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Randomized Controlled Trial

Effects of pomegranate juice consumption on blood pressure and lipid profile in patients with type 2 diabetes: A single-blind randomized clinical trial

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SUMMARY

Pomegranate juice (PJ) has abundant anti-oxidative polyphenolic compounds which are assumed to have cardioprotective effects such as hypotensive properties. This study aimed to investigate the effects of PJ consumption on blood pressure and lipid profile F variables in patients with type 2 diabetes. Sixty subjects (30 in intervention group and 30 in control group) were recruited in this single-blind placebo-controlled randomized clinical trial. The volunteers were randomly assigned to one of two groups. Treatment group consumed 200 ml/day PJ for 6 weeks, while control group received no intervention. Systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) and triglyceride (TG) concentrations were measured following 12–14 h of fasting at baseline and at the end of the study. After 6 weeks of intervention, SBP (13.5 ± 1.5 mmHg vs. 12.3 ± 2.5, $P < 0.001$) and DBP (7.7 ± 1.6 vs. 7.2 ± 1.6 mmHg, $P < 0.05$) significantly decreased in the intervention group. Similarly, SBP and DBP in the intervention group were significantly lower than the control group after intervention ($P < 0.02$ and $P < 0.03$, respectively). At the end of the intervention, TC, TG, LDL-C and HDL-C did not significantly differ between the intervention group and the control group however, TC and LDL-C decreased significantly compared to pre-trial values within the intervention group. It is concluded that PJ consumption could decrease systolic and diastolic blood pressure in patients with diabetes while having no effect on lipid profile. A more definitive result will be obtained if future studies could conducted in hyperlipidemic individuals who might be more prone to respond to the lipid-lowering effects.

1. Introduction

Type 2 Diabetes mellitus (T2DM) is a critical health issue globally. According to International Diabetes Federation report, 415 million people in 2015 suffered from diabetes and its prevalence is estimated to reach 642 million by 2040 [1]. The most prominent cause of mortality in patients with diabetes is cardiovascular disease (CVD) and diabetes could lead to a two to four-fold increase in the risk of developing CVD [2]. This amplified hazard is partially due to the high prevalence of CVD risk factors such as hypertension and dyslipidemia among individuals with diabetes [2,3]. Hypertension affects 40%–80% of the population with diabetes. In the Framingham study, The adjusted hazard ratio for hypertension showed a 57% elevation in the risk of any cardiovascular event and 25% increase in the risk of death for any cardiovascular events in the population with diabetes [4]. Furthermore, there is some evidence indicating that dyslipidemia characterized by raised triglycerides (TG) and small, dense low-density lipoprotein (LDL) as well as reduced high-density lipoprotein (HDL) levels could feasibly correspond to CVD risk and mortality from CVD in T2DM [5].

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In spite of some contradictory and null clinical findings on the effects of antioxidants such as polyphenols and nutrients such as vitamin C, on lipid profile [6–10] and blood pressure [11,12], some studies have proposed that antioxidants might improve hypertension [13,14] and lipid profile biomarkers [15,16]. Pomegranate juice (PJ) has a substantial amount of soluble polyphenols comprising principally anthocyanins and tannins (e.g. ellagitannins (mainly punicalagin), ellagic acid, gallic acid and catechins). These polyphenols have antioxidant and anti-inflammatory characteristics [17] and many of them have been shown to have the capability of ameliorating hyperlipidemia [18–20], and hypertension [21,22]. In addition, PJ has exhibited biological activities such as inhibition of angiotensin converting enzyme [23]. In a study on hypertensive males, 150 ml/day PJ following a 12 h fasting significantly reduced both systolic blood pressure (SBP) and diastolic blood pressure (DBP) by 7% and 6%, respectively [24]; however, it did not affect lipid profile parameters after 2 weeks [25]. Similarly, in another investigation, consumption of 500 ml/day PJ significantly attenuated SBP as well as DBP after 2 and 4 weeks, while plasma lipid concentrations were not altered [26]. On the other hand, following administrating 40 g concentrated PJ to patients with both diabetes and hyperlipidemia for 8 weeks, total cholesterol (TC), LDL-C, LDL-C/HDL-C ratio and TC/HDL-C ratio were significantly decreased. However, serum TG and HDL-C were not affected [27]. Few other studies which assessed the impact of PJ consumption did not have a control group [27], used healthy subjects as control [28] or studied the short-term effects of PJ consumption on different diabetic variables [29].

