The Effects of β-Hydroxy-β-Methylbutyrate (HMB) and HMB/Creatine Supplementation on Indices of Health in Highly Trained Athletes

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This study aimed to investigate the effects of 6 wk oral supplementation of β-hydroxy-β-methylbutyrate (HMB) and HMB combined with creatine monohydrate (HMBCr) on indices of health in highly trained athletes. Elite, male rugby league players (n = 28) were allocated to 1 of 3 groups: a control group (n = 6), a HMB group (3 g/d; n = 11), or a HMBCr group (3 g/day HMB, 3 g/d Cr; n = 11). Testing prior to, and immediately following, supplementation included a full blood count, plasma testosterone and cortisol, blood electrolytes, lipids, urea and glucose, sperm count and motility, and assessment of psychological state. A 3 × 2 factorial ANOVA revealed no effect of HMB or HMBCr on any of the measured parameters except minor changes in blood bicarbonate and blood monocyte and lymphocyte counts. Blood bicarbonate was significantly decreased in the HMB post-supplementation sample compared to the control and HMBCr groups. Blood monocyte and lymphocyte counts showed no within-group changes for HMB or HMBCr supplementation but were significantly different from the control. However, the majority of these readings remained within normal range. HMB and HMBCr were concluded to have no adverse effects on the parameters evaluated in this study when taken orally by highly trained male athletes over a 6-wk period.

Key Words: supplements, ergogenic, health, rugby league

Introduction

It has been suggested that β-hydroxy-β-methylbutyrate (HMB), a metabolic derivative of the amino acid leucine, acts as an anticitabolic agent to enhance recovery from exercise (20). A small number of human studies have shown significantly greater strength increases in trained and untrained subjects consuming HMB compared to a placebo (19–21). However, the ergogenic benefits of HMB are equivocal, as a number of studies have reported no effect of HMB on strength (8, 14, 22). Given that sales of HMB in the United States alone reached $50–60 million in 1998 (27), HMB appears to be widely used. It is therefore important to examine the possibility of adverse effects from this supplement.

Nissen et al. (18) performed a meta-analysis on nine studies in which subjects consumed 3 g/d HMB for periods of 3–8 wk. Blood biochemistry and hematological indices were evaluated with no negative effects found. Furthermore, Gallagher et al.
showed no harmful effects of 76 mg/kg body weight dose of HMB (approximately equal to 6 g/d) over 8 wk on hematological, hepatic, and renal function in untrained subjects. Another study investigating the effects of HMB on health reported no negative effects of 3 g/d HMB in 6 active subjects over a 14-d period evaluated by a daily illness log recorded by the subjects (28). Very few studies have examined psychological health during HMB supplementation. However, the meta-analysis performed by Nissen et al. (18) reported no negative effects on the emotional profile of subjects consuming HMB for periods up to 8 wk. Indeed, the Nissen et al. (18) study reported a decrease in negative mood after HMB supplementation as evaluated by the Circumplex Model of Affect. Given the scarcity of literature available, there is a clear need for further studies into the effects of HMB on both physical and psychological health.

The mechanism underlying the proposed ergogenic effects of HMB remains unclear. HMB has been reported to have no effect on urine levels of the anabolic hormone, testosterone, after 14 d supplementation (28). However, the majority of research has been aimed at establishing HMB as an anticatabolic agent rather than an anabolic agent. In support of the anticatabolic hypothesis, markers of muscle damage, including creatine phosphokinase and lactate dehydrogenase, were reduced after HMB supplementation (13). However, the cause of this reduction in catabolic markers has not been established. One possible anticatabolic effect could be a decrease in the catabolic hormone, cortisol. However, to date there have been no reported investigations into the effects of HMB on plasma cortisol levels. Other hypotheses include an increase in cholesterol synthesis as a result of HMB supplementation and the possibility that HMB acts as a structural component of cell membranes (20). These hypotheses require investigation.

Creatine monohydrate (Cr) is another popular dietary supplement about which controversy exists. Oral supplementation with Cr has been shown to increase the amount of free Cr and creatine phosphate stored in the muscle (2, 11). Thus, a greater availability of creatine phosphate will facilitate greater work and greater gains in muscle size and strength (6, 15, 29). Past studies have examined the effects of loading doses (20–25 g/d) for up to 14 d or maintenance doses (2–5 g/d) supplemented over periods of up to 10 wk, with very few Cr studies examining longer-term supplementation (2, 24).

