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Raw red onion intake and insulin resistance markers in overweight or obese patients with polycystic ovary syndrome: a randomized controlled-clinical trial

Mehranghiz Ebrahimi-Mamaghani[1], Maryam Saghafi-Asl[2], Mitra Niafarc, Mohamma[3] Asghari-Jafarabadi[4], Mehran Mesgari-Abbasi[5]

[1]Nutrition Research Center, Department of Nutrition in Community, School of Nutrition & Food Sciences, Tabriz University of Medical Sciences, Tabriz 5166614711, Iran; [2]Nutrition Research Center, Department of Biochemistry and Diet Therapy, School of Nutrition & Food Sciences, Tabriz University of Medical Sciences, Tabriz 5166614711, Iran - E-mail: saghafiaslm@gmail.com; [3]Imam Reza hospital, Tabriz University of Medical Sciences, Tabriz 5166614711, Iran; [4]Department of Statistics and Epidemiology, Road Traffic Injury Research Center, School of Health, Tabriz University of Medical Sciences, Tabriz 5166614711, Iran; [5]Drug Applied Research Center, Tabriz University of Medical Sciences, Tabriz 5166614711, Iran

Summary. *Background:* Insulin resistance (IR) plays a pivotal role in the development of polycystic ovary syndrome (PCOS). Though hypoglycemic and hypolipidemic effects of onion have been suggested in type 2 diabetes mellitus, still, lack of data exist to investigate its hypoglycemic effect in PCOS. *Objective:* to assess the effects of raw red onion consumption on IR markers in PCOS. *Methods:* In this randomized controlled-clinical trial, 53 overweight or obese non-diabetic patients with PCOS were randomly allocated to either group of 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) for an 8 weeks. Fasting and 2-hour blood sugar, insulin, total testosterone, and progesterone, as well as homeostasis model of insulin resistance (HOMA-IR) and quantitative insulin sensitivity check index (QUICKI) were measured at baseline and after treatment. IR was defined as HOMA-IR≥3.8 in PCOS. Anthropometric indices and dietary intake were also evaluated. *Results:* After 8 weeks, no differences were observed in the IR markers including HOMA-IR neither within nor between the HO (from 3.53±1.22 to 4.08±1.70; P=0.090) and LO groups (from 3.58±1.75 to 3.32±1.36; P=0.338). Anthropometric and dietary parameters did not differ between the two groups (P>0.050). However, a non-significant increase was observed in the rate of menses occurrence in HO (17%) compared to LO group (6%) after 8 weeks. *Conclusions:* Although raw red onion intake could not significantly improve IR markers in non-diabetic patients with PCOS, it could increase the chance of menses occurrence. Further investigations are warranted to determine the effects of onion in these patients.

Key words: Polycystic ovary syndrome, insulin resistance, onion, diet, body mass index

Abbreviations

BMI, body mass index; FBS, fasting blood sugar; G: I ratio, glucose to insulin ratio; HO, high-onion; HOMA-B, HOMA of β-cell function; HOMA-IR, homeostasis model of insulin resistance; IGT, Impaired glucose tolerance; IR, insulin resistance; LO, low-onion; OGTT, oral glucose tolerance test; PCOS, Polycystic ovary syndrome; QUICKI, Quantitative insulin check index; QR, quercetin; RCT, randomized controlled-clinical trial; SD, standard deviation; SMCS, S-methyl cysteine sulfoxide; T2DM, type 2 diabetes mellitus.

Introduction

Polycystic ovary syndrome (PCOS), the most common endocrinopathy, affects 5-10% of reproductive-aged patients, depending on the diagnostic criteria used (1). PCOS is a pre-diabetic state (2), with decreased insulin sensitivity. Afflicted patients have an earlier onset of glycemic abnormalities and type 2 diabetes mellitus (T2DM) (3). Thus, the increased prevalence of impaired glucose tolerance (IGT) and T2DM has been attributed to the insulin resistance (IR), as the common characteristic of the syndrome (4).

