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Effects of Physical Exercise with and without Pomegranate Concentrate Consumption on the HbA1c and C-peptide Levels in the Middle-aged Women with Metabolic Syndrome

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ABSTRACT

Introduction: Metabolic syndrome is defined as a cluster of metabolic disorders, which may lead to type II diabetes and cardiovascular diseases. Promotion of healthy lifestyle and use of herbal supplements with anthocyanin and phenols are recommended for the treatment of metabolic syndrome. The present study aimed to investigate the effects of eight weeks of combined aerobic and resistance exercises and pomegranate concentrate consumption on the levels of HbA_{1c} and C-peptide in women with metabolic syndrome.
Methods: This study was conducted on 30 middle-aged women with metabolic syndrome, who were randomly assigned to two groups of exercise (E; n=15) and exercise with pomegranate concentrate (EPC; n=15). The exercise protocol was conducted at 60-80% intensity of the maximal heart rate and 60-80% of one-repetition maximum. Data analysis was performed in SPSS version 20 at the significance level of $P \leq 0.05$.
Results: HbA1C levels significantly reduced in the EPC group ($P<0.05$), while no significant difference was observed between the groups in terms of the C-peptide and HbA1C levels ($P>0.05$). In addition, the within-group comparison indicated no significant changes in the C-peptide levels in the E and EPC groups ($P>0.05$).
Conclusion: According to the results, regular physical exercises along with the consumption of pomegranate concentrate could be effective in reducing HBA1c. Improving a number of metabolic syndrome indices (e.g., insulin resistance) could prevent the complications of metabolic syndrome in middle-aged women.

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Introduction

As anticipated by the World Health Organization (WHO), non-contagious chronic diseases will account for three-quarters of mortalities in developing countries by 2020 (1). Metabolic syndrome is a prevalent, non-contagious disease, which is caused by several risk factors for cardiovascular diseases and type II diabetes, such as obesity, increased serum triglyceride and high-density lipoprotein (HDL), elevated fasting glucose, and hypertension. In fact, the majority of patients with metabolic syndrome are obese and physically inactive with high plasma glucose levels.

The prevalence of metabolic syndrome has risen within the past two decades across the world. Moreover, the prevalence of this syndrome has been reported to be higher in adults and women. Insulin resistance reduces the cellular absorption of blood glucose, insulin secretion, and cell sensitivity to insulin (2, 3).

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C-peptide refers to the level of endogenous insulin production. Patients with metabolic syndrome generally have normal or high levels of C-peptide, which indicate higher insulin levels and no relative insulin sensitivity (4). Currently, measurement of glycated proteins prior to serum hemoglobin and proteins has added another dimension to blood glucose testing. Glycol hemoglobin, which is also known as glycosylated hemoglobin, HbA1c or A1C, is defined as the secondary or stable combinations of hemoglobin. These compounds are resulted from a combination of hemoglobin and glucose gradually and without enzyme mediation. The amount and rate of HbA1c formation is directly correlated to peripheral glucose concentration. Since erythrocytes are totally penetrable by glucose, HbA1c illustrates the blood glucose status within the past 120 days, representing the average age of the erythrocyte. In other words, HbA1c paints a clear picture of the controlled blood glucose within the past 2-3 months and has become the key index of evaluating blood glucose control (5).

The recent recommendations by the WHO for the prevention and treatment of metabolic syndrome include increasing the frequency of physical activity, reducing body weight, and consumption of healthy foods. Regular physical activity plays a pivotal role in regulating the physical shape. Depending on their type, intensity, and duration, physical exercise helps lower fats and increase the fat-free mass, thereby preventing the unfavorable changes in the constituents of metabolic syndrome (6).

Regular physical exercise is indispensable to the clinical management of metabolic syndrome. According to the literature, the main risk factors for metabolic syndrome include cholesterol, body weight, insulin level, blood glucose, and insulin resistance, which could decrease as a result of aerobic exercises (7). For instance, the findings of a review study conducted by Vissers et al. suggested that aerobic exercises without limitation in calorie intake could reduce visceral fat and the symptoms of metabolic syndrome (8).

