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Active Status of HMB Supplementation on Aerobic Capacity, Blood Parameters, Low and High Intense Body Muscle Oxygen and Energy Ergometer: A Systematic Review and Fixed Model Effect Meta-Analysis

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Özet
HMB (β-hydroxy-β-methylbutyric acid) ergojenik takviyesi, insanın aerobic vücut metabolizması, düşük ve yüksek yoğun kas oksijeni ve enerji ergometresi üzerinde oldukça etkilidir. Ancak, HMB takviyesinin aerobic kapasite, kan laktat birikimi ve diğer kan enzim aktivite düzeyleri üzerindeki aktif durumu sporcularda ve fiziksel bireylerde belirsizdir. Bu çalışma, sabit model etkili meta-analiz altında gerçekleştirilmiştir. HMB takviyesinin aktif durumu, sporcular ve fiziksel bireyler için çalışmalarla (n=194) önyargı çözme riskinin metadolojik kalitesi aracılığıyla analiz edildi. Sabit model etkisi için kullanılan ortak popülasyon etki büyüklüğü, ortalama farkı ve etki büyüklüğü yerine getirildi, ayrıca sadece örneklem düzeyi ve minimum etki analiz edildi. Parametrik değişkenler için popülasyon etki büyüklüğü Cohen'd kullanıldı, ancak bu çalışmada VO_2max ES= 0.32 orta, heterojenite I^2 =70.41, ortalama fark = -0.12, ayrıca diğer parameter HR_{VT} ES= 1.61 büyük, heterojenite I^2 = 9.01, ortalama fark = 1.65 bulunmuştur.

Anahtar kelimeler: HMB, Aerobik kapasitesi, Sporcular, Bireyler

Active Status of HMB Supplementation on Aerobic Capacity, Blood Parameters, Low and High Intense Body Muscle Oxygen and Energy Ergometer: A Systematic Review and Fixed Model Effect Meta-Analysis

Abstract
The HMB (β-hydroxy-β-methylbutyric acid) ergogenic supplement, highly effective on human aerobic body metabolism, low and high intense muscle oxygen and energy ergometer, however, active status of HMB supplementation on aerobic capacity, blood lactate accumulation, and other blood enzyme activity level is unclear in athletes and physical individuals. This study performed under fixed model effect meta-analysis. Active status of HMB supplementation analyed through metadologic quality of risk of bias solvementation with studies (n=194) for athletes and physical individuals. Common population effect size used for fixed model effect was fulfill into mean different and effect size, also was analyzed only sample level and minus effect. Population effect size Cohen'd was used for parametric variables was used, but in this study have been resulted VO2max ES=0.32 medium, heterogeneity I2=70.41, mean difference = -0.12, also other parameter HRVT ES=1.61 large, heterogeneity I2=9.01, mean difference=1.65.

Keywords: HMB, Aerobic capacity, Athletes, Individuals

Abbreviation
HMB – β-hydroxy-β-methylbutyric acid
α-KIC – α-ketoisocaproate
BCATc – Branched-chain aminotransferase cytosolic
BCATm – Mitochondrial branched chain aminotransferase
BCKDC – Branced-chain alpha-keto acid dehydrogenase complex
MC-CoA – β-Methylcrotonyl-CoA
ATP – Adenosine triphosphate
ADP – Adenosine diphosphate
AMPK-FoxO$_3$ – Adenosine monophosphate-activated protein kinase
PGC-1α – Gamma co-activator 1-alpha
VO2max – Maximum oxygen consumption
HRmax – Heart rate maximum
VT – Ventilatory threshold
TVT – Time to reach at ventilatory threshold
WVT – Watt at ventilatory threshold
HRVT – Heart rate at ventilatory threshold
LDH – Lactate dehydrogenase
CK – Creatine kinase

INTRODUCTION

β-hydroxy-β-methylbutyric acid (HMB), is one of energy producing and ergogenic aid, enhancing metabolite amino acid of leucine and its α-ketoisocaproate (α-KIC) into skeletal muscle protein synchronization, their metabolite is isovaleryl-CoA inside liver mitochondria concluded with 95% probability, hence cytosolic HMB converted β-hydroxy-β-methylbutyric CoA and acetoacetyl-CoA only 5% of leucine, which be metabolite mevalonate and de novo cholesterol synthesis (Albert et al., 2015).

