methods

Studies for this narrative review were found primarily through a systematic search of the electronic databases MEDLINE, PubMed, and EMBASE, using terms, title words, and abstract words such as "exercise", "physical activity", "athletes", "athletic performance", "nutrition supplements", "ergogenic aids", "bicarbonate sodium" and "b-alanine." We also employ past review articles, as well as references from original studies and related books, in our computer analysis. Physical activity, athletic performance, exercise, health, bicarbonate sodium, and b-alanine were all used as keywords. We looked for studies that used the above terms and were published in the English language between January 1985 and December 2021. Studies were considered if they offered information on bicarbonate sodium or b-alanine consumption in athletes, evaluated their potential efficacy in terms of athletic performance and/or health, or detailed the mechanism of action, administration procedures, safety, and recommendations. Each qualified article's title and abstract were examined, and full-text articles were retrieved in circumstances where inclusion was in doubt. The final eligibility of publications included in the systematic review was determined using PRISMA guidelines.

3. ß-hydroxy-ß-methyl-butyrate (HMB)

Reduced muscle degeneration during exercise and proper recuperation after sports training are critical for athletes' health and good performance. Rest and sufficient nutrition are the two most important aspects of healing. HMB is a vital nutritional ergogenic supplement that aids in the prevention of muscle deterioration during exercise. In the mid-1990s, HMB made his debut in the sports world. It was marketed at first as "the most useful bodybuilding supplement, even more beneficial than creatine." About 20 years ago, Jeff Stout published the first popular HMB review [13].

3.1 Action Mechanism

The amino acid leucine is used to make HMB in both animals and humans. The branched-chain amino acid transferase enzyme reversibly demineralizes leucine to -keto-isocaproic acid (KIC) as the initial step in the synthesis of HMB. KIC is primarily converted to isovaleryl-CoA, with only around 5% of leucine being transferred to HMB. Isovaleryl-coenzyme A is metabolized further to become -hydroxy-methylglutaryl-coenzyme A (HMG-CoA) [9]. HMB, like HMG-CoA, can be transformed to HMG-CoA, a precursor of cholesterol. To achieve the quantity of leucine (60 g) required creating the normal daily dose of 3 g of HMB used in human studies, the average individual (68 kg) would need to ingest more than 600 g of high-quality protein. HMB is usually boosted through supplementation because consuming this amount of protein is not realistic for athletes [9]. The mechanism of HMB absorption in the intestine is unknown. HMB has a half-life of roughly 2.5 hours [9]. HMB is available in the form of HMB-Ca/calcium monohydrate as a dietary supplement. The quantity and speed HMB manifests itself after intake is determined by the dose and whether it is taken with other substances [14]. According to Vukovich *et al.* (2001), treatment of 1 g of HMB-Ca resulted in the highest concentration (peak) in the blood 2 hours later, whereas administration of 3 g resulted in the maximum concentration 60 minutes later and at a 300 percent higher concentration (487 vs. 120 nmol/ml). When HMB-Ca was coupled with 75 g of glucose, the maximum HMB concentration was delayed by one hour and was much lower (352 nmol/ml) [15]. The addition of glucose to the stomach may slow gastric emptying or hasten HMB clearance [15]. Another method of delivering HMB, such as free acid, has been examined. HMB-free acid is the name given to the new type (HMB-FA). HMB-FA is a gel, whereas HMB-Ca is a powder that comes in capsules. When 0.8 g HMB-FA and 1.0 g HMB-Ca (equal levels in HMB) were tested, HMB-FA produced twice the peak plasma concentration of the chemical in 14 times (30 vs. 120 min). In addition, the concentration of HMB 180 minutes after treatment was 91-97% greater in HMB-FA than in HMB-Ca, and the uptake and utilization in tissues were 25% higher in HMB-FA than in HMB-CA [16]. The plasma clearance of the substance, which is suggestive of substance absorption and utilization, was 25% higher in the HMB-FA form compared to HMB-Ca [16], which was perhaps the most noteworthy discovery in the study. As a result, the HMB-FA form is recommended as the most effective for drug administration. However, HMB-Ca has been used in the majority of research to date [17]. The mechanisms of HMB's effect on athletic performance can be explained in three ways. In a nutshell, the routes increase protein synthesis, decrease protein degradation, and increase the substrates required in cell membrane repair. The result/end product of protein synthesis and breakdown in skeletal muscle proteins is the rate of exhaustion and replacement (turnover) of muscle proteins [9, 17]. There is a pure synthesis of skeletal muscle proteins when protein synthesis exceeds protein degradation [4]. When protein degradation outnumbers protein synthesis, however, skeletal muscle proteins are clearly broken down [4]. Both protein synthesis and skeletal muscle breakdown have been demonstrated to be affected by HMB [9, 17].

3.2 How Does HMB Affect Athletic Performance?

The following are some of the suggested effects of HMB on athletic performance. In chronic diseases and the elderly, it (a) enhances protein synthesis, (b) lowers protein breakdown, (c) boosts strength, (d) reduces muscle fatigue, and (e) maintains lean body mass [17]. We should also consider the following to better understand the oscillations as well as the results of study (good or negative) that investigated the effect of HMB on athletic performance. The putative ergogenic effects of HMB (e.g., reduction of protein catabolism) have been investigated using several markers such as creatine kinase, lactic dehydrogenase, and urea markers [6-7, 10, 17]. Muscle pain and felt weariness after exercise, with or without HMB, were investigated for the same aim. Also used were various administration protocols (1 day to 6 weeks), ages (19-50 years), exercise regimens, and people with various training levels [6-7, 10, 17]. In other research, only HMB and additional supplements like creatine were used. Some studies [7, 10, 17] have incorporated diet and activity, but not all. In the literature, the level of training is a variable that has gotten a lot of attention. According to Kreider *et al*. (1999), the action of HMB is likely to interact with both the exercise stimulus and the athlete's exercise training level [18]. Several studies have demonstrated that HMB can impact skeletal muscle injury and protein breakdown when the intensity of training and nutrition is taken into account [19-20].