According to few and conflicting studies concerning PJ influences on dyslipidemia and hypertension in T2DM, this study was carried out to evaluate the effects of PJ consumption on systolic and diastolic blood pressure and lipid profile variables including TC, TG, LDL-C and HDL-C in patients with type 2 diabetes.

2. Materials and methods

2.1. Study design and subject selection

This study was a randomized, single blind clinical trial on patients with type 2 diabetes. It was carried out at Health Faculty of Tehran University of Medical Sciences. Having diabetes was defined by having fasting blood glucose higher than 126 mg/dl [1]. Medical records of patients in Iran's Charity Foundation for Special Diseases and Iranian Diabetes Society were carefully reviewed (Fig. 1). Of those, 62 non-smoking 40-65-year-old patients with diabetes who didn't suffer from any other chronic diseases and hadn't taken estrogen or progesterone (if female) or any supplements for last 3 months and also insulin for diabetes control, were recruite using convenience sampling. Goals of the study were explained for all subjects and each participant provided informed written consent. Ethics approval for the trial was obtained from the ethical committee of the Tehran University of Medical Sciences (No: ir.tums.112546). The trial was registered in the Iranian Registry of Clinical Trials at http://www.clinicaltrials.gov, registration no. NCT02559843. Patients were stratified by sex and randomly assigned to PJ consuming group (intervention group) and control group, using computer generated random number table. Subjects in both groups were asked to maintain their usual activity levels during the entire study.

2.2. Dietary intervention and compliance

Subjects in both groups were instructed not to modify their regular diet. The intervention group was asked to consume 200 ml of PJ (without sugar or additives) daily for 6 weeks while the control group received no intervention. The juices were delivered to the participants every two weeks. Compliance was checked by weekly

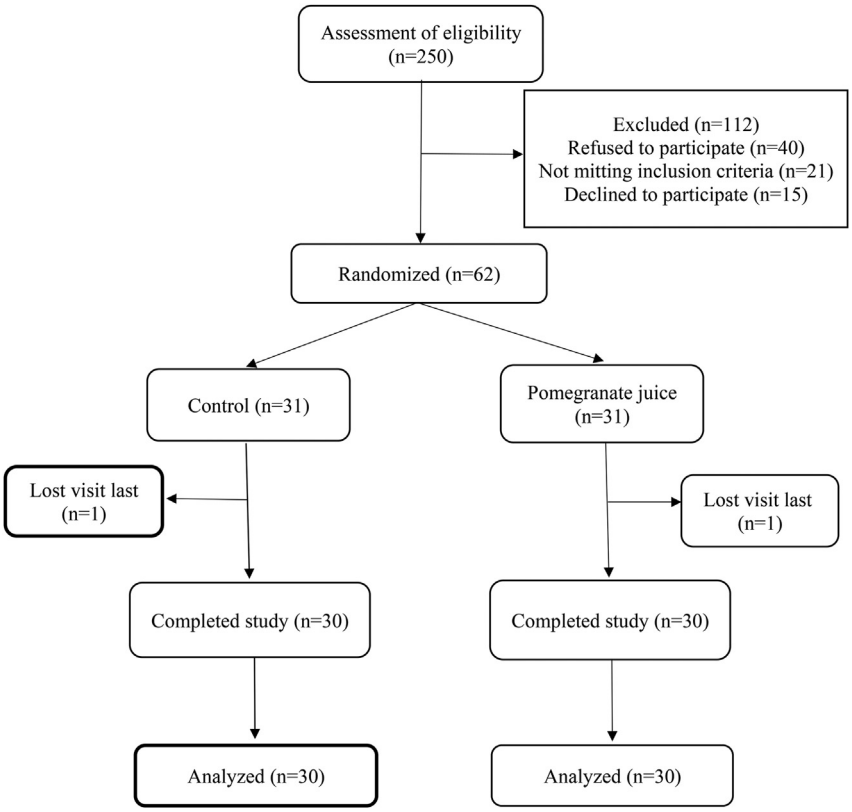

Fig. 1. Flow chart of study.

contact. To ascertain patient adherence to the study protocol, we provided each patient with a fixed number of PJ bottles and instructions to return the unused bottles at the end of the study. Based on the number of returned bottles by each patient, their compliance was determined, which was 90% for our participants.

