Original Article

REN

https://doi.org/ 10.34785/J019.2022.524

Research in Exercise Nutrition 2022; 1(1): 15-21

Effects of β-Hydroxy-β-Methylbutyrate Supplementation on IL-4, IL-10 and TGF-β1 during Resistance Exercise in Athletes

Mohammad Rahman Rahimi[1]✉, Hamid Shoker-Nejad[2]

Received: 2021/10/31 **Accepted: 2022/03/19**

Abstract

The aim of this study was to investigate the effect of β-Hydroxy-β-methylbutyrate (HMB) supplementation on anti-inflammatory cytokines including IL-4, IL-10 and TGF-β during an acute bout of resistance exercise (RE) in young resistance trained men. Ten resistance-trained men in a randomized, double-blind, placebo-controlled and crossover study, were administered a 7-day HMB supplementation (3×1 g.d^{-1} of HMB) and placebo (3×1 g.d^{-1} of Maltodextrin) with a 7 days washout period. After supplementation periods, subjects performed three sets of bench press, lat pull down, leg extension, leg curl, biceps curl, triceps curl and shoulder press to failure with 85% of one repetition to maximum (1RM). Blood samples were obtained before- (Pre), immediately post- (IP) and 1 hour-post RE (1h P) to assess serum concentrations of IL-4, IL-10 and TGF-β1. The data were analyzed using 2 (treatment: HMB and Placebo (PL)) × 3 (time points: Pre, IP and 1hP) repeated measures analysis of variance (ANOVA) followed by the Bonferroni post hoc test with a significant level of $p<0.05$. Serum IL-4 was significantly higher at IP resistance exercise in HMB compared to placebo. Circulating IL-4 and TGF-β1 were significantly raised at IP compared to Pre in both HMB and placebo treatments. No significant differences between treatments were observed for IL-10 and TGF-β1at any time points. In conclusion, HMB supplementation increased the circulating level of IL-4 during RE in resistance-trained men, which may attenuate inflammatory markers and facilitate adaptation to RE.

Keywords: β-Hydroxy-β-Methylbutyrate, anti-inflamatory cytokines, resistance exercise

[1] Associate Professor of Exercise Physiology, Department of Exercise Physiology, University of Kurdistan, Sanandaj, Iran.

✉ **Corresponding author:** mohammad.rrahimi@yahoo.com

[2] MSc of Exercise Physiology, Department of Exercise Physiology, University of Kurdistan, Sanandaj, Iran.

1. Introduction

It is generally accepted that chronic resistance exercise (RE) is associated with reduced risk of low grade systemic inflammation in atherosclerosis, obesity and insulin resistance [1], paradoxically, a single bout of RE appears to promote inflammation [2, 3]. Tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), IL-1 and C reactive protein (CRP) are considered as low grade systemic inflammatory cytokines [4]. Studies examining the acute effect of RE on inflammatory markers revealed significant elevations [5, 6] and no changes [2, 7] in inflammatory cytokines. The inflammatory responses to a single bout of RE may be due to RE-induced muscle damage [8]. In addition to muscle damage, RE may trigger cytokine production by other physiological factors such as neuroendocrinological factors (i.e. adrenaline, noradrenaline, growth hormone and cortisol), ROS production, acidosis and the rise in muscle temperature [9-11].

Recently, the concept of anti-inflammatory effects of exercise has attracted particular attention in sport science community [12]. The anti-inflammatory cytokines including IL-4, IL-10 and TGF-β1 are able to attenuate inflammation by limiting inflammatory cytokine production, up-regulating their soluble antagonist binding proteins, and suppressing inflammatory cell activity [13, 14]. IL-4 and IL-10 are produced

Citation:

Rahimi MR, Shoker-Nejad H. Effects of β-Hydroxy-β-Methylbutyrate Supplementation on IL-4, IL-10 and TGF-β1 during Resistance Exercise in Athletes. Research in Exercise Nutrition. 2022 May 22;1(1):15-21. https://doi.org/10.34785/J019.2022.524.

largely by the T_{H2} subset of lymphocyte and TGF-β1 is produced mainly by regulatory T cells [14]. The anti-inflammatory cytokines (Il-4 and IL-10) responses to acute RE are equivocal [3]. However, there are no studies reporting TGF-β1 response to an acute RE in athletes. Recently, it was demonstrated TGF-β1 increased immediately after acute RE at low intensity (50% of 1 RM; 2x18 rps) in Coronary Artery Disease patients [15]. In addition to the effect of exercise on the immune system, previous studies have shown that diet and nutritional supplements can reinforce the immune system in athletes [6, 16-18].

