DOI: 10.7860/JCDR/2019/41201.13066

Original Article

Physiology Section

The Effect of a 16-week Home-based Aerobic Exercise Program on Serum High-sensitivity C-Reactive Protein (Hs-CRP) and Insulin Resistance in Polycystic Ovary Syndrome

NAHID MOHAMMADI JAVID[1], NASER BEHPOUR[2], VAHID TADIBI[3]

ABSTRACT

Introduction: Polycystic Ovarian Syndrome (PCOS) is one of the most common hormonal disorders that affect 10 to 15% of women of reproductive age. Women with PCOS are at risk for complications such as pregnancy poor outcomes, insulin resistance, Type 2 Diabetes Mellitus (T2DM), metabolic syndrome, cardiovascular diseases and some malignant conditions where increase in serum C-reactive protein (CRP) level is known to be a marker.

Aim: To investigate the effect of a 16-week home-based aerobic exercise program on high-sensitivity CRP (hs-CRP) and insulin resistance index in females with PCOS.

Materials and Methods: In this quasi-experimental study, 24 female patients with PCOS were included and were divided into experimental (a home-based aerobic exercise program for 16 weeks) group (12 subjects) and control group (no intervention, 12 subjects). Serum hs-CRP and insulin resistance index (HOMA-IR) were measured and compared between the two groups. The paired t-test was used to compare the variables at baseline and after 16-weeks.

Results: Mean (±SD) hs-CRP level in experimental group at baseline was 6.31 (±2.64) mg/L which decreased to 3.91 (±1.59) mg/L (p=0.004). Mean (±SD) HOMA-IR in the experimental group at baseline was 3.24 (±1.3) which decreased to 1.87 (±0.47) after 16-weeks. However, no significant change in hs-CRP or HOMA-IR was seen in control group.

Conclusion: The home-based aerobic exercise program had a beneficial effect on improving insulin sensitivity (decrease in HOMA-IR) and reduction in hs-CRP in women with PCOS. This exercise could be recommended as a safe treatment for these patients.

Keywords: Exercise, Inflammation, Polycystic ovarian syndrome

INTRODUCTION

PCOS is the most common endocrine disorder at reproductive age (20 to 40 years of age) which affects about 10% of females [1]. PCOS prevalence has been estimated as 15.2% among Iranian women [2]. This condition, which is also called Stein-Leventhal syndrome after gynaecologists Stein and Leventhal who described the condition in 1935, is manifested by appearance of poly-cystic ovaries on ultrasound and on the other side, it is manifested by obesity, hyperandrogenism, menstrual abnormalities, and infertility [2]. Metabolic disorders including increased levels of Lutein Hormone (LH), testosterone and insulin is common in PCOS and affect health status of these patients in long-term [3]. At one end, morphological characteristics of PCOS is seen on ultrasound examination including more than 9 mm increase in ovarian size, existence of 10 or more 2-8 mm cysts in one surface, and increased stromal density. At the other side, clinical symptoms such as oligomenorrhea, hirsutism, anovulation or low ovulation and laboratory findings such as increased serum androgens, impaired glucose tolerance test and dyslipidemia are seen. PCOS is a form of ovarian hyperandrogenism. This hyperandrogenism appears during puberty but in fact, stems in childhood and even in fetal period and is due to dysregulation of androgen production by thecal cells [2,4].

The symptoms of PCOS include ovarian dysfunction, multi-cystic ovaries, biochemical hyperandrogenism, and/or clinical symptoms (hirsutism and acne). Women who suffer from this disease show metabolic abnormalities such as insulin resistance, obesity, dyslipidemia and are at risk of developing cardiovascular and Type 2 Diabetes mellitus (T2DM) as well [3]. The insulin resistance mechanism in PCOS is not known clearly; however, mild chronic inflammation has been suggested as one of the possible aetiologies [5].

Mild chronic inflammation is associated with higher than normal levels of some cytokines including Tumour Necrosis Factor-alpha (TNF-α), Interleukin-6 (IL-6), and High-Sensitivity C-Reactive Protein (Hs-CRP) [6]. Evidence shows that inflammatory biomarkers are increased in PCOS patients and there is a close association between the inflammatory markers and infertility as well as metabolic and cardiovascular complications. This shows that the process of inflammation plays an important role in insulin resistance pathogenesis in PCOS patients [7].

