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ORIGINAL ARTICLE

Beneficial Effects of Pomegranate Peel Extract Treatment on Anthropometry and Body Composition of Overweight Patients With Diabetes Mellitus Type-2: a Randomised Clinical Trial

Milkica Grabež,[1, 2] Ranko Škrbić,[3] Miloš P Stojiljković,[3] Vesna Rudić-Grujić,[1, 2] Katarina Šavikin,[4] Nebojša Menković,[4] Gordana Zdunić,[4] Nađa Vasiljević[5]

(1) Department of Hygiene, Faculty of Medicine, University of Banja Luka, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina.
(2) Department of Hygiene, Public Health Institute of Republic of Srpska, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina.
(3) Department of Pharmacology, Toxicology and Clinical Pharmacology, Faculty of Medicine, University of Banja Luka, Banja Luka, the Republic of Srpska, Bosnia and Herzegovina.
(4) Institute for Medicinal Plant Research "Dr Josif Pančić", Belgrade, Serbia.
(5) Institute of Hygiene and Medical Ecology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia.

Correspondence:
MILKICA GRABEŽ
E: milkica.grabez@med.unibl.org
T: +387 51 234 100

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Abstract

Background/Aim: Polyphenol compounds obtained from pomegranate have beneficial pharmacological activities in the treatment of diabetes mellitus type 2 (DMT2). Most of DMT2 patients are overweight or obese and obesity by itself is very much related to insulin resistance and abnormalities in insulin secretion. This clinical study aimed to evaluate the pomegranate peel extract (PoPEx) activity on anthropometric parameters and body composition of overweight patients with DMT2.
Methods: Sixty patients with DMT2 on continuous metformin therapy were involved in this double-blind, placebo-controlled, randomised clinical trial. Patients from the study group (n=30) were treated with capsules containing PoPEx (250 mg) twice a day for 8-week period, while those ones from the placebo group (n=30) received placebo capsules for the same period. Anthropometric characteristics (body weight, waist circumference, fat mass percentage, visceral fat level) were measured at the beginning and at the end of the study.
Results: Eight-week treatment with PoPEx resulted in significant changes in BMI (mean value ± standard deviation: 0.18 ± 0.30 kg/m^2) and body mass (0.48 ± 0.93 kg). The intake of PoPEx produced a significant decrease in waist circumference ($z = -4.613$, $p < 0.001$, $r = 0.60$) indicating a large effect size using Cohen's d-test, and a non-significant decrease in the level of visceral fat. The results showed a non-significant reduction in fat mass percentage in PoPEx group (-0.58 ± 2.21 %, $p = 0.159$) compared with the placebo group (0.14 ± 1.24 %, $p = 0.546$).
Conclusion: The eight-week supplementation with PoPEx had a beneficial effect on anthropometry and body composition of overweight diabetic patients.

Key words: pomegranate peel extract; overweight; obesity; diabetes mellitus type 2; anthropometry.

Introduction

Nearly half a billion people worldwide or 9.3 % of all adults globally have diabetes mellitus (DM). The most common type of DM belongs to type 2 (DMT2), accounting for about 90 % of all diabetes cases and the prevalence of this disease is rising.[1] Hyperglycaemia is the most common clinical sign of DMT2 that occurs as a result of decreased insulin secretion and the inability of the body to fully respond to insulin, known as insulin resistance.[1, 2]

Obese patients are at higher risk for non-communicable diseases including DM.[3] Most DMT2

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patients are overweight or obese and obesity by itself is linked to insulin resistance and abnormalities in insulin secretion.[3, 4] One of the most significant risk factors for metabolic disorders and its predisposition to DMT2 is abdominal distribution of fat.[5] Having in mind that DM is one of the leading causes of death worldwide and that DMT2 and obesity together increase the mortality, it is not surprising that the prevention and treatment of DM and obesity are important public health measures.[1, 6]

Diabetes can be managed by different approaches, including antidiabetic medication, nutrition, physical activity or herbal remedies.[7, 8] There is an increasing interest in identifying herbal compounds that have lipid-lowering activities or properties to reduce obesity.[9] According to some studies, polyphenols exert very potent anti-inflammatory effects and can improve metabolic conditions.[8] Pomegranate is an excellent source of polyphenols (flavonoids, condensed tannins and hydrolysable tannins) with beneficial pharmacological properties and potential for treatment of various disorders including DM.[10-13] According to the literature data, pomegranate peel extract (PoPEx) can affect adipocyte differentiation.[9] Adipocytes, on the other hand, are very important in the development of metabolic disturbances that are related to obesity and DM.[9, 14] A recent clinical study, performed in obese patients with DMT2, clearly showed that PoPEx, containing ellagitannins had a very potent hypolipaemic, hypoglycaemic and anti-hypertensive effects, but had no effect on body mass index (BMI), body weight, fat mass and fat-free mass.[15] However, the animal and cell culture studies suggest that dietary polyphenols may have a pronounced anti-inflammatory effect associated with a reduction of body weight and FM.[16, 17]

Therefore, this clinical trial, as an arm of the existing clinical investigation, was aimed to study the effects of PoPEx on anthropometry and body composition in overweight patients with DMT2.