There have been a number of anecdotal reports of negative side effects associated with the use of Cr, but few well-controlled studies exist to support or refute these claims (for review, see 24). However, two recent studies have investigated the effects of Cr supplementation on the health of athletes (26, 30). One retrospective study evaluated serum enzymes and hormones and the incidence of past side effects in active athletes, including 7 controls and 19 athletes who had regularly taken Cr for up to 4 yr (26). There was no significant difference in liver enzyme levels, testosterone, cortisol, or human growth hormone levels or in the incidence of past side effects between the two groups. The authors concluded that long-term Cr supplementation did not result in adverse health effects. The second study examined hepatic stress in 8 nationally competitive athletes who consumed a loading dose of Cr for 5 d followed by a 5-wk maintenance dose whilst weight training (30). All measured parameters, including serum liver enzyme levels, did not change significantly with Cr supplementation and remained within normal clinical range.

Although HMB and Cr are often supplemented together, few studies have examined the combined effects of these supplements. One of the few studies in this area compared 3 wk supplementation with Cr, HMB, or HMB combined with Cr
This study did not specifically investigate indices of health but reported that urine and blood urea levels were unchanged with HMB combined with Cr and with Cr alone but were significantly lowered with HMB. The authors concluded that protein turnover was decreased with HMB supplementation alone. However, blood urea may also provide an indirect measure of liver function indicating no negative effects of HMB combined with Cr.

As few studies have examined whether HMB has any adverse health effects in highly trained athletes, the current study aimed to investigate oral HMB supplementation in this population. In an attempt to elucidate the mechanism by which HMB works, plasma testosterone and cortisol were also measured. As HMB is often sold as a mixture with Cr, and little is known about the health effects of combining these two supplements, this study also investigated the effects of supplementing HMB in combination with Cr. A 6-wk supplementation period was chosen to allow comparison with past HMB and Cr maintenance dose studies. Therefore, this study examined the effects of 6 wk supplementation of HMB (3 g/d) and HMBCr (3 g/d HMB + 3 g/d Cr) on hematology, blood biochemistry, hormone levels, psychological mood and affect, and fertility in a group of highly trained, male athletes undergoing a weight training program. It was expected that these doses of HMB and HMBCr would have no negative effects on these parameters.

**Methods**

**Subjects**

The participants in this study were 28 male subjects recruited from an Australian National Rugby League team. The average (±SE) age, body weight, and percent body fat (25) of the subjects was 24.9 ± 0.7 yr (range, 18–32 yr), 94.8 ± 1.6 kg (range, 74.0–116.8 kg), and 13.8 ± 0.7%, respectively. All subjects had been playing Rugby League (competitive at a national or state level) for at least 2 yr prior to the study. The subjects were all familiar with the weight training techniques used and had been participating in a regular weight training program for at least 4 yr. All subjects were asked to avoid any other supplements and excessive consumption of caffeine during the study. The subjects were given clear instructions on the procedures involved in the study and gave their written informed consent. Ethics approval for the project was granted from the James Cook University Ethics Committee.

**Procedure**

A repeated measures design was employed, where subjects underwent baseline testing followed by a 6-wk supplementation period at the end of which the baseline tests were repeated. All subjects underwent the same strength and conditioning program throughout the 6-wk supplementation period. This minimized differences in variables such as training intensity, duration, volume, and frequency. The training program consisted of three total body weight-training sessions and one speed/power session per week. This was supplemented by four skills and/or conditioning sessions per week. All training sessions were fully supervised, and loads were determined for each subject for every weight session. Weight sessions were periodized for strength (2–6 reps) and consisted of 25–30 sets per session at an intensity of 80–95% 1RM. This study was performed in conjunction with other investigations of
strength, power, body composition, and aerobic and anaerobic power responses to HMB and HMBCr.

Due to ethical and religious reasons, some of the athletes declined to be included in a supplement group. Thus, it was not possible to employ a double-blind protocol. Those subjects who declined to take a supplement were included in the control group \((n = 6)\), and the remaining subjects were allocated to one of two supplement groups. The subjects in the supplement groups were unaware of whether they were taking HMB (3 g/d of the calcium salt of HMB; Quality of Life Products, Adelaide, Australia; \(n = 11\)) or a HMB/creatine monohydrate mix (12 g/d of HMBCr composed of 3 g calcium-HMB, 3 g Cr, and 6 g carbohydrates; Quality of Life Products, Adelaide, Australia; \(n = 11\)). Although Quality of Life Products guarantees the purity of its products, the supplements utilized in this study were not independently evaluated for purity of composition. Since the subjects were not blinded as to groupings, the control group \((n = 6)\) did not receive a placebo. The HMB subjects received daily doses of HMB or HMBCr as a powder, which they were instructed to dissolve in juice or sports drink and consume in the morning. Compliance with taking the supplement was verbally confirmed with all subjects on each training day.

**Blood Sampling.** A qualified technician from a commercial pathology laboratory obtained two 5-ml venipuncture blood samples prior to, and at the completion of, the 6-wk supplementation period. To minimize any effects of training on the measured parameters, the samples were taken on a rest day from training at least 12 hours after the last exercise session. All subjects reported to the pathology laboratory for pre- and post-supplementation testing at the same time of day, between 9 AM and 12 noon on the rest day.