On the other hand, studies show that an average weight loss through limiting calorie intake is associated with improving health factors in PCOS [8]. Nevertheless, despite the well-known advantages of physical exercises in the general population, limited studies have been performed in PCOS. Based on the limited reports, it appears that physical exercise improves body preparatory status, physical preparation, fasting insulin, menstrual cycles and ovulation [9-13]. Notwithstanding, in this limited studies, the mechanism of such beneficial effects of training in PCOS patients is not clear. Most previously conducted studies focused on the effect of exercise on factors such as lipid profile and blood pressure and few studies assessed the effect of exercise on inflammation [14]. Thus, in view of the role attributed to inflammation in PCOS pathogenesis and the results of the previous studies, further studies are required to investigate the efficacy of exercise on inflammatory markers in these patients. The objective of the current study was to study the effects of a 16-week home-based aerobic exercise program on serum hs-CRP level and insulin resistance among PCOS patients.

MATERIALS AND METHODS

This quasi-experimental study was performed at Imam Reza Hospital, which is a University Hospital affiliated to Kermanshah

University of Medical Sciences, Kermanshah, Iran. The study lasted from March to September 2017.

The study population consisted of female patients diagnosed with PCOS. The diagnosis was made by a board certified endocrinologist after obtaining laboratory tests, clinical examination and ultrasound of the ovaries using the Rotterdam criteria [15]. According to the criteria, two of three items namely oligo-and/or anovulation, clinical and/or biochemical signs of excess androgen, polycystic ovaries detected on ultrasound should be present to make the diagnosis of PCOS. Inclusion criteria included females with PCOS aged 20 to 40 years. Exclusion criteria were inability to perform physical exercise, cigarette smoking, infection and taking any medication by the patient which can affect laboratory tests. A total of 24 patients were consecutively included into the study. The subjects were divided into experimental group (aerobic exercise group, 12 patients) and control group (no intervention, 12 cases).

The details of the study and objectives of the protocol were explained to the patients and informed consent was obtained. The participants were allowed to leave the study whenever they were reluctant to continue. The study protocol was approved by our university Deputy of Research and Ethics Committee (Code: IR.KUMS.REC.1397.572).

Aerobic Exercise Program

The experimental group participated in a daily aerobic exercise program. The participants were asked to perform the stepping program at home following the schedule every morning at 11 o'clock in the morning. To guide the participants, an audio file was prepared and delivered to the experimental group subjects via cell phone which contained 88 acoustic signals per minute for a four-stroke stepping and a rhythm of 22 steps per minute. In order to monitor and ensure that the aerobic exercise program was completed correctly and on a daily basis, the exercises of five participants which were selected randomly every day were monitored.

The goal of the exercise program was to achieve the specific Exercise Energy Expenditure (ExEE) at each session. ExEE is amount of energy required by an individual to perform exercise. Specific ExEE during the first four weeks of the exercise program was equivalent to 4% of the estimated individual energy needed to maintain weight, which during the fifth to the eight weeks of the exercise increased to 6%, and during the weeks 9 to 12 increased to 8%, and during the weeks 13 to 16 increased by 10% [16]. The required energy was also calculated from the equation for the energy required to maintain weight for subjects with routine lifestyle [16]:

Energy requirement (kilocalories per day)=1625+31.8 (fat free mass in kilograms)+1.5 (fat mass in kilogram)–187 (for females).

Considering one minute of stepping with specific height and number of steps, the amount of oxygen consumed per minute was determined. With determining ExEE, by dividing it to VO2, the required time for stepping to reach exercise oxygen consumption was determined. After estimating the ExEE for each session, and after converting it to exercise oxygen consumption (VO2), the obtained value was put into a formula suggested by the American College of Sports Medicine to determine stepping ergometry, the required time for stepping to achieve the calculated required energy was determined [17]:

VO2 (mL.kg-1.min-1)=(0.2×f)+(1.33×1.8×f×h)+3.5 mL.kg-1.min-1, f is the stepping frequency in minutes; H is step height in metres; the height=16.25 inches or 41.275 cm for each step and a total number of 22 steps per minute.

After determining the required time for stepping for each individual, a table was designed which included schedule of stepping for the study period.