Although PCOS patients were reported to have basal hyperinsulinemia, studies that exactly assessed β-cell function have indicated impaired early-phase insulin secretion in obese PCOS women (5-7). In these patients, insulin secretory responses to meals could be remarkably reduced (6). Moreover, they had β-cell dysfunction to respond to oscillations in plasma glucose (7).

PCOS treatment is a big challenge due to medications side effects. Therefore, improving metabolic profile with dietary options seems to be favorable. Amongst, onion (*Allium cepa L.*), mainly made up of sulfur compounds and flavonoids such as quercetin (QR), has been extensively investigated for its therapeutic properties (8). Several studies have established insulinotropic (9, 10), and insulin-sensitizing (11) effects of onion either in diabetic or hypercholesterolemic animal models or human-based studies. Some researchers indicated the hypoglycemic and insulin-sensitizing capacity of onion peel extract containing high QR in high-fat diet/ diabetic rats (11). Additionally, in a cross-over clinical trial on 20 well-controlled diabetic patients, consumption of 20 g of fresh onion (three times daily) for one week could significantly reduce fasting blood sugar (FBS) (10). While it was previously reported that onion does not reduce blood sugar levels in healthy non-diabetic people (12).

So far, little attention has been paid to the study of the effects of whole onion consumption (13) on IR markers in experimental studies. Amongst, T2DM and hypercholesterolemia were more targeted in animals (13, 14) and rarely in human (10, 15). Only hypocholestrolemic effects of raw red onion was reported in our previous work on PCOS patients (16). Therefore, this randomized controlled clinical trial was undertaken to evaluate the effects of raw red onion consumption on IR markers along with anthropometric measures and dietary intake in PCOS patients.

Materials and Methods

Study subjects

In this randomized controlled-clinical trial (RCT), 65 non-diabetic PCOS patients with overweight or obesity were recruited from January 2011 to August 2012 in Clinics of Tabriz University of Medical Sciences, Tabriz, IR. Iran. Approval for this trial was obtained from the Ethics Committee of Tabriz University of Medical Sciences (reference number: 906, IRCT registration number: IRCT201105306652N1). Written informed consent was taken from each participant. Sample size estimation was based upon 80% power and α-error of 5%. Based on these estimations, it was predicted that 26 patients in each group would detect changes in insulin sensitivity (as the primary outcome). Allowing for 20% dropout over 8 weeks of intervention, the total sample size required for the study was 63 patients.

The revised Rotterdam criteria (2003) (17) was used for the diagnosis of PCOS in which the fulfillment of two of the three following criteria were required: (1) oligo- and/or anovulation (<8 menstrual periods per year) (18), (2) clinical signs of hyperandrogenism i.e. hirsutism (Ferriman-Gallwey score>8) and/or laboratory findings i.e. hyperandrogenemia (serum testosterone level above 2.08 nmol/l) (19) and (3) polycystic ovary morphology on ultrasound (i.e. the presence of 12 or more peripheral follicles measuring 2–9 mm in diameter at least in one ovary and/ or an ovarian volume of more than 10 mL) (20) and exclusion of other comorbidities (androgen-secreting tumors, Cushing's syndrome, hyperprolactinemia, thyroid dysfunction, and congenital adrenal hyperplasia (serum 17-hydroxy progesterone (17-OHP) above 4.8 nmol/l) (21). Transabdominal pelvic or vaginal ultrasonography, as appropriate, was performed only on patients who did not fulfill the diagnostic criteria. The inclusion criteria were PCOS patients diagnosed by the aforementioned criteria (17), aged 17 to 37 years, body mass index (BMI) between 25 to 40 kg/m^2, be-

ing medication-free for at least two months before the trial, applying non-drug contraceptive methods, no tendency to pregnancy during the study, and low intake of liliaceous vegetables (<93g) (22). Patients with hypoglycemia, diabetes mellitus, gastrointestinal disorders (e.g. peptic ulcer), hypertension or those taking dietary supplements or any drug known to affect glucose or insulin metabolism within 2 months before the enrollment were excluded. Besides, pregnant, lactating, menopause or athletic women, smokers and alcohol users, and dieters within the six months before the study were considered as excluded criteria (Fig. 1).