**Hematology and Blood Biochemistry.** The commercial laboratory performed all blood analysis. The following blood biochemistry parameters were assessed using the Beckman Coulter CX7 (Beckman Coulter, Sydney, Australia): potassium, sodium, chloride, bicarbonate, and anion gap (5). The Beckman Coulter CX5 and CX7 were used to assess blood urea, creatine phosphokinase, glucose, total cholesterol, high-density lipoproteins (HDL), low-density lipoproteins (LDL), and very low–density lipoproteins (VLDL; 5). The HDL:LDL cholesterol ratio was determined according to the following formulas: HDL cholesterol = total cholesterol − HDL − (0.45 × triglycerides) and LDL cholesterol = 0.45 × triglycerides (5). The hematological parameters including hemoglobin, red and white blood cell numbers, packed cell volume (PCV), mean cell volume (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), and neutrophil, lymphocyte, monocyte, and platelet numbers were assessed using the Beckman Coulter MaxM (Beckman Coulter, Sydney, Australia). The MaxM uses the same protocols as the Coulter STKS (4).

**Hormone Analysis.** Hormone levels were assayed by the commercial pathology laboratory. Plasma testosterone levels were analyzed using the Abbott Architect methodology (Abbott Diagnostics Division, Sydney, Australia). Plasma cortisol levels were assessed using the Abbott TDX methodology (Abbott Diagnostics Division, Sydney, Australia).

**Fertility.** Sperm count and sperm motility were assessed as an indicator of fertility. The subjects were given a sterile plastic vial and asked to provide a semen
sample at home and deliver it to the commercial laboratory for testing within 1 hour. The samples were analyzed for sperm count and motility using a manual count with the Makler counting chamber (Sefi-Medical Instruments, Haifa, Israel). Due to ethical and privacy reasons, it was deemed unnecessary to obtain a semen sample from the control subjects.

**Psychological Profile.** Subjects completed the Symptom Checklist-90-R (SCL-90-R) both prior to and following the supplementation period. The SCL-90-R is a 90-item self-report inventory designed to identify psychological and somatic symptomology (7). The inventory is scored on nine primary symptom dimensions and three global indicators. The symptom dimensions include Interpersonal Sensitivity, Obsessive-Compulsive, Somatization, Depression, Hostility, Anxiety, Phobic Anxiety, Paranoic Ideation, and Psychoticism. The three global indicators include Global Severity Index, Positive Symptom Total, and Positive Symptom Distress Index. The SLR-90-R is a valid measure as both a screening device and an outcome measure in clinical and research contexts. The appropriateness of the measure in pharmacotherapeutic drug trials revealed the sensitivity of the instrument to detect therapeutic change (7).

**Statistical Analyses**

All data were analyzed using a 2 × 3 (time × group) factorial analysis of variance with repeated measures for time using the SPSS for Windows version 9.0 software. The alpha level was set at \( p < .05 \). When less than five values were available for analysis, comparisons were made using the non-parametric Kruskal-Wallis test. Values found to be significantly different underwent post hoc analysis using the Tukey test. All data are presented as mean ± standard error (SE).

**Results**

The groups were well matched for age and body weight with no significant differences in these two parameters among the three groups prior to supplementation (\( p > .05 \)).

HMB and HMBCr supplementation had no significant effect on the blood levels of glucose, urea, triglycerides, or lipids when compared to pre-supplementation levels (\( p > .05 \); see Table 1). Furthermore, there was no significant difference in these parameters for the HMB and HMBCr groups when compared to the control group (\( p > .05 \)). Supplementation with either HMB or HMBCr had no effect on blood CK levels. However, CK levels were significantly higher in the control group compared to the HMB and HMBCr groups at pre-supplementation, which was maintained post-supplementation (\( p < .05 \); see Table 1). The mean blood CK level for the control group was skewed by an outlier, with 1 subject having an average blood CK level of 2782 units/L. When the data from this outlier was discarded and the data re-analyzed using the Kruskal-Wallis test, there were no significant differences among the three groups (\( p > .05 \); control pre-supplementation CK 484.5 ± 210.3 units/L, post-supplementation CK 950.0 ± 104.8 units/L without outlier).