Methods

Study population

This study was designed as a randomised, double-blind, placebo-controlled clinical trial in overweight patients with type 2 diabetes mellitus. Patients were recruited at the Department Endocrinology of the University Clinical Centre of the Republic of Srpska, Banja Luka. All participants (40 - 65 years of age) were overweight (BMI ≥ 25 kg/m^2), had poor glycaemic control (glycosylated haemoglobin, HbA1C ≥ 6.5%) and were treated with metformin for the period of at least one year before being enrolled in the study. Patients not enrolled in the study were those with inflammatory diseases, with chronic kidney or liver disease or those on hormone replacement therapy and antioxidant supplements. Patients on insulin treatment were not considered for the study.

Ethical Considerations

All the subjects interested in participating in this study had to sign an informed consent. They were informed about the study purpose and protocol, as well as on the possible risks or benefits of treatment. This clinical study was approved by the Ethics Committee of the Faculty of Medicine, University of Banja Luka No 01-9-604-2/17 and the study was conducted according to the Declaration of Helsinki.

Study design and medication

After randomisation, sixty patients were allocated into two groups. The study group (n=30) received capsules (250 mg) containing PoPEx twice daily for 8-weeks period, and the placebo group (n=30) received capsules containing the same quantity of placebo. Participants had to follow the study protocol without changing their dietary habits, physical activities and medication regimens during the study period. They participants

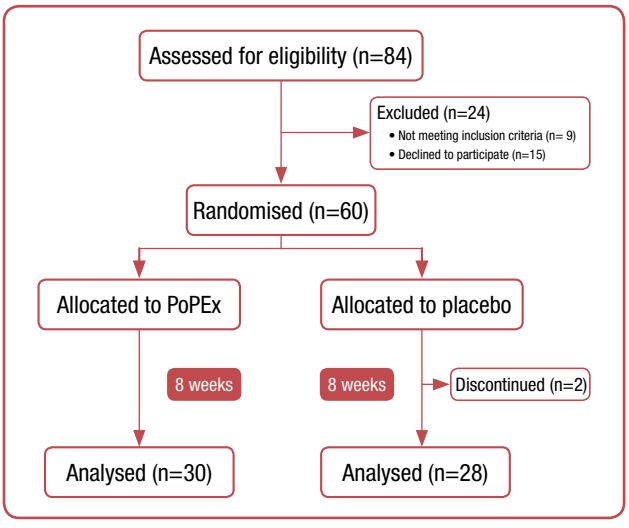

Figure 1: The study design and the participants flow diagram

were provided with a fixed number of capsules needed for the course of treatment. The participant flow diagram and study design are presented in Figure 1.

Pomegranate peel extract

PoPEx was provided by Institute for Medicinal Plant Research "Dr Josif Pančić", Belgrade, Serbia. Pomegranate fruits were obtained from Herzegovina, a southern region of Bosnia and Herzegovina. After being separated from the fruit, peels were dried at room temperature (4 - 6 days). The dried peels were grounded with a laboratory mill to obtain the powder. Powdered pomegranate peel was extracted with 50% ethanol. After filtration, the extract was evaporated to dryness and put in capsules. Each capsule (250 mg) contained polyphenols (punicalagin, punicalin, ellagic acid, and gallic acid) in defined quantities. The detailed