Study protocol

At trial entry, all subjects were randomized (block size 4) in a single-blind manner (i.e. patients were unaware of the treatment assignment), using a computer-generated randomization list. The patients were randomly assigned in a 1:1 ratio to either the 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. The two groups consumed one onion with lunch and another with dinner for 8 weeks, followed by a 7-day run-out period for liliaceous vegetables. They were asked to receive their usual diet and also limit the consumption of liliaceous vegetables (<93g/day) (22) during the trial. The amounts of onions were selected based on most of the previous human-based studies in which the effects of onion were revealed using at least 25 g/d and often at two to four times that amount (10, 23).

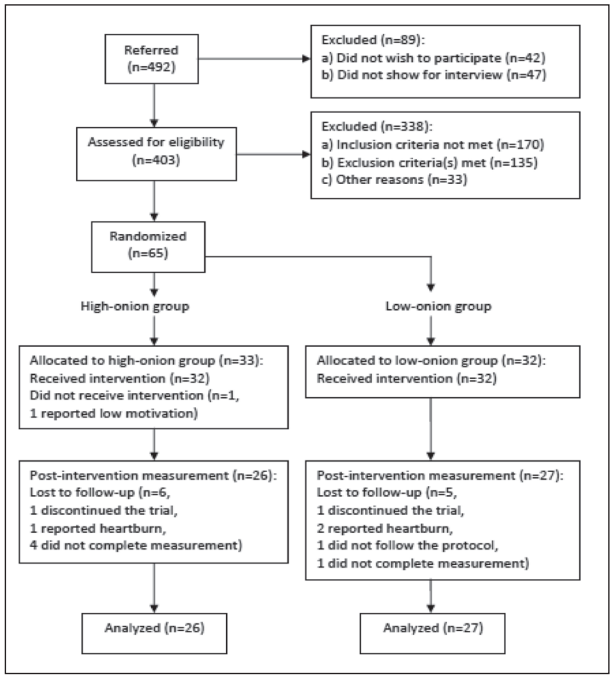

Figure 1. Flowchart of the trial

Dietary intake was measured using a 3-day (including one weekend day) food record. A specific checklist was used to assess the intake of liliaceous vegetables (including onions, garlic, spring onion, leek, water-cress and shallot). This checklist was completed at baseline, in the middle and at endpoint of the study to get ensured about low intake of such vegetables. Height without shoes was measured to the nearest 0.1cm, using a wall-mounted stadiometer. Weight was measured by a calibrated Seca scale (Itin Scale Co., Inc., Germany) to the nearest 0.1 kg with subjects wearing light clothing without shoes. BMI was calculated as weight (kg) divided by the square of height (m) (24). Waist circumference (WC) (cm) was measured with a plastic tape at a level midway between the lower rib margin and the iliac crest with the subject standing at the end of gentle expiration (25) and hip circumference (HC) (cm) at the widest point between the iliac crest and buttock (26). The circumferences were measured in a standing position and to the nearest 1 mm. The WC was divided by the HP to give a ratio of waist to hip (WHR) (27). Body fat (%) was estimated using a Body Composition Analyzer (BC 418MA, TANITA® Europe GmbH, Sindelfingen, Germany). Dietary and laboratory assessments were conducted at baseline and after 8 weeks. The way of onion consumption and storage (in a cool and dark place) was explained to each patient. They were recommended to ingest fresh-cut onions. They were also encouraged not to alter their usual dietary habits, exercise, and lifestyle throughout the study.

The standard oral glucose tolerance test (OGTT) was carried out two hours after administration of 75 g glucose for each patient (28). Impaired glucose tolerance (IGT) was defined as an elevated fasting blood sugar (FBS) (110 mg/dL ≤ G_0 ≤ 125 mg/dL) or an elevated 2-hour blood sugar (BS2h) (140mg/dL≤ G_{120} ≤ 199 mg/dL) (29). Quantitative insulin sensitivity check index (QUICKI) was calculated as 1/(log serum fasting insulin×log serum fasting glucose in mg/

dl) (30). Therefore, higher QUICKI indicates lower IR. Serum fasting glucose to insulin (G: I) ratio less than 4.5 was considered abnormal (31). IR was defined as the homeostasis model of insulin resistance (HOMA-IR) value≥3.8 (28). HOMA-IR was calculated as (fasting serum glucose (mmol/L)×fasting serum insulin (μU/mL)/22.5) (32), while the HOMA of β-cell function (HOMA-B) was computed in the form of (20×fasting serum insulin (μU/mL)/ fasting serum glucose (mmol/L)-3.5). This formula has been proposed as an appropriate measure of β-cell function (33).