β-Hydroxy-β-methylbutyrate (HMB) is a metabolite of the amino acid leucine that has previously been shown to increase protein synthesis, strength and power, and decrease circulating markers of muscle damage [19]. To date, three studies only have been evaluated the effect of HMB on immune function during RE in humans [6, 17, 18]. Recently, it was proposed that HMB may exerts immunoregulatory effects including increased the anti-inflammatory cytokine IL-10 and decreased pro-inflammatory cytokine IFN-γ and IL-1β after resistance training [17]. In addition, it was reported that HMB could reduced TNF-α and monocyte TNF-α receptor 1 expression after strenuous RE [6]. In a vitro study, a decrease in inflammatory cytokine IFN-γ in T-lymphocytes demonstrated which was incubated with varying concentrations of HMB [20]. Due to the lack of information regarding to the effect of HMB supplementation on anti-inflammatory cytokines during RE in athletes, the purpose of this study was to investigate the effects of HMB on IL-4, IL-10 and TGF-β1 during intense RE in athletes.

2. Methods

2.1. Participants

Ten resistance-trained men voluntarily participated in this randomized, double-blind, placebo-controlled and crossover study (Table 1). The study protocol was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board for the human participants. All procedures, risks and benefits of this study were explained to participants, and then participants provided written informed consent. Participants had at least 2 years of resistance-training experience. Exclusion criteria were smoking, taking supplements (i.e., creatine, HMB, lucine, or other amino acids), anabolic and catabolic hormones, and anti-inflammatory agents. The participants were asked to refrain from engaging in any exercise for 48 h before each resistance exercise bout as well as to complete 2-day food diary before the first RE bout and repeat it before the subsequent RE bout.

Table 1. Baseline anthropometrics of subjects

Variable	Mean±SD
Age (**yr**)	22±1.32
Weight (**kg**)	76.45±9.13
Height (**cm**)	179.33±4.33
Body mass index (**kg/m^2**)	23.7±1.99
Body fat mass (**%**)	12.5±4.08

2.2. Study design

To investigate the effect of one week HMB supplementation on anti-inflammatory cytokines during heavy RE, participants ingested HMB (3 capsules of 1 g per day) or placebo (3 capsules of 1 g Maltodextrin per day) three times a day for one week prior to intense resistance exercise in a randomized, double-blind, placebo-controlled and crossover study. Participants were called to the Exercise Physiology Laboratory on three different sessions. In the first session, maximal strength tests based on one repetition maximum for bench press, lat pull down, leg extension, leg curl, biceps curl, triceps curl and shoulder press test were performed using methods described previously (Table 2) [21]. During the second and third sessions, participants performed intense resistance exercise that included of three sets of bench press, lat pull down, leg extension, leg curl, biceps curl, triceps curl and shoulder press to failure with 85% of 1RM and 2 min of rest between sets and exercises. During two supplementation periods, participants in a randomized, double-blind, placebo-controlled and crossover design received one week HMB (Olimp, Poland) and placebo that separated by a one week washout period. Both HMB and placebo (PL) capsules were identical in shape, size and color. At the end of each period, the participants performed heavy RE with 85% of 1RM. Prior to resistance exercise protocols, all participants performed warm-up, which consisted of 3 min running, 5-10 repetitions at 50% of perceived maximum and stretching.