In addition to aerobic exercises, previous studies have confirmed the effects of resistance training and combined aerobic and resistance exercises on some of the key risk factors for metabolic syndrome, such as blood glucose and insulin resistance (9, 10). However, since the duration of exercises and calorie intake are higher in combined exercises than each type of exercise alone, it has been recommended that aerobic and resistance training be performed together (9).

Evidence suggests that combined exercises (aerobic and resistance) decrease the level of glycosylated hemoglobin (key index of glucose control), thereby reducing the risk of type II diabetes and cardiovascular diseases and enhancing insulin resistance (11).

Pomegranate (*Punica granatum*) belongs to the *Punicaceae* family and is an abundant source of flavonoids; this fruit is native to many countries. Some of the important metabolites found in pomegranate are organic acids, various carbohydrates, alkaloids, polyphenols, anthocyanins, fatty acids, and vitamins (12). Furthermore, pomegranate juice has important biological properties, such as antioxidative activity (13), cardiovascular protection (14), and hyperlipidemia amelioration (15).

Pomegranate concentrate is a product that contains no additives and is used in pomegranate juice production after sieving and separation from the particles of the fruit (16). The antioxidant compounds found in pomegranate juice have remarkable effects on the reconstruction and repair of pancreatic beta cells and play a key role in reducing the incidence of diabetes and its complications (17).

Previous studies have investigated the effectiveness of training interventions and consumption of pomegranate in the treatment of diabetes and cardiovascular risk factors (17). However, the interactive effects of these approaches on glucose indices (e.g., C-peptide and glycosylated hemoglobin) remain unclear in patients with metabolic syndrome.

The present study aimed to investigate the effects of physical exercise combined with pomegranate concentrate consumption on C-peptide and glycosylated hemoglobin in middle-aged women with metabolic syndrome.

Material and methods

The study protocol was approved by the Ethics Committee of Mashhad University of Medical Sciences, Mashhad, Iran (IR.MUMS.MEDICAL.REC.1397.064), and the trial was also registered on the Iranian

Registry of Clinical Trials (IRCT20181029041491N1).

Participants

This study was conducted on 30 physically inactive middle-aged women with metabolic syndrome, who were selected via purposive and convenient sampling and randomly allocated to two groups based on the inclusion criteria. Written informed consent was obtained from the participants prior to enrollment.

Inclusion Criteria

The health status of the subjects was assessed using the American College of Sports Medicine (ACSM) health/fitness questionnaire and international physical activity questionnaire (IPAQ) (18). The inclusion criteria of the study were as follows: 1) no medication use; 2) non-smokers; 3) absence of chronic diseases (e.g., cardiovascular, renal, and thyroid disorders); 4) no menopause; 5) no visceral obesity (i.e., abdominal circumference of >80 centimeters plus two indices of metabolic syndrome [HDL cholesterol of <50 mg/dl, triglyceride of ≥150 mg/dl, blood glucose of <120 mg/dl, and 130/85 mmHg< blood pressure] based on the guidelines of the International Diabetes Federation (IDF) (19) and 6) no exercises within a minimum of two months prior to the research.

Exclusion Criteria

The exclusion criteria of the study were as follows: 1) presence of digestive disorders; 2) absence of more than three consecutive days in the exercise program; 3) inadequate consumption of the pomegranate concentrate and 4) consumption of dietary supplements containing antioxidants.

Anthropometric Measurements

The height of the participants was measured using Seca height gauge (Germany) with the error margin of five millimeters. Waist circumference was measured in a standing position, midway between the lower costal margin and iliac crest using a measuring tape with the error margin of five centimeters. Body weight and body mass index (BMI) were measured using a bioelectrical impedance device (model: In Body 720, Biospace Industry, Seoul, South Korea). All the measurements were performed after a minimum of four hours of nil per os (NPO) with empty gastrointestinal tract and bladder. The baseline characteristics of the participants are represented in Table 1.

