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The Effects of Raw Red Onion Consumption on Serum Levels of Adiponectin, Leptin, and hs-CRP in Overweight/Obese Females with Polycystic Ovarian Syndrome: A Randomized Controlled-Clinical Trial

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Abstract

Background: Chronic low-grade inflammation has been confirmed to be a major etiological factor in polycystic ovarian syndrome (PCOS). The anti-inflammatory effects of quercetin, a major flavonol in onion, have been suggested by experimental studies. However, lack of data exists to investigate the effects of onion on inflammatory markers in PCOS.
Objectives: This study aimed at assessing the effects of raw red onion consumption on inflammatory markers in PCOS.
Methods: Fifty-four overweight/obese patients with PCOS were randomly assigned to either High-Onion (HO; raw red onions: 2 (40 - 50 g/day) for overweight and 2 (50 - 60 g/day) for obese patients) or Low-Onion (LO; raw red onions: 2 (10 - 15 g/day)) group over 8 weeks in this randomized controlled trial (RCT). Serum adiponectin, leptin, and high-sensitivity C-reactive protein (hs-CRP) levels and their correlations with metabolic and anthropometric parameters were assessed at baseline and endpoint.
Results: The 2-month treatment with onion could not significantly effect mean serum levels of adiponectin, leptin, or hs-CRP. However, the percentage change of serum adiponectin was significantly different between the two groups after 8 weeks (-11.9% in LO vs. 48.32% in HO; P = 0.026). Percentage change of serum leptin and hs-CRP showed no significant differences between the 2 groups. Leptin had significant correlations with most anthropometric and metabolic variables of insulin resistance (P < 0.05). Adiponectin concentration correlated significantly with fasting glucose (r = -0.35; P < 0.05), while log hs-CRP had significant correlations with most of the anthropometric markers (P < 0.05).
Conclusions: The 8-week intervention with red onion could increase percentage changes of serum adiponectin level in overweight/obese females with PCOS. However, no such effect was observed for serum leptin as well as hs-CRP levels.

Keywords: Polycystic Ovary Syndrome, Inflammation, Adiponectin, Leptin, CRP, Onion, Quercetin

1. Background

Polycystic ovarian syndrome (PCOS), as the most common endocrine abnormality, results in anovulatory infertility in females (1). It is frequently associated with abdominal obesity and glucose intolerance (2). Abdominal obesity usually alters the secretion of several adipocytokines, the production of which effects insulin sensitivity (3). Regarding the frequent observation of obesity and Insulin Resistance (IR) in PCOS (2), the adipokines have been shown to play a role in the pathogenesis of PCOS (4).

Adiponectin, as the most abundant adipokine, is mainly expressed in adipose tissue (4) and is down-regulated in obesity (5). Plasma levels of adiponectin have been shown to negatively correlate with IR (6).

Similar to adiponectin, leptin is mainly secreted from adipose tissue (7) and seems to help regulate insulin sensitivity (8). Serum leptin levels are highly correlated with body fat percentage (9). In PCOS, the main determinant of leptin levels seems to be adiposity rather than IR (10). This may be owing to the dominant effect of the adipose tissue mass on serum leptin levels.

The hs-CRP is a biomarker of low-grade chronic inflammation. A number of previous studies have reported that PCOS is associated with increased hs-CRP levels (11). It is now clear that PCOS is a proinflammatory state, and chronic low-grade inflammation is accounted for the development of metabolic aberrations and ovarian dysfunction in this disorder (12).

Allium vegetables have been used in traditional medicine for a long time to treat various diseases. Onion (Allium cepa L.), as one of these vegetables, has been examined for its therapeutic attributes due to its sulfur compounds and flavonoids, such as quercetin (QR) (13).

Supplementation of onion extract for obese rats has influenced the transcriptional level of adipokine expression by decreasing the amounts of mesenteric fat, indicating the modulatory effect of onion extract on obesity-induced

inflammation (14). In the authors' previous research, raw red onion consumption could decrease serum total cholesterol in PCOS patients (15). In another study, QR could prohibit high fat diet (HFD)-induced adipose tissue inflammation in mice (16). Quercetin also reduced the expression of human CRP in mice *in vivo* (17). Contrary to the findings of others, quercetin had no effect on reduction of adipose tissue inflammation in obese mice (18).