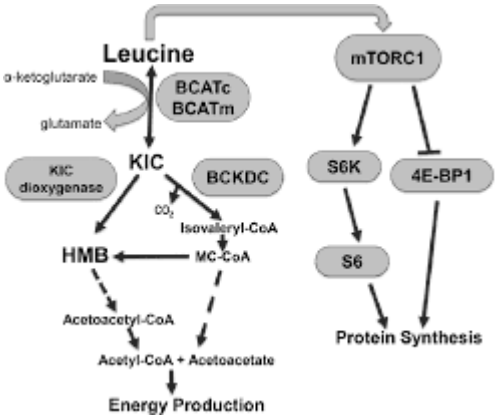

Fig 1A. Active status of HMB supplementation with leucine is lactic acid production, occured form muscle glycogen metabolism, is the first example of leucine degradation by transferring nitrogen from leucine to α-ketoglutarate included in BCATc and BCATm so-called glycolytic regulation, meanwhile glutamate regulation of CNS and KIC prevent catabolism. Thenafter, leucine is energy metabolized with KIC, KIC is both metabolized into isovaleryl-CoA by BCKDC and into HMB by an enzyme referred as to KIC dioxygenase. After, one into muscle apoptosis elimination of derivatives of isovaleryl-CoA, MC-CoA is cell creating converts into HMB. Thus, these muscle cell metabolites by acetoacetyl-CoA and acetoacetate and used for autogenic energy production.

HMB supplementation is used to promote intrinsic muscle recovery, glycogen regulation and aerobic muscle oxygen mechanism through replacement of energy substrates, this mechanism of mitochondrial produces ATP by means of roles in electron transport system and oxidize energy molecules (Holecek, 2017). Furthermore, HMB specifically improves metabolic time regulated performance and aerobic capacity, enhances mitochondrial biogenesis by gamma co-activator 1-alpha (PGC-1α) protecting muscle mass and higher oxygen consumption, thus promoting higher fat oxidation via carbohydrate acetyl CoA cycle in aerobic transient muscle ergometrics (Tadaishi et al., 2011; Durkalec-Michalski et al., 2017; Broatch, 2019). For over two decades, increased higher fatty acid oxidation has been able to be an indicator of the effective mitochondrial function, low and high intense muscle oxygen and energy ergometer

of athletes and physical individuals, additionally generated skeletal muscle activation in individual aerobic capacity development (Wilson et al., 2013). In contrast, deterioration of resting mitochondrial function may have negative effects of HMB intake 3g/day excreted 29% on the body autogenic energy mechanism (Deutz et al., 2013; Vukovic and Dreifort, 2001). A high dose HMB intake in aerobic working muscles exposed to proteolysis during low and high muscle intense exercises may decrease protein degradation (Kaczka et al., 2019). This muscle oxygen and energy ergometers reflective of more efficient maintenance of the ATP:ADP re-sentez ratio by reduced degradation of adenine nucleotides, which plays a key role to metabolic adaptation of exercise capacity (O'Connor and Crowe, 2003). Muscle energetic PCr, Pi breakdown due to the mitochondrial stress relationship during exercises, muscle protein breakdown, proteolysis and decreased ATP production in the proteasome systems also activate adenosine monophosphate-activated protein kinase (AMPK)-FoxO3 pathways in ATP activation and causes increased protein breakdown (Herzig and Shaw, 2018). Muscle enzyme, muscle glycogen and nutritial enyzmatic in aerobic exercises can change these conditions for example, AMPK activation can be seen in low and high intense exercises over 60% VO_2max associated with CK activity, hemoglobin (Rothschild et al., 2021). Regulation of mitochondrial biogenesis and regulation of skeletal muscle energy adaptation provided on activation of AMPK and PGC-1α in molecular muscle mass (He et al., 2015). Active status of HMB on effect of aerobic capacities and energy production of skeletal muscles must be clarified in aerobic endurance muscle working intensities (Robinson et al.., 2014). Because, low and high intense aerobic working on muscle oxygen functions and energy ergometers could be an indicator of optimal use of HMB (Durkalec-Michalski and Jeszka, 2015). To aerobic capacity and power working on performance has been determined HMB effective at high dose 3 g/day intake (Hung et al., 2010; Lamboley et al., 2007; Robinson et al., 2014). For this reason, the purpose of analyzing the effect of HMB is to explain how aerobic status comprise on energy production by muscle working following recommendation for not occur muscle exhaustion at HRmax, time to reach of VT produce mechanic muscle power, HMB included mechanical threshold metabolic adaptation transient (Durkalec-Michalski et al., 2017). In studies of threshold sequences, only cyclists and rowers, HMB intake provide reported that increased VO_2max, VT, VO_2peak, time to reach VO_2peak, HRmax and Watt of VT, while lactate accumulation decreased considerably (Vukovic and Dreifort, 2001; Durkalec-Michalski et al., 2015). The ineffectiveness of lactate peaks in the other parameters where blood lactate accumulation mechanisms are observed explains based on the time-dependent increase or decrease by muscle aerobic performance (Vukovich and Dreifort, 2001; O'Connor and Crowe, 2003). Aerobic capacity of skeletal muscles is energy production and homeostasis mechanisms implicated low blood activity decrease level LDH and CK (Knitter et al., 2000). Considering that, aerobic capacity parametrics of highly trained and blood cycle fulfill increasing time to reach VT ($p<0.001$), threshold load ($p=0.0017$), threshold heart rate ($p<0.0001$), HRmax ($p<0.025$), Watt of VT ($p<0.006$), no differences were represented blood lactate accumulation and other blood activities (Durkalec-Michalski et al., 2017). Indeed, aerobic ranges evolved VO_2peak and VT to determine aerobic thresholds use to combined approaches between fat-free mass and aerobic capacity were recorded while considered VO_2max increased from fatty acid oxidation simultaneously after HMB observed on long time period (Robinson et al., 2014; Durkalec-Michalski and Jeszka, 2016). To short