Blood electrolytes remained unchanged after HMB or HMBCr supplementation (\( p > .05 \); see Table 2) with the exception of the blood bicarbonate levels (\( p < .05 \)). Post hoc analysis revealed that the blood bicarbonate levels significantly decreased in the HMB group from pre- to post-supplementation (\( p < .05 \)). In comparison
Table 1  Mean (±SE) Blood Glucose, Urea, Creatine Phosphokinase, and Lipids for the Control, HMB, and HMBCr Groups Pre- and Post-supplementation

<table>
<thead>
<tr>
<th>Blood parameter</th>
<th>Control</th>
<th></th>
<th></th>
<th>HMB</th>
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<th></th>
<th>HMBCr</th>
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<tr>
<td></td>
<td>Pre</td>
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<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
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<tr>
<td>Glucose (mmol/L)</td>
<td>5.20 (0.31)</td>
<td>5.00 (0.65)</td>
<td>4.87 (0.14)</td>
<td>4.97 (0.18)</td>
<td>4.96 (0.19)</td>
<td>5.24 (0.22)</td>
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<tr>
<td>Urea (mmol/L)</td>
<td>5.92 (1.00)</td>
<td>7.42 (0.78)</td>
<td>6.35 (0.29)</td>
<td>7.75 (0.32)</td>
<td>6.44 (0.35)</td>
<td>6.82 (0.35)</td>
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<tr>
<td>Creatine phosphokinase (units/L)</td>
<td>1175.6 (710.0)</td>
<td>1084.8 (157.3)</td>
<td>551.6 (82.9)</td>
<td>465.6 (67.4)</td>
<td>442.2 (95.0)</td>
<td>729.0 (117.2)</td>
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<td>Cholesterol (mmol/L)</td>
<td>4.38 (0.60)</td>
<td>4.06 (0.66)</td>
<td>4.32 (0.20)</td>
<td>4.42 (0.20)</td>
<td>4.56 (0.26)</td>
<td>4.22 (0.27)</td>
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<tr>
<td>HDL (mmol/L)</td>
<td>1.14 (0.13)</td>
<td>1.14 (0.09)</td>
<td>1.11 (0.06)</td>
<td>1.10 (0.05)</td>
<td>1.13 (0.09)</td>
<td>1.18 (0.11)</td>
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<tr>
<td>LDL (mmol/L)</td>
<td>2.92 (0.53)</td>
<td>2.64 (0.53)</td>
<td>2.96 (0.21)</td>
<td>3.02 (0.20)</td>
<td>3.17 (0.20)</td>
<td>2.77 (0.24)</td>
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<tr>
<td>VLDL (mmol/L)</td>
<td>0.32 (0.06)</td>
<td>0.28 (0.06)</td>
<td>0.23 (0.03)</td>
<td>0.29 (0.04)</td>
<td>0.26 (0.02)</td>
<td>0.27 (0.03)</td>
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<tr>
<td>LDL:LDL</td>
<td>3.94 (0.58)</td>
<td>3.48 (0.39)</td>
<td>3.99 (0.31)</td>
<td>4.10 (0.28)</td>
<td>4.14 (0.26)</td>
<td>3.72 (0.27)</td>
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<tr>
<td>Triglycerides (mmol/L)</td>
<td>1.60 (0.34)</td>
<td>1.38 (0.25)</td>
<td>1.19 (0.15)</td>
<td>1.52 (0.21)</td>
<td>1.32 (0.08)</td>
<td>1.26 (0.17)</td>
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</table>

Note. HDL = high-density lipoprotein; LDL = low-density lipoprotein; VLDL = very low-density lipoprotein.
to the control group, there were also no significant differences in the blood electrolyte levels between the HMB and HMBCr groups (p > .05) with the exception of significantly lower blood bicarbonate in the HMB group than in the control group at pre- and post-supplementation and the HMBCr group at pre-supplementation (p < .05; see Table 2).

Table 3 illustrates the hematological parameters that were unchanged after supplementation with HMB or HMBCr (p > .05). There was also no difference between the HMB and HMBCr groups compared with the control group in the hematological parameters (p > .05), with the exception of the monocyte and lymphocyte counts. Post hoc analysis revealed that the monocyte count of the HMB and HMBCr groups were significantly higher than that of the control group at post-supplementation (p < .05). The lymphocyte count of the control group at pre-supplementation was significantly higher than the control group at post-supplementation and of the HMB and HMBCr groups at both pre- and post-supplementation (p < .05). All monocyte and lymphocyte counts were within normal clinical range except the lymphocyte counts of 5 subjects (1 control and 4 HMBCr subjects) who were just below normal range.

Plasma testosterone levels were unchanged after HMB or HMBCr supplementation (HMB 13.99 ± 1.65 vs. 16.08 ± 1.90 mmol/L; HMBCr 16.18 ± 1.38 vs. 17.62 ± 1.54 mmol/L; p > .05). Further, the plasma testosterone levels of the HMB and HMBCr groups were not significantly different to those of the control group (12.82 ± 3.41 vs. 15.04 ± 2.86 mmol/L; p > .05). Similarly, cortisol levels were unchanged by HMB or HMBCr supplementation (HMB 351.5 ± 42.1 vs. 295.5 ± 20.3 mmol/L; HMBCr 296.9 ± 35.7 vs. 283.5 ± 27.3 mmol/L; p > .05) and were not significantly different from the control group (280.8 ± 40.6 vs. 295.2 ± 56.7 mmol/L; p > .05). Similarly, sperm count (HMB 55.5 ± 11.0 × 10^6/ml vs. 58.7 ± 10.2 × 10^6/ml; HMBCr 78.1 ± 12.7 × 10^6/ml vs. 71.0 ± 13.3 × 10^6/ml; p > .05) and sperm motility (HMB 67.6 ± 3.3% vs. 69.7 ± 5.0%; HMBCr 75.6 ± 2.4% vs. 71.5 ± 4.1%; p > .05) were also unchanged by HMB or HMBCr supplementation.