2. Objectives

Though interest towards the use of quercetin in obesity, infertility, diabetes, etc. has increased, no trial has examined the consumption of whole onion in PCOS. Therefore, regarding the effects of onion bioactive substances on inflammation and the wide usage of onions in Iran, the current researchers aimed at investigating the effects of raw red onion consumption on serum adiponectin, leptin, and hs-CRP levels in overweight or obese females with PCOS. In addition, the correlations of these inflammatory markers were examined with anthropometric and metabolic parameters.

3. Methods

3.1. Subjects

In this RCT, carried out from January 2011 to August 2012, 54 patients with PCOS and overweightness or obesity were recruited from all major referral clinics of Tabriz University of Medical Sciences, Tabriz, IR Iran, after public announcement. The ethics committee of Tabriz University of Medical Sciences approved the protocol for the study (Reference Number: 906, IRCT Registration Number: IRCT201105306652N1). Written informed consent was obtained from each subject. The entire study protocol complied with the ethical guidelines of the 1975 Declaration of Helsinki. Using literature-derived data (19) and the below formula, sample size was estimated to be 27 patients in each group based upon 80% power and α-error of 5%: $n = ((z_{1-\alpha/2}) + (z_{1-\beta}))^2 (SD1^2 + SD2^2 / (\mu 2 - \mu 1)^2$. All of the patients fulfilled the revised Rotterdam criteria (2003) (20), which includes the presence of any 2 of the following criteria: (i) oligo/anovulation, (ii) clinical signs of hyperandrogenism and/or hyperandrogenemia, and (3) polycystic ovaries on sonography and exclusion of other comorbid conditions (such as hyperprolactinemia, androgen-secreting tumors, Cushing's syndrome, and thyroid dysfunction). The inclusion criteria were those recognized as PCOS by the Rotterdam criteria, with Body Mass Index (BMI) between 25 and 39 kg/m^2, age of 17 to 37 years, taking no medication or supplements for at least the 2 prior months, applying non-drug contraceptive methods, and consuming low liliaceous vegetables (< 93 g/day) (21). Patients with diabetes mellitus, gastrointestinal disorders, hypertension or pregnancy, lactating, menopause or athletic females, smokers and alcohol users, and dieters within the preceding 6 months were excluded.

3.2. Protocol of the Study

The patients were randomly allocated to either HO or LO group, using a computer-generated program. The HO (intervention) group received 2 (40 to 50 g/day) onions for overweight and 2 (50 - 60 g/day) onions for obese patients, whereas the LO (control) group received 2 (10 - 15 g/day) onions. They consumed onions twice a day i.e. at lunch and dinner for 8 weeks, followed by a 7-day run-out period for liliaceous vegetables. The patients were recommended to receive their usual diet along with limited consumption of liliaceous vegetables (< 93 g/day) (21). The amounts of onions were selected based on previous studies, using at least 25 g/d and often at 2 to 4 times that amount (15, 22).

A checklist was prepared to assess the intake of liliaceous vegetables, such as onions, and a 3-day (including 1 weekend day) food record was used to assess dietary intake. Weight and height were measured by standard methods (23) and BMI was calculated as weight (kg) divided by the square of height (m). All the measurements were taken by 1 observer at baseline and after 8 weeks, using calibrated equipment based on the NHANES guideline. The participants were encouraged not to alter their usual dietary habits and lifestyle throughout the study.

3.3. Laboratory Analysis

After a 12-hour overnight fast, all patients underwent blood sampling in the follicular phase of their menstrual cycle (i.e. serum progesterone level < 2.5 ng/mL) (24). In the case of elevated progesterone level either at onset or endpoint, all measurements were repeated. All of the blood samples were centrifuged at 3000 rpm for 5 minutes and were kept frozen at -70°C for the assays. Levels of serum adiponectin and leptin (BioVendor kit; Brno, Czech Republic) and hs-CRP (DRG Instruments GmbH, Germany) were measured using Enzyme-Linked Immunosorbent Assays (ELISAs).