time aerobic capacities (+15.5% at VO_2max), similar was no significant difference (Lamboley et al., 2007). Therefore, this study aimed at critical active status to determine the effective use of HMB on aerobic capacity, blood parameters, low and high intense muscle aerobic performance.

MATERIAL AND METHOD

The research was concluded methodological quality and risk of bias by critical for common population effect used only fixed model resolved from the studies the risk of bias was evaluated by two authors. Comprehensive approaches of the study concluded PRISMA guidelines is an evidence based minimum set of items for reporting in systematic reviews and meta-analyses (Figure 2B). Research propered randomize allocation concealment, blinding of outcome, incomplete outcome data, selective outcome reporting, other sources of bias and overall risk of bias; 2 low, 3 medium, 4 high risk of bias was evaluated as the quality of Cochrane collaboration' s tool for assessing randomize trials (Table 1) (Higgins, 2011). Randomize population heterogeneity percentage calculated I^2 =25% small; 50% medium; 75% large heterogeneous (Borenstein et al., 2009). Cochran's Q heterogeneity statistic was calculated according to the formula I2: (Q-df)/Qx100% using SPSS v.13 (Thorlund et al., 2012). The fixed model solved weight mean different ($\omega i = \frac{e1\sigma1+e2\sigma2+\cdots en\sigma n}{e1+e2+\cdots en}$) is only one sample level and population minus effect (Borenstein et al., 2009). The research databases included PubMed (n=9), Google Scholar (n=3180), and Web of Science (n=505) were data publications including with no limitations, additionally sample size (n=194) obtained from total studies. Keywords of studies determined β-hydroxy- β- methylbutyrate OR b-hydroxy-b-methylbutyrate OR beta-hydroxy-betamethylbutyrate; AND aerobic capacity OR aerobic performance OR physical performance; AND blood parameter OR Lactate OR LHD OR CK. All times included from 2000 to 2017 years. The Cochrane Collaboration quality controversial resolved author, method, sample size, aerobic parameters. The same dose using was formed in all studies. All observations had evaluated mean, standard deviation and confidence interval investigated significant parametrics was set the effect size references; 0.00 < 0.20 very weak, 0.20 < 0.50 weak, 0.50 < 0.80 moderate, 0.80 < 1.20 strong, 1.20 < 2.00 very strong and 2 or > 2 concluded as extremely strong effect size (Sawilowsky, 2009)

