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ORIGINAL ARTICLE

Effects of conjugated fatty acid supplementation on central obesity and blood pressure in women with benign breast disease: a randomized controlled-clinical trial

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Summary. *Objective:* Health benefits of conjugated fatty acids, particularly conjugated linolenic acid (CLNA), have recently provide substantial insights in a variety of obesity-related tumorigenesis including breast neoplasia. This study aims to investigate the effects of CLNA-contained oil (CLNAO) supplementation on central obesity indices and blood pressure in women with benign breast disease (BBD). *Methods:* Forty six pre-menopausal women with BBD were randomly allocated to intervention group (n=23) or placebo (n=23). Patients in the intervention group received 1000 mg/day CLNAO capsule and the placebo group received 1000 mg/day inert oil-contained capsule during 13 weeks. Measures of blood pressure and some anthropometric variables were performed at the baseline and end of study. *Result:* Systolic (P<0.01) and diastolic (P<0.05) blood pressures decreased within CLNAO group on subjects whom were overweight. Normal weight participants who received placebo showed significant increases in total body fat (P<0.05), waist circumference (P<0.05), and waist circumference to height ratio (P<0.05), meantime CLNAO group showed no changes on both variables. Intervention with CLNAO caused no significant increases on skinfolds of abdomen and suprailiac, whereas these measures were remarkably increased in placebo (P<0.001 and P<0.05, respectively). *Conclusion:* Findings from this study show that CLNAO can attenuate development of central fat acquisition in the BBD patients who weighted normally. Administration of CLNAO decline systolic and diastolic blood pressures of overweight subjects.

Key words: Benign breast disease, conjugated fatty acid, central obesity, blood pressure

Introduction

Great numbers of breast disorders have a network to benign lesions of breast (1). Premenopausal women experience benign breast disease (BBD) by a far more frequent rate than breast carcinoma (BC) (2). Fibrocystic change and fibroadenoma are the most common benign lesions that occur in breast (3). Women with lobular/ductal proliferative tumors indicates larger risk for later developing of breast cancer (BC) (4, 5). Indicators related to excess deposition of fat in abdomen, including waist circumference (WC) and WC to hip ratio (WHR) grant strong risks for breast neoplasia (6-8). Increase in circulating insulin and insulin like growth factors, and inflammatory dysfunction of adipocytes are considered as risk factors for developing BC in either obese pre/postmenopausal women (9, 10). It is reported that WC to height ratio (WHtR) is a useful predictor employed along with WHR to assess the risk of metabolic disorders (11). Epidemiological studies revealed an expressive relation among blood pressure, central obesity, and breast neoplasia (12-14). Obesity represses circulating amount of adiponectin, as a predictor condition for later hypertension, even among normotensive people (15, 16).

Moreover, it is reported that prevalence of hypertension was significantly higher in BC-affected patients versus BBD subjects, despite of same distribution of body fat (12). In fact, hypertension can also be a tumorigenic factor associated with disturbance of circulating androgen to estrogen ratio (13).

There are growing research findings concerning in protective effects of conjugated fatty acids (CFA) against a variety of disorders ranging from obesity to breast tumorigenesis (17-19). CFA referred to two isomeric types of linoleic and linolenic acid (CLA and CLNA), which may contain cis (c) and/or trans (t) bonds (20, 21). Evidences from interventional clinical literatures suggest an anti-adipogenic role for CLA/CLNA in healthy people who were overweight and obese (22-24). These findings even have been supported by experimental animal studies concerned CLNA in rodents exposed to a high-fat diet (25, 26). Currently, mitigating efficacy of CLA in the obesity-related hypertension has been shown in the interventional human studies and animal experiments (27, 28). However, a literature worked on healthy non-obese subjects described no significant change in blood pressure after CLA consumption (29).

Considering the BC-specific turmoil in BBD patients, examining control strategies for this disease can be very important in health care of patients. Therefore, in this study, we tend to check the interaction between centrally distributed body fat and variations in blood pressure in BBD patients who received CLNAO supplement.