Table 2. Baseline 1RM in resistance exercises

1RM (kg)	Mean±SD
Bench Press	80±18.5
Lat Pull Down	71.5±15.6
Leg Extension	43±12.29
Leg Press	169±62.97
Biceps Curl	35.5±7.97
Triceps Curl	69±25.65
Shoulder Press	44±10.21

2.3. Blood sampling

Blood samples were obtained from a forearm vein at Pre, IP and 1h P into serum vacutainer tubes that allowed clotting at room temperature for 30 min and afterward centrifuged at 3000 g for 15 min at 4°C. Serum tubes were stored at – 80 °C for later analysis. IL-4, IL-10 and TGF-β1 were measured using enzyme-linked immunosorbant assays (ELISA kits with Catalogue No.: abx050119; abx050094 and abx252257, United States), with sensitivities of 1.5 pg/mL, 0.5 pg/mL and 18.75 pg/mL.

2.4. Statistical analysis

Statistical analysis of the data was performed using IBM SPSS Statistics 20.0 software for windows (SPSS Inc., Chicago, Illinois). P value less than 0.05 were considered statistically significant. The Shapiro–Wilk test confirmed the normal distribution of the data. The data were analyzed using 2 (treatment: HMB and PL) × 3 (time points: Pre, IP and 1hP) repeated measures analysis of variance (ANOVA). A Bonferroni post hoc test was used for pairwise comparisons when the *F*-statistic revealed a significant *p*-value. Data are reported as mean ± standard deviations (SD) for all values.

3. Results

Figure 1 illustrates serum concentration of IL-4 at pre-, immediately post (IP)- and 1h post (1h P)-resistance exercise in resistance-trained men for both HMB and PL conditions. Repeated measures of ANOVA demonstrated a significant time effect for treatment ($F_{(2,\ 32)=}$ 16.82, P=0.0001, η^2=0.51), time × treatments interaction ($F_{(2,\ 32)=}$ 3.31, P=0.04, η^2=0.17) and between treatments ($F_{(1,\ 16)=}$ 1.98, P=0.0001, η^2=0.29). Serum IL-4 significantly increased at immediately post RE in HMB supplementation compared to placebo; with no significant difference at 1h post RE between both conditions.

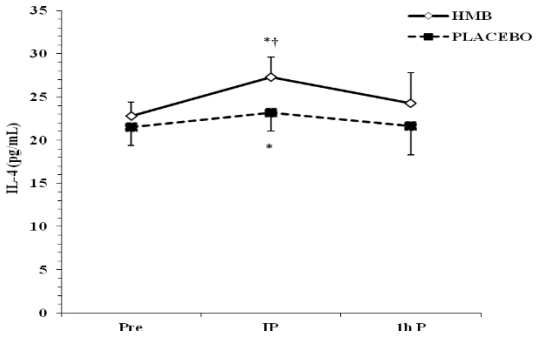

Figure 1. Effects of HMB supplmentation on serum concentration of IL-4 at pre-, immediately post- and 1h post-resistance exercise in resistance-trained men

* siginficant difference (P≤0.05) from corresponding pre-RE value.

† siginficant difference (P≤0.05) between HMB and placebo at corresponding time point.

Figure 2 shows serum concentration of IL-10 at pre-, immediately post- and 1h post-resistance exercise in resistance-trained men for both HMB and placebo conditions. Repeated measures of ANOVA demonstrated no significant time effect for treatments ($F_{(2,\ 32)=}$ 0.99, P=0.38, η^2=0.058), time × treatments interaction ($F_{(2,\ 32)=}$ 0.23, P=0.79, η^2=0.014) and between treatments ($F_{(1,\ 16)=}$ 0.098, P=0.75, η^2=0.006). However, greater increase (4.5%) in IL-10 immediately post RE was observed after HMB supplementation compared to placebo.

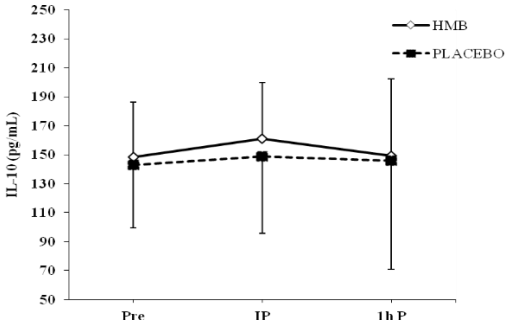

Figure 2. Effects of HMB supplmentation on serum concentration of IL-10 at pre-, immediately post- and 1h post-resistance exercise in resistance-trained men.

