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ORIGINAL ARTICLE

Oral carnitine supplementation influences mental health parameters and biomarkers of oxidative stress in women with polycystic ovary syndrome: a randomized, double-blind, placebo-controlled trial

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Abstract

Introduction: Limited data are available assessing the effects of oral carnitine supplementation on mental health parameters and biomarkers of oxidative stress of women with polycystic ovary syndrome (PCOS).This study was designed to determine the effects of oral carnitine supplementation on mental health parameters and biomarkers of oxidative stress in women with PCOS.

Methods: In the current randomized, double-blind, placebo-controlled trial, 60 patients diagnosed with PCOS were randomized to take either 250 mg carnitine supplements ($n = 30$) or placebo ($n = 30$) for 12 weeks.

Results: After 12 weeks' intervention, compared with the placebo, carnitine supplementation resulted in a significant improvement in Beck Depression Inventory total score (-2.7 ± 2.3 versus -0.2 ± 0.7, $p < 0.001$), General Health Questionnaire scores (-6.9 ± 4.9 versus -0.9 ± 1.5, $p < 0.001$) and Depression Anxiety and Stress Scale scores (-8.7 ± 5.9 versus -1.2 ± 2.9, $p = 0.001$). In addition, changes in plasma total antioxidant capacity (TAC) ($+84.1 \pm 151.8$ versus $+4.6 \pm 64.5$ mmol/L, $p = 0.01$), malondialdehyde (MDA) (-0.4 ± 1.0 versus $+0.5 \pm 1.5$ μmol/L, $p = 0.01$) and MDA/TAC ratio (-0.0005 ± 0.0010 versus $+0.0006 \pm 0.0019$, $p = 0.003$) in the supplemented group were significantly different from the changes in these indicators in the placebo group.

Conclusions: Overall, our study demonstrated that carnitine supplementation for 12 weeks among patients with PCOS had favorable effects on parameters of mental health and biomarkers of oxidative stress.

Keywords

Carnititine, mental health, oxidative stress, polycystic ovary syndrome

History

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Introduction

Recent studies have demonstrated that the risk of mental health disorders such as depression and anxiety is increased in women with polycystic ovary syndrome (PCOS) [1,2]. The prevalence of depression in women with PCOS was reported up to 35% depending on the questionnaire [3,4]. Psychiatric disorders associated with PCOS have been shown to cause a reduction in psychosocial well-being, decreased sexual self-worth and sexual satisfaction, and increased emotional distress [5]. Furthermore, PCOS is associated with oxidative stress in which increased production of free radicals and reactive oxygen species (ROS) are followed by decreased total antioxidant levels [6]. Increased oxidative stress may play a role in the dysregulation of the theca-interstitial compartment and the development of cardiovascular disease [7,8].

Carnitine plays a substantial role in both carbohydrate and lipid metabolism, and the amelioration of the insulin-resistant state [9]. In addition, there is evidence regarding beneficial effects of carnitine in improvement of depression symptoms. Previous studies have suggested the efficacy of carnitine in mitigating depressive symptoms in major depressive disorder (MDD) [10], in the treatment of mild cognitive impairment and Alzheimer's disease [11,12]. L-carnitine also plays an important role in preventing the accumulation of end-products of lipid peroxidation due to its antioxidant effects [13]. According to the previous studies, a significant reduction in oxidative stress was observed following the supplementation with 2 g/day L-carnitine for 3 months in patients with type 2 diabetes mellitus (T2DM) [14] and 1 g/day L-carnitine for 3 months among patients with coronary artery disease [15]. However, carnitine supplementation in women with knee osteoarthritis did not influence biomarkers of oxidative stress [16].

Although there is evidence to indicate that carnitine supplementation may improve mental health parameters and biomarkers

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of oxidative stress in PCOS women, the beneficial effects of carnitine supplementation in PCOS patients on these markers compared with the control group, to our knowledge, has not yet been firmed. Therefore, we hypothesized that taking carnitine might improve mental health parameters and biomarkers of oxidative stress of PCOS population. This study aimed, therefore, to determine the effect of carnitine supplementation on improve mental health parameters and biomarkers of oxidative stress among women with PCOS.

