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Research Article

Effect of 8-week simultaneous metabolic resistance training and Chlorogenic acid supplement on the expression level of BMP2, BMP4, BMP6, and BMP7: A randomized open label clinical trial

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Abstract

Background: BMP has critical role in development, growth, and differentiation of cell. There is enough evidence regarding the role of BMPs in lipid accumulation and homeostasis The current study aimed to evaluate the simultaneous effect of eight weeks of metabolic resistance training (MRT) and Chlorogenic Acid (CGA) supplementation on expression level of BMP2, BMP4, BMP6, and BMP7 in overweight women.

Materials and Methods: We carried-out a randomized clinical trial performed on 40 overweight women in Iran 2020. We randomly assigned the study participants into four groups including combined 8-week course of metabolic resistance training (MRT) training and 400 mg chlorogenic acid (CGA) supplementation, 8-week course of MRT, CGA supplement, and the control group. Intervention included three MRT training sessions per week and the duration of each session was 45 minutes. The training exercise intervention was 10 minutes of warm-up, 30 minutes of metabolic resistance training, and 5 minutes of cool-down. The supplementation arms were also received 400 mg / day CGA extracted from green coffee beans. Expression level of BMP2,4,6, and 7 was the main interested outcome that assessed pre and post intervention.

Results: We observed significant decrease in BMP2 level in combined intervention group in compared with the control group (Regression coefficient= -2.7, 95% CI=-5.0, -0.4). Moreover, we observed that combined intervention has decreased BMP4 level and the observed difference was statistically significant (Regression coefficient= -6.2, -1.7, -10.6). No significant effect for MRT and CGA group was reported regarding BMP2, and BMP4. Neither combined nor separate form of CGA and MRT had no significant effect on BMP6 and BMP7 (P-value>0.05).

Conclusion: Simultaneous MRT exercises and CGA supplementation prohibited expression levels of BMP2, and BMP4. However, they had no significant effect separately. There was no association between the interventions and expression level of BMP6, and BMP7.

Keywords:
metabolic resistance training, green coffee, obese and overweight women, Bone/body morphogenic proteins

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1. Introduction

Obesity is a global health problem with an increasing trend over the past decade across the world (1). It increases risk of many chronic diseases and also is associated with higher risk of all-cause mortality (2). Lack of physical activity, sedentary lifestyle, and high calories fast-food and diet are possibly the main risk factors of obesity (3).

Exposure to exercise and dietary factors could regulate neurogenesis in adults that involves in different phases of cell cycle including cell proliferation, differentiation, survival and integration into functional circuits(4, 5). Bone/body morphogenic proteins (BMPs) are type of growth factors that are affected by such exposures. Although inducing bone and cartilage formation are the original ability of the BMPs, there are enough evidence regarding the role of BMPs in lipid accumulation and homeostasis (6, 7). BMP family has at least 20 members with different roles in development, growth, and differentiation. For instance, BMP8 is known as a driver of thermogenic response in brown adipose tissues and BMP7 could lead fat browning through regulation of insulin signaling (8, 9). On the other hand, BMP2 and BMP4 have already been shown as regulator of insulin sensitivity (10, 11). According to previous studies BMPs could regulate insulin resistance and they are correlated with metabolic syndrome, as well (10, 12, 13).

As it already mentioned exposure to exercise and some specific dietary supplement could regulate level of BMPs. Previous studies reported that exercise training has various effects on different member of BMP family. It could induce expression of BMP7 (14), while it had inhibitory effects on BMP2 and BMP4 (10).

Despite from lack of evidence, the results of previous studies regarding the effect of exercise on BMPs are controversial. Moreover, dietary supplement like chlorogenic acid (CGA) was almost ignored and simultaneous effects of these two factors have never been investigated. In the current study, we aimed to investigate the effect of 8-weeks metabolic resistance training (MRT) and CGA supplement on level of different BMPs including BMP2, BMP4, BMP6, and BMP7. We also determined the effect of simultaneous MRT and CGA on level of the investigated BMPs.