3.4. Statistical Analysis

The Kolmogorov-Smirnov test and histograms were used to check the normality of the data distribution. The authors used the method of "per protocol" for analysis. Data were expressed as Mean $\pm$ Standard deviation (SD) for continuous variables. Paired t-test and independent samples t-test were performed to determine the significance of

differences within and between groups, respectively. For abnormal data, a log 10 transformation of the data was carried out. Correlation between parameters was checked using Pearson's bivariate correlation coefficient. Statistical analysis was carried out through SPSS 17.0 for Windows (SPSS Inc., Chicago, IL, USA). P values of < 0.05 were considered statistically significant.

4. Results

4.1. Baseline Characteristics

The flowchart of the study is indicated in Figure 1. No clinical adverse effect was reported over the trial, except for heartburn, which was reported in one patient from the intervention group, and two patients from the control group.

The majority of the patients in the HO group and all of them in the LO group had oligo/anovulation (P = 0.118). Only 4 out of 53 PCOS non-diabetic patients (1 from the LO group and 3 from the HO group) had impaired glucose tolerance (BS2h: 142 to 215 mg/dL).

At baseline, the LO and HO groups were similar in terms of age (26.70 $\pm$ 5.58 in the LO group vs. 26.44 $\pm$ 5.93 years in the HO group), BMI (30.83 $\pm$ 3.92 in the LO group vs. 31.27 $\pm$ 3.90 kg/m^2 in the HO group), IR status (29.6% in the LO group vs. 46.2% in the HO group), and intake of energy (2328.18 $\pm$ 591.36 in the LO vs. 2468.48 $\pm$ 654.42 kcal/day in the HO group), and total onion (16.51 $\pm$ 13.90 in the LO vs. 15.56 $\pm$ 11.48 g in the HO group). The baseline demographic, metabolic, and some hormonal features have been published earlier (15).

At baseline, serum levels of adiponectin, leptin, and hs-CRP were similar in the LO and HO groups (Table 1). The significant correlations of leptin with most of anthropometric and IR parameters are presented in Table 3. Adiponectin concentration correlated significantly with only fasting glucose ($P < 0.05$), while log hs-CRP had a significant correlation with most of the anthropometric markers ($P < 0.05$) (Table 3).

4.2. Changes After Onion Treatment

The 2-month treatment with either high-dose or low-dose raw red onion could not significantly effect mean serum levels of adiponectin, leptin, or hs-CRP (Table 1). However, the percentage change of serum adiponectin was significantly different between the 2 groups after 2 months (-11.9% in LO vs. 48.32% in HO; P = 0.026). Percentage change of serum leptin and hs-CRP showed no significant difference between the 2 groups (Figure 2). The results of subgroup analysis into overweight and obese PCOS patients revealed that only in overweight patients with PCOS, the changes in serum adiponectin level were significant between the LO and HO groups (percentage change: -26.8% vs. 107%; P = 0.012) and (mean difference: -1.62 $\pm$ 1.06 μg/mL vs. 1.50 $\pm$ 0.89 μg/mL; P = 0.04), respectively (Table 2). This subgroup analysis also indicated no significant within- or between-group changes in IR markers (data not shown).

Table 1. Changes in Serum Adiponectin, Leptin, and hs-CRP Levels Between the Two Groups After 8 Weeks