According to research evidence in trained persons HMB may not be helpful if exercise intensity and volume are not required to generate muscle damage, [6-7, 21]. Based on Ahtiainen *et al*., (2003), modifications due to HMB administration occur at a slower rate in trained persons than in untrained individuals [22]. HMB may be most useful in these individuals when the exercise lasts longer than 6 weeks, although HMB appears to moderately boost strength in free resistance training regimens that last longer than 6 weeks [22]. The outcomes of the study (Kraemer *et al*., 2009) in 17 healthy trained men (mean age: 22.9±3.8 years) showed that after 12 weeks of resistance training, lean body mass and total fat improved in both groups, i.e. in the HMB group as well as the placebo group [23]. HMB treatment was also observed to improve lean body mass, muscle strength, and muscle strength considerably more than the placebo group after 12 weeks ($p<0.05$) [23]. In another study, 28 trained persons were given either a placebo or 3.0 g HMB per day and were asked to lift weights for 2-3 hours six days a week for seven weeks, while their lean body mass was determined using the electrical conductivity of the body method [24]. According to the findings, the group that received HMB gained considerably more lean body mass after the 15th day and up to the 40th day [24]. In addition, Wilson *et al*., (2014) found that 12 weeks of resistance training and simultaneous administration of placebo or HMB-FA resulted in an increase in lean body mass in both groups, with the HMB-FA group gaining considerably more (7.4±4.2 vs. 2.1±6.1 kg, $p<0.001$) than the placebo group [25]. The results of the same study showed that after 12 weeks of training, overall strength increased in the HMB-FA group by 77.1±18.4 kg vs. 25.3±22.0 kg, $p<0.001$) compared to the placebo group [25]. Finally, a 12-week study by Lowery *et al*., (2016) in trained men who exercised with resistance for 12 weeks while receiving either placebo, ATP (400 mg), HMB-FA (3 g), or a combination of 3 g HMB-FA with (400 mg) ATP found that, while lean body mass increased significantly in the HMB group compared to the control group, the combination HMB-FA/ATP resulted in a 12.7 percent greater improvement ($p<0.001$) compared to the HMB group [26]. Conclusively, the researchers speculated that combining HMB-FA and ATP with resistance training promotes lean body mass and muscle strength, and that the combination of HMB-FA and ATP may benefit those who train at a high level on a regular basis, such as elite athletes and military personnel [26].

The majority of studies employing HMB as an ergogenic supplement lasted four weeks or fewer in both trained and untrained participants. HMB treatment has been found to increase lean body mass and strength in untrained persons in just three weeks [6]. Given that HMB operates by speeding up the repair of skeletal muscle tissue injury, these findings are not surprising. In untrained individuals, evidence reveals that the first few weeks of exercise produce the most muscle damage [9]. In untrained persons, research has shown that taking HMB for three weeks while exercising simultaneously lowers the risk of skeletal muscle injury and protein breakdown in a dose-dependent way, with significant favorable improvements in lean body mass [11]. According to research data, the rate of progress among novice weightlifters slows as their coaching expertise grows [27-28]. Thus, after 8 weeks, the size of the effect of HMB against placebo in beginners' increases modestly, compared to the first 3-4 weeks [27-28]. In addition, in untrained persons, a dose of 3 g/day confers better benefits than a dose of 1.5 g/day, although a dose of 6 g/day confers no greater benefit than a dose of 3 g/day [22]. Finally, a study of 41 untrained individuals who were divided into three levels of HMB (0, 1.5, or 3.0 g HMB/day) and exercised with weights for 1.5 hours, three days per week, for three weeks found that changes in total body muscle strength were significantly higher in the HMB group compared to the control group from week one to week three [24]. In the same study, exercise-induced increases in muscle proteolysis were found in participants who exercised with weights and were given 3 g of HMB-Ca at the same time compared to the control group in the first two weeks [24].

As a result of the current scientific findings, the following conclusions can be drawn: (a) In untrained persons, HMB can increase muscle hypertrophy and strength in as little as three weeks; (b) in trained individuals, it's vital to remember that modifications take longer than in untrained individuals. As a result, HMB will likely be more useful for lengthier training (>6 weeks) in trained persons. A meta-analysis concluded that because of the duration of training protocols (10 days to 12 weeks), the type of training programs (free or supervised), the method of training (machines or free weights), the dose administered (1.5 to 6 g per day), the combination with other substances (e.g. creatine, arginine, and glutamine), and the impact assessment indicators that were measured differ, no overall conclusions can be drawn for untrained and trained individuals together on the effect of HMB, although the direction of the results is favorable for both categories [17]. While HMB has long been known to be an anti-catabolic agent that aids in the restoration and improvement of athletic performance, new research suggests that HMB supplements may have additional metabolic effects relating to energy metabolism [29-30]. HMB has been demonstrated to help endurance athletes in previous studies. In a study of 8 high-level athletes cycling 300 miles per week, Vukovich et Dreifort (2001) discovered that eating 3 g of HMB-Ca for 6 weeks enhanced endurance parameters compared to the control group [31]. The mechanisms underlying HMB's favorable effects on aerobic exercise and body fat loss are unknown. HMB supplements, on the other hand, have been demonstrated to boost fatty acid oxidation and the activity of many proteins in adipocytes and skeletal muscle, improving mitochondrial biogenesis, fat oxidation, energy metabolism, and the immune system [32]. Finally, data suggest that HMB administration may benefit obesity, insulin resistance, and diabetes, as well as athletes looking to increase their aerobic performance [9, 14, 29, 32].

3.3 Administration of HMB and its beneficial effects on health

According to a review of 9 trials in healthy persons HMB is safe and has a favorable effect on health indicators (such as a reduction of 7.3 % in LDL cholesterol, 10% in cardiovascular risk, and 3% in blood pressure) [33]. Men and women, young and elderly, trained and untrained, participated in the studies, which lasted 3 to 8 weeks [33]. Finally, it appears that, in addition to athletic performance, HMB treatment can have good impacts on other health indicators.

3.3.1 HMB in athletes who train on a low-calorie diet

HMB supplements' effects on cell regeneration and fat metabolism make them a viable option in a variety of situations when skeletal muscle is compromised. The effect of HMB, for example, has been studied in situations of exercise combined with calorie restriction. In bodybuilders and weightlifters, calorie restriction is customary before a race. Calorie restriction can result in a loss of lean mass and athletic performance [34]. Body weight was lowered less in the HMB group than in the control group in female judokas who followed a 3-day calorie restriction. There was a lesser drop in lean body mass and maximum strength in the same group (HMB). Overall, the findings imply that HMB administration may prevent future loss of lean body mass in people who are on a moderate calorie restriction and thus be helpful [34, 35].

3.3.2 Adolescents and young people receiving HMB

HMB aids recovery in stressful situations and may thus be advantageous to younger populations. During the first seven weeks of training, elite volleyball participants (13-18 years old) were given three grams of HMB-Ca every day. In comparison to the control group, HMB-Ca treatment enhanced lean body mass and decreased body fat. In addition, the HMB-Ca group had greater upper and lower limb maximum strength and power [36]. Due to drug delivery, no changes in hormone profile (testosterone, cortisol, growth hormone, and IGF-1) or inflammatory indicators (interleukin-6 and interleukin-1 receptor antagonist) were found [36]. While there isn't enough data to back up the use of HMB to improve sports performance in adolescents, taking supra-physiological levels may cause unwanted side effects [37]. To summarize, deteriorating results at these ages revealed that, despite the positive effect of administration, HMB did not improve resistance exercise-induced changes in body composition or muscle strength in young people [38].