2. Materials and Methods

The current study was an open-label randomized clinical trial that was performed on 40 overweight women. The study participants were taken using a convenient sampling scheme among women with a body mass index between 25 and 28 who participated in a fitness gym in Tehran-Iran. Having physical activity in the past six months, Not using dietary supplements, or medications, having underlying diseases related to the investigated variables, and not having any pulmonary diseases were the other inclusion criteria. Women with no willingness to participate were excluded from the study. This study was reviewed and approved by XXX ethics committee and all study participants completed a written informed consent prior to the study. The study participants were allowed to leave the study at any phase.

We investigated the effect of CGA supplement, MRT exercise, and simultaneous supplement and exercise versus a control group and the study participants were randomly assigned to one of these groups using a stratified balanced block randomization approach. The training exercise intervention was 10 minutes of warm-up, 30 minutes of metabolic resistance training, and 5 minutes of cool-down. The intensity of the exercise was 60-70 percent of the maximum heart rate of the participants (15). The overall duration of each training session was 45 minutes and it was repeated three times a week. We also used Chlorogenic Acid (CGA) extracted from green coffee as the dietary supplement. Each participant in the supplement group received 400 mg of the green coffee extract on daily basis (16). More detail about sampling, randomization, and interventions are described elsewhere.

We collected data on Demographic and biometric data including age, weight, height, BMI, medical history, and volume of physical activity for each participant. Moreover, data on lipid profiles were also collected as baseline characteristics. Lipid profile was determined using a blood sample taken at baseline and repeated after an 8-weeks study period. All study participants were fasting over the last 12 hours before sampling and sampling was done from their right-hand vein at 8 AM. BMPs expression levels including BMP2, BMP4, BMP6, and BMP7 were the main investigated outcomes that were assessed using DNA extraction. Real-time RT-PCR was used to determine the expression level of BMPs. All procedures were repeated at the end of the study after an 8-weeks intervention.

Statistical analysis

We checked the normality assumption and provided the mean and standard deviation (SD) if this assumption was met. Otherwise, we presented the continuous variables as the median and interquartile range (IQR). For dichotomous variables frequency proportion was reported. The baseline characteristics were compared over the four investigated groups to assure that randomization generated comparable groups. We used one-way ANOVA or its non-parametric equivalence for continuous variables and the between-group difference of dichotomous variables was compared using the Chi-square test. Pre and post-study within-group variability was investigated using the U-Mann Whitney test. We also used multiple linear regression to investigate the effect of each intervention on the expression level of BMPs after adjustment for potential confounders. Age, BMI, baseline BMP, HDL, LDL, and TG were entered into the model and then we sued backward approach to generate the best fitted model. We created separate regression model for each investigated BMP. All statistical analysis was performed using Stata software (Ver 17.0, College Station, Texas, USA). P-values <0.05 were considered significant.

3. Results

We enrolled 40 overweight women into the four groups including control, CGA supplement, MRT training, and CGA/MRT combined group. Table 1 compared the baseline characteristics including age, weight, BMI, HDL, and LDL. And TG among the compared groups and found no statistically significant difference (P-value>0.05) (Table 1).

The average BMP2 expression level at baseline was 26.1 (5.8) in the control group. It was 25.4 (5.1) in the CGA group, 23.9 (5.4) in the MRT group, and 24.9 (3.4) and the combined MRT/CGA group. After 8 weeks, the BMP2 expression level in the control group, CGA, MRT, and combined groups reached 25.7 (6.3), 25.5 (4.7), 22.4 (6.5), and 21.9 (4.9), respectively (Figure 1). The median of the effect size in the combined CGA/MRT group was 2.9 which was statistically significant (P-value= 0.013). No statistical pre and the post-intervention difference was observed in other groups (P-value>0.05) (Table 2).