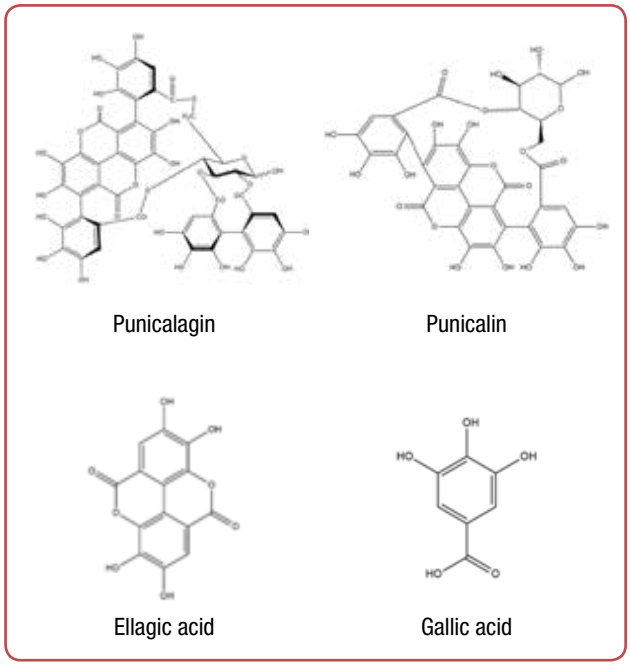

Figure 2: Chemical structures of main pomegranate peel polyphenols

methods of preparation and quantification of phenolic compounds of PoPEx were described in detail in a recently published paper.[15] The chemical formulae of these polyphenols are presented in Figure 2.

Energy and nutrient intake

Using a 3-day food diary records, the dietary intake was assessed at the beginning and at the end of the treatment period. The energy and nutrition intake were estimated every day using the Serbian Food Composition Database, harmonised with the European Food Information Resource (Euro FIR) standards and integrated into the Euro FIR Food Platform and Balkan Food Platform.[18] The participants were advised not to change their usual daily diet.

Anthropometric measurements

The anthropometric measurements were performed at the beginning and the end of the study period by the same trained investigator. All measurements were taken in the morning hours on subjects wearing underwear only. Height was measured using a stadiometer (accuracy of 1 mm), waist circumference (WC) with a non-stretchable tape and the body mass by standard scale (accuracy of 100 g). Body composition (FM, fat-free mass, visceral fat level, and phase angle) was determined using a Tanita bioelectrical impedance analyser (Tanita Corporation, Tokyo, Japan). For skinfold thickness, Harpenden skinfold caliper (SF) was used. Triple measurements were taken on the right side of the body in four standard places (biceps, triceps, subscapular and suprailiac), and the average value was used. BMI was calculated using the following formula: [weight (kg)/height (m)^2].

Statistical analyses

For statistical analyses, the IBM SPSS 20 software was used (Chicago, IL, USA). All results were expressed as mean ± standard deviation and $p < 0.05$ was considered significant. For comparisons between the groups, Student t-test and Mann-Whitney U test were used. The distribution of variables was assessed by Shapiro-Wilk's test. For the power of statistical significance, Cohen's test was used, and the analysis of differences was performed by paired sample t-test or Wilcoxon Signed Rang test. Pearson and Spearman correlation coefficients were used to assess the correlation between body mass change.

Results

Two patients (3.33 %), out of 60 enrolled in the study, did not complete the study. At baseline, there were no differences in age and DM and metformin therapy duration between the PoPEx group and the placebo group (57.9 ± 6.1 years

versus 56.9 ± 6.7 years; 74.00 ± 49.2 months versus 74.8 ± 53.0 months; 56.3 ± 38.0 versus 64.1 ± 49.8 months, respectively). In both study groups, no adverse effects were observed during the follow-up period. The baseline characteristics of the PoPEx and the placebo groups are presented in Table 1. There were no significant differences in anthropometric variables between the PoPEx and the placebo group at baseline.

Table 1: The baseline anthropometric characteristics of patients with diabetes mellitus type 2 (mean values and standard deviations, SD)

	PoPEx group		Placebo group	
	Mean	SD	Mean	SD
Body mass (kg)	90.00	16.58	93.20	16.03
WC (cm)	106.25	11.50	108.71	9.92
BMI (kg/m^2)	30.96	4.37	31.75	4.86
Fat mass (%)	29.85	7.19	30.73	8.59
Fat free mass (%)	66.88	6.61	65.90	8.24
Visceral fat (level)	11.53	3.69	11.67	9.91
Phase angle	5.85	0.67	5.88	0.77

Mean energy intake at baseline was similar in both groups (2333.6 ± 307.9 kcal and 2265.6 ± 343.4 kcal, respectively). The 3-day diary food intake showed no significant changes in the energy and macronutrient intake during the study period. The mean fat energy intake was 920.2 ± 99.3 kcal in the PoPEx group and 881.1 ± 83.8 kcal in the placebo group, accounting for nearly 40% of fat energy. The average daily intakes of saturated fat the energy were 289.6 ± 31.5 kcal and 296.7 ± 30.6 kcal in the PoPEx group and the placebo group, respectively (Table 2).