Materials and Methods

Subjects and design

The present study is a randomized controlled clinical trial conducted as a parallel design, double blind study. The study was started in June 2014 and continued till May 2015, lasting 11 months. Inclusion criteria included BMI <35 kg/m², lack of breastfeeding and pregnancy during the intervention and over the past year, not taking supplements that confuse outcomes, such as omega-3, evening primrose oil, and weight loss supplements, and not receiving derivatives of estrogen and progesterone hormones (over the past 6 months) or drugs such as glucocorticoids, anti-diabetic, and blood pressure controlling drugs. Exclusion criteria were history of any malignancy or receiving conventional treatment for cancer, thyroid disorders, liver dysfunction, gastro-intestinal diseases, and hormonal disorders. Additionally, people with moderate to severe physical activity, smokers and alcoholics were excluded. Objectives and methodology of the study were described to the patients. A questionnaire about medical history and demographic information was completed in participants by a skilled interviewer at the beginning of the study. Study subjects were also asked about physical activity level using a metabolic equivalent of task (MET)-hour-based physical activity questionnaire. Women with confirmed fibrocystic disease (n=42) fibroadenoma (n=1) or both types of lesions (n=3) on pathologic or sonographic examination, aged 25-47 years, from NoureNejat hospital outpatient clinic at Tabriz (North-West Azerbaijan province of Iran) participated in the study (Figure 1). Questionnaires about physical activity level and used drugs or supplements were repeated to ask in the weeks 4, 8, and the end of study. At the enrolment, all participants were trained to complete their daily food record for three days (two typical working days and one weekend day) by using sample of utensil units and list of foods with serving size. Dietary records were returned by patients in baseline, weeks 4, 8, and the end of trial. Recorded foods were converted into grams using household scales by an expert nutritionist. Finally, the average intake of each certain nutrient was obtained by means of Nutritionist IV software (version 3.5.2; 1994, N-Squared Computing, San Bruno, CA).

This study received approval of Ethics Committee of Tabriz University of Medical Sciences (Ethics no: 936). The clinical trial was conducted after with registration at Iranian Registry of Clinical Trials (IRCT) (IRCT no: IRCT2014050411335N3). A written informed consent form was provided by each participant prior to the recruitment. Patients were assured that their personal information will be confidential.

Intervention

Each of study subjects received a unique code. Opaque packages containing capsules were encoded A and B by factory to observe triple-blind state of the study. Two groups, intervention and placebo, were