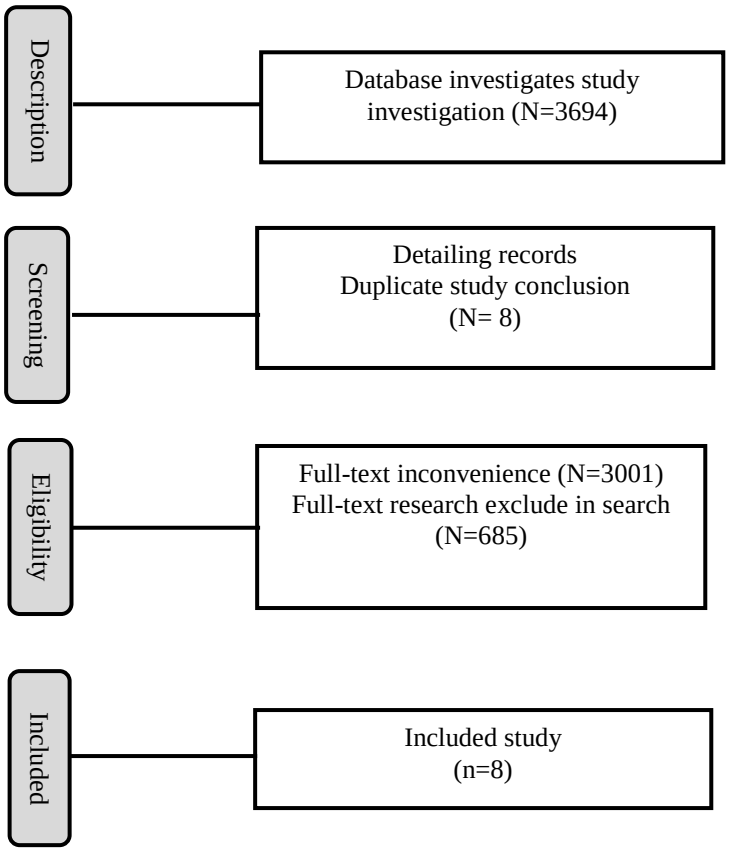

Fig 2B. Flow diagram (PRISMA) guideline

RESULTS

Our study showed that population effect must improved, thus aerobic endurance performances, blood parameters, ATP dynamic sequences, muscle activation, and reactive transient mostly up screen in other athletic population and individual people energy formation. But limitation and risk of bias concluded only 8 study had that over only allow HMB supplement using for muscle bioenerjitic, nutrition limitation no different other supplement as far as highly increased risk urgent. HMB supplement highly effective energy metabolism, anaerobic thresholds power sequence, glycogen regulation. Results were evaluated aerobic protocol, blood lactate accumulation as muscle energy production, specificity VO2max and HRVT same is effect levels in incremental progressive testing or protocols. But, muscle contraction mechanics all of individual capacity from VT in the time changes blood parameters.

