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Original Article

Effects of Eight Weeks of Resistance Training and Consumption of Pomegranate on GLP-1, DPP-4 and Glycemic Statuses in Women with Type 2 Diabetes: A Randomized Controlled Trial

Mohsen Akbarpour[1], Fazlollah Fathollahi Shoorabeh* [2], Mahnaz Mardani[3], Fatemeh Amini Majd[4]

1- Associate Professor Department of Physical Education and Sport Sciences, Faculty of Literature and Humanities, University of Qom, Qom, Iran

2-Department of Nutrition, School of Health and Nutrition, Lorestan University of Medical Sciences, Khorramabad, Iran

3- Professor, Nutritional Health Research Center, Lorestan University of Medical Sciences, Khorramabad, Iran

4- Department of Physical Education and Sport Sciences, Faculty of Literature and Humanities, University of Qom, Qom, Iran

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ABSTRACT

Background and Objectives: Diabetes is one of the metabolic diseases with a significant increase rate in recent decades. The aim of this study was to investigate effects of eight weeks of resistance training and consumption of pomegranate juice on Glucagon-like peptide-1(GLP-1), dipeptidyl peptidase 4(DPP-4) and glycemic statuses in women with type 2 diabetes (a randomized controlled trial).

Materials and Methods: Samples included 40 women with type 2 diabetic aged 45–55 years, who were randomly selected and divided into four major groups of control (n = 10), resistance training (n = 10), pomegranate juice consumption (n = 10) and resistance training and pomegranate juice consumption (n = 10) groups. Resistance training group and resistance training and pomegranate juice consumption group carried out three resistance training sessions for eight weeks, each week with a maximum intensity of 30%. By the end of the Week 18, groups reached 80% of the maximum repetition. The pomegranate juice group received 100 ml of pomegranate juice every day. Analysis of variance (ANOVA) was carried out using SPSS Software v.21.

Results: Results showed that eight weeks of resistance training with pomegranate juice consumption significantly increased GLP-1, HDL, insulin (p = 0.0001) and decreased DPP-4, LDL and glucose (p = 0.0001) levels in women with type 2 diabetes. Furthermore, results showed that resistance training significantly increased GLP-1 and decreased DDP-4 levels in these women. No significant changes were seen in control group and pomegranate juice consumption in the study variables.

Conclusions: Based on the results of this study, resistance training with consumption of pomegranate juice effectively improves insulin secretion and glycemic control. This improvement can be attributed to increases in GLP-1 and DDP-4 levels.

Keywords: Type 2 diabetes, Pomegranate juice, Resistance exercise, Glucagon-like peptide-1, Inhibitors of dipeptidyl peptidase 4

Introduction

Diabetes is one of the metabolic diseases, which has increased in recent decades. In previous decades, the disease prevalence was higher in developed countries, while it has recently been higher in developing countries. Diabetes is a serious medical problem that is spreading dramatically (1). Nearly 370 million people suffer from the disease worldwide. This is expected to increase to 552 million by 2030. Studies have shown that weight gain, obesity and inactivity are the major causes of diabetes and its associated disorders. Numerous dietary, pharmacological and lifestyle changes have been described by nutritionists and metabolic physicians to prevent diabetes as well as cardiovascular disorders (2). Major treatments for diabetes include decreasing insulin resistance and stimulating insulin secretion through dietary modification, exercise and drug therapy (3). Researchers have investigated effects of exercise programs on enzymes and hormones associated with diabetes to suggest the best

***Address for correspondence:** Fazlollah Fathollahi Shoorabeh, Assistant Prof, Department of Nutrition, School of Health and Nutrition, Lorestan University of Medical Sciences, Khorramabad, Iran. E-mail address: f.fathollahi1984@gmail.com

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treatment methods. One of these hormones is glucagon-1-like peptide (GLP-1), which has been shown to play an important role in controlling body weight (4). Hormones are responsible for secreting 50–70% of the insulin that is released after eating glucose. In fact, GLP-1 includes direct and indirect effects on increasing insulin and decreasing blood sugar. Directly through receptors on pancreatic cells, GLP-1 increases expression of insulin genes and their synthesis. Direct effects on GLP-1 receptors of the pancreatic beta cells, as well as indirectly effects through the nervous system and portal vein of the liver, increase insulin secretion. (5) In addition, GLP-1 slows down gastric emptying and absorption of glucose, preventing sudden increases in blood sugar. By inducing feeling of fullness, GLP-1 decreases consumption of foods and thus plays roles in decreasing diabetes and obesity.