Table 2: Energy and macronutrient intakes of patients with diabetes mellitus type 2, at baseline and at the end of the study

	Week 0		Week 8		
	Mean	SD	Mean	SD	P-value
PoPEx					
Energy intake (kcal)	2333.6	307.9	2342.8	298.7	0.422
Protein energy (kcal)	495.3	48.6	524.8	51.2	0.568
Fat energy (kcal)	920.2	99.3	904.32	91.2	0.356
SF energy (kcal)	289.6	31.5	294.7	28.3	0.751
CH energy (kcal)	1181.9	131.4	913.4	111.2	0.532
Placebo					
Energy intake (kcal)	2265.6	343.4	2284.3	346.6	0.492
Protein energy (kcal)	471.2	46.4	484.2	47.3	0.588
Fat energy (kcal)	881.1	83.8	890.2	88.7	0.411
SF energy (kcal)	296.7	30.6	287.8	29.3	0.682
CH energy (kcal)	913.3	101.2	909.9	91.3	0.512

PoPEx, pomegranate peel extract; SF, saturated fat; CH, carbohydrate; p values-paired t-test

After the intervention period, significant increase in BMI (0.18 ± 0.30 kg/m^2) and body mass (0.48 ± 0.93 kg) were noticed in the PoPEx group; z = -2.646, p = 0.008 (r = 0.34) and z = -2.391, p = 0.016 (r =0.30), respectively. However, at the same time, the intake of PoPEx produced a significantly decreased WC, z = -4.613, p < 0.001 (r = 0.60), indicating a large effect size using Cohen's test and a non-significant decrease in the level of visceral fat. In the placebo group, there were no statistical differences in the anthropometric characteristics at the end of the intervention period (Table 3).

Table 3: Changes in the outcomes of anthropometric characteristics in patients with diabetes mellitus type 2

	PoPEx group		Placebo group	
	Mean	SD	Mean	SD
Body mass (kg)	0.48 *	0.43	-0.32	1.52
WC (cm)	2.17 ***	1.82	-0.97	2.71
BMI (kg/m^2)	0.18 **	0.30	-0.10	0.51
Fat mass (%)	-0.58	2.21	0.14	1.24
Fat free mass (%)	0.61	2.50	-0.21	1.31
Visceral fat (level)	-0.20	0.92	0.11	0.50
Phase angle	0.78	0.24	-0.01	0.24

*PoPEx, pomegranate peel extract; WC, waist circumference; BMI, body mass index. *p < 0.05 Wilcoxon signed rank test; **p < 0.01; ***p < 0001*

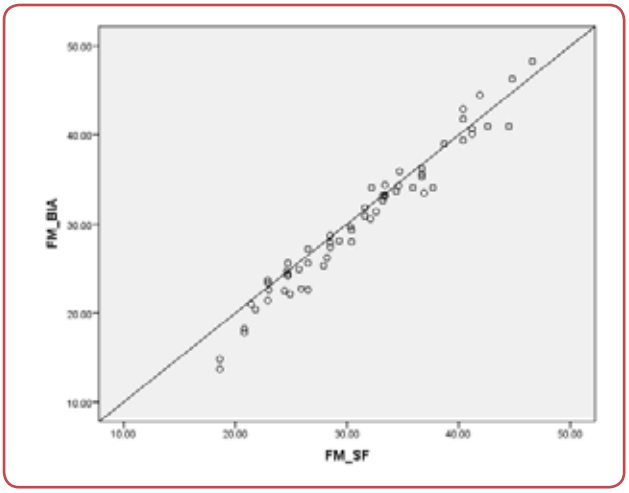

Figure 3: Correlation between two methods, bioelectrical impedance analysis (BIA) and skinfold thicknesses (SF) for estimating the percentage of fat mass in diabetes mellitus type 2 patients r = 0.887; p < 0.001

The relation between the bioelectrical impedance analysis (BIA) and skinfold thicknesses (SF) caliper measurements are illustrated in Figure 3. The correlation factor was high in the total sample (r = 0.887; p < 0.001), but it was lower

for women compared with men (r = 0.93). The results showed a non-significant reduction in fat mass percentage in the PoPEx group (-0.58 ± 2.21 %, p = 0.159) compared with the placebo group (0.14 ± 1.24 %, p = 0.546). Besides, changes in phase angle value and fat-free mass were non-significant (0.78 ± 0.24 and 0.61 ± 0.25).