3.3.3 HMB administration in the elderly without exercise

Many researches have looked into the effect of HMB on skeletal muscle mass in the elderly without exercise. Flakoll *et al*. (2004) found that giving HMB, arginine, and lysine to 50 older people for 12 weeks enhanced lean body mass and strength compared to the placebo group [39]. In addition, when 77 adults over the age of 65 were given HMB, arginine, and lysine for a year, they saw a significant gain in lean body mass and a decrease in adipose tissue compared to the control group [40]. Leucine supplementation can partially overcome anabolic resistance, which is more prominent in the aged, and it has been claimed that this is related to the conversion of leucine to HMB. These findings point to the potential benefits of HMB supplementation in the elderly [41]. Overall, HMB appears to be able to reduce body fat while increasing muscular mass and strength in the elderly.

3.3.4 Exercise and HMB administration in senior athletes

In the elderly, the effects of HMB in combination with resistance training have been studied. In a research of men and women aged 70 years who exercised with resistance for 8 weeks and drank HMB at the same time, the control group exhibited increased lean body mass, decreased fat mass by 8%, and increased strength by 15-20 percent in both groups [31]. Furthermore, Lin *et al*. (2021) postulated in a recent review and meta-analysis in older adults that HMB supplementation is beneficial for improving body composition, while the effect of HMB supplementation combined with exercise training to improve muscle mass is not clear [42]. In summary, HMB administration has the same favorable effects in older persons who exercise as it does in younger people.

3.4 Protocols for administering HMB

According to current recommendations, a daily dose of 38 mg/kg body weight (BW) HMB should be taken at least 2 weeks before the race to be most effective [17]. HMB-Ca and free acid HMB have been the most often used versions of HMB to date (HMB-FA). As previously noted, HMB-FA may boost plasma absorption and retention of HMB to a greater extent than HMB-CA; nevertheless, scientific study on HMB-FA is still in its early stages, and there are inadequate results to determine which of the above forms predominates. According to Ahtiainen *et al*., (2003), 38 mg/kg BW/day, administered in 2-3 doses, provides the appropriate amount of HMB to accelerate muscle adaption processes, with HMB-FA administration increasing HMB levels in the blood faster and at a higher point than HMB-Ca administration [23]. The research led to the following instructions in more detail:

- HMB administration has an instant and long-term effect.
- The immediate effect of HMB is dependent on when it is taken prior to exercise. HMB-FA has a faster and more significant effect than HMB.
- If HMB-FA is given, 1-2 g should be ingested 30-60 minutes before severe exercise, and 60-120 minutes before exercise if HMB-Ca is given.
- HMB should be consumed with glucose at least 2 hours prior to activity.
- A dose of 3 g per day, in three equal doses (3X1 g), for at least two weeks prior to the physically demanding event is required for best long-term impact.
- It comes in the form of a capsule that also contains calcium and contains 250-750 mg HMB per capsule.

3.5 Side effects and safety

HMB is a legitimate ergogenic dietary supplement that is not one of the championship's banned substances. Even in huge doses, current scientific findings do not show considerably serious side effects. In addition, long-term

HMB use appears to be safe for both young and old persons. Consumption of 6 g/day HMB for one month had no effect on cholesterol, hemoglobin, leukocytes, blood glucose, kidney or liver function [30]. In addition, in the elderly, consumption of 2-3 g/day HMB-Ca in combination with amino acids for a year did not result in alterations in kidney or liver function [17]. Finally, review studies conclude that HMB is safe and has no negative effects on health or athletic performance [17, 33, 43].

3.6 Recommendations

- In both trained and untrained populations, HMB aids recovery by reducing exercise-induced muscle injury.
- HMB consumption can be advantageous for untrained people who conduct high-intensity resistance training.
- Consumption of HMB near the time of activity will benefit an athlete.
- The effect of the substance on muscle damage is determined by the timing of HMB administration prior to exercise, the kind of HMB, the duration of HMB administration prior to exercise, the dose, and the individuals' training level. If provided in the form of HMB-FA, 1-2 g should be consumed 30–60 minutes before activity, and 60–120 minutes before exercise if administered in the form of HMB-Ca.
- HMB works best when taken at a dose of 3 g per day for 2 weeks prior to a high-intensity racing exertion that induces muscle injury.
- There are promising findings that HMB promotes muscle hypertrophy, strength, and power in both trained and untrained people, depending on the level of training required.
- In the elderly, physically sedentary people, and older athletes, HMB promotes lean body mass and function.
- When HMB is used with a planned training regimen, fat mass can be reduced more effectively.
- HMB can help athletes on a calorie-restricted diet maintain lean body mass.
- By slowing the rate of protein breakdown, HMB appears to produce favorable conditions for muscle development following training.
- Finally, despite the lack of evidence, HMB treatment appears to improve aerobic performance [17].

4. Creatine

Creatine was first used as a potential ergogenic in the Soviet Union and former Eastern Bloc countries in the 1960s and 1970s. The earliest studies on the effects of creatine on sports performance were conducted in the United States and the United Kingdom in the 1990s. Linford Christie (100m) and Sally Gunnell (400m hurdles) were British Olympians who used creatine in 1992 in Barcelona. Creatine sales in the United States grew from $ 30 million to $ 180 million in just four years, from 1995 to 1998. Several thousand kilos are consumed annually in the United States alone, according to estimates. According to research conducted in the United States, the frequency of creatine consumption among young athletes (high school students) was 14-16 percent, whereas the frequency of consumption among adult professional athletes, particularly men, varied from 40 to 50 percent [44, 45].

4.1 Action Mechanism

Because phosphocreatine (PCr) is the direct source of energy for high-intensity exercise and explosive muscle activity, creatine is important in muscle metabolism and athletic performance. However, the muscle "empties" of PCr in the first 6-10 seconds of a maximum effort due to its limited storage and high rate of breakdown [4]. In muscles, PCr is the most direct and smallest source of ATP production. At maximum effort for a few seconds, it is the primary source of ATP reconstitution (up to about 7 sec). For the immediate power supply of speed and power sports, the ATP-PCr energy system is critical [46]. During and after strenuous exercise, the energy required to rephosphorylate adenosine diphosphate (ADP) to adenosine triphosphate (ATP) is largely determined by the PCr stores stored in the muscles [47]. Due to the inability to re-synthesize ATP at the pace required to maintain high-intensity exercise, available energy is limited as PCr reserves are depleted during severe activity. As a result, the ability to maintain a high level of exercise effort is harmed [47]. The amount of energy produced during short-term and high-intensity exercise is influenced by PCr availability in the muscle. Furthermore, increasing muscle creatine content through creatine administration is thought to increase PCr availability, allowing for a faster rate of ATP resynthesis during and after high-intensity, short-term exercise [1]. Creatine supplementation in training persons could theoretically lead to more training adjustments by increasing the intensity and volume of work done. Creatine supplementation, which increases PCr stores and rate of regeneration during interval training, stimulates athletes' and coaches' interest in strength, speed, and power sports, as well as team sports that require long effort times during race and training [48-49].