The average expression level of BMP4 was 22.7 (4.4) at baseline and 25.1 (7.1) after an 8-weeks study period. The average level of BMP4 in the CGA supplement group was 23.4 (4.6) and 23.8 (5.2) at baseline and after the 8-week intervention. We observed 3.1 units decrease in the BMP4 expression level in the exercise group where the average BMP4 was 23.9 (4.6) at baseline and 20.8 (9.1) at the end of the study. However, the observed difference was not statistically significant (P-value=0.072). Moreover, the average level of BMP4 was 24.6 (7.3) at baseline and decreased to 17.5 (15.5) after 8 weeks of CGA/MRT intervention. This decrease in the BMP4 level was statistically significant (P-value=0.021) (Table 2) (Figure 1).

We also compared the expression level of BMP6 and BMP7 before and after the study period and observed no statistically significant group within the all investigated groups (Table 2).

The effect size of each intervention was compared versus the control group adjusted for all possible confounders. According to table 1, the combined CGA/MRT has led to a 2.7 decrease in the BMP2 expression level and it was statistically significant in comparison to the control group (0.021). The post-test average expression level of BMP4 in the combined intervention arm was also 6.2 units (95% CI= 1.7, 10.6) lower than the control group and the observed difference was statistically significant (P-value=0.008). We also spotted a non-significant decrease in the expression level of BMP2 and BMP4 in the exercise group compared with the control group (P-value>0.05) (Table 3). We found no statistically significant association between the expression level of BMP6 and the applied interventions including CGA, MRT, and combined CGA/MRT. Such a pattern was observed regarding BMP7 expression level in the multiple linear regression model, as well (Table 3).

Table 1: Study participants baseline characteristics by type of intervention

Characteristics	Control	Supplement	Exercise	Exercise/Supp	P-value
Age, year	39.6 (4.7)	40.6 (7.0)	41.1 (4.9)	40.4 (5.9)	0.948
Weight, Kg	67.1 (5.2)	69.8 (3.3)	69.2 (5.1)	68.3 (3.5)	0.632
BMI, Kg/m^2	26.5 (1.4)	26.6 (1.3)	26.9 (1.2)	26.1 (1.2)	0.555
HDL, mg/dL	65.3 (6.8)	64.1 (5.4)	64.3 (8.1)	63.9 (9.3)	0.977
LDL, mg/dL	99.9 (19.9)	104.0 (20.3)	100.4 (25.6)	103.5 (22.5)	0.990
TG, md/dL	108.7 (35.8)	104.3 (22.9)	108.9 (15.9)	113.1 (36.1)	0.170

All variables presented as mean and standard deviation.

Table 2: Pre and post-intervention expression of BMP2, BMP4, BMP6, and BMP7 by each arms of the study

	BMP2		BMP4		BMP6		BMP7	
Group	Post-Pre	P-value	Post-Pre	P-value	Post-Pre	P-value	Post-Pre	P-value
Control	-0.2 (3.1)	0.714	0.5 (10.9)	0.556	3.6 (17.7)	0.375	-1.3 (12.4)	0.769
Supplement	0.04 (2.1)	0.752	0.4 (8.0)	1.00	-3.6 (16.9)	0.161	-3.5 (8.7)	0.130
Exercise	-2.0 (0.7)	0.075	-3.1 (6.8)	0.130	1.8 (16.9)	0.878	-6.1 (9.6)	0.322
Ex/Supp	-2.9 (3.6)	0.013	-7.1 (7.5)	0.019	0.8 (6.1)	0.798	0.02 (20.2)	0.734

The effect sizes are provided be median and interquartile ranges.

Table 3: Multiple linear regression to investigate the effect of each intervention on expression level of UCP1 adjusted for possible confounders

	BMP2		BMP4		BMP6		BMP7	
Group	Reg (95% CI)	P-value	Reg (95% CI)	P-value	Reg (95% CI)	P-value	Reg (95% CI)	P-value
Control	Reference		Reference		Reference		Reference	
Supplement	0.4 (-1.8, 2.6)	0.716	-2.5 (-8.7, 3.5)	0.557	-5.6 (-13.2, 1.8)	0.135	-0.01 (-7.7, 7.7)	0.996
Exercise	-1.2 (-3.4, 0.1)	0.261	-2.3 (-6.3, 2.2)	0.442	-2.4 (-9.8, 4.8)	0.495	-3.8 (-11.5, 3.9)	0.323
Supp/Exercise	-2.7 (-5.0, -0.4)	0.021	-6.2 (-1.7, -10.6)	0.008	-3.1 (-10.6, 4.3)	0.402	-3.9 (-12.1, 4.3)	0.339