Subjects and methods

Trial design

The current study was a 12-week randomized, double-blind, placebo-controlled clinical trial.

Participants

This study was performed among 60 patients with PCOS aged 18–40 years old referred to the Kosar Clinic in Arak, Iran, between March 2016 and June 2016. Diagnosis of PCOS was done according to the Rotterdam criteria [17]: those with the two of the following criteria were considered as having PCOS: (1) oligo- and/or anovulation (defined as delayed menses >35 days or <8 spontaneous hemorrhagic episodes/year), (2) clinical [hirsutism using modified Ferriman-Gallwey (mFG) score of ≥ 8] [17] and/or biochemical signs of hyperandrogenism [18] and (3) polycystic ovaries (12 or more follicles in each ovary measuring 2–9 mm in diameter, and/or increased ovarian volume $>10\,ml^3$) [17]. We excluded pregnant women, individuals with metabolic diseases, thyroid disease, hyperprolactinemia, hypercortisolemia, renal and liver diseases in the study.

Ethics statements

The current study was conducted in accordance with the Declaration of Helsinki and informed consent was obtained from all participants. The research was approved by the Ethics Committee of Arak University of Medical Sciences (AUMS) and was recorded in the Iranian website for registration of clinical trials (http://www.irct.ir: IRCT201605225623N81).

Study design

At the onset of the study, all individuals were matched according to age, phenotypes of PCOS and BMI at the study baseline. Participants were then randomly divided into two groups to take either carnitine supplements ($n=30$) or placebo ($n=30$) for 12 weeks. Participants were requested not to change their ordinary physical activity and not to take any nutritional supplements during the 12-week trial. All participants completed 3-day food records and three physical activity records at weeks 0, 3, 6, 9 and 12 of the intervention. Daily macro- and micro-nutrient dietary intakes were analyzed by nutritionist IV software (First Databank, San Bruno, CA).

Intervention

In the treatment group, persons received 250 mg carnitine supplements for 12 weeks. Carnitine supplements and its placebos (cellulose) were similar in shape and size and manufactured by Avecina (Tehran, Iran) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively.

Treatment adherence

The use of carnitine and the placebo during the study was checked by asking participants to return the medication containers. To increase compliance, all participants received brief daily cell phone reminders to intake the supplements.

Assessment of anthropometric measures

Height and weight (Seca, Hamburg, Germany) were determined by standard protocols without shoes by a trained midwife. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2).

Assessment of outcomes

In our study, parameters of mental health were considered as the primary outcome and biomarkers of oxidative stress were considered as the secondary outcomes.

Assessment of mental health

Mental health was judged with Beck Depression Inventory (BDI), General Health Questionnaire-28 (GHQ-28) and Depression Anxiety and Stress Scale (DASS) at the beginning and the end of study. BDI is a self-compiled questionnaire of 21 items in multiple choice format [19]. On each item, there are four statements and the persons were instructed to choose the one that best described their situation during the last 2 weeks. The declarations are given the scores of 0, 1, 2 and 3, with ''0'' for the ''normal'' or least depressive statement and ''3'' for the most depressive statement. We calculated the total BDI score by adding together the scores of each item. The GHQ-28 comprises 28-item consisting of 4 subscales: somatic symptoms, anxiety and insomnia, social dysfunction and severe depression [20]. DASS questionnaire consists of three 14-item self-report scales that measure depression, anxiety and stress [21].

Biochemical assessment

Ten milliliters fasting blood samples were taken at the onset of the study and 12 weeks after intervention at Arak reference laboratory in a fasting status and centrifuged to separate plasma. Then, the samples were stored at $-80\,^{\circ}C$ before analysis. Plasma total antioxidant capacity (TAC) concentrations were determined by the method of ferric reducing antioxidant power developed by Benzie and Strain [22], total glutathione (GSH) were determined using the method of Beutler et al. [23] and malondialdehyde (MDA) concentrations were determined by the thiobarbituric acid reactive substances spectrophotometric test [24]. All inter- and intra-assay CVs for TAC, GSH and MDA concentrations were less than 5%.