2.3. Pomegranate processing and characteristics

Pomegranate juice was processed and packed by Takdaneh Company in Iran. Pomegranates were hand-picked in the farm. Subsequently, they were washed, chilled to 4 °C and stored. The edible parts of pomegranate fruit were separated by machine, squeezed and treated enzymatically with pectinase to yield the PJ including the seeds and 10% of inner peels. The juice was filtered, pasteurized at 80 °C, concentrated and stored at −18 °C. Concentrated PJ was diluted to yield PJ, packed in tetra pack sachet and kept in cold storage. PJ contains 5.9 g glucose in 100 ml. The characteristics of PJ which was used in this study indicated in our previous study [30]. The phenols were determined by the Folin–Ciocalteu reagent, using Gallic acid as a standard [31]. Total flavonoid content was measured by the aluminum chloride colorimetric assay using catechin as a standard [32]. The PJ contains 2125 mg/l total polyphenol and 385 (lg/ml) for total flavonoid.

2.4. Dietary assessment

Dietary intake was assessed using a 3-day dietary recall (including two-week days and one weekend day) for each subject at the beginning and at the end of 6 weeks trial. Dietary recalls were analyzed by Food Processor II software modified for Iranian foods.

2.5. Anthropometric measurements

Each subject's weight was recorded while wearing light clothing and no shoes, using digital scales (Sohenle, Germany) to the nearest 100 g. Height was measured using a plastic tape attached to the wall to the nearest 0.5 cm. Body mass index (BMI) was calculated as weight (kg) divided by square of height (m).

2.6. Blood pressure measurement

SBP and DBP were measured using a standard mercury sphygmomanometer (Rishter, Diplomat 1002, Germany), on the right arm after a 15-min rest in a sitting position. Two measurements were taken at 1-min intervals and the average of measurements was recorded as the participant's blood pressure. If the second measurement was a lot different to the first, it was measured for the third time and the average of two more closest No was considered as the participant's blood pressure.

2.7. Lipid profile measurements

At the beginning and at the end of the study, 10 ml of venous blood was drawn following 12–14 h of fasting. After keeping for 30–45 min at room temperature, blood samples were centrifuged at a rate of 2000 round per minute in order to separate blood serum. Serums were kept in −80 °C until the time of performing experiments. Precipitation of serum HDL-C was done using phosphotungstate and magnesium chloride solution (MAN company kit) and separation of serum LDL-C was done by heparin-sodium citrate solution (Randox company kit). Serum HDL-C, LDL-C, TC and TG concentrations were measured by the enzymatic method using MAN company kits. Inter- and Intra-assay coefficient of variations of all assays were <5%.

2.8. Statistical analysis

Data were analyzed using Statistical Program for Social Sciences (SPSS) (version 12). The sample size was designed to detect a 25 mg/dl difference among groups in total cholesterol with 95% CI and 90% power. With regard to the possible loss of the participants, the calculated sample size was 30 patients in each group.

Paired T-test was used to detect changes within each group. Adjustment for differences in the baseline covariates and changes in variables during the study was performed by analysis of covariance using general linear models. Statistical significance was defined as P-value <0.05. All values are expressed as mean ± S.D.