Model is adjusted for age, baseline BMI, and baseline BMP level. CI= Confidence Interval

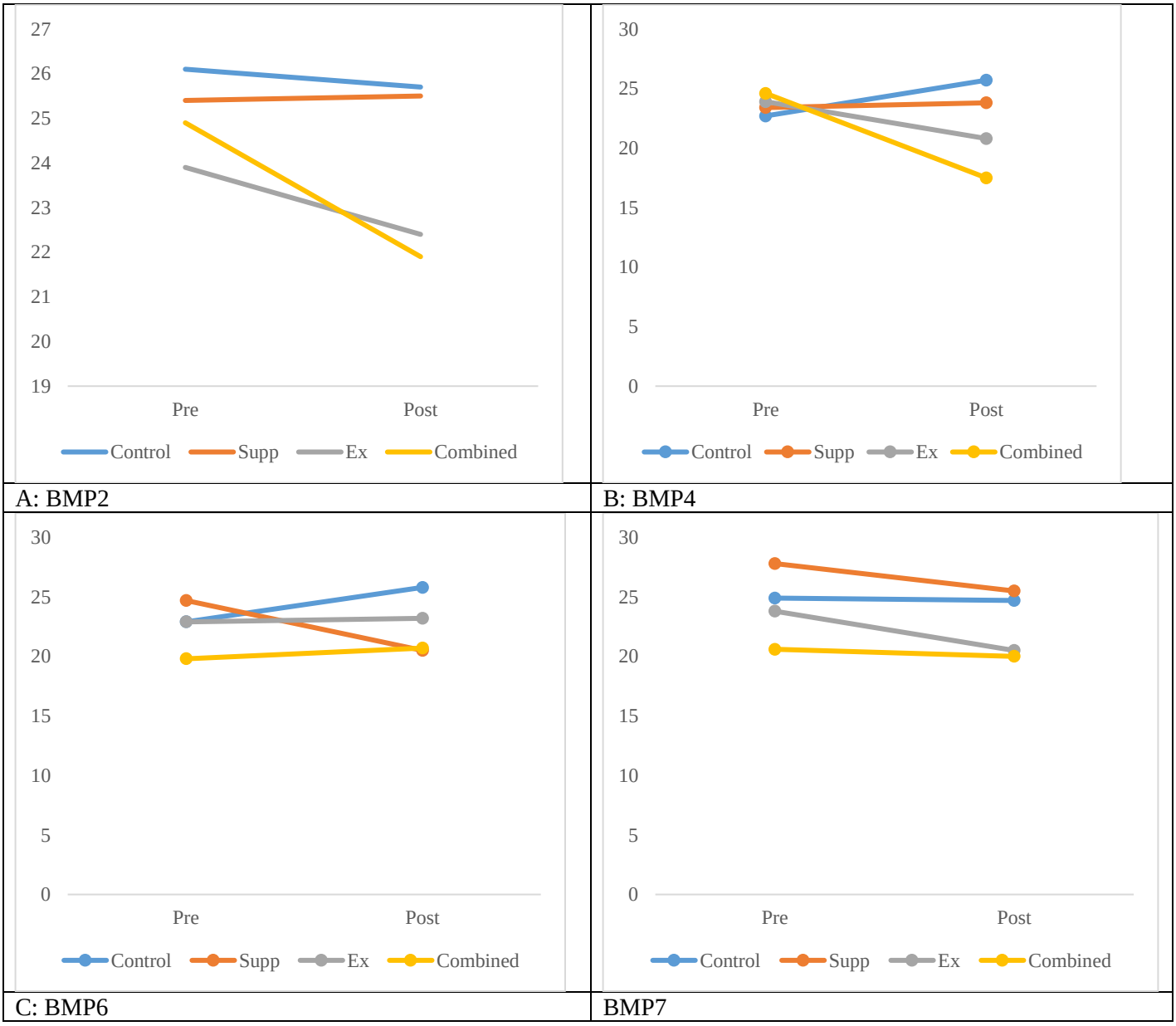

Figure 1: Average expression level of BMP2, BMP4, BMP6, and BMP7 before and after 8-weeks study period by type of intervention