Figure 3 indicates serum concentration of TGF-β1at pre-, immediately post- and 1h post-resistance exercise in resistance-trained men for both HMB and placebo conditions. Repeated measures of ANOVA demonstrated a significant time effect for treatments ($F_{(2,\ 32)=}$ 6.46, P=0.004, η^2=0.28), with no significant time × treatments interaction ($F_{(2,\ 32)=}$ 0.103, P=0.90, η^2=0.006) and between treatments ($F_{(1,\ 16)=}$ 0.115, P=0.73, η^2=0.007). Serum TGF-β1 significantly increased in both HMB (14.25%) and placebo (11.94%) condition at immediately post RE compared to pre RE in resistance trained men.

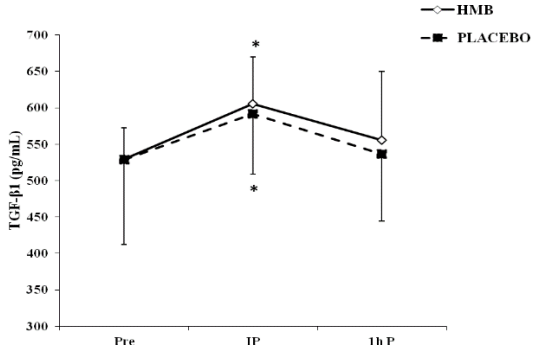

Figure 3. Effects of HMB supplmentation on serum concentration of TGF-β1 at pre-, immediately post- and 1h post-resistance exercise in resistance-trained men.
* siginficant difference (P≤0.05) from corresponding pre-RE value.

4. Discussion

The primary aim of the present study was to evaluate the effect of HMB supplementation in a randomized, double-blind, placebo-controlled and crossover design in resistance-trained men on anti-inflammatory cytokines during intense RE. The main finding of the present study was that short-term HMB supplementation (3 $g.d^{-1}$ for 7 days) significantly raised circulating IL-4 at immediately post RE in resistance-trained men. IL-4 is an important anti-inflammatory cytokine which leads to polarization of T helper (Th) cell differentiation toward Th2-like cells [14]. These cells are able to secretes anti-inflammatory cytokines of IL-4 and IL-10 that cause to suppression of Th1 responses as well as block the secretion of inflammatory cytokines including IL-1, TNF-α, IL-6 and IL-8 produced by monocytes [14, 22]. Furthermore, it has been demonstrated that IL-4 can directly stimulate myogenesis, which is due to enhance myoblast fusion [23].

HMB supplementation increased circulating IL-4 by 19.75% immediately after heavy RE in resistance-trained men, which may be attributed to anti-inflammatory effect of HMB that supported by previous studies [6, 24, 25]. Consistent with our findings, previous study has shown that HMB exerts anti-inflammatory effect by attenuating elevations in circulating TNF-α immediately after acute bout of heavy RE and as well as reducing TNFR1 expression on human monocytes at 30 min post RE [6]. In another study, a single dose of 3 $g.d^{-1}$ prior to RE attenuated C-reactive protein (CRP) 24 h post-RE in resistance-trained men [24]. In addition, HMB-free acid administration can attenuate complement receptor type 3 (CR3) at 30 min post heavy RE with 70-80% of 1RM in resistance-trained men [25]. Inflammatory cytokine responses to 23 days of HMB supplementation during heavy military training with sleep deprivation revealed decreases in circulating IL-6, IL-8, IL-10, IL-1ra, CX3CL1 and G-CSF [26]. In contrast, 7 weeks of HMB supplementation in elite volleyball players had no significant effect on inflammatory markers of IL-6 and IL-1 after the first 7 weeks of the volleyball season [27].