3. Results

From 62 subjects who enrolled, 60 individuals (30 in intervention group and 30 in control group) completed the study. A subject in the control and a subject in the intervention group were excluded because of missing the blood collecting date and smoking, respectively. According to Table 1, baseline characteristics including sex, age, duration of diabetes and BMI were not significantly different between two groups. Nutrients and fiber intake derived from 24-h dietary recalls were also similar between two groups at baseline. Mean BMI, nutrients and fiber intake (except vitamin E), type and dosage of medications used and also physical activity level of participants had not changed during the study (Table 2). All analyzes were adjusted for Vitamin E intake by Covariance analysis. As shown in Table 3, within the PJ consuming group, there was a significant difference in mean SBP ($P < 0.001$) and mean DBP ($P < 0.05$) after PJ administration compared to the baseline values. Mean SBP ($P < 0.02$) and DBP ($P < 0.03$) were also different between two groups after intervention. Fasting blood sugar (FBS) mean concentration in PJ group was significantly lower than the control group but mean changes between two group didn't have a significant difference (data not shown) [30]. Furthermore, within PJ consuming group, post-trial TC and LDL-C concentrations compared to pre-trial values differed significantly. Nevertheless, no significant differences were seen concerning mean TC, TG, LDL-C and HDL-C between control and intervention group after treatment with PJ (data are shown in Table 4). It is worth mentioning that before the intervention, a significant discrepancy in terms of

Table 1
Baseline characteristics of participants according to the study groups.

Demographic variable	Intervention group (n = 30)	Control group (n = 30)
	N (%)	N (%)
Sex		
Women	15 (50)	15 (50)
Men	15 (50)	15 (50)
Physical Activity Level		
Sedentary	8 (26.7)	7 (23.3)
Light	7 (23.3)	10 (33.3)
Moderate	15 (50)	13 (43.4)
Oral Hypoglycemic Drugs		
Glybenclimide	8 (26.7)	6 (20)
Metformin	1 (3.3)	3 (10)
Both	18 (60)	16 (53.3)
None	3 (10)	5 (16.7)
Lipid Lowering Drugs		
No	23 (76.7)	25 (83.3)
Yes	7 (23.3)	5 (16.7)
Anti-hypertensive Drugs		
No	24 (80)	23 (76.7)
Yes	6 (20)	7 (23.3)

*Values are shown in number and percentage.
**There was no significant difference between groups by chi-square.

Table 2
Means and standard deviations of independent quantitative variables according to study groups.

Quantitative variable	Intervention group (n = 30)	Control group (n = 30)
Age (yrs)	54.6 ± 8.4	55.3 ± 8.5
BMI (kg/m^2)		
Before	27.2 ± 3.4	26.5 ± 3.6
After	27.1 ± 3.5	26.4 ± 3.6
Duration of diabetes (months)	94.4 ± 64.7	91.2 ± 84.6
Energy (Kcal/d)		
Before	1479.2 ± 422.4	1552.2 ± 419.9
After	1512 ± 352.7	1398.9 ± 457.4
Calcium (mg/d)		
Before	811.2 ± 376.3	994.9 ± 582.1
After	797.1 ± 360.7	849 ± 550.4
Magnesium (mg/d)		
Before	284.6 ± 110.5	322.9 ± 107.3
After	287.6 ± 100.2	295.3 ± 101.8
Potassium (mg/d)		
Before	2476.7 ± 982.2	2665.7 ± 916.6
After	2378.7 ± 775.1	2344.2 ± 885.9

BMI: body mass index.
*Values are shown in mean ± SD.
**There was no significant difference between groups by Independent t-test.

Table 3
Effect of 6 weeks pomegranate juice consumption by patients with diabetes on blood pressure.

Blood pressure	Intervention group N = 30	Control group N = 30	P values	
			P**	P*
Systolic Blood Pressure				
Before	13.5 ± 1.5	13.0 ± 2.0		
After	12.3 ± 2.5	12.6 ± 2.2	<0.02	<0.001
Diastolic Blood Pressure				
Before	7.7 ± 1.6	7.9 ± 1.4		
After	7.2 ± 1.6	7.8 ± 1.5	<0.03	<0.05

Values of systolic and diastolic blood pressure are demonstrated as mean ± SD.
P* p values are for paired comparison of pre- and post-trial values within PJ consuming group (paired t-test).
P** P values are for comparison between two groups after intervention (co-variance analysis).

mean serum TC concentration existed between the two groups ($P < 0.02$).