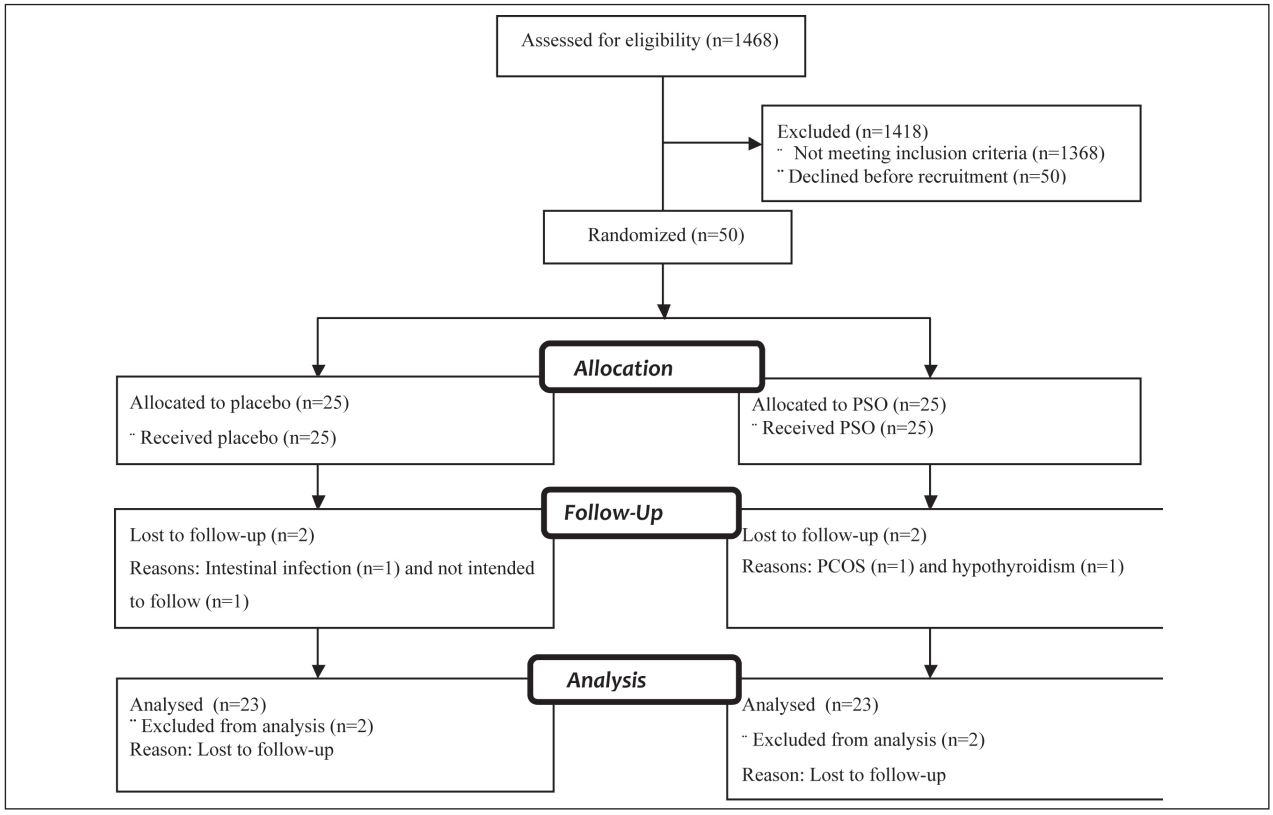

Figure 1. Consort Flow Chart of Treatment

formed using a random list obtained from random allocation software. The third person who was unaware of the grouping was responsible for distributing supplements. In this study, 1000 mg/day pomegranate seed oil (PSO), which contained 75% c9, t11, c13-CLNA, in the form of a soft gel capsule was given to the intervention group. Subjects were asked to keep their usual diet and life style during the study. The placebo group received soft gel capsules containing 1000 mg of inert oil (containing 350 mg sunflower oil, 350 mg palm olein and 300 mg corn oil) based on common oils used in Iranian families (30). The oil content of placebo and supplements were combined with10 IU αtocopherol (Nature Made, USA) and changed into soft gel capsules in Barij Essence pharmaceutical company, Kashan, Iran. Palm olein, sun flower and corn oil respectively were provided by NahanGol, Oila, and Famila companies (Tehran, Iran). Intervention and placebo pearls were similar in terms of shape, size and color. The run-in period for all patients was considered to be 2 weeks, in which they were not supposed to use compounds such as flaxseed, soy bean/protein, green tea, nuts or broccoli. The mean durations of intervention in the placebo and intervention groups were 90.56 and 93 days (average 13 weeks), respectively. Capsules were offered in an opaque container for 4 weeks. The patients were asked to complete the checklist of capsules taken during this period and return the rest that were not taken at the end of 4 weeks. If the patients had taken less than 85% of capsules intended for each individual, they were excluded. The patients were followed up using telephone calls weekly to control abnormal reactions due to the use of supplements.

Supplement safety and content

The fatty acid composition of cold-press extracted seed oil was analyzed by gas chromatography. Punicic acid (PA), c9, t11, c13-CLNA, and its isomers formed 75% of oil compounds. In addition, a fat oxidation test showed 0.3 mg of potassium hydroxide per gram of oil

(<0.7 mg KOH: g oil as normal value) and the Kreis test (to check for epihydrin aldehyde/malonaldehyde) for oil compound was negative.