Laboratory assays

In the follicular phase of the menstrual cycle (i.e. serum progesterone level lower than 2.5 ng/ml) (34), 10 ml blood was obtained after a 12-hour overnight fast. In the case of high progesterone level, either at baseline or after treatment period, the whole measurements were repeated in the first or second following weeks during which onion consumption continued. After centrifugation at 3000 rpm for 5 min, the whole blood samples were analyzed either immediately or during the first week at the same lab after supplying in -20˚C.

Serum glucose was analyzed using the standard enzymatic-colorimetric method (Pars Azmoon kit; Pars Azmoon Inc., Tehran, Iran, CV inter-assay=0.9%), while serum insulin (CV inter-assay=3.9%), total testosterone (CV inter-assay=5.3%), serum insulin levels (CV inter-assay=3.9%), and progesterone (CV inter-assay=9.6%) were measured using chemiluminescence method (Liaison®; DiaSorin S.P.A., Saluggia, Vercelli, Italy). 17-OHP (DRG Instruments GmbH, Germany, CV inter-assay=6.7%) was measured using enzyme-linked immunosorbent assays (ELISAs) method.

Statistical analysis

To ensure the normal distribution of variables, Kolmogrov-Smirnov tests and histograms were applied. Data were expressed as frequency (%) for categorical variables and mean±standard deviation (S.D.) for continuous variables. Chi-square test was used for categorical variables, while the paired t-test and independent samples t-test were performed for within or between groups comparison of continuous variables, respectively. SPSS ver. 17.0 for Windows (PASW Statistics; SPSS Inc., Chicago, IL, USA) was used for statistical analysis. *P*-value less than 0.05 was considered significant.

Results

Of 65 patients randomized to receive either high- or low-dose onion, 53 completed the study. Fig. 1 displays the flow diagram of the progress of all participants through the trial.

Baseline characteristics of the patients are shown in Table 1. There were no basal differences in terms of age, BMI, intake of energy and Liliaceous vegetables

Table 1 Baseline characteristics of overweight or obese PCOS patients

Variable	HO	LO	*P**
	(n=26)	(n=27)	
Age (y)	26.85±5.66	26.70±5.58	0.927
Age at menarche (y)	13.02±1.71	13.42±1.23	0.338
Blood pressure (mmHg)			
Systolic	112.30±8.78	107.17±22.97	0.344
Diastolic	74.33±10.16	70.33±16.57	0.345
PCOS duration (y)	10.50±5.14	8.60±4.90	0.204
Liliaceous vegetables intake (g/day)	25.50±16.41	25.36±19.92	0.979
Total onion intake (g/day)	16.00±11.86	16.51±13.90	0.887

*Values are expressed as Means±SD.; *Independent samples t-test; HO=high-onion, LO=low-onion*

including onion (Table 1). The percentage of patients with repeated laboratory assays at baseline (p=0.290) and endpoint (p=0.320) are shown in Fig. 2. Both groups consumed around 14g/day onion (raw and/ or cooked) before the study (p=0.790) (Fig. 3). After 8 weeks, no difference was observed in the anthropometric measures or dietary intake between the two groups (Table 2). However, energy intake (p=0.003), dietary carbohydrates (p=0.014) and protein (p=0.035) decreased significantly within HO group (Table 2).

Basal serum levels of progesterone, 17OH-progesterone, and prolactin were similar between the two groups. IR was also not significantly different between the two groups (46.2% in HO- *vs.* 29.6% in LO-group). In addition, decreased insulin sensitivity (glucose to insulin ratio<4.5) was similarly prevalent between LO and HO groups (22.2% *vs.* 23.1%, respectively) (p=0.599).