Peptidase-4 (DPP-4) dipeptide is an important cytokine involved in metabolic syndrome and type 2 diabetes (7). Furthermore, DPP-4 enzyme is a protein-rich glycogen membrane enzyme that is expressed throughout the body, including skeletal muscles, liver and adipose tissues (7). Chemical activity of DPP-4 with genetic inactivation of DPP-4 increases biological activities of GLP-1 and GIP. In addition, continuous inhibition of DPP-4 decreases blood sugar through insulin stimulation and glucagon secretion inhibition and is associated with maintaining beta cell mass (8). The DPP-4 has been reported to disrupt signaling of insulin at protein kinase B (Akt) level in skeletal muscles; thereby, resulting in glucose tolerance and increased risk of metabolic syndrome (9). Based on several researches on effects of various training programs on blood indicators, insulin resistance and decreased drug use, it seems that participating in regular well-organized exercise programs can play major roles in decreasing effects of diabetes and hence drug uses (10). It has been shown that regular exercises decrease fat accumulation and improve insulin resistance and glucose homeostasis (2). Effects of exercise training on changes in endocrine hormones have been described (10). In humans, acute aerobic exercises have been shown to affect incretins, including GLP-1. Findings have suggested that exercises may be physiological regulators for the function or secretion of invertins (11). Recent studies have shown that GLP-1 from alpha-pancreatic helium cells increases and improves insulin secretion, leading to decreased blood sugar (12). Effects of exercise and physical activity on GLP-1, DPP-4 and insulin resistance have been less studied and need further investigations. In similar limited studies, contradictory results have been reported. Both increased (13) and lack of significant changes in GLP-1 (14) are followed by impaired training. Moreover, DPP-4 has been reported to combine low-fat diets with increased aerobic physical activities, decreasing DPP-4 plasma in overweight children (15). However, findings are less common in adults especially women at risk and information on the role of exercise in regulating DPP-4 and GLP-1 are generally limited. In addition to exercises, healthy eating patterns are the most important factors in lifestyle and play important roles in controlling and treating diabetes and cardiovascular diseases (CVD).

Numerous studies have investigated effects of diets such as fruits, vegetables and meats on inflammatory markers (2). Foods containing flavonoids such as pomegranate decrease blood pressure in people with hypertension and can be recommended as a preventative measure for CVD in patients with type 2 diabetes. Due to nutritional and medicinal properties of pomegranate, it is important in the routine diets (16). Pomegranate (*Punica granatum* L.) is one of the Iranian native fruits and has been used for centuries to prevent and treat human disorders and diseases. Pomegranate contains several phenolic compounds such as flavonoids and anthocyanins and includes antioxidant, anti-inflammatory and anti-cancer properties (17). Pomegranate juice has been shown to decrease effects of diabetic oxidative stress by decreasing blood sugar as well as having antioxidant compounds such as flavonoids. The fruit increases activity of the catalase enzyme; thereby, decreasing effects of diabetes such as weight loss (18). Daily consumption of the pomegranate paste can include good effects on lipid profile and inflammatory factors in type 2 diabetic patients (19). Studies have shown that consumption of pomegranate juice concentrate and exercise include significant effects on heart rate indicators. However, effects of combining pomegranate juice concentrate with aerobic exercise on these indicators were higher in women with type 2 diabetes. Another study has demonstrated that pomegranate juice includes no effects on fasting blood sugar (FBS) and glycosylated hemoglobin but decreases insulin resistance. In this study, pomegranate juice did not include significant effects on hs-CRP (20). In a study, Akbarpour et al. (1398) showed that resistance training with pomegranate juice consumption decreased oxidative factors and increased oxidation and improvement of lipid and sugar profile in women with diabetes (2). Sports activities with use of medicinal plants have been recommended as an appropriate solution for diabetes management in recent decades. However, no studies have been carried out to investigate effects of resistance training and pomegranate juice consumption on the studied variables. Therefore, the aim of this study was to investigate effects of eight weeks of resistance training and consumption of pomegranate juice on GLP-1, DPP-4 and sugar profile in women with type 2 diabetes.