HMB and HMBCr had no significant effect on the SCL-90-R subscale or global measures when compared to pre-supplementation levels and compared to the control group (p > .05). The global severity index averaged 4.39 ± 6.93, 6.00 ± 1.15, and 4.13 ± 8.24 pre-supplementation and 3.84 ± 9.66, 5.33 ± 1.26, and 4.61 ± 1.27 post-supplementation for the control, HMB, and HMBCr groups, respectively. The total positive symptom averaged 25.00 ± 3.94, 37.82 ± 6.34, and 25.33 ± 7.72 pre-supplementation and 25.33 ± 7.22, 31.36 ± 6.25, and 26.27 ± 6.92 post-supplementation for the control, HMB, and HMBCr groups, respectively. The positive symptom distress index averaged 0.14 ± 1.35, 0.13 ± 7.10, and 0.12 ± 6.42 pre-supplementation and 0.12 ± 6.31, 0.13 ± 1.24, and 0.13 ± 1.26 post-supplementation for the control, HMB, and HMBCr groups, respectively.

**Discussion**

The current study showed that HMB (3 g/d) or HMBCr (3 g/d HMB + 3 g/d Cr) had no adverse effects on the hematological, fertility, or blood chemistry parameters of well-trained male subjects over a 6-wk period of resistance training.

Blood HMB and muscle Cr were not measured in the current study. However, previous studies have clearly shown that oral HMB taken at doses of 1.5, 3, or 6 g/d cause significant elevations in blood HMB levels (13, 14, 20). Similarly, oral
Table 2  Mean (±SE) Blood Electrolytes for the Control, HMB, and HMBCr Groups Pre- and Post-supplementation