Table 1. Descriptive Statistics of Participants

Group \ Variable		CT (ml/dl)	LDL (ml/dl)	HDL (ml/dl)	TG (ml/dl)	BP (mmHg)	WHC (cm)	BMI (Kg/m2)	Weight (Kg)	Height (cm)	Age (y)
E	Mean	190.58	104.16	54	132.16	120.17	88.41	31.00	77.34	158.00	46.1
	SD	33.67	32.44	14.81	47.64	17.03	8.25	11.67	11.67	5.46	4.5
EPC	Mean	190.25	112.58	50.66	136	114.50	88.00	30.07	74.90	157.83	43.5
	SD	17.11	17.24	6.38	52.52	16.17	7.54	4.50	12.02	5.42	2.5

CT: total cholesterol, **LDL:** low-density lipoprotein, **HDL:** high-density lipoprotein, **TG:** triglyceride, **BP:** blood pressure, **WHC:** waist-to-hip circumference, **BMI:** body mass index, **E:** exercise; **EPC:** exercise with pomegranate concentrate consumption

Blood Sampling and Laboratory Measurements

Blood samples were obtained 24 hours prior to the exercises and 48 hours after the last exercise session from the right-hand vein in a sedentary and relaxing position using the venipuncture method. The concentration of fasting serum glucose was measured via calorimetry (GOD-PAP) using a commercially available glucose kit (Pars Azmoon, Tehran, Iran) with the error margin of 5 mg/dl.

Plasma fasting insulin levels were measured via radioimmunoassay using a commercially available kit (Demeditec, Germany) with the error margin of 1.76 micIU/ml. The concentration of glycosylated hemoglobin (HbA1c) was determined using a commercially available kit (Nyco Card, England) with the error margin of 3%. Serum C-peptide level was measured using the ELISA technique with a commercially available kit (Demeditec, Italy) and the error margin of 0.01 ng/ml. In addition, insulin resistance was measured based on the homeostasis model assessment (HOMA-IR) formula, as follows:

Glucose (mg/dl) × insulin (micIu/ml)/405

Exercise Protocol

In the current research, the participants were divided into two groups of exercise (E) and exercise with pomegranate concentrate (EPC), and the study groups received a combination of aerobic and resistance exercises for eight weeks. The exercise program consisted of three sessions per week, each of which involved 10 minutes of warm-up, 20 minutes of aerobic exercises, and three minutes of rest. Afterwards, resistance exercise was performed for 20 minutes, followed by seven minutes of cool-down (11). The intensity of the aerobic and resistance exercises in the first week was set at 60% of the maximal heart rate (HRmax) and 60% of one-repetition maximum (1-RM).

In the second, fourth, sixth, and eighth week, the intensity of the aerobic exercises increased by 5%, and in the third, fifth, and seventh week, the intensity of resistance exercises also increased by 5%. The resistance exercises involved weight training focused on the large muscles, including bench press, latissimus dorsi pull, and leg extension. Each movement was performed in three sets of 8-12 repetitions. The active resting intervals between the movements and sets were two and one minutes, respectively.

Pomegranate Concentrate

In addition to the exercise protocol, the participants in the EPC group were supposed to consume a daily amount of pomegranate concentrate (50 g) with two 25-gram meals after lunch and dinner (20). In the current research, the pomegranate concentrate was obtained from Razavi Food Product Co. in Razavi Khorasan, Iran. The pomegranate concentrate was composed of the fruit products cultivated in the gardens in Shiraz and Ferdows and physically kept chilled in 220-liter gallons so as to reach the desired concentration. According to the analysis of the pomegranate concentrate in the research center laboratory, the level of anthocyanin (cyanidin-3-glucoside) was 376.28 mg/100 g of juice, the level of total polyphenols was estimated at 200.86 mg/100 g of juice, and the level of regenerative sugar in the juice was 12.50%.