Materials and Methods

The sample volume of this study included 40 women with type 2 diabetes. This study was approved by the Ethics

Committee (IR.QOMREC.1398.013). To select study participants, after initial coordination with the centers for the implementation of study as well as announcements issued in Khorramabad City, eligible people were invited to participate in the study. Then, participants were asked to measure their height and weight. Inclusion criteria for the participants were type 2 diabetes over 2, menopause, body mass index (BMI) of 25–30 kg per square meter and blood sugar of 160–250 mg (17). Lack of regular exercises over the past six months, no histories of CVD and no smoking were other inclusion criteria. In total, 40 people were selected as the study participants. The participants we randomly divided into four major groups of ten (resistance training, pomegranate juice, resistance training and pomegranate juice and control groups). The G* Power Software was used to analysis sample size and study power and showed that the sample size of ten participants in each group included power of 70%. It is noteworthy that none of the participants received insulin or oral metformin/ glibenclamide during the study.

Measurement of blood indicators

After 10–12 h of overnight fasting, 4 ml of anterior vena cava blood were collected from the participants at 8:00 AM. Blood sera were separated and FBS and lipid profiles were assessed. Then, sera were stored at -70 °C until use. The training program started 48 h after the initial data collection and continued for 8 w. nearly 48 h after the last training session, anthropometric and laboratory measurements were carried out in similar conditions and times. Serum GLP-1 was assessed with a sensitivity of 25 pg per ml using ELISA kits (Abcam, UK). Moreover, DPP-4 was assessed with a sensitivity of 10 ng per ml using endometrial fluorometric technique (Abcam, UK).

The exercise protocol

Strength training was carried out for 8 w using three sessions per week. Resistance included two sets of ten repetitions and 30% of the maximum repetition, which increased to three sets with six repetitions and 80% of the maximum repetition at the end of the training period. Between each repetition, participants received 2-min breaks. Trainings included bench press, Leg press , lunch and latissimus dorsi pulldown. The forearm and bilateral traction downward involved the large muscles of the upper torso and lower torso. To study principles of overload and gradual progress within 2, 4 and 6 w, these movements were measured 1RM (One-repetition maximum) (2). The resistance exercises were carried out between 4 and 6 PM.

Consumption of pomegranate juice

Individuals in the pomegranate juice group received 1 l of frozen pomegranate juice once every ten days. Pomegranate juice groups consumed 100 ml of the pomegranate juice daily (2).

Statistical analysis

In this study, SPSS21 Software v.21 (IBM Analytics, USA) of descriptive statistics and inferential statistics were used to analyze data. Smirnov-Kolmograph test was used to check the normality of data as well as one-way analysis of variance (ANOVA). A significant level was reported when $\alpha \leq 0.05$.

Results

Characteristics of the participants are shown in Table 1. Based on the results of Table 1, no significant differences were seen between the height, weight and BMI of the study groups ($p < 0.05$).

Results of intragroup data analysis showed GLP-1 in the control group with non-significant decreases (p = 0.714). Furthermore, results of intragroup analysis showed increases of GLP-1 in pomegranate juice consumption group with no significances (p = 0.577). Results of the resistance training group demonstrated that eight weeks of resistance training significantly increased GLP-1 values. In addition, eight weeks of resistance training with pomegranate juice supplementation significantly increased GLP-1 levels (p = 0.001). Intragroup and intergroup results revealed that DDP-4 increased in control group with no significances (p=0.633). Moreover, results of pomegranate juice group showed that DDP-4 levels included insignificant increases (p=0.056), compared to control group (p=0.711). Results showed that eight weeks of resistance training significantly increased DPP-4 (p=0.0001). Findings showed that DDP-4 levels increased significantly between group and intragroup of resistance training group and pomegranate juice consumption group (p=0.0001). Findings also demonstrated that eight weeks of resistance training with pomegranate juice consumption significantly increased HDL (p= 0.0001) and insulin (p=0.0001) levels. Furthermore, eight weeks of resistance training significantly decreased levels of LDL (p=0.0001) and glucose (p = 0.0001) in women with type 2 diabetes.