Anthropometric measurements

Actual body weight, height, WC and hip circumference (HC) of the patients were measured at the baseline and 13 weeks following the intervention. The patients' height without shoes was measured using a stadiometer (Seca, Germany) with an accuracy of 0.5 cm. The patients' weight with light clothing and without shoes was measured using a digital scale (Seca, Germany) with an accuracy of 0.1 kg. The body mass index (BMI) was calculated by dividing patients' weight (kg) by their height (m^2). WC was evaluated with an accuracy of 0.1 cm in the narrowest region between the last rib and the iliac crest bone when the person was at the end of her natural expiration. HC was measured using a tape measure with an accuracy of 0.1 cm and WHR and WHtR were obtained through mathematical calculation. Total body fat percent (TBF) measurement was done using the body fat analyzer (EZ-Care-BF108E, Taiwan) after measuring twice at intervals of 5 minutes. Skinfolds were also measured on the right side of body using a skinfold caliper over the abdomen and the suprailiac, 3 times at intervals of 5 minutes. Average measured values were used for analysis.

Measuring blood pressure

Systolic and diastolic blood pressures were measured after 10 minutes of relaxation, with subjects in sitting position at a comfortable room, using a digital sphygmomanometer (Beurer-BM60, Germany). Blood pressure was measured on the right arm placing at the right atrium level, three times at intervals of 5 minutes and the average of the second and third measures was recorded for analysis.

Statistical methods

Data were analyzed by means of SPSS software (version 13). Distribution of data was checked by histogram and the Kolmogorov-Smirnov test. Normal quantitative variables were reported by mean and standard deviation (S.D.) and qualitative variables by frequency and percentage. Independent t-test and Mann-Whitney U test were used to compare the means between the two groups. Paired t-test and repeated measure of analysis of variance (RM-ANOVA) was used to compare mean values of the quantitative variable in each group. Correlation coefficient between variables was performed by bivariate Pearsons' correlation test. Chi-square analysis was done for ordinal and nominal scale data. Analysis of covariate (ANCOVA) was employed to provide adjusted outputs. Subgroup analysis was carried out to detect subgroup of participants that displayed differential treatment effect. $P<0.05$ was considered statistically significant level.

Results

Forty six patients (92%) completed this 13-week study, with 23 patients in each group (Figure 1). Weekly monitoring of patients reported no side effects of the supplements. The baseline demographic and clinical characteristics of study population are summarized in Table 1. The mean age of the placebo and intervention groups (years ± S.D.) were 32.6±6.2 and 34.2±6.9. Comparing the average dietary intake (including daily amounts of macro- or micro-nutrients and total calorie intake) and physical activity levels at baseline, weeks 4, 8, and after 13 weeks showed no statistically significant difference (data not shown). The mean values of blood pressure and anthropometric variables are represented in table 2. There were no significant differences in anthropometric indices (Weight, BMI, TBF, WC, HC, WHR, WHtR, abdominal and suprailiac skinfolds) and blood pressure (systolic and diastolic blood pressures) between the two groups at the beginning and end of study. However, both PSO and control groups showed a significant increase in abdominal skinfold ($P<0.01$ in both groups) during the study. The mean values of systolic and diastolic blood pressures significantly decreased within both groups ($P<0.05$ in both groups) as compared with baseline values. After covariate adjustment for potential possible confounder (actual body weight and baseline values), no statistical significant changes in absolute treatment effects were detected.

Table 3 shows a subgroup analysis for the variable "body weight", which participants were categorized into 2 groups based on their baseline median values. Comparison of dietary intake between the two sub-

Table 1. Demographic and clinical characteristics of the intervention and placebo groups at the baseline of study.