IL-10 known as an important anti-inflammatory cytokine which is a potent inhibitor of Th1cytokines, including IL-2 and IFN-γ [14] as well as inhibits nuclear factor ҡB (NF-ҡB), cell surface expression of major histocompatibility complex class II molecules, B7 accessory molecules and signal molecule CD14 [14, 28]. In addition, it appears that the anti-inflammatory effects of exercise is mediated by elevations in circulating IL-10 and to be beneficial for recovery [4]. Thus, it has been shown that circulating IL-10 can attenuate adaptive immune response and reduced the damage to tissue caused by inflammation in response to exercise [29]. In the present study greater increase (4.5%) in IL-10 immediately post RE was observed after HMB supplementation compared to placebo but this change did not reach statistically significant. Few studies have evaluated HMB supplementation on IL-10 and their results are conflicting [24, 26]. Similar to our results, HMB supplementation in resistance-trained men did not alter IL-10 post lower body RE [24]. In contrast, HMB supplementation was shown to attenuate circulating IL-10 response to military training with sleep deprivation [26]. Also, regarding other nutritional supplements have been demonstrated that carbohydrate beverage intake reduces exercise-induced increases in circulating IL-10 compared to placebo [30-32]. In addition, carbohydrate supplementation during hypoxia condition didn't change serum IL-10 concentration in healthy male who exercised for 60 min at an intensity of 50% VO_{2peak} [33]. Quercetin ingestion (1000 mg/day for 24 days) in trained male cyclists significantly reduced blood leukocyte IL-10 mRNA expression but without effect on plasma IL-10 after prolonged cycling [31]. However, it was demonstrated that caffeine ingestion (6 $mg.kg^{-1}$ body weight) lead to higher increases in circulating IL-10 after 15-km run competition.
Few studies observed raises in IL-10 levels after following resistance training [5, 34]. Moreover, 12 weeks of isokentic training significantly increased the protein expression of IL-10 in skeletal muscle [35]. In contrast, Peake et al., [36] reported no change in IL-10, IL-1ra, TNF-α after submaximal and maximal RE protocols. In addition, a single bench press exercise with different intensities ranging from 50 to 110 % of 1RM didn't alter IL-10, IL-1β and IL-6 [7].

TGF-β1 like IL-4 and IL-10 is an important anti-inflammatory cytokine which suppresses the proliferation and differentiation of T and B lymphocyte cells and reduces IL-2, IFN-γ and TNF-α secretion [14, 37]. Higher circulating levels of TGF-β1 after exercise contribute to mediating anti-inflammatory effects of exercise. Our findings show that circulating TGF-β1 significantly increased in both HMB (14.25%) and placebo (11.94%) condition at immediately post RE in

resistance trained men, with no differences between conditions. We observed a trend towards a greater increase in TGF-β1 (2.31%) following HMB intake compared to placebo at immediately post RE in resistance trained men. To our knowledge there are no data on TGF-β1 response to HMB supplementation during RE in athletes. In addition, little research has examined the effect of acute RE on TGF-β1in humans [38]. Our findings are in line with a previous study showing an increase in serum TGF-β1 following an acute bout of RE with 50% of 1RM in coronary artery dieses patients [38]. It has been reported a rise in circulating TGF-β1 level after chronic resistance training in healthy adults [39] and in patients with type 2 diabetes [40, 41]. However, other studies reported no change in TGF-β1 level following resistance training in the elderly [42] and in older adults [43]. Our results indicate that intense RE with 85% of 1RM lead to a rise in serum TGF-β1 in resistance-trained men, which may indicate a protective effect leading to prevention or reduction of atherosclerosis progression [38, 44].

5. Conclusion

In conclusion, to the best of our knowledge this is the first study to investigate the effect of HMB supplementation on anti-inflammatory cytokines during strenuous RE in resistance-trained men in a randomized, double-blind, placebo-controlled and crossover design. Our findings revealed that short-term HMB supplementation lead to significant increment in IL-4 level after acute strenuous RE in resistance-trained men, which can directly stimulate myogenesis [23]. Moreover, a trend towards greater increase in circulating IL-10 (4.5%) and TGF-β1(2.31%) were observed in HMB supplementation compared to placebo at immediately after RE in resistance-trained men. Taken together, our results show that short-term HMB supplementation during RE can amplify anti-inflammatory effects of exercise as shown by significant increase in IL-4 and non-significant increase in TGF-β1and IL-10. Additional study is needed to directly investigate how HMB exert anti-inflammatory effects during acute strenuous RE in resistance-trained men.

Acknowledgments: We would like to thank the participants for contribution to the study.