Table 1. Weight, height and BMI changes in the study groups before and after eight weeks

	Weight			Height	BMI		
	pre	post	p-value		pre	post	p-value
Control	71.52±4.11	71.50±4.50	p<0.758	166.12±4.55	24.83±2.1	24.9±2.33	p<0.721
Pomegranate juice	68.14±3.12	68.16±3.21	p<0.687	168.17±2.17	23.6±3.22	23.97±4.50	p<0.589
Resistance training	65.17±4.77	67.11±3.18	p<0.644	165.45±3.11	23.77±3.77	24.97±3.46	p<0.616
Resistance training and pomegranate juice	66.35±3.44	68.98±2.11	p<0.745	165.22±2.55	23.77±2.35	25.65±2.9	p<0.512

Table 2. Changes in pre and post-test study variables

Index	Time	Control group (*n*=10)	Pomegranate juice group (*n*=10)	Resistance training group (*n*=10)	Resistance training group + pomegranate juice (*n*=10)	*p*-value
GLP-1 "pg/ml"	pre-Test Post- Test	728.52±102.36 725.11±98.95	798.52±122.79 978.99±125.55	685.74±77.63 963.32±100.56*‡	755.65±77.65 1136.11±101*‡	"p<0.001"
DPP-4 (International unit per liter)	pre- Test Post- Test	415.85±77.40 417.55±78.11	475.77±89.25 390.86±1.63	415.33±55.55 302.12±42.54*‡	432.74±66.71 216.63±2.32*‡	"p<0.001"
HDL "mg/dL"	pre- Test Post- Test	35.23±2.19 35.16±2.22	37.25±2.78 40.23±2.19	37.24±3.19 40.36±2.11	36.63±2.25 45.24±1.39*‡	"p<0.001"
LDL "mg/dL"	pre- Test Post- Test	87.25±5.22 88.21±5.35	87.11±3.35 81.47±3.39	88.63±4.33 81.54±5.88	87.24±2.22 65.42±5.55*‡	"p<0.001"
Glucose "mg/dL"	pre- Test Post- Test	198.34±15.39 198.1±14.38	188.7±13.71 170.11±10.45	200.1±18.87 180.44±12.1	195.15±12.54 160.1±7.25*‡	"p<0.001"
Insulin (μU.ml)	pre- Test Post- Test	6.16±1.22 6.17±1.25	7.1±1.93 7.52±2.28	6.24±2.14 8.39±2.89	5.46±1.19 8.1±2.77*‡	"p<0.001"

* Indicates a significant difference from pre-test to post-test (P <0.05)
+ Indicates a significant difference with the control group (P <0.05)

Discussion

In general, the aim of this study was to investigate effects of eight weeks of resistance training and consumption of pomegranate juice on GLP-1 and DPP-4 levels and glycemic statuses in women with type 2 diabetes. Results of this study showed that eight weeks of resistance training with pomegranate juice consumption significantly increased levels of GLP-1, HDL and insulin in women with type 2 diabetes. Results also showed that eight weeks of resistance training in combination with pomegranate juice consumption significantly decreased DPP-4, LDL and glucose levels in these women. Taybi Rad et al. (2019) investigated effects of aerobic exercises on dipeptidy peptidase-4 and peptide-like glucagon-1 in obese women with diabetes. They showed that aerobic exercises decreased DPP-4 and increased GLP-1 in obese women with type 2 diabetes (5). Similarly, Nejati et al. (2019) studied effects of twelve weeks of combined exercises on GLP-1 and insulin resistance in women with type 2 diabetes. They demonstrated that GLP-1 levels increased and insulin resistance decreased significantly in exercise groups, compared to control group. However, no statistically significant differences were seen between aerobic-resistance and aerobic-resistance training groups (13). Results of the present study were also similar to those of a study by Ueda et al. (2019) on obese people; by which, GLP-1 levels were shown to be consistent after aerobic exercises with 50% max VO_2 on ergometer bikes (21). Based on the results by Akbarpour et al. (2019), who investigated effects of eight weeks of resistance training and pomegranate juice consumption on inflammation, anti-inflammatory factors and sugar profiles were consistent. Akbarpour et al. reported that consumption of pomegranate juice and carrying out resistance training decreased glucose and LDL and increased insulin and HDL in women with type 2 diabetes (2).