Variable	LO (N = 27)	HO (N = 27)	P Value[a]
Adiponectin, μg/mL			
Before	4.50 $\pm$ 2.78[b]	3.06 $\pm$ 2.31	0.093
After	3.62 $\pm$ 2.33	3.71 $\pm$ 2.81	0.853
P value[c]	0.154	0.214	
Mean difference	-0.87 $\pm$ 2.63	0.65 $\pm$ 2.02	0.064
Leptin, ng/mL			
Before	22.70 $\pm$ 11.81	20.97 $\pm$ 13.30	0.803
After	23.10 $\pm$ 12.94	23.38 $\pm$ 13.03	0.753
P value	0.895	0.357	
Mean difference	0.40 $\pm$ 15.08	2.40 $\pm$ 12.26	0.618
log hs-CRP, μIU/mL			
Before	0.29 $\pm$ 0.40	0.30 $\pm$ 0.38	0.998
After	0.38 $\pm$ 0.46	0.36 $\pm$ 0.46	0.776
P value	0.288	0.502	
Mean difference	0.08 $\pm$ 0.39	0.07 $\pm$ 0.50	0.917

Abbreviations: HO, High-Onion; hs-CRP, High-Sensitivity C-Reactive Protein; LO, Low-Onion.
[a] Independent Samples t-test.
[b] Mean $\pm$ SD.
[c] Paired t-test.

5. Discussion

Polycystic ovarian syndrome is now regarded as a low-grade inflammatory state. Therefore, its management should be aimed at the correction of metabolic imbalance of adipokines. In the present study, the authors examined possible effects of raw red onion on some inflammatory markers, which demonstrated a 2-months onion treatment could make significant percentage changes in serum adiponectin, yet not serum leptin or hs-CRP levels, in overweight or obese females with PCOS.

This is the first study in which the effects of raw red onion are reported on inflammatory markers in PCOS. Previous studies have been mostly carried out on QR (25-27), an important flavonol in onion. Therefore, we had to compare the results of the present study with QR-based researches.