Creatine reserves in an average young guy weighing 70 kg are around 120-140 g, differ from person to person and are determined by the type of muscle fibers and the amount of muscle mass present in each [50-51]. The body's creatine removal is compensated for by endogenous generation and food intake [50, 51]. In general, oral creatine use raises creatine levels in the body [52]. Creatine is eliminated from the bloodstream by being stored in a variety of organs or being cleared in the kidneys. The majority of creatine is absorbed into the bloodstream when a creatine supplement is consumed and enters the intestines [4]. Insulin-regulated active transport transports blood creatine to skeletal and cardiac muscles. A portion of the creatine is combined with phosphates after absorption to form PCr [1, 4]. Creatine and PCr storage enables the quick recombination of ATP to fulfill energy demands via a mechanism mediated by creatine kinase [1, 4]. The CreaT1 transporter is the only one that transports more creatine to cells. Many factors influence creatine absorption, including phosphorylation, glycosylation, and intracellular and extracellular levels of the molecule [4, 53-54]. Crea T1 is very sensitive to both external and intracellular creatine levels, and it is activated when the total creatine content inside the cell falls. In addition to cytosolic creatine, the presence of a mitochondrial isoform of Crea T1 allows creatine to be transported into the mitochondria, indicating that there is another intramitochondrial store of creatine that appears to play an important role in transmitting light from mitochondria to the cytoplasm [4, 53-54].

Increasing PCr concentrations in muscle: (a) aids rapid ATP synthesis via the creatine kinase response; (b) increases PCr diffusion between mitochondria and myosin heads; (c) reduces muscle acidity via the absorption of H^+ during the conversion phase of ADP to ATP, allowing the muscle to accumulate more lactic acid before "catching" the restrictive muscle pH, extending the duration of high-intensity exercise; and (d) causes osmotic changes in muscle cells, which increases the water content in the cells [52, 55-57].

4.2 Creatine's Impact on Athletic Performance

4.2.1 Strengthening effect of creatine administration

When creatine is combined with intense resistance training, athletic performance, lean body mass, and muscle morphology improve. The bulk of studies on creatine administration show that it increases the body's creatine reserves, and that there is a link between creatine intake/absorption and athletic performance. Increased total creatine leads to faster ATP regeneration between sets in intense resistance training, allowing athletes to maintain a higher training intensity and improve training quality throughout. Creatine was given to adult men for at least 8 weeks along with intense resistance exercise, and several studies found a significant improvement in muscle strength [58-61]. In addition, a meta-analysis found that combining creatine with resistance training improved 1 maximal repetition (1RM) and strength endurance (maximum repetitions in a given percentage of 1RM) by +8% and +14 %, respectively, when compared to placebo groups [52]. Overall, creatine supplementation combined with resistance training improves maximum performance, strength endurance, and muscular hypertrophy [52, 62-63].

4.2.2 Anaerobic exercise and creatine administration

In short-term, anaerobic intermittent activity, creatine improves neuromuscular performance. For example, creatine supplementation improves anaerobic performance in elite male rowers, regardless of the effect of intensive endurance training [64]. Furthermore, in a meta-analysis, Branch J (2003) found that its administration had an effect size (ES) of 0.24±0.02 for activities lasting 30 seconds [52]. Also, it has no effect on exercise that is done repeatedly, at a high intensity, and for a short length of time (less than 30 seconds), while, creatine had a 0.19±0.05 effect on anaerobic endurance exercise (>30-150 sec) when compared to placebo groups [52]. Overall, creatine has the greatest effect in high-intensity, short-duration (the 30s) intermittent exercise [48, 57].

4.2.3 Muscle hypertrophy and creatine administration

Creatine supplementation has been linked to muscle hypertrophy when combined with severe resistance training. Creatine (21 g/day) combined with resistance training for 5 days improved the muscle anabolic environment (mRNA, GLUT4, Myosin heavy chain IIA) in 9 healthy men [61]. Creatine injection mixed with intensive resistance exercise increased the levels of insulin-like growth factor 1 (IGF-1) in muscle and muscle hypertrophy [65]. In the same study, vegetarians had a higher gain in lean mass than non-vegetarians (2.4 and 1.9 kg, respectively) [65]. These findings, according to the authors, do not support the theory that a low-amino-acid standard vegetarian diet reduces IGF-1 production [65]. On the whole, creatine administration and subsequent increases in total creatine and PCr may result in increased muscle IGF-1 production and protein synthesis, resulting in greater muscular hypertrophy [66-68].

4.2.4 Creatine supplementation and aerobic exercise

There have been some research discoveries that show creatine has a beneficial effect on aerobic exercise. A meta-analysis concluded that the ergogenic effect of creatine on aerobic endurance exercise declines as the length of the activity grows above 150 seconds [48]. In addition, the administration of 20 g of creatine for 5 days resulted in a significant decrease in lactic acid concentration and an increase in the lactic threshold in high-level male rowers [64]. Overall, creatine's putative benefits in endurance performance are more closely linked to a rise in the lactation threshold [69].

4.2.5 Glycogen storage and creatine administration

Creatine has been shown to increase muscle glycogen accumulation and the expression of GLUT4 (glucose transporter type 4, insulin-regulated glycogen transporter) when given to a person who is performing an exercise that depletes muscle glycogen [70, 71]. Creatine by itself does not appear to improve muscle glycogen storage. Creatine administration had a positive effect on boosting the original and maintaining a higher level of muscle glycogen during 2 hours of cycling in male cyclists [72]. It is widely accepted that when exercising causes muscle glycogen depletion, a high-carbohydrate diet should be combined with creatine administration to increase reserves [48-49, 69].

4.3 Creatine and the body's health

Creatine administration, according to the scientific literature, can help maintain total creatine stores during the recovery period after an injury, mitigate muscle damage caused by prolonged endurance exercise, and act as an effective antioxidant after very intense resistance exercise [69].

4.3.1 Cardiovascular and hormonal changes that may occur as a result of creatine consumption

Creatine administration has no effect on blood pressure, heart rate, or oxygen consumption. Although, some studies have found a reduction in total cholesterol and triglycerides, the validity of these recent findings is debatable [73]. In addition, creatine administration has no effect on testosterone or cortisol levels, while, significantly increasing growth hormone and aldosterone [74-75]. Finally, scientific evidence suggests that it has no effect on renin, angiotensin, or insulin levels [76].

4.3.2 Creatine's impact on general health and the elderly

Creatine supplementation boosts cognitive and neurological performance. Creatine appears to raise the levels of creatine and PCr in the brain [49]. Creatine levels in the brain have been linked to better neuropsychological performance, while, it can help improve cognitive function that has been delayed due to sleep deprivation and physical impairment due to aging [74-75]. It is unknown what the optimal creatine dose is for maximum brain uptake. Other potential benefits of creatine consumption, particularly for the elderly's health and well-being, include increased fatigue resistance, strength, muscle mass, bone density, and daily activity performance. The majority of these advantages must occur in the absence of exercise [75, 77]. Recommendations for creatine administration propose that patients should be given 40 g/day to improve their health [49, 69].