<table>
<thead>
<tr>
<th>Blood electrolyte</th>
<th>Control</th>
<th></th>
<th>HMB</th>
<th></th>
<th>HMBCr</th>
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<tr>
<td></td>
<td>Pre</td>
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<tr>
<td>Potassium (mmol/L)</td>
<td>4.24 (0.07)</td>
<td>4.16 (0.15)</td>
<td>4.16 (0.08)</td>
<td>4.24 (0.07)</td>
<td>4.42 (0.11)</td>
<td>4.16 (0.05)</td>
</tr>
<tr>
<td>Sodium (mmol/L)</td>
<td>138.2 (0.9)</td>
<td>138.2 (1.1)</td>
<td>138.3 (0.6)</td>
<td>141.4 (1.0)</td>
<td>139.4 (0.4)</td>
<td>140.4 (1.1)</td>
</tr>
<tr>
<td>Chloride (mmol/L)</td>
<td>103.2 (1.2)</td>
<td>102.6 (0.6)</td>
<td>104.4 (0.4)</td>
<td>104.7 (0.6)</td>
<td>105.6 (0.6)</td>
<td>104.8 (0.6)</td>
</tr>
<tr>
<td>Bicarbonate (mmol/L)</td>
<td>27.20 (0.73)</td>
<td>28.00 (0.55)</td>
<td>27.91 (0.48)</td>
<td>24.27* (0.82)</td>
<td>27.55 (0.53)</td>
<td>26.55 (0.58)</td>
</tr>
<tr>
<td>Anion gap (mmol/L)</td>
<td>7.80 (1.62)</td>
<td>7.60 (1.36)</td>
<td>6.00 (0.19)</td>
<td>12.27 (1.53)</td>
<td>6.18 (0.50)</td>
<td>9.00 (1.24)</td>
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Note. *Significantly lower than all pre-supplementation values (p < .05). #Significantly lower than control group at post-supplementation (p < .05).
<table>
<thead>
<tr>
<th>Hematological variable</th>
<th>Control</th>
<th></th>
<th></th>
<th>HMB</th>
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<th>HMBCr</th>
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<td>Pre</td>
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<tr>
<td>Hemoglobin (g/L)</td>
<td>142.33 (1.96)</td>
<td>137.17 (2.82)</td>
<td></td>
<td>147.27 (2.07)</td>
<td>142.73 (1.89)</td>
<td></td>
<td>145.82 (2.60)</td>
<td>140.91 (1.80)</td>
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<tr>
<td>RBC ($\times 10^{12}$)</td>
<td>4.63 (0.06)</td>
<td>4.63 (0.09)</td>
<td></td>
<td>4.91 (0.08)</td>
<td>4.79 (0.07)</td>
<td></td>
<td>4.91 (0.09)</td>
<td>4.83 (0.06)</td>
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<tr>
<td>PCV (%)</td>
<td>40.8 (0.5)</td>
<td>40.5 (0.7)</td>
<td></td>
<td>42.4 (0.6)</td>
<td>41.3 (0.6)</td>
<td></td>
<td>42.0 (0.7)</td>
<td>41.3 (0.6)</td>
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<tr>
<td>MCV (fL)</td>
<td>87.67 (0.33)</td>
<td>87.83 (0.48)</td>
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<td>86.36 (0.54)</td>
<td>86.18 (0.52)</td>
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<td>85.73 (0.84)</td>
<td>85.27 (0.93)</td>
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<tr>
<td>MCH (pg)</td>
<td>30.67 (0.42)</td>
<td>29.83 (0.31)</td>
<td></td>
<td>30.09 (0.25)</td>
<td>29.64 (0.28)</td>
<td></td>
<td>29.91 (0.39)</td>
<td>26.67 (2.65)</td>
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<tr>
<td>MCHC (g/L)</td>
<td>348.33 (1.73)</td>
<td>340.17 (2.73)</td>
<td></td>
<td>348.45 (2.05)</td>
<td>345.27 (2.04)</td>
<td></td>
<td>348.00 (1.84)</td>
<td>342.73 (1.40)</td>
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<tr>
<td>Total WBC count ($\times 10^9$)</td>
<td>7.02 (0.77)</td>
<td>7.70 (0.86)</td>
<td></td>
<td>5.66 (0.33)</td>
<td>6.41 (0.31)</td>
<td></td>
<td>5.58 (0.44)</td>
<td>7.08 (0.40)</td>
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<tr>
<td>Neutrophils ($\times 10^9$)</td>
<td>4.04 (0.73)</td>
<td>5.08 (0.97)</td>
<td></td>
<td>3.18 (0.22)</td>
<td>3.86 (0.23)</td>
<td></td>
<td>3.21 (0.41)</td>
<td>4.40 (0.44)</td>
<td></td>
</tr>
<tr>
<td>Lymphocytes ($\times 10^9$)</td>
<td>2.34* (0.19)</td>
<td>2.02 (0.19)</td>
<td></td>
<td>1.76 (0.08)</td>
<td>1.87 (0.09)</td>
<td></td>
<td>1.80 (0.23)</td>
<td>1.96 (0.21)</td>
<td></td>
</tr>
<tr>
<td>Monocytes ($\times 10^9$)</td>
<td>0.50 (0.06)</td>
<td>0.44* (0.05)</td>
<td></td>
<td>0.51 (0.04)</td>
<td>0.56 (0.03)</td>
<td></td>
<td>0.46 (0.03)</td>
<td>0.56 (0.03)</td>
<td></td>
</tr>
<tr>
<td>Platelets ($\times 10^9$)</td>
<td>211.2 (6.6)</td>
<td>208.0 (7.0)</td>
<td></td>
<td>232.1 (9.5)</td>
<td>227.5 (12.6)</td>
<td></td>
<td>228.6 (9.3)</td>
<td>244.1 (9.7)</td>
<td></td>
</tr>
</tbody>
</table>

Note. RBC = red blood cell count; PVC = packed cell volume; MCV = mean cell volume; MCH = mean cell hemoglobin; MCHC = mean cell hemoglobin concentration; WBC = white blood cell. *Significantly higher than all other means ($p < .05$). #Significantly lower than HMB and HMBCr groups at post-supplementation ($p < .05$).
supplementation with 3–20 g Cr per day has been shown to increase muscle Cr levels (2, 11). As the current study utilized doses of 3 g/d HMB and 3 g/d Cr, it was assumed that blood HMB and muscle Cr levels were significantly elevated.

The exact mechanism of the proposed antecedatal effect of HMB is unknown. Nissen et al. (20) have shown that over one half of HMB ingested was metabolized in the body. This finding, combined with previous work on HMB, lead Nissen et al. (20) to hypothesize that HMB is most likely converted to β-hydroxy-β-methylglutarate-Co-A in the body, which can potentially donate carbons for cholesterol synthesis. An alternative hypothesis suggested by the Nissen et al. (20) group is that HMB functions as a structural component within tissues or membranes by polymerizing and forming covalent links with cell membrane components. If these hypotheses are correct, and post-exercise muscle repair is enhanced by HMB, then markers of muscle damage should be reduced. In support of this hypothesis, previous studies have shown lower levels of markers of cell catabolism, including 3-methylhistidine (20), lactate dehydrogenase (13), and creatine phosphokinase (13, 20) in subjects supplemented with HMB compared to a placebo. In contrast with this hypothesis, the current study found no effect of HMB on creatine phosphokinase levels. One possible reason for this contrasting finding may relate to the training background of the subjects. The current study used well-trained athletes with an extensive resistance training background. Long-term resistance training has previously been suggested to decrease muscle damage and resulting protein turnover (16, 23). Thus, the subjects in the current study may not have gained any antecedatal benefits from HMB, whereas the Nissen et al. (20) subjects, who were untrained and unaccustomed to resistance exercise, had decreased levels of muscle catabolism markers. Untrained subjects may have greater capacity to benefit from the antecedatal effects of HMB. The subjects in the Knitter et al. (13) study were endurance trained, running at least 48 km/wk. It may be that the antecedatal effects of HMB in this population function differently to those of resistance-trained athletes. The different responses of antecedatal markers to HMB require further investigation in endurance and resistance trained athletes.