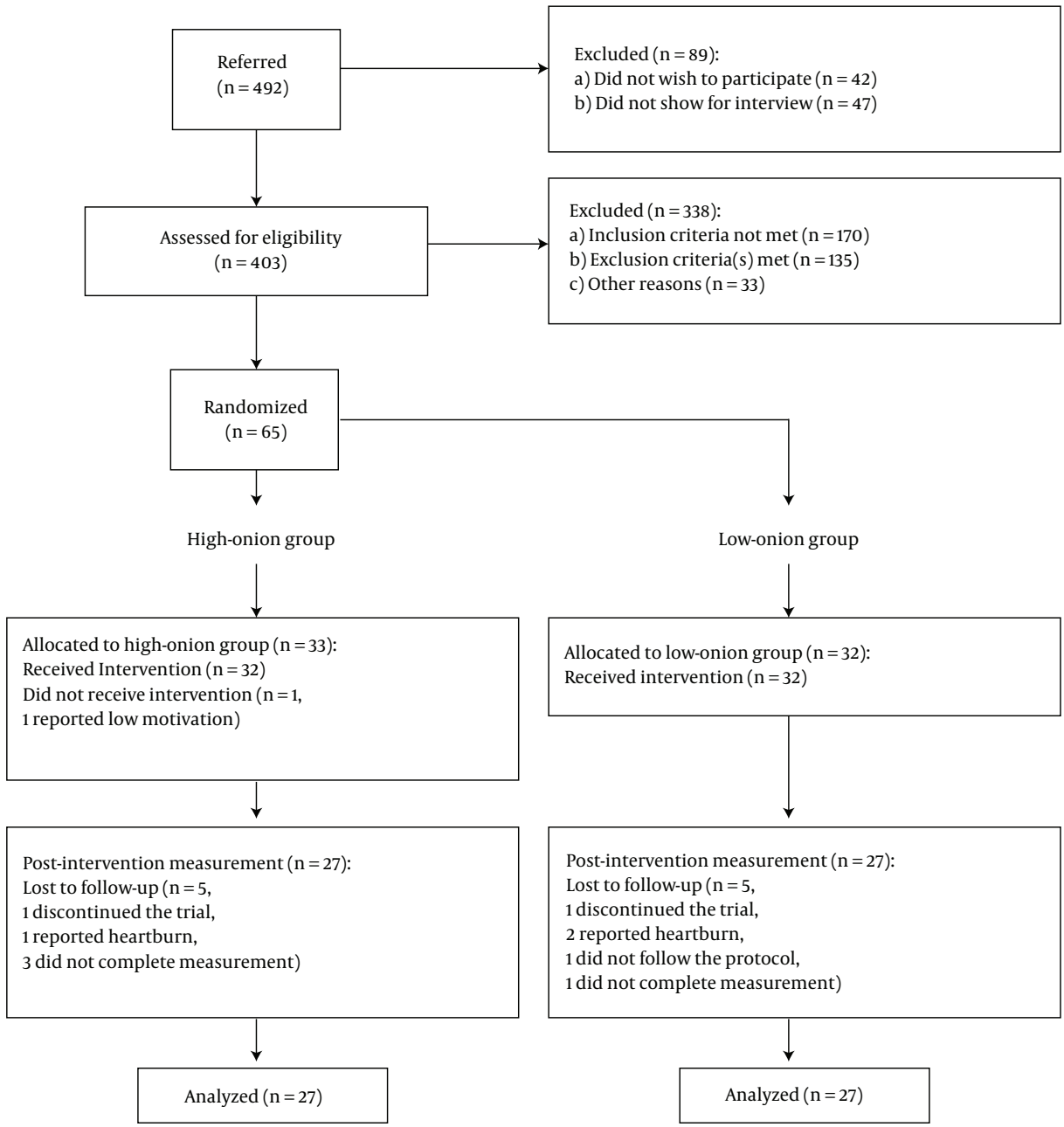


Figure 1. Flowchart of the Study

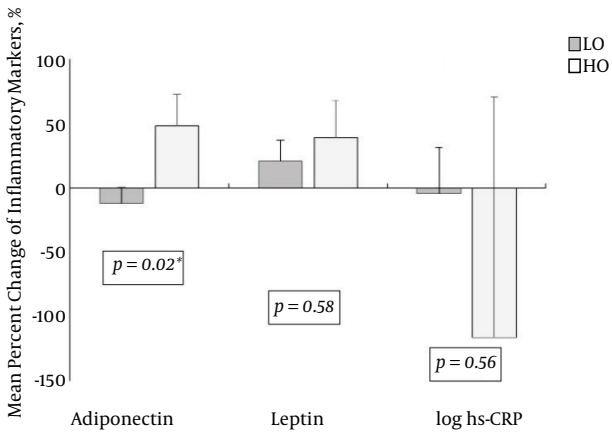
In one study, QR increased levels of secreted adiponectin in tumor necrotising factor (TNF)-α-treated 3T3-L1 adipocytes (28) as well as in diet-induced obese rats (29). Furthermore, Kim et al. (14) reported that quercetin-rich onion peel extract (OPE) supplementation increased the transcriptional level of adiponectin expression in the high-fat diet-induced obese rats, suggesting that quercetin-rich OPE has modulatory effect on the inflammatory processes in obesity. In another study (27), level of adiponectin increased in OPE-treated and placebo groups, compared to baseline values. However, there were no significant differences between the 2 groups, consistent with the study of Brull et al. (27), in which QR could not significantly affect serum levels of adiponectin and leptin,

Table 2. Mean Differences and Percentage Changes of Serum Adiponectin, Leptin, and hs-CRP Levels Between the Two Study Groups According to Their BMI Categories

Variable	$25 \leq$ BMI < 30 kg/m^2			BMI ≥ 30 kg/m^2		
	LO (n = 10)	HO (n = 14)	P value[a]	LO (n = 16)	HO (n = 14)	P value[a]
Adiponectin, μg/mL						
MD	-1.62 ± 3.00[b]	1.50 ± 2.38	0.046	-0.37 ± 2.35[b]	0.00 ± 1.52	0.664
Percentage change	-26.80 ± 38.30	106.9 ± 123.5	0.012	-1.94 ± 63.84	2.70 ± 34.41	0.846
Leptin, ng/mL						
MD	3.70 ± 11.87	1.95 ± 13.73	0.754	-2.64 ± 17.46	2.74 ± 11.58	0.363
Percentage change	25.07 ± 77.20	63.11 ± 210.2	0.566	16.85 ± 90.75	20.54 ± 53.27	0.901
log hs-CRP, μIU/mL						
MD	0.13 ± 0.96	0.30 ± 1.02	0.412	0.018 ± 0.47	-0.098 ± 0.91	0.438
Percentage change	25.07 ± 163.72	63.11 ± 488.3	0.648	7.20 ± 123.45	-63.16 ± 613.7	0.451