4. Discussion

We performed the current study to investigate the effect of CGA supplementation and MRT exercises on the expression level of the BMP family including BMP2, BMP4, BMP6, and BMP7. We also aimed to assess the effect of 8-week simultaneous CGA supplementation and MRT exercises on the BMPs expression levels. According to our data, we found simultaneous CGA supplementation and MRT exercises could significantly inhibit the expression of BMP2 and BMP4. The such decreasing pattern was also observed for the MRT group. However, the observed association was not statistically significant indicating that the CGA supplement might work as a booster. Moreover, we found no significant effect for CGA and MRT intervention either solely or in the combined form regarding the expression level of BMP6 and BMP7.

We found that the combined CGA and MRT intervention could inhibit BMP2 and BMP4 expression levels. According to our findings average expression level of BMP2 and BMP4 in the CGA/MRT group was 2.9 and 7.8 units lower than the control group. However, such effects were not observed in the exercise and supplement group when they were given to the participants separately. There is limited evidence regarding the effect of exercise and CGA supplements on the BMP family. However, according to previous studies, BMP has a critical role in the regulation of hemostasis (17). BMP2 and BMP4 as the closest relatives have already been shown as factors promoting white adipogenesis through the induction of peroxisome proliferator-activated receptor (PPAR) (18, 19). According to the Leipzig Cohort, there was a positive correlation between BMP2 and BMI and diabetic status, especially in visceral adipose tissues(20).

Such findings were consistent with ours since we showed reducing BMP2 has led to weight and BMI reduction. Sadeghi et al, reported that different intensities of resistant training had no effect on the expression level of BMP4 (10). They also observed a downward non-significant trend between the intensity of resistance training and the post-intervention level of BMP4 (10). Their findings were in favor of the current study as we found no association between resistant training and BMP4. The data regarding the effects of CGA supplements on BMP2 and BMP4 was limited. In one study by Fujita et al. CGA had no effect on the expression of BMP4 that was similar to our findings (21). However, as we added the CGA supplement our data in CGA/MRT group was unique and we found a significant reduction in BMP4 level in this group. In another study by Majerczak et al no association between BMP4 level in the heart muscle of mics and exercise was observed that confirmed our findings (22). They also illustrated that exercise training could significantly reduce the level of BMP4 in the tibia indicating that the effect of exercise on BMP4 level might depend on the type of tissue(22). It has been argued that BMP4 tended to be accumulated in obese and overweight people since it could inhibit insulin secretion from beta cells (10). There are also evidences regarding the association between BMP4 level and Insulin resistance (23). Activation of IRS-1 inhibitors and insulin signaling was the proposed contribution of BMP4 in the upregulation of insulin resistance (17). Increasing the BMP4 level could reduce lipolysis and consequently increase the weighting of adipose tissues through Smad signaling pathway (17).

We also investigated the effect of resistance training and CGA supplement on the expression level of BMP7 and BMP6 and observed no statistically significant association in this regard. Rodrigues et al. against our findings have shown that training exercises could upregulate the level of BMP7(14). They also showed BMP7 was inversely correlated with body weight2(14). It seems that BMP7 leads to full activation of brown adipogenesis and affects processes such as the induction of primary regulators of brown fat such as PRDM16 and PGC-1. Also, the BMP7 protein increases the number of specific markers of brown fat (UCP1), adipogenic transcription factor PPARy, CCAAT binding proteins, and induction of p38 mitogen-activated mitochondrial kinase biogenesis and PGC-1α-dependent pathways (14). However, the studies conducted on the effect of exercise training on the expression level of BMPs were limited and there are serious differences in the method of conducting these studies. Also, the conducted studies were mostly performed on animals and the generalization of their findings to humans has serious limitations. These reasons can be considered the main reasons for the differences observed in the findings of the present study with previous studies.