Conflicts of Interest: The authors declare no conflict of interest.

References

[1] N. Mathur, B.K. Pedersen, Exercise as a mean to control low-grade systemic inflammation, Mediators of inflammation 2008 (2009).

[2] T.W. Buford, M.B. Cooke, D.S. Willoughby, Resistance exercise-induced changes of inflammatory gene expression within human skeletal muscle, European journal of applied physiology 107(4) (2009) 463.

[3] M.C. Calle, M.L. Fernandez, Effects of resistance training on the inflammatory response, Nutrition research and practice 4(4) (2010) 259-269.

[4] A.M.W. Petersen, B.K. Pedersen, The anti-inflammatory effect of exercise, Journal of applied physiology 98(4) (2005) 1154-1162.

[5] L. Smith, A. Anwar, M. Fragen, C. Rananto, R. Johnson, D. Holbert, Cytokines and cell adhesion molecules associated with high-intensity eccentric exercise, European journal of applied physiology 82(1-2) (2000) 61-67.

[6] J.R. Townsend, M.S. Fragala, A.R. Jajtner, A.M. Gonzalez, A.J. Wells, G.T. Mangine, E.H. Robinson, W.P. McCormack, K.S. Beyer, G.J. Pruna, β-Hydroxy-β-methylbutyrate (HMB)-free acid attenuates circulating TNF-α and TNFR1 expression postresistance exercise, Journal of Applied Physiology 115(8) (2013) 1173-1182.

[7] M.C. Uchida, K. Nosaka, C. Ugrinowitsch, A. Yamashita, E. Martins Jr, A.S. Moriscot, M.S. Aoki, Effect of bench press exercise intensity on muscle soreness and inflammatory mediators, Journal of sports sciences 27(5) (2009) 499-507.

[8] M. Sousa, V.H. Teixeira, J. Soares, Dietary strategies to recover from exercise-induced muscle damage, International journal of food sciences and nutrition 65(2) (2014) 151-163.

[9] S. Arbogast, M.B. Reid, Oxidant activity in skeletal muscle fibers is influenced by temperature, CO2 level, and muscle-derived nitric oxide, American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 287(4) (2004) R698-R705.

[10] B.K. Pedersen, L. Hoffman-Goetz, Exercise and the immune system: regulation, integration, and adaptation, Physiological reviews 80(3) (2000) 1055-1081.

[11] S.K. Powers, M.J. Jackson, Exercise-induced oxidative stress: cellular mechanisms and impact on muscle force production, Physiological reviews 88(4) (2008) 1243-1276.

[12] M. Gleeson, N.C. Bishop, D.J. Stensel, M.R. Lindley, S.S. Mastana, M.A. Nimmo, The anti-inflammatory effects of exercise: mechanisms and implications for the prevention and treatment of disease, Nature reviews. Immunology 11(9) (2011) 607.

[13] D.C. Kluth, A.J. Rees, Inhibiting inflammatory cytokines, Seminars in nephrology, 1996, pp. 576-582.

[14] S.M. Opal, V.A. DePalo, Anti-inflammatory cytokines, Chest Journal 117(4) (2000) 1162-1172.

[15] K.A. Volaklis, I. Smilios, A.T. Spassis, C.E. Zois, H.T. Douda, M. Halle, S.P. Tokmakidis, Acute pro- and anti-inflammatory responses to resistance