4.3.3 Adolescents and children's use of creatine

During high-intensity activity, a child's body has a lower ability to regenerate high-energy phosphates (ATP & CP) than an adult [1]. As a result, creatine supplementation can improve the pace and efficiency with which creatine phosphate and ATP are re-phosphorylated. Short-term and high-intensity exercise performance, on the other hand, can be enhanced through training, therefore supplements may not be necessary [78]. There are insufficient findings based on limited performance and safety data, and creatine ingestion is not suggested, at least in children and early adolescence [49, 78]. Creatine supplementation in teenagers under the age of 18 has not been well studied in terms of sports performance [49]. Nonetheless, young athletes under the age of 18 are given creatine. Sixty-two of the 1103 students who participated in a study (Metzl *et al*., 2001) [80] on a sample of youths (10-18 years old) in the United States used creatine [79]. The researchers attributed the aforementioned conclusion to two possible reasons: first, the safety of administration at these ages has not been explored, therefore creatine is not suggested, and second, its intake is regarded to lead to the usage of harmful anabolic steroids as an intermediate step [80].

Adolescent/young athletes (over 16-17 years old) can take creatine if the following conditions are met, according to the International Society of Sports Nutrition recommendations [49]:

1. The athlete engages in scheduled, intense, competitive exercise and participates in a sport that can benefit from creatine supplementation.
2. The athlete eats a well-balanced diet that helps him or her perform better in sports.
3. The athlete and his parents are fully aware of the consequences of its use.
4. The athlete's parents have given their permission for it to be used.
5. Its management should be overseen by parents, coaches, and doctors.
6. High-quality materials are used.
7. Athletes do not exceed the doses recommended by the manufacturer [49].

If all of the following parameters are met, adolescent/young athletes (over 16-17 years old) may use a creatine supplement, but only with their physicians' and coaches' permission. The use of permitted substances under international rules could be a safe and effective dietary "aid" in the fight against illegal anabolic steroids and other potentially harmful drugs. In contrast, if none of the above terms/conditions apply, creatine administration may not be necessary.

4.3.4 Administration of creatine to responders vs. non-responders

In all individuals, the same amount of creatine does not elevate intramuscular creatine and PCr levels to the same extent. Syrotuik et Bell (2004) found that there are three categories of people who respond to creatine administration: (a) those who respond (responders), (b) those who almost respond (quasi responders), and (c) those who respond very little (non-responders) in amateur men with resistance who have a history of taking the substance (loading dose was 0.3 g/kg BW/day, for 5 days) [81]. Responders are defined as people who have (a) lower baseline total Cr muscle levels, (b) a higher type II fiber population, and (c) a greater ability to improve creatine responsiveness. In addition, like many other ergogenic supplements, creatine administration has a different effect on men and women, with men having a higher response [82].

4.4 Creatine supplementation in combination with other substances

Although creatine can be purchased on its own, it is frequently found mixed supplements with other nutrients. Creatine + carbohydrates, creatine + proteins, creatine + carbohydrates + proteins, creatine + caffeine, creatine + taurine, and creatine +-alanine are the most common combinations. Nutrients that increase insulin levels and/or improve insulin sensitivity have piqued researchers' interest. The inclusion of specific macronutrients appears to boost muscle creatine retention considerably. Green *et al*. (1996) found that mixing 93 g of carbohydrates with 5 grams of Creatine monohydrate (CM) enhanced total muscle creatine by 60% [70]. Similarly, Steenge *et al*., (2000) proposed that adding 47 g of carbohydrate and 50 g of protein to CM was as effective as adding 96 g of carbohydrate in boosting creatine levels [83]. Another study speculated that adding dextrose to the mix increased creatine levels [84]. Overall, it appears that the best results come from combining creatine monohydrate with carbohydrates or creatine with carbohydrates and proteins [49, 85, 86]. A large number of scientific researches have found no favorable results after using the drug to improve athletic performance. Insufficient statistical power, high variability in initial creatine values, athletic performance testing tests may be unreliable, athletic performance testing tests may be incorrect, the effect of the substance is too weak to detect, and the substance does not "manage" to increase creatine levels are all possible reasons why creatine administration does not always produce positive results in research.

4.4.1 Creatine Myths

To date, there are a few "myths" about the effect of creatine on athletic performance:

- Water retention is the cause of the total body weight gain during its administration.
- It puts a load on the kidneys when taken.
- It causes cramping, dehydration, and electrolyte imbalance when consumed.
- The long-term consequences of its administration are unknown.

Newer creatine formulations are more helpful and have fewer adverse effects than CM [49]. Despite the fact that creatine has been recognized by the international scientific community as a safe and useful ergogenic aid to athletic performance, there are still a lot of misconceptions about how to use it. For example, there is no scientific data that suggests that taking CM for a short or long period of time has any negative impact on healthy people. Despite the fact that the aforementioned beliefs have been debunked by scientific research, the public is nevertheless exposed to the media's perspectives, which may or may not be factual [87].

4.5 Side effects and safety

While weight gain is the only clinically significant side effect reported in the research literature, many anecdotal reports of side effects, such as dehydration, cramps, kidney and liver damage, musculoskeletal injury, and persistent gastrointestinal media and non-scientific reports have been made. Despite the fact that creatine athletes are more likely to have some of these symptoms, scientific evidence suggests that they are not at substantial risk. The risks of side effects are extremely low. Specifically, during the charging period, there have been reports of minor gastrointestinal pain (the most common consequence), increased body mass (due to water retention in the muscle cell due to osmotic shifts), and decreased urine volume. Overall, no significant adverse events have been reported when using the lowest ergogenic doses (up to 30 g/day) for up to 5 years. Its use in sports is deemed safe and legal [49].

4.6 Administration Protocols and Recommendations

- A typical administration protocol includes a charging phase of 20 g CM/day or 0.3 g CM/kg BW/day divided into four daily 5 g intakes, followed by a maintenance phase of 3-5 g CM/day or 0.03 g CM/kg BW/day for the duration of the administration.
- A 5-day charging protocol with 20 g CM in 1 g doses (even if taken at 30-minute intervals) may be a better way to achieve maximum intramuscular creatine replenishment (+13 percent compared to the standard protocol of 4x5 g/day for 5 days). This method (multiple low doses throughout the day) could lead to a significant increase in weight gain.
- A single dose of 3-6 g or 0.03-0.1 g/kg BW/day is also used, though this method takes longer to produce an ergogenic effect (21-28 days).
- Consuming 0.3 g/kg BW/day for 3-7 days followed by 3-5 g/day for the remaining weeks is perhaps the quickest way to increase muscle creatine stores. Lower doses of creatine monohydrate (e.g. 0.2–0.3 g/kg BW/day) will increase muscle creatine reserves after 3–4 weeks, but the performance benefits are less comprehensive.
- Adding carbohydrates or a combination of carbohydrates and proteins to creatine administration improves muscle reserves, but the effect on performance does not appear to be superior than CM alone [49].
- The athlete must maintain a healthy lifestyle (adequate physical rest, hydration, proper nutrition, etc.).