The current study is one of the first attempts to investigate the simultaneous effect of MRT training and CGA supplementation on BMPs expression. In this sense, the findings of this research were unique as we had a comprehensive approach regarding BMPs and investigated the expression level of BMP2. BMP4, BMP6, and BMP7. Conducting the study on a human sample with no lost-to follow-up cases in all intervention and control groups was the main strength of the current study. However, the interpretation of our findings must be done in light of our limitations.

The impossibility of blinding was the main limitation of the current study, which could bias the findings of the present study. However, in this study, we tried to avoid contact between the intervention and control groups, and the people of these groups participated in their exercise programs separately. Moreover, the small sample size was the other limitation that reduced our power.

Conclusion

Simultaneous MRT exercises and CGA supplementation prohibited expression levels of BMP2, and BMP4. However, they had no significant effect separately. We also found no association between MRT exercise/CGA supplement with BMP6 and BMP7 either in combined or separate form. More human studies are required.

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Compliance with ethical standards

Conflict of interest None declared.

Ethical approval the research was conducted with regard to the ethical principles.

Informed consent Informed consent was obtained from all participants.

Author contributions

Conceptualization: M.T., F.GH., SH.S., KH.E.; Methodology: M.T., F.GH., KH.E.; Software: M.T., F.GH., SH.S., KH.E.; Validation: M.T., F.GH., SH.S.; Formal analysis: F.GH., SH.S., KH.E.; Investigation: F.GH., SH.S., KH.E.; Resources: M.T., F.GH., SH.S.; Data curation: M.T., F.GH., KH.E.; Writing - original draft: M.T., F.GH., SH.S., KH.E.; Writing - review & editing: M.T., SH.S., KH.E.; Visualization: M.T., F.GH., SH.S., KH.E.; Supervision: M.T., SH.S., KH.E.; Project administration: M.T., SH.S.; Funding acquisition: M.T., SH.S., KH.E.

References

1. Riyahi Malayeri, S., Saei, M. Changes in Insulin resistance and serum levels of resistin after 10 weeks high intensity interval training in overweight and obese men. Sport Physiology & Management Investigations, 2019; 10(4): 31-42. http://www.sportrc.ir/article_82662.html?lang=en.

2. Ashtary-Larky D, Kashkooli S, Bagheri R, Lamuchi-Deli N, Alipour M, Mombaini D, Baker JS, Ramezani Ahmadi A, Wong A. The effect of exercise training on serum concentrations of chemerin in patients with metabolic diseases: a systematic review and meta-analysis. Arch Physiol Biochem. 2021 Mar 2:1-10. doi: 10.1080/13813455.2021.1892149. Epub ahead of print. PMID: 33651961.

3. Farazandeh Nia, D., Hosseini, M., Riyahi Malayeri, S., Daneshjoo, A. Effect of Eight Weeks of Swimming Training with Garlic Intake on Serum Levels of IL-10 and TNF-α in Obese Male Rats. Jundishapur Scientific Medical Journal, 2018; 16(6): 665-671. doi: 10.22118/jsmj.2018.57830

4. Riyahi Malayeri S, Kaka Abdullah Shirazi S, Behdari R, mousavi Sadati K. Effect of 8-week Swimming training and garlic intake on serum ICAM and VCAM adhesion molecules in male obese rats. JSSU 2019; 26 (10): 867-878.URL: http://jssu.ssu.ac.ir/article-1-4695-en.html.

5. Gobeske KT, Das S, Bonaguidi MA, Weiss C, Radulovic J, Disterhoft JF, Kessler JA. BMP signaling mediates effects of exercise on hippocampal neurogenesis and cognition in mice. PLoS One. 2009 Oct 20;4(10):e7506. doi: 10.1371/journal.pone.0007506. PMID: 19841742; PMCID: PMC2759555.