Laboratory Assays

Blood samples were taken two times to measure fasting glucose, fasting insulin, and hs-CRP. First, blood samples were obtained 24 hours before the first exercise session. The second time that blood samples were obtained was 48-hours after the last session of the exercise program. In both the occasions, the blood samples were obtained after 12-hours of fasting via collection of 3 cc of anterior brachial vein blood. The blood samples were taken in certain hours of day (8-10 am) to ensure that diurnal variations do not affect blood insulin and hs-CRP levels. The blood samples were centrifuged for 15 minutes (3000 rpm) for plasma separation and were frozen and kept at -80°C. Insulin level was measured using Sandwich ELISA (Isotope, Sweden). To assess insulin resistance, Homeostatic Model of Assessment of Insulin Resistance (HOMA-IR) was derived using fasting glucose and insulin levels using the following formula [18]:

HOMA-IR={fasting plasma glucose (mmol/L)×fasting insulin concentration (μU/mL)}/22.5

Serum hs-CRP level was measured using immuno-turbidimetric method (Pars Azzmoon Co., Iran).

The participants were weighted using Seca Digital Weigh with 0.1-kg precision. The subject's height was measured by using measurement tape fixed on the wall with minimum 0.1 centimetres. The Body mass index (BMI) was calculated as body weight in Kg divided by height in metres squared.

STATISTICAL ANALYSIS

To study the changes of hs-CRP and HOMA-IR index before and after the study, the paired t-test was used. To determine the differences of hs-CR and HOMA-IR index between the experimental and control groups, the independent t-test was used. The significance level was set at 0.05. All analyses were performed by SPSS software (ver. 22.0, IBM, US).

RESULTS

The [Table/Fig-1] presents characteristics of the subjects. As observed, no significant difference was detected regarding age, height, weight, and BMI between the two groups.

Variables	Experimental group	Control group	p-value
Age (year)	31.64 (±4.28)	28.31 (±4.52)	0.49
Height (cm)	174.38 (±5.19)	177.22 (±7.46)	0.71
Weight (kg)	64.17 (±5.67)	66.67 (±7.39)	0.37
BMI (kg/m^2)	21.71 (±1.76)	20.96 (±2.09)	0.51

[Table/Fig-1]: Comparison of demographic characteristics between experimental and control groups.
Data are presented as mean (±standard deviation); BMI: Body mass index

Mean (±SD) fasting glucose and insulin levels at baseline in the experimental group decreased after 16-weeks of home-based aerobic exercise. However, in control group, no such decrease was observed. There was a significant decrease in hs-CRP (38.03% decrease from baseline) and HOMA-IR (42.2% decrease from baseline) in the experimental group after the aerobic exercise program. However, no significant change was observed in hs-CRP (0.42% change from baseline) and HOMA-IR (4.2% change from baseline) in control group [Table/Fig-2].

DISCUSSION

PCOS not only leads to infertility, but also can cause cardiovascular diseases [19]. Non-pharmacologic interventions in particular physical exercise and diet are the primary modalities to prevent cardiovascular diseases [20]. The goal of the present research was to study the effects of a 16-week home-based aerobic exercise program on hs-CRP and insulin resistance in PCOS women. The findings showed that the aerobic exercise program had significant effect on decreasing hs-CRP and insulin resistance index among PCOS

		Baseline	After 16 weeks	p-value
Experimental group	Fasting glucose, mmol/L	5.06 (±0.97)	4.26 (±1.13)	<0.001*
	Fasting insulin, µIU/mL	13.98 (±8.14)	9.92 (±8.76)	0.006*
	HOMA-IR	3.24 (±1.3)	1.87 (±0.47)	0.02*
	hs-CRP, mg/L	6.31 (±2.64)	3.91 (±1.59)	0.004*
Control group	Fasting glucose, mmol/L	4.98 (±0.89)	5.12 (±1.03)	0.13
	Fasting insulin, µIU/mL	13.56 (±8.52)	14.02 (±9.12)	0.23
	HOMA-IR	3.09 (±1.11)	3.22 (±1.39)	0.15
	hs-CRP, mg/L	7.01 (±2.84)	7.04 (±2.28)	0.11