4. Discussion

The current study was carried out to examine the effects of 200 ml/d PJ consumption for 6 weeks on cardiovascular risk factors encompassing hypertension and dyslipidemia in T2DM patients. A significant reduction was observed in systolic blood pressure as well as diastolic blood pressure in the PJ administrated group compared to the control group after the intervention. Nonetheless, no significant difference was seen regarding mean TC, TG, LDL-C and HDL-C between control and intervention group after treatment with PJ. These findings are consistent with the results of several studies conducted previously. For instance, a recent trial indicated a significant decline in SBP and DBP in hypertensive and normo–lipid profile subjects following 2 weeks of 150 ml/d PJ intake. Also, similar to our study, no significant influence was seen on lipid profile variables in that study [25]. The greater effect of PJ on SBP in the mentioned study could be due to the higher baseline SBP values of the hypertensive subjects. The same amount of a single dose PJ also reduced SBP and DBP by 7% and 6%, respectively in a single arm study in hypertensive males [24]. In a crossover trial, Tsang et al. investigated the effects of 500 ml/d PJ or placebo

Table 4
Effect of 6 weeks pomegranate juice consumption by patients with diabetes on lipid profile parameters.

Lipid profile parameters	Intervention group N = 30	Control group N = 30	P values	
			P*	P**
Total cholesterol (mg/dL)				
Before	236.1 ± 50.8[a]	205.9 ± 46.7	<0.02[b]	NS
After	215.7 ± 48.8	199.9 ± 46.7		
Triglycerid (mg/dL)				
Before	176.2 ± 70.1	159.3 ± 72.6	NS	NS
After	175.3 ± 77.2	152.2 ± 68.6		
HDL-C (mg/dL)				
Before	46.3 ± 11.5	45.2 ± 7.9	NS	NS
After	45.8 ± 11.2	44.5 ± 8.5		
LDL-C (mg/dL)				
Before	148.8 ± 38.4	128.8 ± 39.7	<0.03[c]	NS
After	134 ± 44.6	125.1 ± 35.9		

HDL-C: high density lipoprotein cholesterol; LDL-C low density lipoprotein cholesterol; NS: nonsignificant.
Values of lipid profile concentration are demonstrated as mean ± SD.
P* p values were for paired comparison of pre- and post-trial values within PJ consuming group (paired t-test).
P** P values were for comparison between two groups after intervention (independent t-test).
[a] Significant difference between two groups before intervention ($P < 0.02$) seen with independent t-test.
[b] Significant difference of pre and post-trial values within PJ consuming group ($P < 0.02$) seen with paired t-test.
[c] Significant difference of pre and post-trial values within PJ consuming group ($P < 0.03$) seen with paired t-test.

consumption for 1 month in 28 overweight or obese subjects who did not have metabolic syndrome. A significant reduction was demonstrated in SBP and DBP; however, lipid profile markers remained unchanged as they were in the normal range from the initiation [26]. Similarly, another study on obese patients exhibited no significant modification in lipid profile ensuing consumption of 120 ml/d PJ in a fasted state for 1 month [33]. Furthermore, Lyn et al. reported a significant decrease in SBP and DBP after consuming 330 ml/d PJ for 1 month in healthy adults in an open-label placebo-controlled trial [34]. In addition, Aviram et al. examined effects of 50 ml/d PJ supplementation in 10 atherosclerotic patients with carotid artery stenosis for 1 year whom five of them continued PJ consumption for 3 years [35]. After 1 year, SBP decreased by 12% and no further decline was seen within 3 years [35]. DBP, TC, LDL and HDL were not significantly affected; however, TG and VLDL levels rose (by 16% and 12%, respectively) after 1 year but the increased values were still in the normal range [35]. On the contrary, another study which was conducted on patients with coronary heart disease showed that consuming 240 ml/d of PJ for 3 months had no significant influence on neither their blood pressure nor their plasma lipids [36].

A quasi-experimental study on the effects of 40 g/d concentrated PJ consumption for 8 weeks on lipid profile in diabetic subjects with hyperlipidemia showed a significant reduction in TC, LDL, LDL/HDL and TC/HDL; however, TG and HDL were not altered [27]. The observed significant cholesterol-lowering effect may be due to the fact that all the patients had hyperlipidemia at baseline [27]. On the other hand, since the study had no control group it is feasible that the observed difference in TC and LDL levels may be due to within-group changes rather than PJ consumption as what we found in our study [27]. We observed the same significant reduction in TC and LDL levels in the intervention group but these changes were not significant compared to the changes in the control group.