6. Wu MY, Hill CS. Tgf-beta superfamily signaling in embryonic development and homeostasis. Dev Cell. 2009 Mar;16(3):329-43. doi: 10.1016/j.devcel.2009.02.012. PMID: 19289080.

7. Clark JF, Ciccarelli EJ, Kayastha P, Ranepura G, Yamamoto KK, Hasan MS, et al. BMP pathway regulation of insulin signaling components promotes lipid storage in Caenorhabditis elegans. PLoS genetics. 2021;17(10):e1009836. https://doi.org/10.1371/journal.pgen.1009836.

8. Whittle AJ, Carobbio S, Martins L, Slawik M, Hondares E, Vázquez MJ, Morgan D, Csikasz RI, Gallego R, Rodriguez-Cuenca S, Dale M, Virtue S, Villarroya F, Cannon B, Rahmouni K, López M, Vidal-Puig A. BMP8B increases brown adipose tissue thermogenesis through both central and peripheral actions. Cell. 2012 May 11;149(4):871-85. doi: 10.1016/j.cell.2012.02.066. PMID: 22579288; PMCID: PMC3383997.

9. Riyahi Malayeri S, Abdolhay S, Behdari R, Hoseini M. The combined effect of resveratrol supplement and endurance training on IL-10 and TNF- α in type 2 diabetic rats. RJMS 2019; 25 (12) :140-149.URL: http://rjms.iums.ac.ir/article-1-5526-en.html.

10. Sadeghi Eshtehardi F, Peeri M, Azarbayjani MA. The effect of Different Intensity Circuit Resistance Training on the Levels of Selected Adipokines (WISP-1, WISP-2, BMP4) in Obese Postmenopausal Women. Razi Journal of Medical Sciences. 2022;28(12):15-27. URL: http://rjms.iums.ac.ir/article-1-6983-en.html.

11. Mao H, Li L, Fan Q, Angelini A, Saha PK, Wu H, Ballantyne CM, Hartig SM, Xie L, Pi X. Loss of bone morphogenetic protein-binding endothelial regulator causes insulin resistance. Nat Commun. 2021 Mar 26;12(1):1927. doi: 10.1038/s41467-021-22130-2. PMID: 33772019; PMCID: PMC7997910.

12. Chattopadhyay T, Singh RR, Gupta S, Surolia A. Bone morphogenetic protein-7 (BMP-7) augments insulin sensitivity in mice with type II diabetes mellitus by potentiating PI3K/AKT pathway. Biofactors. 2017 Mar;43(2):195-209. doi: 10.1002/biof.1334. Epub 2017 Feb 10. PMID: 28186649.

13. Xu X, Li X, Yang G, Li L, Hu W, Zhang L, Liu H, Zheng H, Tan M, Zhu D. Circulating bone morphogenetic protein-9 in relation to metabolic syndrome and insulin resistance. Sci Rep. 2017 Dec 13;7(1):17529. doi: 10.1038/s41598-017-17807-y. PMID: 29235531; PMCID: PMC5727514.

14. Rocha-Rodrigues S, Rodríguez A, Gouveia AM, Gonçalves IO, Becerril S, Ramírez B, Beleza J, Frühbeck G, Ascensão A, Magalhães J. Effects of physical exercise on myokines expression and brown adipose-like phenotype modulation in rats fed a high-fat diet. Life Sci. 2016 Nov 15;165:100-108. doi: 10.1016/j.lfs.2016.09.023. Epub 2016 Sep 28. PMID: 27693382.

15. Takhty M, Ghazalian F, Sohili S, Ebrahim K. Simultaneous Effect of Eight Weeks of Metabolic Resistance Training and CGA Supplementation on Weight Loss and Fat Profile of Overweight Women. RJMS 2022; 29 (7) :23-32.URL: http://rjms.iums.ac.ir/article-1-7593-fa.html.