Data analysis was performed in SPSS version 20, and the normal distribution of the data was confirmed using the Shapiro-Wilk test. Moreover, paired-samples t-test and independent-samples t-test were applied for the inter- and intra-group comparison of the mean scores at the significance level of P≤0.05.

Results

The results of independent-samples t-test indicated no statistically significant divergence between the groups in terms of glucose concentrations (P=0.47) (Table 2). However, insulin concentration and insulin resistance (HOMA-IR) significantly decreased in the EPC group compared to the E group (P=0.01 and P=0.02, respectively). No significant difference was observed between the groups in terms of the levels of HbA1C and C-peptide (P=0.02 and P=0.29, respectively).

Table 2. Results of Paired-samples T-test and Independent-samples T-test

Variable	E Group Pretest	E Group Posttest	P-value (paired t-test)	EPC Group Pretest	EPC Group Posttest	P-value (paired t-test)	P-value (independent t-test)
FBS (mg/dl)	93.33±11.86	84.25±12.55	0.03*	92.50±10.43	86.66±13.44	0.03*	0.47
Insulin (micIU/ml)	9.75±5.35	6.80±4.50	0.06	10.48±8.50	6.45±5.10	0.01*	0.01*
IR (mg/dl)	2.20±1.26	1.46±1.14	0.01*	2.26±1.90	1.54±1.37	0.04*	0.02*
HbA1c (%)	5.48±0.63	5.29±0.76	0.52	5.50±0.81	4.84±0.66	0.02*	0.2
C-peptide (ng/ml)	1.53±0.60	1.53.0.69	0.98	1.53±0.38	1.35±0.22	0.1	0.29

FBS: fasting blood sugar, **IR:** insulin resistance, **HbA1c:** hemoglobin A1c
*Statistically significant difference
Data expressed as mean±standard deviation

The results of paired-samples t-test indicated a significant difference within the exercise group in terms of fasting blood glucose and insulin resistance (Table 2). Similarly, significant within-group differences were observed in the EPC group compared to the E group in terms of fasting blood glucose, insulin resistance, insulin concentration, and HbA1c level ($P<0.05$). However, no divergence was observed in the study group regarding the level of C-peptide ($P>0.05$).

Discussion

The major findings of the current research were the significant reduction of insulin level and insulin resistance, as well as the non-significant reduction of HbA1C and C-peptide, in the EPC group compared to the E group. Furthermore, a significant reduction was denoted in the HbA1C level at posttest compared to the pretest in the EPC group.

Insulin resistance is considered to be the key clinical symptom of metabolic syndrome, which occurs due to the reduced capability of insulin, affecting target tissues such as skeletal muscles, adipose tissue, and hepatic tissue. Insulin resistance is relative since the values above the normal level in blood circulation convert the plasma glucose into the normal level. If insulin resistance continues, glucose consumption is disrupted in the target tissues that are sensitive to insulin, which in turn increases the hepatic glucose output. Consequently, the blood glucose increases, thereby leading to the glycation of proteins such as hemoglobin.

HbA1c is an index referring to the quality of controlled blood glucose. The results of the present study indicated the reduction of HBA1c in both groups, with the EPC group showing significantly lower HbA1c compared to the E group. The significant within-group difference in the HbA1c level in the EPC group could be due to the anthocyanin compounds in the pomegranate concentrate. Evidence attests to the effectiveness of anthocyanin compounds in the reduction or inhibition of non-enzymatic glycosylation, which could be due to the competition between anthocyanin compounds and glucose in reaction to protein (21-23). The anthocyanin glucose in the pomegranate concentrate used in the present study was cyanidin 3-glucoside, and the extra glucose in blood seemed to bind to aglycon, thereby resulting in the glycosylation of anthocyanin, preventing the formation of HBA1c, and lowering the HbA1c values. Moreover, the gallic acid found in pomegranate acts as a natural phytochemical, affecting AMP-activated protein kinase and PGC1-a, as well as insulin resistance and weight control, as gallic acid is involved in the inhibition of adipogenesis (24, 25). Therefore, pomegranate concentrate may be involved in some signaling pathways, via which it could significantly reduce insulin resistance and HbA1C in the middle-aged women with metabolic syndrome in the current research.