Abbreviations: BMI, Body Mass Index; hs-CRP, High-Sensitivity C-Reactive Protein; HO, High-Onion; LO, Low-Onion; MD, Mean Difference.
[a] Independent Samples t-test.
[b] Mean ± SD.

Figure 2. Mean Percentage Changes of Serum Adiponectin, Leptin, and hs-CRP in the Two Groups After 8 Weeks



*Independent Samples t-test. hs-CRP, High-Sensitive C-Reactive Protein; LO, Low-Onion; HO, High-Onion.

compared to placebo in obese patients after 6 weeks.

Reduced levels of adiponectin expression in patients with PCOS may be partly attributed to IR (30). A recent study also showed that adiponectin levels are related to the degree of glucose intolerance and IR (31). However, in the present study, adiponectin level was not associated with IR markers, except for fasting glucose ($r = -0.35$, $P < 0.05$). It is noteworthy to add that raw red onion consumption could not make a significant change in serum insulin level (unpublished data), despite increasing adiponectin level. Similar to this, is the result reported by Lee et al. (32) in which Valsartan increased circulating adiponectin levels without changing HOMA-IR in patients diabetic patients. In addition, adiponectin plasma levels are not always associated with IR (33). In fact, in insulin-resistant PCOS patients with normal weight, serum level of adiponectin is comparable with that of control lean subjects; on the other hand, patients with PCOS with and without obesity have similarly low levels of adiponectin, showing that the amount of increased body fat is much more important than the IR status (33). Furthermore, only 4 patients had glucose intolerance and IR was present only in one-third of the patients with PCOS. Overall, the findings on adiponectin add further beneficial effects beside the hypocholesterolemic effect of raw red onion, found in a previous report (15).

After an 8-week treatment, there was no significant change in serum levels of leptin, as a pro-inflammatory cytokine (34). Data from the present study are in line with most of the literature regarding the effects of QR on inflammatory parameters in different clinical conditions. In this regard, a study (27) showed that OPE supplementation could not significantly change serum leptin level. Also, 162 mg/d QR from OPE could not make significant changes in parameters of adipose tissue and systemic inflammation as well as insulin and glucose in overweight/obese individuals with pre-hypertension after 6 weeks (28). In other research (35), QR supplementation for 4 weeks did not effect plasma leptin concentration in HFD-fed rats. However, in another animal model, QR reduced both plasma and expression level of leptin in adipose tissue of mice fed Western diets (30).

In the present study, leptin was significantly correlated with most of the anthropometric and metabolic parameters. However, it was confirmed to be more significantly

correlated with BMI at baseline (r = 0.532, P < 0.001) and endpoint (r = 0.400, P = 0.003), than serum insulin only at baseline (r = 0.356, P < 0.04). However, the result on serum leptin is parallel with that of IR markers, reported in this research, as both remained unvaried over the study.

The strong linear correlation between BMI and leptin, observed in this and previous studies (10), demonstrates that adiposity may represent the main determinant of leptin levels in females with PCOS, as in the general population. In the present study, serum leptin and insulin levels are linked to obesity, suggesting their role in the complicated picture of the syndrome in patients with obesity. A hypothesis that can be easily understood is the direct effect of insulin on leptin expression level, triggering the greater inhibitory action of leptin on the ovary as well as the insulin and LH effect on the androgen level (36).

The present study showed no significant changes in hs-CRP level after 8 weeks. It is now clear-cut that PCOS is a proinflammatory state, which triggers metabolic aberrations and ovarian dysfunction (12). Hs-CRP, increased in PCOS (11), is associated with abdominal obesity and metabolic diseases. To the best of our knowledge, only one study (17) has examined the effects of QR on hs-CRP level to date, in which QR reduced the expression of CRP in mice *in vivo*, a result, which may differ in human studies.