[Table/Fig-2]: Comparison of hs-CRP and insulin resistance index before and after high intensity interval training and control groups.
Data are presented as mean (±standard deviation); HOMA-IR: Homeostatic model of assessment of insulin resistance; hs-CRP: high-sensitivity C-reactive protein
*Statistically significant p-value

females. However, no significant difference was found in control group who did not receive any intervention. Thus, improvement in insulin resistance index in the experimental group could be attributed to the aerobic exercise program implemented in this group. Studies on the role of physical exercise in PCOS patients have not been done sufficiently. Vizza L et al., investigated the effect of Progressive Resistance Training (PRT) in PCOS women and reported mean hs-CRP level at baseline as 8.9 mg/L which decreased to 8 mg/dL after 12 weeks of PRT which statistically was not significant (p=0.38) [21]. The authors also investigated HOMA-2 which decreased from 2.62 to 2.56, a small non-significant decrease. This discrepancy can be related to the nature of the PRT which is different from aerobic exercise. Strenuous exercise may in fact cause a short-term increase in CRP but chronic habitual physical activity decrease CRP levels [22]. In another study, including 94 obese women with PCOS, three interventions (diet, diet and aerobic exercise, diet and mixed aerobic-resistance exercise) resulted in decrease in HOMA-IR from 1.87 at baseline to 1.4 after 20 weeks of diet and aerobic exercise [11]. In the present study, calorie intake and diet of the patients were not studied. Although diet alone as intervention in the mentioned study [11] also led to decrease in HOMA-IR, according to our findings aerobic exercise for 16 weeks also decreased HOMA-IR significantly in PCOS patients.

Insulin resistance is a pathologic situation in which, the normal amount of blood insulin is unable to provide a normal biologic response. In fact, insulin signalling is impaired. This decreased response could affect the entire metabolic effects of insulin [23]. As 70-80% of the uptake of circulating glucose is done by the muscles, this tissue has specific importance in insulin resistance development [24]. Glucose absorption in target tissues is carried out by Glucose Transporter 4 (GLUT4). By activating phosphoinositide kinase, insulin changes phosphatidylinositol 4,5-bisphosphonate to phosphatidylinositol (3,4,5-triphosphate and activates other cytosol mediators such as PDK1 (phosphoinositol-dependent kinase-1), AS160 protein, GTPase, protein kinase B, protein kinases C [25].

The findings of the current study showed that aerobic exercise improved insulin resistance in PCOS patients reflected by significant decrease in HOMA-IR after 16 weeks.

Aerobic exercise help in physiologic compatibility such as increasing oxidation enzymes, lowering fat tissues, reducing inflammatory markers such as hs-CRP [26], increasing anabolic hormones such as dihydrotestosterone [27], increasing capillary density, increase in the number of mitochondria, improving maximum oxygen intake and efficiency of cardiovascular system [28]. Increase in resistin level occurs following physical exercise and acts as an antioxidant [29]. Resistin acts as a pre-inflammatory mediator and stimulates release of tumour necrosis factor-alpha, monocyte chemotactic protein-1 and endothelial adhesion molecules [30].

Regular physical activities could improve glucose tolerance in individuals; however, people do not have sufficient time to spend on sports [31]. Aerobic exercises affect fat tissues and stimulate muscular peroxisome Proliferator-activated receptor Gamma Coactivator 1-alpha (PGC-1α), which increases fat oxidative capability and capacity. By aerobic exercise, perhaps the systemic inflammation reduces and insulin function increases; followed by reducing insulin resistance index in subjects; and ultimately, due to increase in tissues reactions towards insulin, the insulin amount of serum is consequently reduced [32]. Physical exercise improves insulin resistance via increase in transfer of glucose transporter (GLUT4) in cell membrane via activating intra-cellular messages after muscle contractions, increase in activity of glycogen synthesise insulin and protein kinase B receptors, and trans-regulation of components engaged in insulin signalling flow [33].