Characteristics	Placebo (n=23)	Intervention (n=23)	P-value
Age (years)a			
At diagnosis (mean±S.D.)	31.91±6.42	32.86±6.89	0.629b
At first delivery (mean±S.D.)	22.62±3.55	23.05±3.56	0.729b
At first menses (mean±S.D.)	13.09±1.30	13.30±1.25	0.580b
At enrolment (mean±S.D.)	32.56±6.25	34.17±6.87	0.411b
Lactation (N (%))c			
≤1	15 (65.20)	15 (65.20)	1.000d
≥2	8 (34.80)	8 (34.80)	
Parity (N (%))c			
≤1	15 (65.20)	15 (65.20)	1.000d
≥2	8 (34.80)	8 (34.80)	
Marital status (N (%))c			
No	5 (21.70)	4 (17.40)	0.710d
Positive	18 (87.30)	19 (72.60)	
Higher education (N (%))c			
No	14 (60.90)	14 (60.90)	0.1000d
Positive	9 (39.10)	9 (39.10)	
Histopathological characteristics (N (%))c			
Fibrocystic	20 (87.00)	22 (95.70)	0.490d
Fibroadenoma	1 (4.30)	0 (0.00)	
Fibrocystic and fibro adenoma	2 (8.70)	1 (4.30)	
Family history of BC (N (%))c			
No	21 (91.30)	18 (78.30)	0.218d
Positive	2 (8.70)	5 (21.70)	
Family history of BBD (N (%))c			
No	19 (82.60)	19 (82.60)	1.000d
Positive	*4 (17.40)*	*4 (17.40)*	

BC, breast cancer; BBD, benign breast disorders. aData were expressed in geometric mean±S.D. bIndependent sample t-test was performed. c Data were expressed in the form of number of participants (relative frequency). d Chi-square test was performed.

group showed participants in the lower half of body weight distribution consumed a significantly higher calorie per kg of body weight (P<0.05) than subjects in upper category at the baseline and after 13 weeks. In patients who were under the subgroup of weight less than the median (body weight≤64.45 kg), their weight, BMI and TBF increased 2.0%, 2.0% and 2.7% in the placebo group, respectively (P<0.05), whereas, PSO caused no significant increases on these measures (Figure 2). Placebo group showed significant increases in WC and WHtR (P<0.05 in both variables) as compared with baseline values, while PSO group experienced no changes on both variables during the study (Figure 2). Accordingly, the placebo group had larger increase in abdominal (11.6%, P<0.01) and suprailiac (7.6%, P<0.05) skinfolds compared to PSO group (mean percentage changes of 7.1% and 6.7%, respectively), from baseline to week 13 (Figure 2).

In the subgroup of patients with a body weight higher than the median (body weight> 64.45 kg), the average systolic (mean percentage change of -5.0%, p<0.05) and diastolic (mean percentage change of -6.0%, P<0.01) blood pressures significantly decreased within the PSO group at week 13 compared with baseline values (Figure 3). However, patients in the placebo group showed no significant change in the systolic (mean percentage change of -2.1%) and diastolic (mean percentage change of -3.3%) blood pressures during the study.

Table 2. Anthropometric and blood pressure variables at baseline and 13 weeks after the intervention in women with BBD who received PSO supplementation (PSO group(versus placebo capsules consumers.