Similar to results of a study by Abolfathi et al. (2016), who investigated effects of acute aerobic exercises with an intensity of 65–75% of the maximum heart rate on treadmills on women with type 2 diabetes, results of this study demonstrated that acute aerobic exercise included no effects on GLP1 levels and was heterogeneous (4). However, these findings were not similar to those by Farzanegi (2014), who carried out a study with eight weeks of aerobic exercises on treadmills with a maximum intensity of 57–75% of oxygen for mice and reported that GLP-1 levels decreased after exercises (22). Heden et al. (2013) showed that 60 min of moderate-intensity aerobic activities did not alter GLP-1 levels (23). Similarly, Dekker et al. (2010) reported that 60 min of walking on treadmills did not alter GLP-1 response after eating. Based on the highlighted studies, further intense exercises, negative energy balances, higher carbohydrates or weight losses with exercises are needed to change the response of incretins after eating (24). Major reasons for this discrepancy included study samples, exercise protocols and supplement consumption. As previously stated, one of the results of this study included decreases in DPP-4 levels. One possible mechanism for these decreases could be attributed to increased insulin sensitivity and fat oxidation, resulting in decreases in body fat proportion and poor BMI (25). Decreased body fat proportion and BMI might lead to suppression of DPP-4, decreasing breakdown of intracrine

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hormones, which were typically low in sugar. Adipocytes have been shown as potential sources of DPP-4 secretion into the bloodstream. Since resistance training decreased fat mass, it decreased DPP-4 mass as well. Decreased DPP-4 might partially be essential to improve exercise-induced insulin sensitivity; therefore, decreases in DPP-4 with weight losses improved hemostasis (26). The exact mechanism; by which, DPP-4 is involved in improving post-exercise insulin sensitivity has not been well established. However, researchers have shown that DPP-4 disrupts skeletal muscle insulin signaling at phosphorylation (27). Links between increased insulin sensitivity and decreased DPP-4 after exercises in previous studies have suggested that exercises decrease effects of DPP-4 on glucose uptakes by the skeletal muscles. Therefore, improvements in exercises in insulin sensitivity might be due to decreases in effects of DPP-4 on skeletal muscle insulin signaling, However, effects of exercises on insulin signaling are controversial (27). Insulin resistance has been reported to decrease after a period of aerobic exercises with low-fat diets and this change in insulin resistance is significantly associated with decreases in DPP-4 (28). Decreases in DPP-4 is linked to changes in the expression of PPAR and SREBP-1c, which are important transcription factors for fat oxidation regulation (29). Decreases in plasma DPP-4 have been shown to significantly be correlated with increased post-workout fat oxidation and weight loss. In fact, DPP-4 prevents increased fat oxidation (30). Therefore, increases in fat oxidation after decreases in exercise-induced DPP-4 improve insulin sensitivity (31).

Another result of this study included significant increases in GLP-1 in resistance training and pomegranate juice consumption group. The current study has shown resistance to GLP-1 increases in diabetes mellitus. Resistance to GPL-1 seems to be caused by visceral fat. Physical activity, including resistance training, increases short-chain fatty acids derived from microbiota (microbiota-derived short chain fatty acids), which improves insulin resistance. Short-chain fatty acids communicate with receptors attached to specific G-proteins such as GPR41 and GRP43. These interact at the level of intestinal L-cells and increase GLP-1 secretion. A further result of this study included increases in GLP-1 in pomegranate juice group and pomegranate juice and resistance training group. Studies have shown that pomegranate juice can increase GLP-1 by increasing antioxidants such as vitamin C, vitamin E and carotenoids. Since the level of free radicals is high in diabetics, free radicals break down DNAs produced by GLP-1, (32) Therefore, GLP-1 level decreases in diabetics. The study also has found that resistance training and consumption of pomegranate juice increase insulin and decrease blood glucose in women with type 2 diabetes. The mechanism of this increase was due to increased levels of GLP-1 in women with type 2 diabetes.

Conclusion

In this study, eight weeks of resistance training and pomegranate juice consumption increased GLP-1, HDL and insulin levels and decreased DPP-4, LDL and glucose levels in women with type 2 diabetes. Therefore, resistance exercises with consumption of pomegranate juice as a therapeutic supplement are suggested in women with type 2 diabetes.

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