Sample size

Using a formula suggested for clinical trials, having 25 participants in each group were adequate while considering a type one error (α) of 0.05 and type two error (β) of 0.20 (power = 80%), 3.5 as SD and 2.8 as the mean distinction (d) of BDI as the key variable [25]. Assuming 5 dropouts in each group, the final sample size was determined to be 30 subjects in each group.

Randomization

Randomization assignment was performed by the use of computer-generated random numbers. Randomization and allocation were concealed from the researchers and patients until the final analyses were completed. The randomized allocation sequence, enrolling participants and allocating them to interventions were conducted by a trained staff at the clinic.

Statistical methods

To evaluate whether the study variables had normally distributed or not, we used the Kolmogrov–Smirnov test. To detect

differences in macro- and micro-nutrient dietary intakes between the two groups, we applied Student's *t*-test to independent samples. To determine the effects of carnitine supplementation on parameters of mental health and biomarkers of oxidative stress, we used one-way repeated measures analysis of variance. To identify within-group differences (pre- and post-supplementation), we used paired-samples *t*-tests. Adjustment for changes in baseline values of biochemical parameters, age and BMI at the baseline was performed by analysis of covariance (ANCOVA) using general linear models. The p values of <0.05 were considered statistically significant. All statistical analyses used the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, IL).

Results

Among participants in the carnitine and placebo groups, 2 patients [withdrawn due to personal reasons ($n=2$)] were excluded (Figure 1). In the end, 56 subjects [carnitine ($n=28$) and placebo ($n=28$)] completed the trial. However, as the analysis was based on the ITT principle, all 60 participants (30 in each group) were included in the final analysis. On average, the rate of compliance in our study was high, such that more than 90% of carnitine supplements were consumed throughout the study in both groups. No side effects were reported following administration with carnitine in PCOS patients throughout the study.

Mean age, height, weight at baseline and after the 12-week intervention were not statistically different between the two groups (Table 1). After the 12-week intervention, carnitine administration led to a significant reduction in weight (-2.9 ± 1.3 versus -0.5 ± 1.1 kg, $p<0.001$) and BMI change (-1.2 ± 0.5 versus -0.2 ± 0.4 kg/m^2, $p<0.001$) compared with the placebo.

Based on the 3-day dietary records obtained at study baseline, weeks of 3, 6, 9 and end-of-trial and throughout the trial, we found no significant difference in mean dietary macro- and micro-nutrient intakes between the two groups (Table 2).

After 12 weeks' intervention, compared with the placebo, carnitine supplementation resulted in a significant improvement in BDI total score (-2.7 ± 2.3 versus -0.2 ± 0.7, $p<0.001$), GHQ scores (-6.9 ± 4.9 versus -0.9 ± 1.5, $p<0.001$) and DASS scores (-8.7 ± 5.9 versus -1.2 ± 2.9, $p=0.001$) (Table 3). In addition, changes in plasma TAC ($+84.1\pm151.8$ versus $+4.6\pm64.5$ mmol/L, $p=0.01$), MDA (-0.4 ± 1.0 versus $+0.5\pm1.5$ µmol/L, $p=0.01$) and MDA/TAC ratio (-0.0005 ± 0.0010 versus $+0.0006\pm0.0019$, $p=0.003$) in the supplemented group were significantly different from the changes in these indicators in the placebo group. We did not observe any significant effect on plasma GSH levels after intake of the carnitine supplements.

Baseline levels of GSH were significantly different between the two groups. Therefore, we controlled the analyses for the

Figure 1. Summary of patient flow.