In addition, the results of the research showed that the aerobic exercises resulted in significant differences between hs-CRP of PCOS patients. However, no significant changes were observed in control group. This improvement in hs-CRP level in experimental group could be attributed to the aerobic exercise. CRP activates the classic complement pathway and, similar to antibodies, causes opsonization, phagocytosis and lysis of invading organisms. It has been an accepted claim in the past decade that inflammatory mechanism plays a key role in the pathologic process of PCOS. It has been well established that PCOS patients show mild chronic inflammatory symptoms [11]. In fact, these findings support the idea that there is a close relation between mild chronic inflammation and high levels of metabolic indices in PCOS women [34]. Most studies have suggested that it is weight reduction, rather than the effect of training itself, that decrease CRP [16]. It has been claimed that small weight loss in obese patients reduces visceral fat mass more than subcutaneous fat mass and this factor is followed by an improvement in all cardiovascular disease risk factors [16]. Weight loss in women has been shown to prevent increase in the inflammatory cytokines and improvement of endothelial disorders [33]. Therefore, it seems that weight loss is one of the main mechanisms in CRP reduction [35]. Due to direct relationship between CRP production with IL-6, serum IL-6 level should also decrease [35]. Some researchers have introduced IL-6 as an inducing factor of insulin excretion in pancreatic beta cells. Constant engagement in intensive interval activities reduces fat. Since fat tissue is one of the major sources in IL-6 production. By lowering fat tissue, the serum level of this cytokine decreases as well. The reduction of serum IL-6 level weakens the signalling path of CRP and insulin production [35].

Many researchers have claimed that improving physical fitness due to the physiology of exercise is the main factor in lowering the CRP level [36]. The relation between increase in physical activities level and decreasing CRP has observed even after controlling BMI and waist-hip-ratio [36]. Therefore, it seems other factors, besides body composition, can be effective in lowering post-interval exercise inflammatory factors; and researchers attribute those factors to the anti-inflammatory characteristics of physical activities [35,36].

Some possible anti-inflammatory characteristics of aerobic exercise could be associated with regulating the cytokines produced from fat tissue, muscles and mononuclear cells [37]. In addition, perhaps intensive interval activities decrease TNF-α, IL-1-α and Interferon Gamma (INFG) production by mononuclear cells and increases the anti-atherogenic cytokines (IL-10, IL-4 and TGF-β-11) [37].

Along those mechanisms, although aerobic exercises lead to an increase in oxidation stress; in long-term, it improves anti-oxidant defense of body by increasing anti-oxidant enzymes. These anti-oxidant characteristics prevent HDL cholesterol oxidation and ultimately prevent endothelial damage and inflammation [38].

LIMITATION

This study had certain limitations. The study period was not long enough to establish long-term effect of aerobic exercise. Authors were not able to include other methods of physical exercise to

compare different exercise programs (resistance training, mixed aerobic and resistance exercise). The present authors did not assess weight change or lipid changes in the patients. Finally, randomisation was not used here to allocate the women to experimental or control groups.

CONCLUSION

A 16-week home-based aerobic exercise program led to decrease in HOMA-IR and hs-CRP in a sample of female patients with PCOS. Although the effect of aerobic exercises in PCOS need more studies, these findings confirm the effective role of aerobic exercises in decreasing inflammation and improving insulin sensitivity in these patients. The present authors recommend aerobic exercise in PCOS patients. Future studies can be done to investigate the effect of aerobic exercises in PCOS patients who have diabetes mellitus to determine whether by improving insulin resistance, similar effects can be seen regarding blood glucose level.

ACKNOWLEDGEMENTS

This article was extracted from the thesis of Dr. Nahid Mohammadi Javid. The authors thank the supervisor Dr Naser Behpour and consultant Dr. Vahid Taidibi. Also, we acknowledge all participants of this study and all staff who helped us in this project.