Discussion

This clinical study was performed to examine the effects of the 8-week treatment with PoPEx on body composition and anthropometric parameters in overweight subjects with DMT2. The results indicated that PoPEx had a beneficial effect on WC, but the effects on body mass and anthropometric characteristics were not consistent. Compared to the placebo group, a significant effect on BMI increase and WC decrease was noticed in the PoPEx group. However, the percentage of FM was decreased (-0.58 %) but the change was statistically not significant. Moreover, the recent results of an additional arm of this study undoubtedly demonstrated hypolipaemic activity of PoPEx treatment with a beneficial effect on fatty acid composition indicating a strong influence on lipid metabolism.[15]

Life-style management, including balanced nutrition and physical activity, are very important keys for improving glucose control in the context of DM self-management.[19] Having that in mind, at the beginning of this study, all participants completed a 3-day food diary and all participants were asked not to change the nutritional pattern. The results showed that diabetic patients had a similar proportion of macronutrients in the diet as the rest of the population which what is in accordance with the 2019 Consensus Report.[20] Nearly 40 % of calories taken originated from fat and saturated fat energy and it was was higher than recommended. Epidemiological studies suggested a positive relationship between the saturated fat intake and plasma cholesterol levels.[21] Furthermore, a meta-analysis of randomised controlled clinical trials on modification of dietary fats on cardiovascular disease (CVD) risk suggested that saturated fat energy reduction might reduce cardiovascular events by 14% in patients with DMT2.[22] In diabetic patients replacing 2% saturated fat energy with polyunsaturated fatty acids (PUFA) energy was associated with a 12 %-decrease in CVD mortality rate.[23] The results of this study clearly showed that at the end of the intervention period, the energy intake and energy macronutrient proportion remained the same in both study groups.

The 8-weeks consumption of PoPEx induced a significant reduction in WC in the treatment group. WC is an independent predictive factor of chronic disease including DMT2.[24] According to Lou et al,[25] a change in WC can decrease the risk for DMT2, despite the lack of change in BMI. Several previous studies showed a significant influence on body mass after pomegranate extract consumption.[26, 27] Our findings are not in accordance with the results obtained from previous animal studies, which have shown that pomegranate induces a weight loss. Intake of pomegranate leaf extracts had demonstrated a significant loss of body weight and a percentage of FM, decreased lipid profile and a decrease in the intestinal fat absorption in the animal model. Lei et al[26, 27] have indicated that one of the possible mechanisms by which leaf extract affects the body mass is similar to the mechanism of drug orlistat (Xenical) causing the decrease in the activity of intestinal lipase, fat absorption, and increase of fat excretion. The administration of the whole pomegranate extract significantly decreased the body mass in overweight people, while there were no changes in the placebo group.[28] Another study noted that intake of 120 mL of pomegranate juice during the 30 days led to a decrease in body mass and total body fat percentage.29 Discrepancies in outcomes of these studies could be explained by the differences in study protocols and treatment regimens (different study designs, different duration of the interventional period, variations among subjects, dosages and forms of pomegranate used).[30] The phase angle value has been reported previously as a biomarker of fat-free mass and changes of phase angle value and fat free-mass in the PoPEX group confirm that assumption.[31, 32]

Concerning the body composition changes in the PoPEx group, average weight gain was 0.48 ± 0.9 kg, but the percent of FM was decreased by 0.58 ± 2.2%. For the assessment of body composition in this study, two measurement tools were used, including BIA and SF caliper. The results showed a highly significant correlation between BIA and SF caliper (p< 0.001, r =0.887).

In DMT2 patients, atherosclerotic CVD is the major cause of morbidity and mortality. Although multiple factors play key roles in the development of CVD in DMT2, obesity is one of the factors that can be modified by dietary interventions.[4] Previous studies investigating the effects of the pomegranate consumption on BMI and body composition are inconsistent. According to Ghefalti et al,[33] supplementation with pomegranate extract showed a tendency to exert a beneficial effect on weight and the percentage of FM. Some *in vivo* and *in vitro* studies suggested that pomegranate had regulatory effects on dyslipidaemia and adipose tissue metabolism in human and animal adipose tissue.[34] Polyphenols as functional food components exert a potential anti-obesity effect through an impact on white adipocyte browning and activation of the brown adipose tissue. Induction of the beige adipocytes may be mediated via the adrenergic membrane receptors, resulting in the stimulation of lipolysis and thermogenesis.[35]

Conclusion

The results of this study showed that eight-week supplementation with PoPEx had a beneficial effect on anthropometry and body composition of overweight diabetic patients. Further studies are needed to explore the potential effect of PoPEx on adipokines and adipocyte functions in obese patients.

Conflict of Interest

None.

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