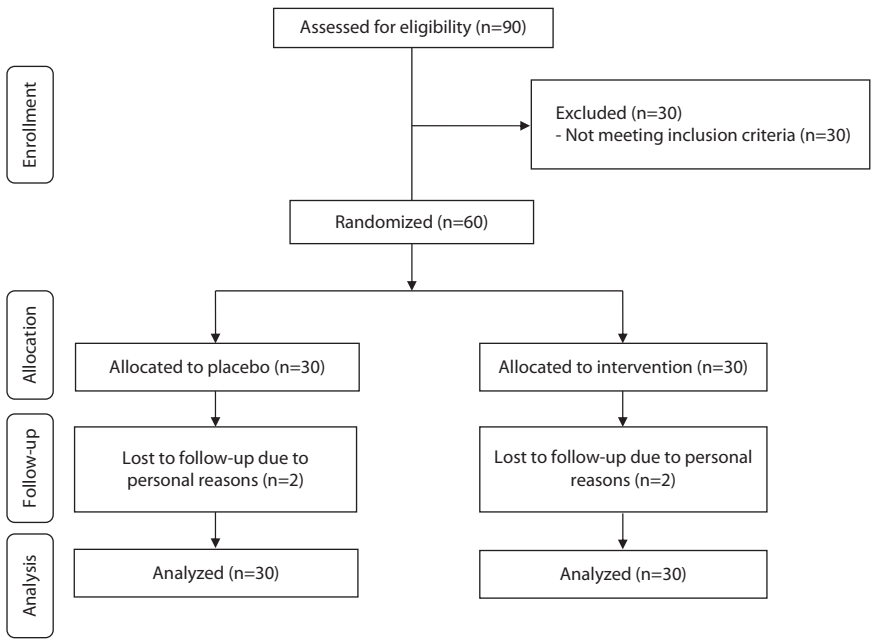

Table 1. General characteristics of study participants.

	Placebo group ($n=30$)	Carnitine group ($n=30$)	p[a]
Age (years)	27.2 ± 5.1	27.1 ± 5.2	0.92
Height (cm)	163.9 ± 6.4	161.5 ± 7.3	0.18
Weight at study baseline (kg)	75.4 ± 13.0	75.3 ± 8.7	0.98
Weight at end-of-trial (kg)	74.9 ± 12.8	72.4 ± 8.1	0.38
Weight change (kg)	-0.5 ± 1.1	-2.9 ± 1.3	<0.001
BMI at study baseline (kg/m^2)	28.0 ± 4.4	29.0 ± 3.5	0.37
BMI at end-of-trial (kg/m^2)	27.8 ± 4.3	27.8 ± 3.2	0.99
BMI change (kg/m^2)	-0.2 ± 0.4	-1.2 ± 0.5	<0.001

Data are means ± SDs.
[a]Obtained from independent *t*-test.
BMI: body mass index.

baseline values of biochemical parameters, age and baseline BMI. However, after this adjustment no significant changes in our findings occurred (Table 4).

Discussion

However, in another study, we have previously shown beneficial effects of carnitine supplementation on insulin metabolism and lipid profiles in patients with PCOS [26], to our knowledge, this trial is the first evaluating effects of carnitine on mental health parameters and biomarkers of oxidative stress in patients with PCOS. We shown that taking carnitine for 12 weeks among patients with PCOS had favorable effects on parameters of mental health, and plasma TAC and MDA levels, but did not affect GSH concentrations.