The current study did not detect any significant changes in total cholesterol, triglycerides, HDL, LDL, VLDL, or the ratio of LDL to HDL after 6-wk HMB or HMBCr supplementation. This finding is in contrast to Nissen et al. (18), who reported significantly lower total cholesterol and LDL levels in response to dietary HMB supplementation. However, the significant reductions in cholesterol only occurred when the subjects were divided into subsets of high and low initial cholesterol levels (cut-off point of 5.17 mmol/L). When the subjects were subdivided into these groups, only the subjects with high initial cholesterol levels showed a significant reduction after HMB supplementation. Those with low initial values did not have significant changes in total cholesterol or LDL. Since the current study utilized healthy, highly trained athletes, their initial total cholesterol and LDL levels were 4.4 ± 0.2 mmol/L and 3.1 ± 0.1 mmol/L, respectively. As with the Nissen et al. (18) report, a starting cholesterol level under 5.17 mmol/L was unaffected by HMB supplementation. The results of the current study, along with those of Nissen et al. (18), question whether HMB can act as an antecedatal agent by increasing cholesterol synthesis in highly trained, healthy subjects.

Blood urea levels were unchanged after HMB or HMBCr supplementation in the current study. If HMB was an effective antecedatal agent able to reduce muscle damage, it would be expected that less protein degradation would occur and blood
urea levels would be significantly lower. However, for blood urea levels to accurately reflect muscle catabolism, protein intake and exercise levels need to remain constant. Variations in exercise volume and intensity were minimized in the current study due to the team training environment. The subjects were also asked not to vary their diet during the study. However, a dietary analysis was not undertaken to verify this due to logistical problems associated with the monitoring of food intake in this group of elite athletes. Therefore, it is not possible to make strong conclusions on muscle catabolism in relation to the blood urea levels determined in this study. Further studies need to address this concern and measure nitrogen balance.

Health concerns over Cr have involved potentially harmful effects on liver and kidney function (for review, see 24). As 6 wk supplementation with HMBCr in the current study did not significantly alter blood urea levels, it can be tentatively concluded that Cr at a dose of 3 g/d, coupled with 3 g/d HMB, does not impair liver function. This supports the findings of Jowko et al. (12), who also reported no effect of Cr on blood urea levels. However, blood urea is only an approximate indicator of liver function; liver enzyme levels provide a better indication of liver function (24). Unaltered liver enzyme activity after Cr supplementation has been reported in abstract form (1), as unpublished observations (24) and, more recently, in a small group of highly trained athletes who consumed Cr for 6 wk (30) and in a retrospective study of athletes who had consumed Cr for up to 4 yr (26). Therefore, these early studies have demonstrated no negative effects of Cr on liver function. However, further long-term studies are needed.

If HMB is an important source of carbon for cholesterol synthesis, then supplementation with HMB may lead to an increase in the anabolic hormones derived from cholesterol such as testosterone. Slater et al. (28) showed no alteration in the urine testosterone to epitestosterone ratio after 2 wk of 3 g/d HMB. The current study supports the findings of Slater et al. (28) with no change in plasma testosterone levels after 6 wk HMB (3 g/d) or HMBCr supplementation (3 g/d HMB + 3 g/d Cr). The observation that Cr does not affect plasma testosterone levels is in agreement with Schilling et al. (26) and supports the hypothesis that Cr increases muscle size by providing a greater pool of Cr phosphate to fuel muscle contraction (6, 15, 29) rather than altering anabolic hormone levels. The current study showed that sperm count and motility were unaffected by HMB and HMBCr. These results on fertility show that HMB and low doses of Cr pose little risk to fertility in highly trained subjects but also give indirect confirmation that there were no effects on testosterone levels. These findings further confirm that HMB does not act through the anabolic agent, testosterone, in enhancing recovery from exercise.