exercise in patients with coronary artery disease: a pilot study, Journal of sports science & medicine 14(1) (2015) 91.
[16] J.M. Wilson, R.P. Lowery, J.M. Joy, J.A. Walters, S.M. Baier, J.C. Fuller, J.R. Stout, L.E. Norton, E.M. Sikorski, S.M. Wilson, β-Hydroxy-β-methylbutyrate free acid reduces markers of exercise-induced muscle damage and improves recovery in resistance-trained men, British Journal of Nutrition 110(03) (2013) 538-544.
[17] W.J. Kraemer, D.L. Hatfield, B.A. Comstock, M.S. Fragala, P.M. Davitt, C. Cortis, J.M. Wilson, E.C. Lee, R.U. Newton, C. Dunn-Lewis, Influence of HMB supplementation and resistance training on cytokine responses to resistance exercise, Journal of the American College of Nutrition 33(4) (2014) 247-255.
[18] W.J. Kraemer, D.R. Hooper, T.K. Szivak, B.R. Kupchak, C. Dunn-Lewis, B.A. Comstock, S.D. Flanagan, D.P. Looney, A.J. Sterczala, W.H. DuPont, The addition of beta-hydroxy-beta-methylbutyrate and isomaltulose to whey protein improves recovery from highly demanding resistance exercise, Journal of the American College of Nutrition 34(2) (2015) 91-99.
[19] D.S. Rowlands, J.S. Thomson, Effects of β-hydroxy-β-methylbutyrate supplementation during resistance training on strength, body composition, and muscle damage in trained and untrained young men: A meta-analysis, The Journal of Strength & Conditioning Research 23(3) (2009) 836-846.
[20] E.A. Nunes, A.R. Lomax, P.S. Noakes, E.A. Miles, L.C. Fernandes, P.C. Calder, β-Hydroxy-β-methylbutyrate modifies human peripheral blood mononuclear cell proliferation and cytokine production in vitro, Nutrition 27(1) (2011) 92-99.
[21] J. Hoffman, Norms for fitness, performance, and health, Human Kinetics2006.
[22] A. Marchant, C. Bruyns, P. Vandenabeele, M. Ducarme, C. Gérard, A. Delvaux, D. De Groote, D. Abramowicz, T. Velu, M. Goldman, Interleukin-10 controls interferon-γ and tumor necrosis factor production during experimental endotoxemia, European journal of immunology 24(5) (1994) 1167-1171.
[23] V. Horsley, K.M. Jansen, S.T. Mills, G.K. Pavlath, IL-4 acts as a myoblast recruitment factor during mammalian muscle growth, Cell 113(4) (2003) 483-494.
[24] A.M. Gonzalez, J.R. Stout, A.R. Jajtner, J.R. Townsend, A.J. Wells, K.S. Beyer, C.H. Boone, G.J. Pruna, G.T. Mangine, T.M. Scanlon, Effects of β-hydroxy-β-methylbutyrate free acid and cold water immersion on post-exercise markers of muscle damage, Amino acids 46(6) (2014) 1501-1511.
[25] A.M. Gonzalez, M.S. Fragala, A.R. Jajtner, J.R. Townsend, A.J. Wells, K.S. Beyer, C.H. Boone, G.J. Pruna, G.T. Mangine, J.D. Bohner, Effects of β-hydroxy-β-methylbutyrate free acid and cold water immersion on expression of CR3 and MIP-1β following resistance exercise, American Journal of Physiology-Regulatory, Integrative and Comparative Physiology 306(7) (2014) R483-R489.
[26] J.R. Hoffman, Y. Gepner, J.R. Stout, M.W. Hoffman, D. Ben-Dov, S. Funk, I. Daimont, A.R. Jajtner, J.R. Townsend, D.D. Church, β-Hydroxy-β-methylbutyrate attenuates cytokine response during sustained military training, Nutrition Research 36(6) (2016) 553-563.
[27] S. Portal, A. Eliakim, D. Nemet, O. Halevy, Z. Zadik, Effect of HMB supplementation on body composition, fitness, hormonal profile and muscle damage indices, Journal of Pediatric Endocrinology and Metabolism 23(7) (2010) 641-650.
[28] S.M. Opal, J.C. Wherry, P. Grint, Interleukin-10: potential benefits and possible risks in clinical infectious diseases, Clinical infectious diseases 27(6) (1998) 1497-1507.
[29] Yan Wang, Research progress of relations between exercise training and obese chronic inflammatory, Journal of Chemical & Pharmaceutical Research 5(2) (2013) 829.
[30] D.C. Nieman, N.C. Bishop, Nutritional strategies to counter stress to the immune system in athletes, with special reference to football, Journal of sports sciences 24(07) (2006) 763-772.
[31] D.C. Nieman, D.A. Henson, J.M. Davis, E.A. Murphy, D.P. Jenkins, S.J. Gross, M.D. Carmichael, J.C. Quindry, C.L. Dumke, A.C. Utter, Quercetin's influence on exercise-induced changes in plasma cytokines and muscle and leukocyte cytokine mRNA, Journal of Applied Physiology 103(5) (2007) 1728-1735.
[32] D.C. Nieman, J.M. Davis, D.A. Henson, J. Walberg-Rankin, M. Shute, C.L. Dumke, A.C. Utter, D.M. Vinci, J.A. Carson, A. Brown, Carbohydrate ingestion influences skeletal muscle cytokine mRNA and plasma cytokine levels after a 3-h run, Journal of applied physiology 94(5) (2003) 1917-1925.
[33] A.V. Caris, E.T. Da Silva, S.A. Dos Santos, F.S. Lira, L.M. Oyama, S. Tufik, R.V.T. Dos Santos, Carbohydrate Supplementation Influences Serum Cytokines after Exercise under Hypoxic Conditions, Nutrients 8(11) (2016) 706.
[34] L. Hirose, K. Nosaka, M. Newton, A. Laveder, M. Kano, J. Peake, K. Suzuki, Changes in inflammatory mediators following eccentric exercise of the elbow flexors, Exerc Immunol Rev 10(75-90) (2004) 20.
[35] P.A. Della Gatta, A.P. Garnham, J.M. Peake, D. Cameron-Smith, Effect of exercise training on skeletal muscle cytokine expression in the elderly, Brain, behavior, and immunity 39 (2014) 80-86.
[36] J. Peake, K. Nosaka, M. Muthalib, K. Suzuki, Systemic inflammatory responses to maximal versus submaximal lengthening contractions of the elbow flexors, Exercise immunology review 12 (2005) 72-85.
[37] M.W. Feinberg, M.K. Jain, F. Werner, N.E. Sibinga, P. Wiesel, H. Wang, J.N. Topper, M.A. Perrella, M.-E. Lee, Transforming growth factor-β1 inhibits cytokine-mediated induction of human metalloelastase in macrophages, Journal of Biological Chemistry 275(33) (2000) 25766-25773.