Only 4 out of 54 patients with PCOS (three from HO and one from LO groups) had IGT (BS2h: 142-215 mg/dl); however, none were diabetic. Hyperandrogenism was less frequent in HO compared to LO group (48% *vs.* 67%, p=0.271). Moreover, around 80% of the patients in each group were hirsute. The majority of the patients in HO group and all of them in LO group had oligo/anovulation (p=0.118) (data not shown).

A non-significant increase was observed in the rate of menses occurrence from 41.7% to 58.3% in HO group and from 36% to 41.7% in LO group (Fig. 4). After 8 weeks, no significant changes were observed in IR markers neither within nor between LO and HO groups (Table 3).

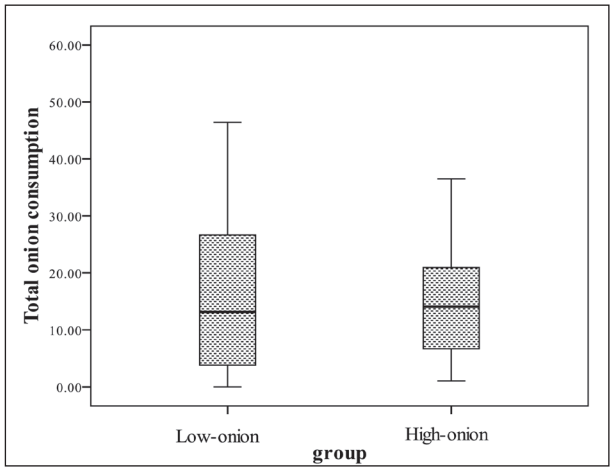

Figure 2. Median (25th and 75th centiles) of daily intake of total onion in the two groups before the study
(P-values: non-significant)

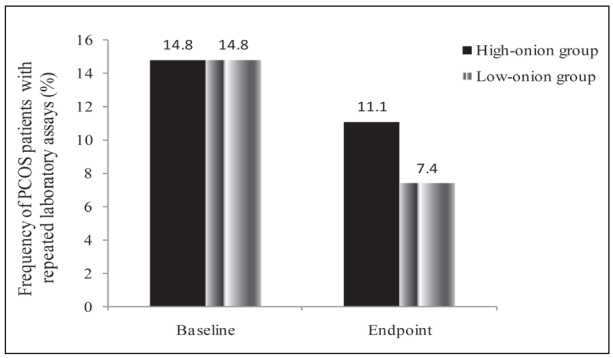

Figure 3. Comparison of the two groups at baseline and endpoint based on the repetition of their laboratory assays (serum progesterone> 2.5 ng/ml) (P-values: non-significant)

Discussion

To the best of our knowledge, this study appears to be the first RCT to examine the effects of raw red onion consumption on IR markers in non-diabetic (including insulin-resistant cases of) PCOS patients with overweight or obesity. The obtained results indicated that intake of high-dose onion could not lead to significant changes in IR markers in PCOS patients, regardless of considering their IR status.

Insulin hypersecretion is suggested to play a role in the pathogenesis of PCOS (35). However, studies that carefully assessed β-cell function have discovered important defects in insulin secretion in PCOS (6, 36). Thus, insulin secretory responses to meals were reported to be markedly reduced (6). It was demonstrated that sulfur-rich compounds of onion such as S-allyl cysteine sulfoxide, S-methyl cysteine sulfoxide (SMCS), diallyl trisulfide, and its other bioactive components have antidiabetic as well as insulinotropic effects in experimental animals (9, 37). Thus, it was assumed that onion consumption might ameliorate IR markers in PCOS women. However, the present study could not reach to such a result.