5. Conclusions

HMB has been proven to affect the strength and lean muscle mass by working largely as an anti-catabolic agent, decreasing muscle breakdown and degradation of muscle proteins after training. Furthermore, for the human body to gain muscle mass, the rate of protein synthesis must be greater than the rate of protein degradation. By reducing the rate of protein degradation, HMB appears to create favorable conditions for muscle growth after training. In addition, HMB may be more effective in high-level athletes when combined with creatine and an amino acid-carbohydrate formulation. In terms of muscle absorption and the ability to boost high-intensity exercise capacity, creatine monohydrate is the most studied and therapeutically beneficial nutritional supplement. Athletes utilize creatine pills to boost their creatine storage and improve their performance. Creatine is not a magic bullet for athletic achievement, but it can help active athletes improve their training in the same way as carbohydrate consumption (charging), energy drinks, and/or charging with carbohydrates can help endurance athletes improve their performance. A combination of 3–10 g/day of CM plus 3 g/day of HMB, for 1–6 weeks had potential positive effects on strength and anaerobic performance, as well as increasing fat-free mass and decreasing fat mass for 4 weeks [88].

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7. References

1. Burke L, Deakin V. Clinical Sports Nutrition, 3rd edition. McGraw Hill, Sydney, Australia, 2006.
2. Spriet LL, Perry CG, Talanian JL. Legal pre-event nutritional supplements to assist energy metabolism. Essays in Biochemistry. 2008;44:27-43.
3. Tambalis K. Nutritional support for athletes (Ergogenic Supplements). Carpe Librum, Athens, Greece, 2016.
4. Brody T. Nutritional Biochemistry, 2nd edition. Academic Press, California, USA, 1999.
5. Kamei Y, Hatazawa Y, Uchitomi R, Yoshimura R, Miura S. Regulation of Skeletal Muscle Function by Amino Acids. Nutrients. 2020;12(1):261.
6. Wilson GJ, Wilson JM, Manninen AH. Effects of beta-hydroxy-betamethylbutyrate (HMB) on exercise performance and body composition across varying levels of age, sex, and training experience: a review. Nutr Metab (Lond). 2008;5:1.
7. Wilson JM, Kim JS, Lee SR, Rathmacher JA, Dalmau B, Kingsley JD, *et al*. Acute and timing effects of beta-hydroxy-beta-methylbutyrate (HMB) on indirect markers of skeletal muscle damage. Nutr Metab (Lond). 2009;6:6.
8. Portal S, Zadik Z, Rabinowitz J, Pilz-Burstein R, Adler-Portal D, Meckel Y, *et al*. The effect of HMB supplementation on body composition, fitness, hormonal and inflammatory mediators in elite adolescent volleyball players: a prospective randomized, double-blind, placebo-controlled study. Eur J Appl Physiol. 2011;111:2261-2269.
9. Kaczka P, Michalczyk MM, Jastrząb R, Gawelczyk M, Kubicka K. Mechanism of Action and the Effect of Beta-Hydroxy-Beta-Methylbutyrate (HMB) Supplementation on Different Types of Physical Performance - A Systematic Review. J Hum Kinet, 2019;68:211-222.
10. Bemben MG, Lamont HS. Creatine supplementation and exercise performance: recent findings. Sports Med. 2005;35(2):107-125.
11. Bird SP. Creatine supplementation and exercise performance: a brief review. J Sports Sci Med. 2003;2(4):123-132.
12. Jowko E, Ostaszewski P, Jank M, Sacharuk J, Zieniewicz A, Wilczak J, *et al*. Creatine and beta-hydroxy-beta-methylbutyrate (HMB) additively increase lean body mass and muscle strength during a weight-training program. Nutrition. 2001;17:558-566.
13. Stout J, Eckerson J, Ebersole K, Moore G, Perry S, Housh T, *et al*. Effect of creatine loading on neuromuscular fatigue threshold. J Appl Physiol. 1985-2000;88(1):109-112.