[38] K.A. Volaklis, I. Smilios, A.T. Spassis, C.E. Zois, H.T. Douda, M. Halle, S.P. Tokmakidis, Acute pro- and anti-inflammatory responses to resistance exercise in patients with coronary artery disease: a pilot study, Journal of sports science & medicine 14(1) (2015) 91-97.

[39] S. Hering, C. Jost, H. Schulz, B. Hellmich, H. Schatz, A. Pfeiffer, Circulating transforming growth factor β1 (TGFβ1) is elevated by extensive exercise, European journal of applied physiology 86(5) (2002) 406-410.

[40] A.-M. Touvra, K.A. Volaklis, A.T. Spassis, C.E. Zois, H. Douda, K. Kotsa, S.P. Tokmakidis, Combined strength and aerobic training increases transforming growth factor-beta1 in patients with type 2 diabetes, Hormones (Athens) 10(2) (2011) 125-30.

[41] P. Gordon, E. Vannier, K. Hamada, J. Layne, B. Hurley, R. Roubenoff, C. Castaneda-Sceppa, Resistance training alters cytokine gene expression in skeletal muscle of adults with type 2 diabetes, International journal of immunopathology and pharmacology 19(4) (2006) 739-749.

[42] I. Bautmans, R. Njemini, S. Vasseur, H. Chabert, L. Moens, C. Demanet, T. Mets, Biochemical changes in response to intensive resistance exercise training in the elderly, Gerontology 51(4) (2005) 253-265.

[43] B. Schober-Halper, M. Hofmann, S. Oesen, B. Franzke, T. Wolf, E.-M. Strasser, N. Bachl, M. Quittan, K.-H. Wagner, B. Wessner, Elastic band resistance training influences transforming growth factor-ß receptor I mRNA expression in peripheral mononuclear cells of institutionalised older adults: the Vienna Active Ageing Study (VAAS), Immunity & Ageing 13(1) (2016) 22.

[44] D.J. Grainger, Transforming growth factor β and atherosclerosis: so far, so good for the protective cytokine hypothesis, Arteriosclerosis, thrombosis, and vascular biology 24(3) (2004) 399-404.