Several mechanisms have been suggested for the blood pressure lowering effect of PJ. First is inhibition of angiotensin converting enzyme (ACE) activity [33]. Aviram et al. discovered that 50 ml/d of

PJ consumption for 2 weeks in hypertensive patients could lead to a 36% decrease in ACE activity as well as a 5% decline in SBP. However, in the aforementioned study of Lyn et al. no influence on serum ACE was found and it was proposed that the polyphenol or potassium content of PJ might account for its hypotensive properties [33]. Another possible mechanism for reducing blood pressure can be related to nutrients intake such as calcium, magnesium and potassium [37]. As shown in Table 2, dietary intake of these nutrients were not shown any significant difference within and between groups before and after the intervention. Therefore, the observed decrease in blood pressure cannot be due to the effect of these nutrients.

As stated before, antioxidants such as polyphenols and vitamin C in PJ have been shown to be capable of lowering blood pressure in myriad studies. Oxidative stress is known to be implicated in the evolution of hypertension. Interaction of reactive oxygen species (ROS) (specifically superoxide onion) with cellular elements, lipids and proteins result in endothelial dysfunction and vascular resistance. Moreover, ROS preclude production and vasodilatory activities of nitric oxide (NO) through diminishing activity of NO synthase and promoting NO breakdown which culminates in hypertension [24]. Another mechanism which has been hypothesized by the aforesaid study of Tsang et al. is the possible inhibition of 11β-hydroxysteroid dehydrogenase type 1 (11β-HSD1) enzyme activity by PJ which converts cortisone to the active steroid, cortisol. The level of cortisol circulating in the body plays a key role in blood pressure regulation and could adversely affect blood pressure and lipid profile via inducing oxidative stress. Since it was shown in the study that cortisol/cortisone ratio decreased in urine and saliva following PJ administration, it was postulated that 11β-HSD1 enzyme was inhibited by PJ consumption and consequently, this led to reducing SBP and DBP [26].

Some studies have reported that polyphenols might be able to inhibit pancreatic lipase [26], increase fecal excretion and decrease absorption of cholesterol. Also, flavonoids may have a direct influence on cholesterol metabolism via an effect on hydroxymethyl glutaryl-CoA reductase or sterol O-acyltransferase enzymes [27]. Nevertheless, in our trial and most of other studies, PJ did not have any significant effect on lipid profile variables except for one trial which showed the cholesterol-lowering effect of PJ in diabetic patients with hyperlipidemia [27].

As patients with diabetes are more susceptible to oxidative stress because hyperglycemia induces free radical production [26] and they are more prone to hypertension (2), recommending consumption of PJ which has anti-oxidative and hypotensive properties to them is tremendously beneficial with no side effects, and without any elevation in Blood glucose level.

One of the limitations of the current study is that the duration of PJ administration was rather short. Also, factors attributed to the endothelial function or ACE activity were not assessed in this study to elucidate the underlying mechanisms. Moreover, longer studies are recommended to corroborate PJ effects on lipid profile and blood pressure in patients with diabetes since solely a few studies have examined PJ effects on these factors in patients with diabetes The lack of using a qualified food frequency questionnaire and evaluation of dietary phytochemicals which cannot be analyzed using the existing dietary data basesand also the lack of placebo drink and blood polyphenols concentrations as indicators of adherence are the other limitations for the present study.

5. Conclusion

In conclusion, the present study demonstrated the effect of 200 ml/day PJ consumption for 6 weeks on systolic and diastolic blood pressure reduction in patients with type 2 diabetes. Nonetheless, no significant effect on lipid profile variables was found following PJ supplementation in this study. A more definitive result will be obtained if future studies could conducted in hyperlipidemic individuals who might be more prone to respond to the lipid-lowering effects.

Conflict of interest

The authors declare that they have no conflict of interest.

Ethical approval

All procedures performed in studies involving subjects recruitment were in accordance with the ethical standards of institutional research committee and Ethics approval for the trial was obtained from the ethical committee of the Tehran University of Medical Sciences (No: ir.tums.112546).

Informed consent

Informed consent was obtained from all individual participant included in the study.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2018.11.013.

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