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The effects of pumpkin seed oil supplementation on arterial hemodynamics, stiffness and cardiac autonomic function in postmenopausal women

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ABSTRACT

Background: Postmenopausal women have a higher prevalence of hypertension than age-match men. Evidence from animal studies have demonstrated the antihypertensive effects of pumpkin seed oil (PSO). We examined the effects of PSO supplementation on vascular function and heart rate variability (HRV) in postmenopausal women with elevated blood pressure (BP).

Materials and methods: Participants were randomly assigned to either a PSO (n = 12) or a placebo group (n = 11). Participants in the PSO group consumed 3 g/day of PSO. Brachial and central BP, wave reflection (augmentation index, AIx), arterial stiffness (SI) and various HRV parameters were measured before and after 6 weeks.

Results: AIx, brachial and central systolic BP significantly ($P < 0.05$) decreased following PSO but not after placebo. SI and HRV parameters remained unchanged after PSO or placebo.

Conclusion: PSO improved arterial hemodynamics in postmenopausal women and therefore might be effective in the prevention and treatment of hypertension in this population.

Clinical trial ID: (NCT03716960).

1. Introduction

Central systolic blood pressure (SBP) is strongly associated with the loading conditions and mass of the left ventricle [1]. Therefore, the rise in central SBP has become as a key indicator of cardiovascular (CV) risk [1,2]. Central SBP elevates with advancing age due a rise in pressure wave reflection from peripheral arteries to the aorta, which is attributed to age-related increases in central stiffness [3] and impaired peripheral artery vasodilation [4]. Notably, postmenopausal women present higher central SBP, stiffness and wave reflection [augmentation index (AIx)] than men of corresponding age [5–8]; which seem to be related with oestrogen deficiency [9]. Therefore, postmenopausal women may have an augmented risk for CV events [7], especially heart failure [10].

Dietary approaches are a widely advocated form of lifestyle modification among worldwide health organizations to avert the age-related increase in CV disease risks [11,12]. This solidifies the appeal to find other preventive strategies using food and dietary supplements in hopes to prevent CV disease and related complications in postmenopausal women. Pumpkin seed oil (PSO), is a natural produce frequently used in folk medicine for the treatment of different CV conditions, including hypertension and atherosclerosis [13]. Indeed, recent studies in rats and humans demonstrated beneficial effects of PSO supplementation on brachial blood pressure and plasma lipids concentration [14–16]. These positive CV impacts seem to be related to a broad range of favorable properties of PSO, which include significant anti-inflammatory, antioxidant, phytoestrogenic, phenolic as well as hypolipidemic activities [14,17–20]. However, existing literature about the benefits of PSO on vascular domains is sparse. Therefore, this investigation aimed to evaluate whether PSO supplementation has favorable effects on central SBP, AIx as well as arterial stiffness in postmenopausal women hypothesizing that PSO will cause improvements in these variables. We also evaluated cardiac autonomic function as a mechanism that might help explain some potential favorable changes in vascular function.

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2. Materials and methods

2.1. Participants

Twenty-three (age 48–64 years) postmenopausal women from Arlington, Virginia, and surrounding areas participated in this study. Recruitment began in September 2017 and continued through July 2018 when the final participant finished the study. Menopause was described as the absence of menstruation for a period of 12 months at the minimum. Potential participants were excluded from the study if they were smokers, had psychiatric disorders or were receiving any psychological care in the past 12 months. In addition, the exclusion criteria included pulmonary, renal, adrenal, pituitary, thyroid, or CV diseases, other than hypertension. It was necessary to further define the exclusion criteria to encompass the use of medications, supplements or hormone replacement therapy during the 12 months prior to our investigation to eliminate possible extraneous influences on the dependent variables. Lastly, women who in the past year, who participated in physical therapy, had exercise habits or experienced any exercise training and dietary changes were excluded to avoid potential confounding effects that could impact the outcomes of this study. All protocols were approved by the Institutional Review Board, registered in Clinicaltrials.gov (NCT03716960) and carried out as stated by the Declaration of Helsinki. Prior to enrollment, all participants obtained complete information about the study specifications and gave their written informed consent.

2.2. Study design

A randomized, double-blind, placebo-controlled parallel experimental design was utilized in the present study. After the first set of screening and familiarization with all the procedures, eligible participants were randomly assigned to a PSO group or a placebo-controlled (Placebo) group. Allocation was stratified for brachial SBP [$\geq 130 < 180$ mmHg (n = 7 in PSO and n = 7 in placebo group) or < 130 mmHg (n = 5 in PSO and n = 4 in placebo group)], and the sequence was generated by a computer-based number. Measurements were taken at baseline and after 6 weeks during the same time of day ($\pm$ 1 h) in the morning following an overnight fast and ~24 h after the last dose of PSO and placebo. The overnight fast included abstinence from caffeinated drinks and alcohol. CV measurements were collected after having the patient relax in supine for at least 10 min in a noiseless, temperature-controlled room (22–24 °C). Participants were educated not to change their regular lifestyle habits during the investigation period, to help maximize the findings of the study.