REFERENCES

[1] Sirmans SM, Pate KA. Epidemiology, diagnosis, and management of polycystic ovary syndrome. Clin Epidemiol. 2013;6:01-13.
[2] Amer SA. Polycystic ovarian syndrome: diagnosis and management of related infertility. Obstetrics, Gynaecology & Reproductive Medicine. 2009;19:263-70.
[3] Hertle E, Van Greevenbroek M, Stehouwer C, Complement C3: an emerging risk factor in cardiometabolic disease. Diabetologia. 2012;55:881-84.
[4] Hoang YD, McTavish KJ, D, Chang RJ, Shimasaki S. Paracrine regulation of theca androgen production by granulosa cells in the ovary. Fertil Steril. 2013;100:561-67.
[5] Farrell K, Antoni MH. Insulin resistance, obesity, inflammation, and depression in polycystic ovary syndrome: biobehavioral mechanisms and interventions. Fertil Steril. 2010;94:1565-74.
[6] Del Giudice M, Gangestad SW. Rethinking IL-6 and CRP: Why they are more than inflammatory biomarkers, and why it matters. Brain Behav Immun. 2018;70:61-75.
[7] Gonzalez F. Inflammation in Polycystic Ovary Syndrome: underpinning of insulin resistance and ovarian dysfunction. Steroids. 2012;77:300-05.
[8] Turner-McGrievy GM, Davidson CR, Wingard EE, Billings DL. Low glycemic index vegan or low-calorie weight loss diets for women with polycystic ovary syndrome: a randomized controlled feasibility study. Nutr Res. 2014;34:552-58.
[9] Nagelberg J, Burks H, Mucowski S, Shoupe D. The effect of home exercise on ovulation induction using clomiphene citrate in overweight underserved women with polycystic ovarian syndrome. Contracept Reprod Med. 2016;1:14.
[10] Jedel E, Labrie F, Odén A, Holm G, Nilsson L, Janson PO, et al., Impact of electro-acupuncture and physical exercise on hyperandrogenism and oligo/amenorrhea in women with polycystic ovary syndrome: a randomized controlled trial. Am J Physiol Endocrinol Metab. 2011;300:E37-45.
[11] Thomson RL, Buckley JD, Noakes M, Clifton PM, Norman RJ, Brinkworth GD, et al., The effect of a hypocaloric diet with and without exercise training on body composition, cardiometabolic risk profile, and reproductive function in overweight and obese women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2008;93:3373-80.
[12] Lass N, Kleber M, Winkel K, Wunsch R, Reinehr T. Effect of lifestyle intervention on features of polycystic ovarian syndrome, metabolic syndrome, and intima-media thickness in obese adolescent girls. J Clin Endocrinol Metab. 2011;96:3533-40.
[13] Aubuchon M, Laughbaum N, Poetker A, Williams D, Thomas M. Supervised short-term nutrition and exercise promotes weight loss in overweight and obese patients with polycystic ovary syndrome. Fertil Steril. 2009;91:1336-38.
[14] Benham JL, Yamamoto JM, Friedenreich CM, Rabi DM, Sigal RJ. Role of exercise training in polycystic ovary syndrome: a systematic review and meta-analysis. Clin Obes. 2018;8:275-84.
[15] Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome (PCOS). Hum Reprod. 2004;19:41-47.
[16] Havel PJ. Update on adipocyte hormones: regulation of energy balance and carbohydrate/lipid metabolism. Diabetes. 2004;53 Suppl 1:S143-51.
[17] McArdle WD, Margel JR, Delio DJ, Toner M, Chase JM. Specificity of run training on VO2 max and heart rate changes during running and swimming. Med Sci Sports 1978;10:16-20.
[18] Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia 1985; 28: 412-19.
[19] Lim SS, Davies MJ, Norman RJ, Moran LJ. Overweight, obesity and central obesity in women with polycystic ovary syndrome: a systematic review and meta-analysis. Hum Reprod Update. 2012;18:618-37.
[20] Moran LJ, Pasquali R, Teede HJ, Hoeger KM, Norman RJ. Treatment of obesity in polycystic ovary syndrome: a position statement of the Androgen Excess and Polycystic Ovary Syndrome Society. Fertil Steril. 2009;92:1966-82.
[21] Vizza L, Smith CA, Swaraj S, Agho K, Cheema BS. The feasibility of progressive resistance training in women with polycystic ovary syndrome: a pilot randomized controlled trial. BMC Sports Sci Med Rehabil. 2016;8:14.
[22] Kasapis C, Thompson PD. The effects of physical activity on serum C-reactive protein and inflammatory markers: a systematic review. J Am Coll Cardiol. 2005;45:1563-69.