Though the patients in this study were already susceptible to developing IR (HOMA-IR≥3.8) due to PCOS condition, only 37.7% of them met the criteria for IR. In addition, only around one fifth of the

Table 2 Changes in anthropometric measures and dietary intake between the two groups after 8 weeks

Variable	HO	LO	p^*
	(n=26)	(n=27)	
BMI (Kg/m^2)			
before	31.21±3.96	30.83±3.92	0.728
after	31.41±4.14	30.72±3.75	0.530
p^{**}	0.052	0.331	
WHR			
before	0.89±0.037	0.89±0.043	0.808
after	0.89±0.050	0.89±0.041	0.951
p	0.633	0.919	
BF (%)			
before	37.52±4.20	37.87±4.33	0.774
after	37.91±4.58	37.35±3.92	0.634
p	0.470	0.145	
Energy (kcal)			
before	2484.8±662.4	2275.0±533.38	0.218
after	2143.1±411.8	2136.0±716.4	0.966
p	0.003	0.270	
CHO (%)			
before	56.08±7.70	58.48±9.82	0.334
after	57.20±7.40	55.50±7.94	0.436
p	0.448	0.156	
Fat (%)			
before	31.92±8.88	29.92±10.14	0.456
after	30.62±7.18	32.46±8.21	0.406
p	0.427	0.209	
Protein (%)			
before	11.84±2.24	11.48±2.84	0.618
after	12.04±2.01	11.92±3.28	0.877
p	0.584	0.482	
CHO (g)			
before	353.07±97.10	343.38±101.78	0.727
after	310.65±73.21	309.95±117.90	0.980
p	0.014	0.087	
Fat (g)			
before	89.22±45.40	81.04±41.96	0.503
after	74.40±23.83	80.33±34.23	0.484
p	0.080	0.942	
Protein (g)			
before	74.50±22.05	64.92±13.52	0.063
after	64.80±14.73	66.07±31.18	0.854
p	0.035	0.752	

*Values are expressed as Means±SD; * Independent Samples T-test; ** Paired t-test; HO=high-onion; LO=low-onion; BMI=body mass index; WHR=waist to hip ratio; BF (%)=body fat percent; CHO= Carbohydrate*

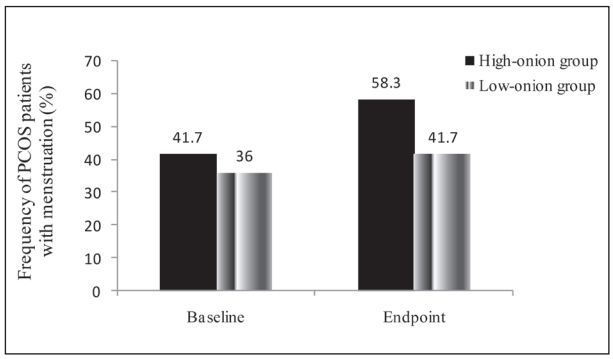

Figure 4. Comparison of the two groups at baseline and endpoint based on the occurrence of their menstruation (P-values: non-significant)

patients had decreased insulin sensitivity at baseline (i.e. fasting glucose to insulin (G:I) ratio<4.5) (data not shown). Therefore, inclusion of high-dose onion in the diet could not affect IR markers. Consistent with this finding, the study of Sharma *et al.* indicated that onion could not reduce FBS level in healthy non-diabetic individuals possibly due to normal basal levels of FBS and BS2h (12). On the other hand, the results of another study showed that fresh onions significantly decreased the average blood sugar (average of FBS and BS2h) during the onion (plus low-fat) diet in *diabetic* patients (10).

Table 3 Effects of 8-week onion consumption on IR markers in the two study groups

Variable	HO	LO	p*
	(n=26)	(n=27)	
FBS (mg/dl)			
Before	92.71±8.67	89.62±6.70*	0.153
after	93.63±10.62	90.55±6.80	0.213
*p***	0.434	0.444	
BS2h (mg/dl)			
Before	109.30±30.52	98.32±20.17	0.176
after	112.36±33.14	100.25±18.89	0.114
p	0.565	0.738	
Insulin (µIU/ml)			
Before	15.45±5.30	16.23±8.13	0.688
after	17.60±6.56	14.91±6.00	0.134
p	0.091	0.330	
HOMA-IR			
Before	3.53±1.22	3.58±1.75	0.790
after	4.08±1.70	3.32±1.36	0.107
p	0.095	0.338	
HOMA-B			
Before	213.58±138.48	239.80±155.12	0.528
after	242.54±169.38	212.76±122.51	0.474
p	0.078	0.341	
QUICKI			
Before	0.32±0.02	0.32±0.02	0.958
after	0.31±0.02	0.32±0.02	0.082
p	0.140	0.606	
G: I ratio			
Before	6.86±2.84	6.73±3.08	0.766
after	5.97±2.10	6.94±2.74	0.230
p	0.127	0.741	