16. Roshan H, Nikpayam O, Sedaghat M, Sohrab G. Effects of green coffee extract supplementation on anthropometric indices, glycaemic control, blood pressure, lipid profile, insulin resistance and appetite in patients with the metabolic syndrome: a randomised clinical trial. Br J Nutr. 2018 Feb;119(3):250-258. doi: 10.1017/S0007114517003439. Epub 2018 Jan 8. PMID: 29307310.

17. Schreiber, I., Dörpholz, G., Ott, CE. et al. BMPs as new insulin sensitizers: enhanced glucose uptake in mature 3T3-L1 adipocytes via PPARγ and GLUT4 upregulation. Sci Rep 7, 17192 (2017). https://doi.org/10.1038/s41598-017-17595-5

18. Tseng YH, Kokkotou E, Schulz TJ, Huang TL, Winnay JN, Taniguchi CM, Tran TT, Suzuki R, Espinoza DO, Yamamoto Y, Ahrens MJ, Dudley AT, Norris AW, Kulkarni RN, Kahn CR. New role of bone morphogenetic protein 7 in brown adipogenesis and energy expenditure. Nature. 2008 Aug 21;454(7207):1000-4. doi: 10.1038/nature07221. PMID: 18719589; PMCID: PMC2745972.

19. Hoffmann JM, Grünberg JR, Church C, Elias I, Palsdottir V, Jansson JO, Bosch F, Hammarstedt A, Hedjazifar S, Smith U. BMP4 Gene Therapy in Mature Mice Reduces BAT Activation but Protects from Obesity by Browning Subcutaneous Adipose Tissue. Cell Rep. 2017 Aug 1;20(5):1038-1049. doi: 10.1016/j.celrep.2017.07.020. PMID: 28768190.

20. Guiu-Jurado E, Unthan M, Böhler N, Kern M, Landgraf K, Dietrich A, Schleinitz D, Ruschke K, Klöting N, Faßhauer M, Tönjes A, Stumvoll M, Körner A, Kovacs P, Blüher M. Bone morphogenetic protein 2 (BMP2) may contribute to partition of energy storage into visceral and subcutaneous fat depots. Obesity (Silver Spring). 2016 Oct;24(10):2092-100. doi: 10.1002/oby.21571. Epub 2016 Aug 12. PMID: 27515773.

21. Fujita K, Otsuka T, Yamamoto N, Kainuma S, Ohguchi R, Kawabata T, Sakai G, Kuroyanagi G, Matsushima-Nishiwaki R, Kozawa O, Tokuda H. (-)-Epigallocatechin gallate but not chlorogenic acid upregulates osteoprotegerin synthesis through regulation of bone morphogenetic protein-4 in osteoblasts. Exp Ther Med. 2017 Jul;14(1):417-423. doi: 10.3892/etm.2017.4491. Epub 2017 May 22. PMID: 28672948; PMCID: PMC5488595.

22. Majerczak J, Filipowska J, Tylko G, Guzik M, Karasinski J, Piechowicz E, Pyza E, Chlopicki S, Zoladz JA. Impact of long-lasting spontaneous physical activity on bone morphogenetic protein 4 in the heart and tibia in murine model of heart failure. Physiol Rep. 2020 Apr;8(8):e14412. doi: 10.14814/phy2.14412. PMID: 32319199; PMCID: PMC7174143.

23. Keller MP, Choi Y, Wang P, Davis DB, Rabaglia ME, Oler AT, Stapleton DS, Argmann C, Schueler KL, Edwards S, Steinberg HA, Chaibub Neto E, Kleinhanz R, Turner S, Hellerstein MK, Schadt EE, Yandell BS, Kendziorski C, Attie AD. A gene expression network model of type 2 diabetes links cell cycle regulation in islets with diabetes susceptibility. Genome Res. 2008 May;18(5):706-16. doi: 10.1101/gr.074914.107. Epub 2008 Mar 17. PMID: 18347327; PMCID: PMC2336811.