2.3. Supplementation

The group ingesting the PSO took in 3 g/day; a 1 g capsule was taken with every main meal (NOW Foods, Illinois, USA). The placebo group had the same regimen of maltodextrin (a polysaccharide), 1 capsule three times a day. The dose and scheduling were based on previous studies that showed positive health trends after PSO supplementation in several populations [20], including decreases in brachial BP in postmenopausal women [16]. When the trial period was over, participants of both groups were told to return unconsumed capsules in order to calculate compliance to the supplementation. This was done by dividing the number of capsules they had left over by the expected number of capsules.

2.4. Anthropometrics

Measurements of height and body weight were done via a stadiometer and Seca scale, respectively. Body mass index was quantified as kg/m [2].

2.5. Arterial hemodynamics and stiffness

A validated automated apparatus (A-PULSE CASPal, Healthstats International, Republic of Singapore) was utilized to assess brachial SBP and DBP and to calibrate waveforms from the radial artery, obtained from a 10s period by means of a noninvasive tonometer. Central SBP and AIx was obtained from central waveforms which were synthesized from radial waveforms [21]. Since HR has a negative influence on AIx, this marker of wave reflection was normalized to a HR of 75 b/min (AIx@75) [22].

A validated digital photoplethysmographer (Angioscan- 01, Angioscan-Electronics LLC, Russia) was used for the measurement of stiffness index (SI), a marker of central stiffness. A 5-min epoch picks up a quantity of waveforms that are then averaged by the system to calculate SI as previously described [23,24].

2.6. Heart rate variability

Cardiac autonomic function was evaluated by means of heart rate variability (HRV) using standard guidelines [25]. HRV measurement was obtained for 5 min from a validated monitor (Polar Electro OY, Kempele, Finland) thru a PC-interfaced chest strap. Total power (TP) and its main elements, low-frequency (LF, mediated by parasympathetic and sympathetic modulations) and high-frequency (HF, an index of parasympathetic activity), were estimated by a power spectrum using autoregressive model and also normalized (nLF and nHF) as a % of the TP. Markers were adjusted as follows: TP (0.00–0.40 Hz), LF (0.04–0.15 Hz) and HF (0.15–0.40 Hz). The ratio of LF to HF (LF/HF) was used as a marker reflecting sympathovagal balance [26].

2.7. Statistical analysis

The Kolmogorov-Smirnov test was performed to examine normal distribution in all parameters. Some of our HRV indexes (TP, LF, HF, LF/HF) did not have a normal distribution, hence a logarithmic transformation (Ln) was done as defined by standard guidelines (Task Force et al., 1996). Group comparisons at baseline were conducted via Student's t-test. A 2 X 2 analysis of variance with repeated measures [group (placebo X PSO) x time (before X after 6 weeks)] was done to establish the effect of PSO and time on dependent variables. A paired *t*-test was carried out for within-group post hoc analysis, if a significant interaction was detected. We implemented Pearson's correlations to examine the association between changes in hemodynamic, SI and HRV variables. Analyses were carried out utilizing SPSS 25.0 for Windows. Data are expressed as mean $\pm$ standard error of the mean (SEM). Statistical significance was fixed at $P < 0.05$. To achieve a difference of 3%–5% between the groups (PSO vs placebo) in SBP with a power of 80%, we needed a sample size of at least 21. This was determined by performing a power analysis calculation [16].

3. Results

Twenty-two participants were incorporated in the statistical analysis as one participant discontinued her participation our study due to time restrictions. Compliance to the supplementation was 94% for the PSO and 95% for placebo groups. Notably, not one of the participants in the PSO group reported any negative symptoms/signs or adverse side effects resulting from PSO.

Participant characteristics, hemodynamics and arterial stiffness at baseline and after 6 weeks for the placebo and PSO groups are presented in Table 1. Baseline values between the two groups were not significantly different ($P > 0.05$). There were significant group $\times$ time interactions ($P < 0.05$) for AIx, AIx@75, brachial SBP, brachial DBP, and central SBP. Mean $\pm$ SEM for AIx (-5 ± 2%), AIx@75 (-5 ± 2%), brachial SBP (-6 ± 1 mmHg), brachial DBP (-3 ± 1 mmHg), and central SBP (-7 ± 2 mmHg) significantly

Table 1
Participant's characteristics, hemodynamics and arterial stiffness before and after 6 weeks of PSO or placebo. Abbreviations: PSO, pumpkin seed oil; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; PP, pulse pressure; AIx, augmentation index; AIx@75, augmentation index adjusted at heart rate of 75 beats/min.*P < 0.05, #P < 0.01 different than before. †P < 0.05 different than control. Data are mean ± standard error of the mean.