	Baseline (n=46)				13-week follow-up (n=46)			P (absolute treatment effect)[b]
Variable	n	Mean	S.D.	Pa	n	Mean	S.D.	Pa	
Weight (kg)									
Control	23	65.91	15.35	0.853	23	65.94	15.34	0.745	0.452
PSO	23	66.71	13.94		23	67.38	14.45		
BMI (kg/m2)									
Control	23	25.75	5.37	0.989	23	25.75	5.31	0.854	0.427
PSO	23	25.77	4.68		23	26.03	5.07		
Waist girth (cm)									
Control	23	87.18	12.15	0.857	23	87.40	12.26	0.848	0.944
PSO	23	87.80	10.96		23	88.07	11.34		
HC (cm)									
Control	23	105	10	0.896	23	105	10	0.993	0.529
PSO	23	105	8		23	105	9		
WHR									
Control	23	0.82	0.04	0.811	23	0.82	0.04	0.664	0.514
PSO	23	0.82	0.05		23	0.83	0.05		
WHtR									
Control	23	0.54	0.07	0.965	23	0.54	0.07	0.955	0.606
PSO	23	0.54	0.06		23	0.54	0.07		
S.SF (mm)									
Control	23	34.86	12.34	0.543	23	35.67	12.37	0.637	0.859
PSO	23	32.89	9.33		23	34.06	10.53		
A.SF (mm)									
Control	23	39.82	13.60	0.475	23	41.97*	12.37	0.672	0.478
PSO	23	37.34	9.34		23	40.50*	11.10		
TBF (%)									
Control	23	33.76	7.41	0.934	23	33.75	7.16	0.791	0.448
PSO	23	33.93	6.71		23	34.32	7.16		
S.BP (mmHg)									
Control	23	113	8	0.343	23	109**	7	0.652	0.814
PSO	23	111	9		23	108**	9		
D.BP (mmHg)									
Control	23	77.13	8.41	0.299	23	73.30**	5.93	0.235	0.509
PSO	23	74.31	9.51		23	70.75**	8.17		

*BMI, body mass index; HC, hip circumference; WHR, waist circumference to hip ratio; WHtR, waist circumference to height ratio; S.SF, suprailic skinfold; A.SF, abdominal skinfold; TBF, total body fat; S.BP, systolic blood pressure; D.BP, diastolic blood pressure. All data were expressed in geometric mean±S.D. Mean values were significantly different within the groups using paired t test: *P<0.01, **P<0.05. a Independent sample t-test was performed between the groups. b Analysis of covariance with 13-week follow-up values adjusted by baseline values and weight.*

Discussion

This study aimed to look at the impact of CLNAO administration on indicators related to central obesity and blood pressure in patients with BBD. To our best knowledge, no human study presently is conducted to examine health benefits of CLNAO in BBD patients in regard with controlling central fatness and blood