The Hs-CRP was significantly correlated with most of the anthropometric measures, including body fat percentage and BMI (Table 3). This result confirms prior findings of the relationship between hs-CRP and obesity in females with PCOS. Elevated hs-CRP in PCOS is ascribed to obesity in some of the previous reports. A research (37) demonstrated that CRP was strongly associated with obesity in healthy females of middle age. In the current research, serum hs-CRP level had no correlation with neither fasting blood glucose, like the study of Ramanand et al. (38), nor HOMA-IR. This may be due to near normal insulin level with the presence of insulin sensitivity in most of our PCOS women.

Table 3. Correlation Coefficients for the Associations of Serum Inflammatory Markers with Anthropometric and Metabolic Measures at Baseline in the Whole Study Group[a]

Variable	Adiponectin	Leptin	log hs-CRP
BMI	0.078	0.532[b]	0.307[c]
Waist circumference	-0.170	0.341[c]	0.315[c]
Hip circumference	-0.010	0.415[b]	0.338
Waist to hip ratio	-0.313	-0.080	0.026
Waist to height ratio	-0.064	0.456[b]	0.303[c]
Body fat (%)	-0.021	0.570[b]	0.384[b]
Fat mass (FM)	-0.040	0.478[b]	0.363[c]
Fasting glucose	-0.355[c]	0.210	0.028
2hBS	-0.150	0.354[c]	-0.031
Fasting insulin	-0.073	0.351[c]	0.210
HOMA-IR	-0.170	0.330c	0.156
QUICKI	0.150	-0.370[b]	-0.116
Triglyceride	-0.048	0.227	0.002
Cholesterol	-0.085	0.433[b]	-0.114
LDL-C	-0.132	0.366[c]	-0.127
HDL-C	0.142	0.150	-0.056

Abbreviations: BMI, Body Mass Index; 2hBS, Blood Sugar After 2 Hours; HDL-C, High Density Lipoprotein Cholesterol; HOMA-IR, Homeostasis Model of Insulin Resistance; Hs-CRP, High-Sensitivity C-Reactive Protein; LDL-C, Low Density Lipoprotein Cholesterol; QUICKI, Quantitative Insulin Check Index.
[a]Using Pearson's correlation coefficient test.
[b]P <0.01.
[c]P < 0.05.

5.1. Conclusions

In conclusion, 8-week intervention of onion could increase percentage changes of serum adiponectin level in females with overweightness or obesity and PCOS. However, no such effect was observed for serum leptin as well as hs-CRP. More extensive studies are warranted with various doses of onion and/or a larger sample.

5.2. Limitations and Strengths

The present study had some limitations. First, though the patients were overweight or obese, most had low levels of inflammation. It seems that the effect of onion consumption may be more common in individuals with high levels of inflammation. Second, the 8-week administration of onion was probably not long enough to find differences in the production of inflammatory markers. However, the present study had some advantages. First, a homogeneous group of non-diabetic overweight or obese females with PCOS at a limited age range was recruited. Second, possible interferences by drugs, including oral contraceptives or those affecting inflammation were removed at least 2 months before the onset of the study. Third, it had enough power to detect the differences between the 2 groups.

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Footnotes

Authors' Contribution: Mehranghiz Ebrahimi-Mameghani, study design/ data interpretation/

manuscript appraisal; Maryam Saghafi-Asl, study design/ sampling/ questionnaire development/ data analysis and interpretation/ drafting and editing the manuscript.

Conflict of Interests: None.

Implications for Health Policy Makers/Practice/Research/Medical Education: In the present study, an 8-week intervention with raw red onion was able to increase serum adiponectin level with no effect on leptin and hs-CRP in overweight/obese females with polycystic ovarian syndrome (PCOS). However, more extensive studies are recommended with various doses of onion and/or a larger sample to determine the effect of onion intake on inflammation.

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