[23] Sone T, Kuriyama S, Nakaya N, Hozawa A, Shimazu T, Nomura K, et al. Randomized controlled trial for an effect of catechin-enriched green tea consumption on adiponectin and cardiovascular disease risk factors. Food Nutr Res. 2011;55.
[24] Fujimoto WY. The importance of insulin resistance in the pathogenesis of type 2 diabetes mellitus. Am J Med. 2000;108 Suppl 6a:9s-14s.
[25] Adamson S, Lorimer R, Cobley JN, Lloyd R, Babraj J. High intensity training improves health and physical function in middle aged adults. Biology (Basel) 2014;3:333-44.
[26] Jorge ML, de Oliveira VN, Resende NM, Paraiso LF, Calixto A, Diniz AL, et al. The effects of aerobic, resistance, and combined exercise on metabolic control, inflammatory markers, adipocytokines, and muscle insulin signaling in patients with type 2 diabetes mellitus. Metabolism. 2011;60:1244-52.
[27] Hawkins VN, Foster-Schubert K, Chubak J, Sorensen B, Ulrich CM, Stancyzk FZ, et al. Effect of exercise on serum sex hormones in men: a 12-month randomized clinical trial. Med Sci Sports Exerc 2008; 40: 223-33.
[28] Kishali NF. Serum leptin level in healthy sedentary young men after a short-term exercise. African J Pharm Pharmacol. 2011;5:522-26.
[29] Harwood HJ. The adipocyte as an endocrine organ in the regulation of metabolic homeostasis. Neuropharmacology. 2012;63:57-75.
[30] Zhang MH, Na B, Schiller NB, Whooley MA. Resistin, exercise capacity, and inducible ischemia in patients with stable coronary heart disease: data from the Heart and Soul study. Atherosclerosis. 2010;213:604-10.
[31] Ghroubi S, Elleuch H, Chikh T, Kaffel N, Abid M, Elleuch MH. Physical training combined with dietary measures in the treatment of adult obesity. A comparison of two protocols. Ann Phys Rehabil Med 2009;52:394-413.
[32] Irvine C, Taylor NF. Progressive resistance exercise improves glycaemic control in people with type 2 diabetes mellitus: a systematic review. Australian J Physiother. 2009;55:237-46.
[33] Cunha VN, de Paula Lima M, Motta-Santos D, Pesquero JL, de Andrade RV, de Almeida JA, et al., Role of exercise intensity on GLUT4 content, aerobic fitness and fasting plasma glucose in type 2 diabetic mice. Cell Biochem Funct. 2015;33:435-42.
[34] Randeva HS, Tan BK, Weickert MO, Lois K, Nestler JE, Sattar N, et al., Cardiometabolic aspects of the polycystic ovary syndrome. Endocr Rev. 2012;33:812-41.
[35] Kim JH, Bachmann RA, Chen J. Interleukin-6 and insulin resistance. Vitam Horm. 2009;80:613-33.
[36] Isasi CR, Deckelbaum RJ, Tracy RP, Starc TJ, Berglund L, Shea S, et al., Physical fitness and C-reactive protein level in children and young adults: the Columbia University BioMarkers Study. Pediatrics. 2003:111:332-38.
[37] Gielen S, Gielen S, Adams V, Möbius-Winkler S, Linke A, Erbs S, et al. Anti-inflammatory effects of exercise training in the skeletal muscle of patients with chronic heart failure. J Am Coll Cardiol. 2003;42:861-68.
[38] Heilbronn, LK, Heilbronn LK, de Jonge L, Frisard MI, DeLany JP, Larson-Meyer DE, et al. Effect of 6-month calorie restriction on biomarkers of longevity, metabolic adaptation, and oxidative stress in overweight individuals: a randomized controlled trial. JAMA. 2006;295:1539-48.

PARTICULARS OF CONTRIBUTORS:
1. PhD, Department of Sport Physiology, Kermanshah Branch, Islamic Azad University (IAU), Kermanshah, Iran.
2. Associate Professor, Department of Exercise Physiology, School of Sports Sciences, Razi University, Kermanshah, Iran.
3. Assistant Professor, Department of Exercise Physiology, School of Sports Sciences, Razi University, Kermanshah, Iran.

NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:
Nahid Mohammadi Javid,
PhD, Department of Sport Physiology, Kermanshah Branch, Islamic Azad University (IAU), Kermanshah, Iran.
E-mail: n.javid76@yahoo.com

FINANCIAL OR OTHER COMPETING INTERESTS: None.

Date of Submission: **Feb 05, 2019**
Date of Peer Review: **Mar 18, 2019**
Date of Acceptance: **Jun 27, 2019**
Date of Publishing: **Aug 01, 2019**