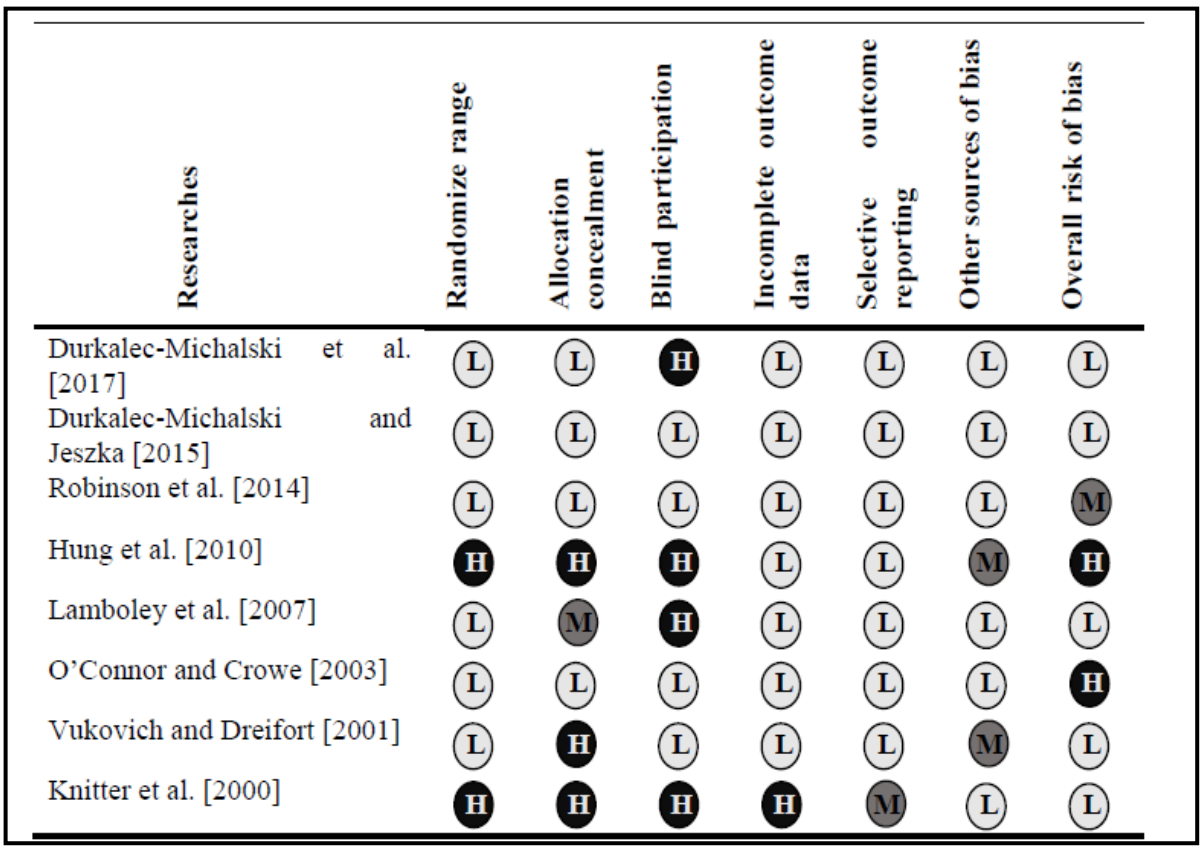

Fig 3C. Research risk of bias quality
Abbreviations: L: Low risk of bias; M: Medium risk of bias; H: High risk of bias.

Table 2. Evaluation of aerobic capacity in HMB intake

Author	Population	Sample	Age	Gender	Desing	Protocol	Variables
Durkalec-Michalski et al. [2017]	Wrestlers Judokas Brazilian jiu-jitsu	HMB= 24 PL= 25	22.8 ± 6.1 yr	M	12 wk; Crossover	Cycloergometer	VO2max (mL/min/kg) TVT (mL/min/kg) HRmax (b.min-1) WVT (W/kg) HRVT (bpm) CK (U/L) LDH (U/L) L (mmol/L)
Durkalec-Michalski and Jeszka [2015]	Rowers	HMB = 10 PL = 6	19.5 ± 1.4 yr	M	12 wk; Crossover	Cycloergometer	VO2max (mL/min/kg) TVT (min) HRVT (bpm) HRmax (bpm) WVT (W.kg-1) CK (U*L-1) LDH (U*L-1)
Robinson et al [2014]	Recreational individual	HMB = 13 PL = 13	22.7 ± 3.1 yr	M/F	4 wk; Crossover	Braked cycle ergometer	VO_2peak (ml/min/kg) VT (ml.kg-1.min-
Hung et al [2010]	Judo	HMB=4 PL=4	21.1 ± 0.6 yr	M	3 day; Parallel	Treadmill	VO2max (mL/min/kg)
Lamboley et al [2007]	Active individual	HMB=8 PL=8	23.40 ±1.2 yr	M/F	5 wk; Parallel	Incremental treadmill	VO2max (mL/min/kg) VT (ml.kg-1.min
O'Connor and Crowe [2003]	Rugby	HMB=10 PL=11	24.9 ± 0.7 yr	M/F	6 wk; Parallel	20 m shuttle run	VO2max (mL/min/kg) L (mmol/L)
Vukovich and Dreifort [2001]	Cyclist	HMB=8	34.2 ± 2.6 yr	M	6 wk; Parallel	Graded cycle ergometer	VO2peak (L/min) L (mmol/L)
Knitter et al [2000]	Physical individual	HMB=8 PL=5	36 ± 2 yr	M/F	6 wk; Parallel	20 km progloned run	LDH (U/L)