14. Albert FJ, Morente-Sánchez J, Ortega FB, Castillo MJ, Gutiérrez Á. Usefulness of B-Hydroxy-B-Methylbutyrate (HMB) Supplementation In Different Sports: An Update and Practical Implications. Nutr Hosp. 2015;32(1):20-33.
15. Vukovich MD, Slater G, Macchi MB, Turner MJ, Fallon K, Boston T, *et al*. beta-hydroxy-beta-methylbutyrate (HMB) kinetics and the influence of glucose ingestion in humans. J Nutr Biochem. 2001;12(11):631-639.
16. Wilson JM, Lowery RP, Joy JM, Walters JA, Baier SM, Fuller JC Jr, *et al*. β-Hydroxy-β-methylbutyrate free acid reduces markers of exercise-induced muscle damage and improves recovery in resistance-trained men. Br J Nutr. 2013;110(3):538-544.
17. Wilson JM, Fitschen PJ, Campbell B, Wilson GJ, Zanchi N, Taylor L, *et al*. International Society of Sports Nutrition Position Stand: beta-hydroxy-beta-methylbutyrate (HMB). J Int Soc Sports Nutr. 2013;10(1):6.
18. Kreider RB. Dietary supplements and the promotion of muscle growth with resistance exercise. Sports Med. 1999;27(2):97-110.
19. Kreider RB. Effects of creatine supplementation on performance and training adaptations. Mol Cell Biochem. 2003;244:89-94.
20. Branch J. Effect of creatine supplementation on body composition and performance: a meta-analysis. Int J Sport Nutr Exerc Metab. 2003;13:198-226.
21. Clarkson PM, Hubal MJ. Exercise-induced muscle damage in humans. Am J Phys Med Rehabil. 2002;81:S52-S69.
22. Ahtiainen JP, Pakarinen A, Alen M, Kraemer WJ, Hakkinen K. Muscle hypertrophy, hormonal adaptations and strength development during strength training in strength-trained and untrained men. Eur J Appl Physiol. 2003;89:555-563.
23. Kraemer WJ, Hatfield DL, Volek JS, Fragala MS, Vingren JL, Anderson JM, *et al*. Effects of amino acids supplement on physiological adaptations to resistance training. Med Sci Sports Exerc. 2009;41:1111-1121.
24. Nissen S, Sharp R, Ray M, Rathmacher JA, Rice D, Fuller JC Jr, *et al*. Effect of leucine metabolite beta-hydroxy-betamethylbutyrate on muscle metabolism during resistance-exercise training. J Appl Physiol. 1996;81:2095-2104.
25. Wilson JM, Lowery RP, Joy JM, Andersen JC, Wilson SM, Stout JR, *et al*. The effects of 12 weeks of beta-hydroxy-beta-methylbutyrate free acid supplementation on muscle mass, strength, and power in resistance-trained individuals: a randomized, double-blind, placebo-controlled study. Eur J Appl Physiol. 2014;114(6):1217-27.
26. Lowery RP, Joy JM, Rathmacher JA, Baier SM, Fuller JC Jr, Shelley MC, *et al*. Interaction of Beta-Hydroxy-Beta-Methylbutyrate Free Acid and Adenosine Triphosphate on Muscle Mass, Strength, and Power in Resistance Trained Individuals. J Strength Cond Res. 2016;30(7):1843-54.
27. Howatson G, Hoad M, Goodall S, Tallent J, Bell PG, French DN. Exercise induced muscle damage is reduced in resistance-trained males by branched chain amino acids: a randomized, double-blind, placebo controlled study. J Int Soc Sports Nutr. 2012;9:20.
28. Jowko E, Ostaszewski P, Jank M, Sacharuk J, Zieniewicz A, Wilczak J, *et al*. Creatine and beta-hydroxy-beta-methylbutyrate (HMB) additively increase lean body mass and muscle strength during a weight-training program. Nutrition. 2001;17:558-566.
29. Bruckbauer A, Zemel MB, Thorpe T, Akula MR, Stuckey AC, Osborne D, *et al*. Synergistic effects of leucine and resveratrol on insulin sensitivity and fat metabolism in adipocytes and mice. Nutr Metab. 2012;9:77.
30. Gallagher PM, Carrithers JA, Godard MP, Schulze KE, Trappe SW. Betahydroxy-beta-methylbutyrate ingestion, part I: effects on strength and fat free mass. Med Sci Sports Exerc. 2000;32:2109-2115.
31. Vukovich M, Dreifort G. Effect of β-Hydroxy β-Methylbutyrate on the Onset of Blood Lactate Accumulation and O2peak in Endurance-Trained Cyclists. J Strength Cond Res. 2001;15:491-497.
32. Wilson GJ, Layman DK, Moulton CJ, Norton LE, Anthony TG, Proud CG, *et al*. Leucine or carbohydrate supplementation reduces AMPK and eEF2 phosphorylation and extends postprandial muscle protein synthesis and rats. Am J Physiol Endocrinol Metab. 2011;301(6):E1236–E1242.
33. Nissen S, Sharp RL, Panton L, Vukovich M, Trappe S, Fuller JC Jr. beta-hydroxy-beta-methylbutyrate (HMB) supplementation in humans is safe and may decrease cardiovascular risk factors. J Nutr. 2000;130(8):1937-1945.
34. Hunga W, Liub T-H, Chenc C-Y, Chang C-K. Effect of [b]-hydroxy-[b]-methylbutyrate Supplementation During Energy Restriction in Female Judo Athletes. J Exerc Sci Fitness. 2010;8:50-53.
35. Zadik Z, Nemet D, Eliakim A. Hormonal and metabolic effects of nutrition in athletes. J Pediatr Endocrinol Metab. 2009;22(9):769-778.
36. Portal S, Zadik Z, Rabinowitz J, Pilz-Burstein R, Adler-Portal D, Meckel Y, *et al*. The effect of HMB supplementation on body composition, fitness, hormonal and inflammatory mediators in elite adolescent volleyball players: a prospective randomized, double-blind, placebo-controlled study. Eur J Appl Physiol. 2011;111:2261-2269.
37. Nemet D, Eliakim A. Banned performance enhancing ergogenic aids in children and adolescent athletes. Harefuah. 2007;146(10):794-799.
38. Jakubowski JS, Nunes EA, Teixeira FJ, Vescio V, Morton RW, Banfield L, *et al*. Supplementation with the Leucine Metabolite β-hydroxy-β-methylbutyrate (HMB) does not Improve Resistance Exercise-Induced Changes in Body Composition or Strength in Young Subjects: A Systematic Review and Meta-Analysis. Nutrients. 2020;12(5):1523.
39. Flakoll P, Sharp R, Baier S, Levenhagen D, Carr C, Nissen S. Effect of betahydroxy-beta-methylbutyrate, arginine, and lysine supplementation on strength, functionality, body composition, and protein metabolism in elderly women. Nutrition. 2004;20:445-451.
40. Baier S, Johannsen D, Abumrad N, Rathmacher JA, Nissen S, Flakoll P. Yearlong changes in protein metabolism in elderly men and women supplemented with a nutrition cocktail of beta-hydroxy-