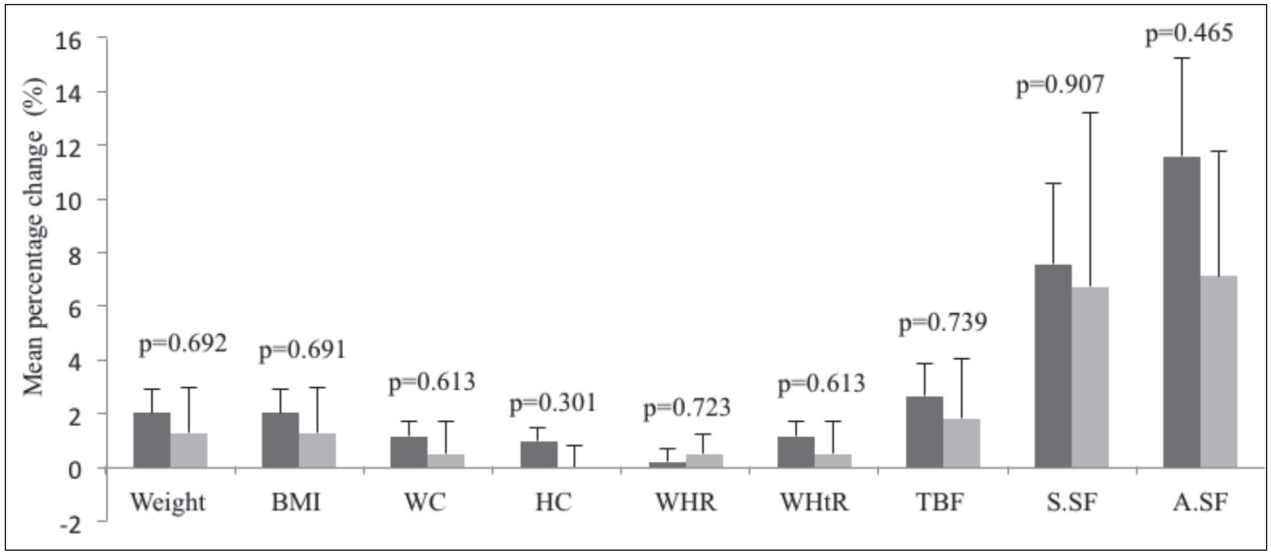

Figure 2. Mean percentage change of anthropometric variables before and after treatment in the placebo (■) and intervention (■) groups for participants with a baseline body weight of ≤64.45 kg. BMI, body mass index; WC, waist circumference; HC, hip circumference; WHR, waist to hip ratio; WHtR, waist circumference to height ratio; TBF, total body fat; S.SF, suprailiac skinfold; A.SF, abdominal skinfold. Independent sample t-test was performed between the groups.

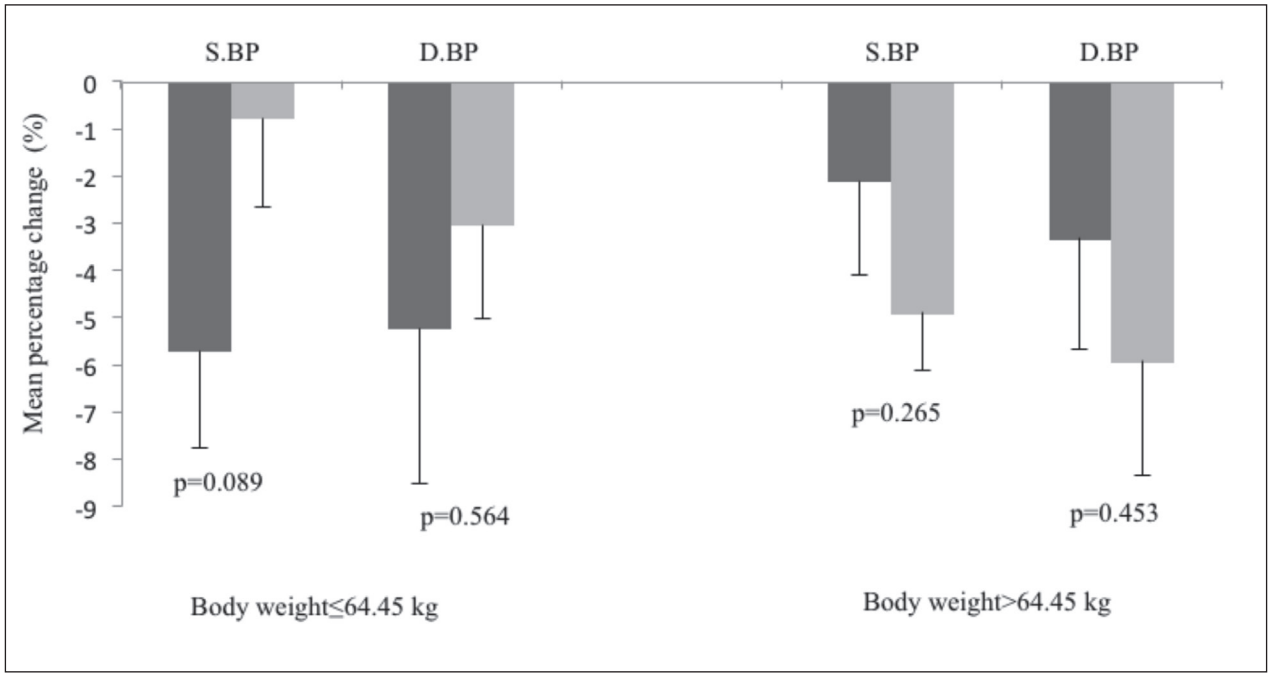

Figure 3. Mean percentage change of blood pressure variables before and after treatment in the placebo (■) and intervention (■) groups participants with a baseline body weight of ≤64.45 kg and >64.45 kg. S.BP, systolic blood pressure; D.BP, diastolic blood pressure. Independent sample t-test was performed between the groups.