Table 3. Active status of HMB supplementation

Authors	VO_2max Post-dif	Mean difference	Effect size	I^2
Durkalec-Michalski et al. [2017]	0.90	-0.12	0.13	70.4
Durkalec-Michalski and Jeszka [2015]	3.00	-0.29	0.38	7.42
Lamboley et al. [2007]	6.60	-0.13	1.14	0.54
O'Connor and Crowe [2003]	2.40	1.93	4.32	0.55
Knitter et al. [2000]	1.80	2.5	0.84	0.35
Authors	**T_{VT} Post-dif**	**Mean difference**	**Effect size**	**I^2**
Durkalec-Michalski et al. [2017]	0.46	-3.16	0.47	1.48
Durkalec-Michalski and Jeszka [2015]	0.66	-4.61	2.78	0.09
Authors	**HRmax Post-dif**	**Mean difference**	**Effect size**	**I^2**
Durkalec-Michalski et al. [2017]	0.00	0.04	0.00	7.0
Durkalec-Michalski and Jeszka [2015]	-1.09	0.94	0.30	0.10
Authors	**WVT Post-dif**	**Mean difference**	**Effect size**	**I^2**
Durkalec-Michalski et al. [2017]	4.00	0.04	0.35	1.30
Durkalec-Michalski and Jeszka [2015]	5.00	1.65	0.66	9.0
Authors	**HRVT Post-dif**	**Mean**	**Effect size**	**I^2**
Durkalec-Michalski et al. [2017]	165	0.10	0.36	0.03
Durkalec-Michalski and Jeszka [2015]	166	11.50	0.51	0.05
Authors	**CK Post-dif**	**Mean difference**	**Effect size**	**I^2**
Durkalec-Michalski et al. [2017]	0.44	8.5	0.20	2.83
Durkalec-Michalski and Jeszka [2015]	0.24	-7.29	0.17	1.42
Authors	**LDH Post-dif**	**Mean difference**	**Effect size**	**I^2**
Durkalec-Michalski et al. [2017]	20.00	-39.18	0.34	0.56
Durkalec-Michalski and Jeszka [2015]	0.00	1.95	0.00	0.52
Knitter et al. [2000]	-3.00	-2.60	0.18	0.45
Authors	**Lactate Post-dif**	**Mean difference**	**Effect size**	**I^2**
Durkalec-Michalski et al. [2017]	0.10	2.25	1.76	0.23
O'Connor and Crowe [2003]	-0.48	0.42	0.87	0.57
Vukovich and Dreifort [2001]	8.1	0.08	0.43	0.30
Authors	**VO2peak Post-dif**	**Mean difference**	**Effect size**	**I^2**
Robinson et al. [2014]	3.80	1.31	1.05	0.38
Vukovich and Dreifort [2001]	47.5	2.40	2.09	0.30
Authors	**VT Post-dif**	**Mean difference**	**Effect size**	**I^2**
Robinson et al. [2014]	4.50	0.28	1.38	0.22
Lamboley et al. [2007]	0.19	0.03	2.08	0.34

$p<0.05$.

Table 4. Difference of comparison of HMB and PL consumption

Variable	Mean±SD	Confidence interval (95%)	t	p	ES
*VO_2max	1.97±0.85	0.91 – 3.03	5.150	**0.007**	0.32
*T_{VT}	56.00±14.14	-71.06 – 183.06	5.600	0.112	No-effect
*HRmax	-1.00±1.73	-5.30 – 3.30	-1.000	0.423	No-effect
*WVT	18.66±10.01	-6.21 – 43.54	3.228	0.084	No-effect
*HRVT	4.33±0.57	2.89 – 5.76	13.000	**0.006**	1.61
*CK	15.00±35.08	-72.15 – 102.15	0.740	0.536	No-effect
*LDH	8.00±11.22	-9.86 – 25.86	1.425	0.249	No-effect
*Lactate	0.07±0.54	-1.26 – 1.41	0.235	0.836	No-effect
*VO2peak	2.65±1.62	-11.96 – 17.26	2.304	0.261	No-effect
*VT	2.34±3.04	-25.03 – 29.72	1.088	0.473	No-effect

$p<0.05$.

The active status of HMB on aerobic capacity and blood parameters were examined in this study. Comparison of HMB and PL studies, determined only VO_2max and HRVT variables explained changes to exercise capacity. For this reason, it is recommended to use HMB for oxygen increases. The use of high doses at intense exercise levels may be effectiveness, because HRVT and VO2max increases at an exercise times by long time into short seconds for expected on long distance.