The findings of the current study also suggest that the mechanism by which HMB functions is not related to a reduction in the catabolic hormone, cortisol. There was no effect of HMB or HMBCr on plasma cortisol levels, indicating it is unlikely that the anticultural effects of HMB operate via this hormone. The finding that HMBCr did not alter cortisol levels supports Schilling et al. (26), who reported normal cortisol levels in subjects who had previously consumed Cr for up to 4 yr. Thus, neither HMB nor Cr, at the stated doses, altered plasma cortisol levels.

An interesting finding of the current study was a significantly lower resting blood bicarbonate level of the HMB group in comparison to their own baseline levels and the bicarbonate levels of the control and HMBCr groups at pre-supplementation and the control group at post-supplementation. However, it is important to note that all bicarbonate measurements for all subjects were within the range of
the normal population. The mechanism underlying this decrease in bicarbonate is unclear and complicated by the fact that subjects in the HMBCr group, who received the same dose of HMB, did not show any change in bicarbonate levels. Bicarbonate is important in maintaining the acid-base balance of the body (10). As the subjects in all three groups underwent the same training regime, the significantly lower bicarbonate levels cannot be attributed to a greater amount of anaerobic activity and, therefore, greater buffering of lactic acid. This is further supported by the fact that blood sampling occurred on a rest day that was at least 12 hours post-activity, at which time blood bicarbonate levels would be expected to be restored to normal (10). As the HMBCr group did not show a significant drop in bicarbonate levels, it may be that there was an interaction between HMB and Cr that neutralized the effects of HMB on blood bicarbonate. However, given that there were 32 dependent variables assessed in the current study, this significant finding could be the consequence of a type I error. Statistically, there is a 1 in 20 chance of making a type I error when alpha is set at 0.05. This effect on bicarbonate needs to be substantiated by further studies.

The hematological parameters of the subjects in the current study were unaffected by 6 wk supplementation with HMB (3 g/d) or HMBCr (3 g/d HMB + 3 g/d Cr). However, blood monocyte and lymphocyte counts varied significantly between the control and supplement groups. Blood monocyte counts remained within normal range but were significantly higher in the HMB and HMBCr groups at post-supplementation compared to the control group. The pre-supplementation lymphocyte count of the control group was significantly higher than all other readings. However, all lymphocyte measurements were within normal clinical range with the exception of low measurements from 1 control subject and 4 HMBCr subjects. Given that there was no consistent trend in these white blood cell variations and that the subjects were highly trained athletes, these variations may reflect the immuno-suppressing effects of the high intensity training undertaken by the athletes (17). Studies have demonstrated that various white blood cell types can be suppressed for up to 72 hours following heavy, intense exercise, which may leave the athlete susceptible to infection (17). Alternatively, as with the blood bicarbonate readings, these significant findings may reflect an increased likelihood of a type I statistical error given that 32 dependent variables were assessed. Past HMB studies (9, 18) have measured hematological parameters and found normal values after supplementation, but few studies exist in this area with Cr supplementation. Although this study indicates that HMB and HMBCr have little effect on hematological parameters, further research should substantiate these findings.

Another indicator of health is psychological well-being. An established scale for measuring current psychological well-being is the SCL-90-R, which has been utilized as a measurement for change in various clinical and research cohorts (3, 7). Results from the current study indicate that psychological measures did not vary for HMB, HMBCr, or control subjects on pre- or post-supplementation measures. These results are in agreement with those of Nissen et al. (18), who utilized the Circumplex Model of Affect and reported no negative effects of HMB on the emotional profiles of respondents. Nissen et al. (18) did report a significant decrease in Unactivated Unpleasant Affect (e.g., feeling dull, tranquil, still, inactive, idle, passive). The current study did not find such a difference; however, the two scales do differ in the attributes they measure. The SCL-90-R does not have a directly comparable subscale to the Unactivated Unpleasant Affect subscale but does contain a broader subscale
of Depression, with some similar attributes. Therefore, this difference between the two studies may be due to differences between the psychometric measures.

The current study found no adverse effects of HMB or HMBCr on indices of health in highly trained athletes over a 6-wk period with the exception of minor changes in blood bicarbonate, lymphocyte, and monocyte counts. However, no long-term studies investigating HMB exist, and there is a need to establish the health effects of this supplement over much longer time periods. The results of this study apply only to well-trained male athletes, and the health effects of HMB and HMBCr need to be substantiated in female athletes as well as endurance athletes, both trained and untrained.

In conclusion, 6 wk supplementation with HMB (3 g/d) or HMBCr (3 g/d HMB + 3 g/d Cr) had no adverse effects on the hematology, blood biochemistry, plasma testosterone, plasma cortisol, and fertility of highly trained male athletes undergoing a resistance training program in comparison to a control group. Furthermore, a number of parameters measured in this study question the validity of HMB as an anticitabolic agent with no effects of HMB on serum creatine phosphokinase, cholesterol, or urea. Further research is required to elucidate the mechanism by which HMB may produce anticitabolic effects.

References