pressure. The findings of this study suggest that among participant with lower body weight, subjects who received PSO remarkably experienced lower elevation in abdominal obesity indexes including WC, WHtR and skinfolds of abdomen and suprailiac compared with subjects in the placebo group. It is reported that weight gain and fat accumulation around the waist and hip in BBD women before menopause is associated with an

increased risk of postmenopausal BC (31).

The major fatty acid of PSO is c9, t11, c13-CLNA (PA), by which involves in many key health benefits attributed to PSO (26). Studies carried out in animal models (25, 26, 32) reported rodents receiving PSO or PA contained oil in their diet (1% of total calorie intake) along with a high-fat diet, showed a significant attenuation in diet-induced acquisition of body fat and weight gain occurrences. While, pomegranate juice seems not to be effective in reducing the acquisition of adiposity induced by high calorie/fat diet (33). Interventional clinical trials strengthened that CLA treatment in healthy-obese and overweight subjects resulted in a significantly lower abdominal adiposity compared with controls (22, 23). An experimental study on human also suggested that receiving PA-contained oil was relevant to reduced level of WC and other anthropometric variables (weight and TBF) in premenopausal women with a BMI ≥25 kg/m^2 (24). Administration of CFA may be protective against body fat gain only in obese/over-weight subjects (22-24). Further evidence is provided by a trial in people with normal BMI, which reported no beneficial effect of CFA on anthropometric indices (34). Accordingly, finding of present study, suggesting the fat-loss effect of PSO only in subjects with normal BMI, was not in line with the findings of previous studies. However, in animal model experiments, an effective fat-loss events due to CLNA/PSO was reported in rodents that received an adipogenic regiment (25, 26, 32). Similarly, in the present study, variable of "total calorie intake per kg of body weight" was significantly higher in the normal-weight participants than overweight ones. Therefore, it is probable that the daily calorie intake can be a more important factor than body fat for CFA-mediated fat-loss events, however this finding needs to replicate in other studies.

In the current study, despite the slimming effect of PSO which was observed for participants in lower half of body weight distribution, systolic and diastolic blood pressures significantly decreased among participants receiving PSO whom were overweight. Declercq et al. studied the effect of CLA isomers on obesity-induced hypertension in obese *fa/fa* Zucker rats and found that t10, c12-CLA-isomer attenuated the increase in systolic blood pressure caused by obesity, after 8 weeks of feeding (27). The results of a clinical trial have shown that with combined administration of isomers mixture of c9, t11-CLA and t10, c12-CLA with Ramipril (inhibitor of angiotensin-converting enzyme) in hypertensive obese patients, clinical response to the drug significantly improved (28), while the use of same isomer mixture in healthy men with normal weight exhibited no change in the systolic and diastolic blood pressures (29). It seems that CLNAO's reducing effect on obesity-related hypertension is independent of improvements that occurred in anthropometric indices, and works by increasing the amount of adiponectin that is secreted by adipocytes (27). There are very limited studies evaluating CLNA and blood pressure in the humans. A trial involving 800 mg PSO supplementation in hyperlipidemic patients showed no significant change in blood pressure during 4 weeks (35). Given the dose-dependent function of CLNA, heterogeneous result can be because of the higher dose that we used. Moreover, CLNA is reported to have a time-dependent action (24, 36). The strength of the present study may be the longer duration of the PSO supplement use. Characteristics of patients enrolled in the study may also affect on results.

Conclusion

Findings from this study showed that administration of PSO improved systolic and diastolic blood pressures of overweight BBD patients. The increasing rate of weight, BMI, TBF and the indices associated with central obesity substantially were attenuated in normal-weight patients who received PSO, yet they consumed more calories per kg of body weight.

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