DISCUSSION AND CONCLUSION

The researchers revealed muscle oxygen and aerobic energy ergometers relationship by eight studies different low and high intense protocol. Metabolic changes considered mitochondrial energy of muscles to investigate for aerobic capacity has effectivelly increased through high dose intake HMB supplementation. To determine aerobic capacity also observed VO_2max higher and LDH and CK lower with effect size. One study reported that HMB have produce augmenting VO2peak actualized in endurance cyclists during short time intensities, however inactive of HMB intake on maximal lactate accumulation based on threshold sequences (Robinson et al., 2014). In contrast, early one study on long time intensity had effective on VO2peak values (Vukovic and Dreifort (2001). Other studies examining aerobic capacity revealed that combined HMB supplementation of endurance exercise and running performance no alter muscle performance. For this reason may be low lactate accumulation similarly those of Durkalec-Michalski and Jeszka (2017), Robinson et al (2014), Hung et al (2010), Lamboley et al (2007), and Vukovic and Dreifort (2001) and Knitter et al (2000). Both short and long time intense responses have been described for endurance athletes using HMB for aerobic endurance intensity. Short time HMB intake may be recommended for same efficiency aerobic performance in high endurance athletes (Robinson et al., 2014). Robinson et al (2014) also revealed that VO_2peak was (9.8%) higher in high intense training group compared to the control group after short time using HMB intake, while VT was approximately (9.3%) higher with the aerobic threshold sequences. Results were observed in 80% to 120% submaximal and supramaximal aerobic endurance training performed 30 min, 1 h, and 3 h after late dosing with an increasing cycle to determine VO_2peak in Watt. In contrast, Lamboley et al. (2007) reported that 8 km/h running speed plateau decreased from VO_2max (+15.47), VT (+11.08) and %VT (-3.77) in physical individuals. Short time HMB intake additionally may be VO2peak (4%) and time to reach VO2peak (3.6%) increase, thus lactate threshold indicates increased VO2peak (8.6%) while (9%) of muscle oxygen uptake

(Vukovich and Dreifort, 2001). Aerobic endurance threshold sequences similarly, results has been indicated on wrestlers, judokas, and Brazilian jiu-jitsu athletes provided with VO2max (+7.01), lactate (+0.39), LDH (+1.0) and CK (-8.0) changes (Durkalec-Michalski et al., 2017). To aerobic capacity changes by Hung et al (2010) concluded on performance (2.5%) judo athletes and hemoglobin (2%) increases. This results obtained from 10-m shuttle runs had decreased shuttle time after 3 day, demonstrated an anaerobic threshold sequences over long aerobic lower intense period. Indeed, muscle oxygen consumption prevents intramuscular proteolysis and muscle homeostasis activity ie. HMB using for performance development. Also, level of high intense aerobic variables and intramuscular enzyme activities provided reduction in LDH and CK associated with increased time to VO_2max and VT (Durkalec-Michalski et al., 2016). Intense aerobic protocols may use for based time recovery in high dose intake HMB implicated on threshold sequences. Other aerobic high intense repeated a 10-km loop run study, Knitter et al (2000) lasted away 10 weeks resulting long term HMB supplementation use occurred measuring LDH, conclusions (152 to 147 U/L) first at 6.5 km changes and (150 to 153 U/L) decrease of middle 6.5 km then late 6.5 km (154 to 151 U/L) detected. Durkalec-Michalski and Jeszka (2016) reported to assessment of VO2max and VT was recorded at low intense (+50W) in aerobic exercise level, producing decreased activity levels of LDH and CK. Results showed that aerobic plateau (+2.7 mL.min.kg.-1) increase and CK was recorded (-87 U/L) and LDH (-15 U/L) and based exercise time determined VT (+1.2) min increase. As seen in the results, a series of eliminations was observed for aerobic capacity with minimal accumulation of lactate, thus muscle oxygen ergometrics change at short and long intense with HMB supplement high dose intake in athletes and physical individuals (O'Connor and Crowe, 2003; Durkalec-Michalski et al., 2017).

Short term use of HMB supplementation for the aerobic thresholds may be effective because mitochondrial homeostasis increased muscle energy capacities. Short term use of HMB supplementation for the aerobic threshold may be effective because mitochondrial homeostasis to organize and muscle oxygen capacities increased. However, long term use of HMB supplementation for aerobic threshold called VO2max, VO2peak reach and Watt of VT most can effective method. Thus, muscle oxygen ergometer was highly aerobic capacity with lactate elimination. Notice that proper high dose intake for longitudinal training, and exercises periods can increase aerobic capacity and muscle oxygen ergometer mechanisms. The active status of HMB supplementation cleared aerobic performance and aerobic capacity but study limitation had intake of 3 g/day in athletes and physical individuals. Our knowledge suggest that low and high intense exercise provides improved muscle oxygen ergometer as well as blood activity mechanism.

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