According to the literature, eight weeks to one year of physical training programs could decrease HBA1c by 6%, as well as the risk of mortality in patients with diabetes, myocardial infarction, and microvascular complications by 21%, 14%, and 37%, respectively (26). As such, physical training programs are considered to be among the most effective interventions for the treatment of metabolic syndrome. According to the results of the present study, two month of the physical exercise program could reduce HBA1c by 3% in the E group and 12% in the EPC group. In general, aerobic exercises have been reported to be an effective approach to weight and glycemia control and HbA1c reduction (27, 28). Furthermore, aerobic exercises combined with resistance training has been associated with ameliorated glycated hemoglobin and reduced insulin resistance (29, 30).

Despite the implementation of combined aerobic and resistance exercises in the current research, the non-significance difference in the level of HbA1c after eight weeks of training is consistent with the studies by George et al. (27) and Bello et al. (28). After 12 and eight weeks of aerobic training, no significant changes were observed in the HbA1c level in the mentioned studies (27, 28).

Our findings also revealed a non-significant reduction in C-peptide in both groups, while the reduction was more significant in the EPC group compared to the E group. The beta cells in the Langerhans islets release C-peptide and proinsulin into the systemic circulation. Following that, the same concentration of C-peptide as insulin is secreted from the pancreatic beta cells into the blood. The plasma concentration of C-peptide in fasting healthy individuals is 0.39±0.12 pmol/l (31), with the half-life of approximately 30 minutes. The physiological action mechanism of C-peptide is remains unclear; however, C-peptide could be effective through binding to the G protein or interacting with the insulin signaling pathway (32).

In a research in this regard, Rosenblat et al.

(2006) investigated the effects of pomegranate juice consumption (50 mg per day) on oxidative stress, blood glucose, and lipid peroxides for three months in 10 patients with type II diabetes with the disease history of 4-10 years. The obtained results indicated no significant effects on HbA1C, blood glucose, and insulin, while serum C-peptide was reported to decrease by 23%, suggesting increased insulin sensitivity (33). In the present study, C-peptide reduced by 0.09% in the E group and 13.8% in the EPC group, which demonstrated the improved function of beta cells and insulin sensitivity. Despite the significant decrease in the glucose level of both groups in the current research, the values were at a physiologically normal concentration.

According to the literature, combined aerobic-resistance training is more effective than each of the exercises alone in controlling the blood glucose, insulin activity, and cardiovascular risk factors (34-36). In general, physical exercises help increase the rate of glucose transporters in the muscles, which in turn improves insulin function and glucose metabolism, thereby decreasing glycated hemoglobin (37). In this regard, Kadoglo et al. (38) and Maiorana et al. (39) have reported a significant reduction in HbA1c after aerobic training, which is inconsistent with the results of the present study. The non-significant reduction in HbA1C in the E group could be due to the small sample size, duration of training, and normal baseline levels of the participants (A1c≤7.6%), which might have altered the effects of physical training (27).

Conclusion

According to the results, the combined effects of exercise and consumption of pomegranate concentrate could give rise to physiological actions, positively affecting the indices associated with metabolic syndrome. Therefore, it could be concluded that pomegranate concentrate could be used as a dietary supplement in the patients with metabolic syndrome who regularly engage in physical training. Further research is required on larger sample sizes with extended training durations to better realize the involved mechanisms. Moreover, such findings could contribute to the development of more accurate exercise programs, which could effectively prevent metabolic syndrome and its complications.

Applicable Remarks

- Metabolic syndrome could potentially increase the risk of type II diabetes and cardiovascular diseases.
- Increased physical activity may improve metabolic syndrome, and the combination of regular exercise and adherence to healthy diets is considered to be a preventive measures to reduce the risk of type II diabetes and cardiovascular diseases.

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