*Values are expressed as Means±SD.; * Independent Samples T-test; ** Paired t-test; IR= insulin resistance; HO=high-onion; LO=low-onion; FBS=fasting blood sugar; BS2h = Blood sugar after 2 hours; HOMA-IR= homeostasis model assessment of insulin resistance; HOMA-B= homeostasis model assessment of ß-cell function; QUICKI=Quantitative insulin check index; G:I ratio=Glucose to insulin ratio*

In line with our results, other evidence indicates that even metformin is not effective on hyperinsulinemia or hyperandrogenemia that is independent of weight loss in obese normal (38) and obese hirsute (39) patients. Ehrrman *et al.* also found that IR, present in obese non-diabetic women with PCOS was not improved by metformin, as assessed by the insulin sensitivity index (Si). In their study, both non-diabetic state and higher degree of obesity may have led to the divergent finding (40). Overall, as most of our PCOS patients were not insulin-resistant, probably they were still not highly affected by metabolic aberrations including ß-cell dysfunction. Since only subtle alterations in ß-cell function in non-diabetic PCOS patients have been previously reported (6).

Several trials previously indicated that insulin sensitizers, such as metformin and Myoinositol, are considered the first-line treatment to restore normal menstrual cycles in PCOS women (41-42). In this regard, our study showed that though onion consumption could not affect IR markers, it could lead to a remarkable increase in the occurrence of menses in HO group (17%) compared to LO group (6%) ($p>0.05$), which may be considered clinically important. This finding also conveys that mechanisms other than insulin resistance may play a role in PCOS menstrual aberrations. As most of the studied patients were afflicted with oligo/anovulation, it seems that intake of high-dose onion may increase the chance of their menses. However, studies with larger sample size are needed to confirm our new finding and clarify the involved mechanisms.

The results of the present study also revealed that intake of energy and liliaceous vegetables including onions were similar between the two groups over the study. However, HO group reduced their energy intake (-344 kcal/d; $p=0.003$) at the endpoint. Regarding similar values of BMI of HO group, it is presumed that the patients in HO group had underreported their total caloric intake. Moreover, Altieri *et al.* did not support the hypothesis of a strong dependence of PCOS on dietary factors (43). In addition, central obesity and IR were not strictly associated with energy intake or dietary macronutrient composition in PCOS women in a separate study (44).

The present study has several advantages. First, a homogeneous group of non-diabetic overweight or obese women with PCOS at a limited age range was recruited. Second, possible interferences by drugs, including oral contraceptives were removed at least 2 months before the study. Third, data collection process was ceased at special occasions such as Ramadan month or Norouz holiday to avoid probable changes in dietary habits. In contrast, there are some limitations as follows: (1) lower prevalence rate of PCOS patients with IR and IGT, (2) no discrimination of onion species, and (3) no data analysis of active components in red onion due to disparity in its species.

In conclusion, our findings showed that the addition of high-dose onion to the diet could not affect IR markers. In fact, IGT and IR were present only in a limited number of patients; hence, the studied women seemed to represent a subgroup of PCOS patients who reflected an early stage in the development of the metabolic aberrations, and therefore, did not respond to onion intervention. Although raw red onion intake could not significantly improve IR markers in non-diabetic patients with PCOS, it could increase the chance of menses occurrence. More extensive investigations are warranted to determine the standard dose and species of onion at larger sample size and longer duration of intervention in which it can exert maximum beneficial effects.

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Correspondence:
Dr. Maryam Saghafi-Asl
Postal address: Department of Biochemistry and Diet Therapy, School of Nutrition & Food Sciences, Tabriz University of Medical Sciences, Tabriz 5166614711, Iran.
+984113357580-3x364 (office)
E-mail: saghafiaslm@gmail.com