Variable	PSO		PLACEBO	
	Before	After	Before	After
Age (years)	57 ± 2	–	56 ± 1	–
Height (m)	1.61 ± 2	–	1.60 ± 2	–
Body weight (kg)	73.3 ± 3.8	73.2 ± 3.7	75.3 ± 4.1	75.5 ± 4.2
BMI (kg/m^2)	28.8 ± 1.6	28.8 ± 1.6	29.4 ± 1.5	29.5 ± 1.5
Brachial SBP (mmHg)	136 ± 3	131 ± 3*†	136 ± 4	135 ± 5
Brachial DBP (mmHg)	78 ± 2	75 ± 2*†	79 ± 2	79 ± 2
Aortic SBP (mmHg)	130 ± 4	123 ± 4#†	130 ± 4	129 ± 5
AIx (%)	38 ± 2	33 ± 3#†	38 ± 3	37 ± 3
AIx@75 (%)	32 ± 3	27 ± 3#†	32 ± 4	31 ± 4
Stiffness Index (m/s)	11.0 ± 0.3	10.7 ± 0.4	11.3 ± 0.4	11.2 ± 0.3

Table 2
Heart rate and heart rate variability measurements before and after 6 weeks of PSO or placebo. Abbreviations: PSO, pumpkin seed oil; Ln, natural logarithm; TP, total power; n, normalized to TP; LF, low frequency; HF, high frequency; LF/HF, LF to HF ratio. Data are mean ± standard error of the mean.

Variable	PSO		PLACEBO	
	Before	After	Before	After
Heart Rate (bpm)	65 ± 3	65 ± 2	66 ± 2	66 ± 2
LnTP (ms^2)	6.7 ± 0.2	6.7 ± 0.2	6.6 ± 0.3	6.5 ± 0.3
nLF (%)	55.3 ± 4.2	54.8 ± 3.9	58.1 ± 4.3	56.8 ± 4.3
nHF (%)	44.5 ± 4.1	45.1 ± 4.0	40.8 ± 4.2	42.3 ± 4.4
LnLF (ms^2)	5.5 ± 0.2	5.4 ± 0.2	5.6 ± 0.2	5.6 ± 0.2
LnHF (ms^2)	5.2 ± 0.2	5.2 ± 0.3	5.2 ± 0.2	5.3 ± 0.2
LnLF/LnHF	1.1 ± 0.1	1.0 ± 0.1	1.1 ± 0.1	1.1 ± 0.1

declined ($P < 0.01$) after PSO compared to placebo. The changes in central SBP were correlated with changes in AIx (r = 0.64, P < 0.05) and AIx@75 (r = 0.66, P < 0.05). No significant changes were seen in SI, weight, BMI, HR and HRV parameters (Table 2), after PSO or placebo.

4. Discussion

Relevant findings of this study are as follows: central SBP and wave reflection significantly decreased after daily incorporation of PSO into the diet of postmenopausal women for 6 weeks. To our knowledge, this has been the only investigation to evaluate the effects of PSO on central hemodynamics in postmenopausal women, a population at a high risk for hypertension and heart failure.

In terms of the effects of PSO on BP, the results of the current investigation revealed a reduction in central SBP in the PSO group, whereas no significant declines were observed in the placebo group. From a clinical standpoint, central SBP is more noteworthy than brachial SBP since it is the pressure applied on the left ventricle [27] in addition to being a more sensitive predictor of adverse CV outcomes [2]. Our investigation showed that our PSO intervention reduced central SBP by roughly 7 mm Hg, without any significant changes in HR, HRV and central stiffness (as shown as no significant change in SI); suggesting that the favorable impact of PSO on central SBP could be explained by attenuated pressure wave reflection. This notion is supported by our observed correlation between central SBP with AIx and AIx@75. The decrease in central SBP after PSO was similar to the elevation in central SBP (7 mm Hg) detected in middle-aged women in a decade follow-up [4]. Additionally, it should be noticed that efficacy of pharmacological interventions on central SBP is not consistent [28]. Therefore, the efficacy of daily PSO intake on reducing central SBP may have important clinical outcomes for postmenopausal women with elevated BP and hypertension.