betamethylbutyrate (HMB), L-arginine, and L-lysine. JPEN J Parenteral Enteral Nutr. 2009;33:71-82.
41. Fitschen PJ, Wilson GJ, Wilson JM, Wilund KR. Efficacy of beta-hydroxybeta-methylbutyrate supplementation in elderly and clinical populations. Nutrition. 2013;29(1):29-36.
42. Lin Z, Zhao Y, Chen Q. Effects of oral administration of β-hydroxy β-methylbutyrate on lean body mass in older adults: a systematic review and meta-analysis. Eur Geriatr Med. 2021;12(2):239-251.
43. Rathmacher JA, Nissen S, Panton L, Clark RH, Eubanks May P, Barber AE, *et al*. Supplementation with a combination of beta-hydroxy-beta-methylbutyrate (HMB), arginine, and glutamine is safe and could improve hematological parameters. JPEN J Parenter Enteral Nutr. 2004;28(2):65-75.
44. LaBotz M, Smith BW. Creatine supplement use in an NCAA Division I athletic program. Clin J Sport Med. 1999;9(3):167-169.
45. Ray TR, Eck JC, Covington LA, Murphy RB, Williams R, Knudtson J. Use of oral creatine as an ergogenic aid for increased sports performance: perceptions of adolescent athletes. South Med J. 2001;94(6):608-612.
46. American College of Sports Medicine. Advanced Exercise Physiology. Lippinkott Williams & Wilkins. Philadelphia, USA, 2006.
47. Clark JF. Creatine and phosphocreatine: a review of their use in exercise and sport. J Athl Train. 1997;32(1):45-51.
48. Cooper R, Naclerio F, Allgrove J, Jimenez A. Creatine supplementation with specific view to exercise/sports performance: an update. Journal of the International Society of Sports Nutrition. 2012;9:33.
49. Kreider RB, Kalman DS, Antonio J, Ziegenfuss TN, Wildman R, Collins R, *et al*. International Society of Sports Nutrition position stand: safety and efficacy of creatine supplementation in exercise, sport, and medicine. J Int Soc Sports Nutr. 2017;14:18.
50. Snow RJ, Murphy RM. Creatine and the creatine transporter: a review. Mol Cell Biochem. 2001;224:169-181.
51. Snow RJ, Murphy RM. Factors influencing creatine loading into human skeletal muscle. Exerc Sport Sci Rev. 2003;31:154-158.
52. Branch J. Effect of creatine supplementation on body composition and performance: a meta-analysis. Int J Sport Nutr Exerc Metab. 2003;13:198-226.
53. Greenhaff PL, Bodin K, Soderlund K, Hultman E. Effect of oral creatine supplementation on skeletal muscle phosphocreatine resynthesis. Am J Physiol. 1994;266:725-730.
54. Greenhaff P, Casey A, Green AL. Creatine supplementation revisited: An update. Insider. 1996;4:1-2.
55. Kreider RB. Creatine in Sports. Essentials of Sport Nutrition & Supplements. Humana Press Inc. Totowa, NJ, USA, 2007.
56. Volek JS, Rawson ES. Scientific basis and practical aspects of creatine supplementation for athletes. Nutrition. 2004;20(7-8):609-614.
57. Hespel P, Derave W: Ergogenic effects of creatine in sports and rehabilitation. Subcell Biochem. 2007;46:245-259.
58. Beck TW, Housh TJ, Johnson GO, Coburn DW, Malek MH, Cramer JT. Effects of a drink containing creatine, amino acids, and protein, combined with ten weeks of resistance training on body composition, strength, and anaerobic performance. J Strength Cond Res. 2007;21:100-104.
59. Carter JM, Bemben DA, Knehans AW, Bemben MG, Witten MS. Does nutritional supplementation influence adaptability of muscle to resistance training in men aged 48 to 72 years? J Geriatric Phys Therapy. 2005;28(2):40-47.
60. Chromiak JA, Smedley B, Carpenter W, Brown R, Koh YS, Lamberth JG, *et al*. Effect of a 10-week strength training program and recovery drink on body composition, muscular strength and endurance, and anaerobic power and capacity. Nutrition. 2004;20:420-427.
61. Deldicque L, Atherton P, Patel R, Theisen D, Nielens H, Rennie M, *et al*. Effects of resistance exercise with and without creatine supplementation on gene expression and cell signaling in human skeletal muscle. J Appl Physiol. 2008;104:371-378.
62. Bemben MG, Lamont HS. Creatine supplementation and exercise performance: recent findings. Sports Med, 2005;35(2):107-125.
63. Bird SP. Creatine supplementation and exercise performance: a brief review. J Sports Sci Med. 2003;2(4):123-132.
64. Chwalbiñska-Moneta J. Effect of creatine supplementation on aerobic performance and anaerobic capacity in elite rowers in the course of endurance training. Int J Sport Nutr Exerc Metab, 2003;13(2):173-183.
65. Burke DG, Chilibeck PD, Parise G, Candow DG, Mahoney D, Tarnopolsky M. Effect of creatine and weight training on muscle creatine and performance in vegetarians. Medicine and science in sports and exercise. 2011;35(11):1946-1955.
66. Farshidfar F, Pinder MA, Myrie SB. Creatine Supplementation and Skeletal Muscle Metabolism for Building Muscle Mass- Review of the Potential Mechanisms of Action. Curr Protein Pept Sci. 2017;18(12):1273-1287.
67. Gibala MJ. Nutritional supplementation and resistance exercise: what is the evidence for enhanced skeletal muscle hypertrophy? Can J Appl Physiol. 2000;25(6):524-535.
68. Valenzuela PL, Morales JS, Emanuele E, Pareja-Galeano H, Lucia A. Supplements with purported effects on muscle mass and strength. Eur J Nutr. 2019;58(8):2983-3008.
69. Wax B, Kerksick CM, Jagim AR, Mayo JJ, Lyons BC, Kreider RB. Creatine for Exercise and Sports Performance, with Recovery Considerations for Healthy Populations. Nutrients. 2021;13(6):1915.
70. Green AL, Hultman E, Macdonald IA, Sewell DA, Greenhaff PL. Carbohydrate ingestion augments skeletal muscle creatine accumulation during creatine supplementation in humans. Am J Physiol. 1996;271:821-826.
71. Sewell D, Robinson T, Greenhaff P. Creatine supplementation does not affect human skeletal muscle glycogen content in the absence of prior exercise. J Appl Physiol, 2008;104:508-512.

72. Hickner R, Dyck D, Sklar J, Hatley H, Byrd P. Effect of 28 days of creatine ingestion on muscle metabolism and performance of a simulated cycling road race. J Int Soc Sports Nutr. 2010;7:26.
73. Clarke H, Hickner RC, Ormsbee MJ. The Potential Role of Creatine in Vascular Health. Nutrients. 2021;13(3):857.
74. Smith RN, Agharkar AS, Gonzales EB. A review of creatine supplementation in age-related diseases: more than a supplement for athletes. F1000Res. 2014;3:222.
75. Fernández-Landa J, Calleja-González J, León-Guereño P, Caballero-García A, Córdova A, Mielgo-Ayuso J. Effect of the Combination of Creatine Monohydrate Plus HMB Supplementation on Sports Performance, Body Composition, Markers of Muscle Damage and Hormone Status: A Systematic Review. Nutrients. 2019; 11(10): 2528.
76. Smith-Ryan AE, Cabre HE, Eckerson JM, Candow DG. Creatine Supplementation in Women's Health: A Lifespan Perspective. Nutrients. 2021;13(3):877.
77. Moon A, Heywood L, Rutherford S, Cobbold C. Creatine supplementation: can it improve quality of life in the elderly without associated resistance training? Curr Aging Sci. 2013;6(3):251-257.
78. Unnithan VB, Veehof SH, Vella CA, Kern M. Is there a physiologic basis for creatine use in children and adolescents? J Strength Cond Res. 2001;15:524–528.
79. Evans MW, Ndetan H, Perko M, Williams R, Walker C. Dietary supplement use by children and adolescents in the United States to Enhance sport performance: results of the national health interview survey. J Prim Prev. 2012;33:3-12.
80. Metzl JD, Small E, Levine SR, Gershel JC. Creatine use among young athletes. Pediatrics. 2001;108:421-425.
81. Syrotuik DG, Bell GJ. Acute creatine monohydrate supplementation: a descriptive physiological profile of responders vs. nonresponders. J Strength Cond Res. 2004;18:610-617.
82. Chilibeck PD, Stride D, Farthing JP, Burke DG. Effect of creatine ingestion after exercise on muscle thickness in males and females. Med Sci Sports Exerc. 2004;36(10):1781-1788.
83. Steenge GR, Simpson EJ, Greenhaff PL. Protein- and carbohydrate-induced augmentation of whole body creatine retention in humans. J Appl Physiol. 2000;89:1165-1171.
84. Greenwood M, Kreider R, Earnest C, Rassmussen C, Almada A. Differences in creatine retention among three nutritional formulations of oral creatine supplements. J Exerc Physiol Online. 2003;6:37-43.
85. Jäger R, Purpura M, Shao A, Inoue T, Kreider RB. Analysis of the efficacy, safety, and regulatory status of novel forms of creatine. Amino Acids. 2011;40(5):1369-1383.
86. Jowko E, Ostaszewski P, Jank M, Sacharuk J, Zieniewicz A, Wilczak J, *et al*. Creatine and beta-hydroxy-beta-methylbutyrate (HMB) additively increase lean body mass and muscle strength during a weight-training program. Nutrition. 2001;17:558-566.
87. Buford TW, Kreider RB, Stout JR, Greenwood M, Campbell B, Spano M, *et al*. International Society of Sports Nutrition position stand: creatine supplementation and exercise. J Int Soc Sports Nutr. 2007;4:6.
88. Fernández-Landa J, Calleja-González J, León-Guereño P, Caballero-García A, Córdova A, Mielgo-Ayuso J. Effect of the Combination of Creatine Monohydrate Plus HMB Supplementation on Sports Performance, Body Composition, Markers of Muscle Damage and Hormone Status: A Systematic Review. Nutrients. 2019;11(10):2528.