In this investigation, we also observed declines in resting brachial SBP and DBP after PSO supplementation. Previous research in rats indicates that PSO supplementation has a significant beneficial hypotensive action leading to decreases in both brachial SBP and DBP [14,15]. Our findings are also consistent with an earlier investigation by Gossell-Williams et al. [16] which reported declines on resting brachial DBP after 12 weeks of PSO supplementation (2 g/day) in postmenopausal women. Conversely, although not significant, a trend towards a reduction in resting brachial SBP (~2 mmHg) was reported in this previous investigation. It is possible that the reductions in brachial SBP after PSO supplementation in postmenopausal women are influenced by dose, as we found a better improvement in brachial SBP (~5 mmHg, Table 1) with a higher PSO dose (3 g/day vs 2 g/day) in a shorter intervention period (6 weeks vs 12 weeks) compared to the previously mentioned investigation [16].

It is notable to point out that our results do not indicate that the effectiveness of the dose of PSO used in this investigation matches the BP lowering effect of antihypertensive medications [28]. It is plausible that higher doses and/or longer interventions may result in additional decreases in both brachial and central BP. Notably, a prior study in rats has shown that concomitant administration of PSO with antihypertensive medications results in potentiated BP lowering effects when compared to either PSO or medications alone [14]. Therefore, future studies focusing in the concomitant administration of PSO with antihypertensive medications in human subjects are clearly warranted. Nevertheless, the changes in BP detected in this investigation are clinically significant because they show that BP can be reduced by the addition of a single dietary element.

Pulse wave reflection by AIx analyses the variance between the late (reflected wave) and early SP respective to central pulse pressure. The high AIx noted in our participants before PSO may be explicated by age as well as vascular dysfunction [4,29]. Although AIx can be reduced by increased HR [22] and decreased central stiffness [30] (measured as SI), these values remain unchanged in our study; therefore, the drop in AIx was more likely influenced by a decline in the magnitude of the reflected wave. Indeed, the reduction of vascular tone by vasodilating agents causes a drop in the size of the reflected wave, resulting in a decline in central SBP and subsequently in AIx [31,32]. Our data agree with previous outcomes showing that despite a diminution in central SBP and wave reflection, vasodilator drugs [4,33] and dietary components [34,35] do not affect central stiffness in older adults, including postmenopausal women. These findings can be rationalized by a significant vasodilatating effect in peripheral but not the central arteries [31,32]. Recent meta-analytic work showed that a 10% rise in AIx would increase the risk for CV events by ~32% [27]. We observed a 5% decline in AIx after PSO supplementation, that may translate into a CV events risk reduction of 16%. Thus, PSO supplementation may reduce CV risk in postmenopausal women.

The mechanisms by which 6 weeks of PSO supplementation might affect BP and wave reflection in postmenopausal women remain unknown. According to our results, we can rule out changes in cardiac autonomic function as one of the possibilities; this is explained by the lack of changes in HRV parameters after our dietary intervention. One possible mechanism is an improved in endothelial function (EF). A previous study by Al Zuhair et al. [14] found that the BP lowering effects of PSO supplementation in spontaneously hypertensive rats is associated to the antioxidants properties of PSO, which prevent the impairment of EF by reactive oxygen species. Additionally, available tocopherols in PSO may play a role in the benefits noted in our study, as tocopherol supplements provide antioxidant protection against lipid-derived free radicals [20]. Furthermore, it is possible that potential

endothelial benefits are related with the phytoestrogens of PSO. Secoisolariciresinol (a key phytoestrogen present in PSO) has been shown to increase endothelial nitric oxide synthase [20], an enzyme catalyzing the production of the important vasodilator nitric oxide. It is therefore possible that consumption of PSO may cause a decline in the risk of vascular complications related with lack of oestrogen.

The interesting outcomes of the present research should be interpreted while considering the following limitations. We did not assess EF, baroreceptor sensitivity and vascular sympathetic activity which would have helped in identifying and/or ruling out mechanisms for the favorable changes in arterial health after PSO. We assessed postmenopausal women, and therefore, the same beneficial adaptations cannot be assumed in other populations. We used a small sample size, although our power calculation was suitable to detect significant differences between groups in hemodynamic markers. The matched parallel placebo-controlled group was used to control different effects that could have influenced our results. However, it could be contended that the interpretation of our outcomes may not completely elucidate for some unclear consequences of observation (i.e., the Hawthorne effect), which is also the case in most scientific investigations using supplements/nutritional strategies.

5. Conclusion

In conclusion, PSO supplementation may help in reducing both brachial and central BP as well as wave reflection in postmenopausal women with elevated blood pressure. This suggests that regular consumption of PSO over the long term could reduce CV risk in this cohort. Further investigations including greater sample sizes and hypertensive participants that are on antihypertensive medications are necessary. Additionally, future studies should investigate the impact of PSO supplementation on vascular EF.

Conflicts of interest

All authors declare having no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ctcp.2019.08.003.

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