Patients with PCOS are predisposed to mental health disorders [1,2], increased oxidative stress [27] and metabolic complications [28]. We found that taking carnitine supplements among PCOS women for 12 weeks led to a significant improvement in parameters of mental health compared with the placebo. However, few studies have evaluated the effects of carnitine and its derivatives on parameters of mental health in various metabolic diseases [29,30]. A study by Malaguarnera et al. [31] was observed that 2 g acetyl-L-carnitine supplementation twice per day for 12 months among office workers with chronic hepatitis C increased daily activity and reduced presenteeism and fatigue. Moreover, acetyl-L-carnitine supplementation among patients with chronic hepatitis C for 12 months reduced both mental and physical fatigue, and improved health-related quality of life [32]. A 3-month supplementation with 2 g acetyl-L-carnitine twice a day in patients with minimal hepatic encephalopathy also resulted in a significant difference in physical function, role physical, general health, social function, role emotional, mental health and BDI scores [25]. In addition, a study by Cuturic et al. [33] was seen that higher total carnitine levels in the stable outpatients compared with acutely hospitalized patients rendered some protection against psychiatric deterioration. Carnitine dysfunction resulted in change in lipid metabolism in mental illness suggesting its possible role in the development of metabolic syndrome [34]. Previous studies have documented decrements in health-related quality-of-life, decreased sexual satisfaction and increased psychological disturbances in PCOS women [5,35]. Obesity is an important factor which can deeply influence quality-of-life in itself, even without the presence of any other clinical symptom in otherwise healthy subjects [36]. In addition, some studies found higher serum levels of androgens in patients with depressive disorders [37,38], whereas the others did not [39]. Abnormal psycho/behavioral aspects in PCOS women might be related to abnormal synthesis of neurosteroids and this might be due to an impaired adrenal function sustained by hyperinsulinemia [40]. Carnitine due to their anti-oxidative actions and the effect on mental health parameters may be useful to decrease psychological disturbances in PCOS women. Carnitine intake may improve parameters of mental health through improved mitochondrial energetic and function,

Table 2. Dietary intakes of study participants throughout the study.

	Placebo group ($n=30$)	Carnitine group ($n=30$)	p^a
Energy (kcal/day)	2438 ± 183	2414 ± 191	0.61
Carbohydrates (g/day)	335.9 ± 38.9	327.9 ± 42.7	0.43
Protein (g/day)	87.2 ± 9.7	85.5 ± 14.3	0.54
Fat (g/day)	86.8 ± 14.2	88.2 ± 14.0	0.69
SFAs (g/day)	24.6 ± 5.1	25.0 ± 5.7	0.76
PUFAs (g/day)	28.6 ± 7.8	28.7 ± 6.8	0.95
MUFAs (g/day)	22.5 ± 5.0	24.8 ± 7.1	0.12
Cholesterol (mg/day)	207.7 ± 113.3	204.1 ± 119.2	0.90
TDF (g/day)	18.7 ± 4.9	17.7 ± 5.1	0.41

Data are means ± SDs.
[a]Obtained from independent *t*-test.
SFAs: saturated fatty acids; PUFAs: polyunsaturated fatty acids; MUF As: monounsaturated fatty acids; TDF: total dietary fiber.

Table 4. Mean adjusted changes in parameters of mental health and biomarkers of oxidative stress in patients with polycystic ovary syndrome that received either carnitine or placebo[a].

	Placebo group ($n=30$)	Carnitine group ($n=30$)	p^b
BDI total scores	−0.2 ± 0.3	−2.7 ± 0.3	<0.001
GHQ scores	−1.0 ± 0.6	−6.8 ± 0.6	<0.001
DASS scores	−1.5 ± 0.8	−8.3 ± 0.8	<0.001
TAC (mmol/L)	4.2 ± 20.8	84.5 ± 20.8	0.009
GSH (μmol/L)	14.6 ± 19.9	64.9 ± 19.8	0.08
MDA (μmol/L)	0.4 ± 0.2	−0.3 ± 0.2	0.02
MDA/TAC ratio	0.001 ± 0.0001	−0.001 ± 0.0001	0.001

[a]All values are means ± SEs.
[b]Obtained from analysis of ANCOVA adjusted for baseline values + age and baseline BMI.
BDI: Beck Depression Inventory; DASS: Depression Anxiety and Stress Scale; GHQ: general health questionnaire; GSH: total glutathione; MDA: malondialdehyde; TAC: total antioxidant capacity.

Table 3. Parameters of mental health and biomarkers of oxidative stress at the study baseline and after 3-month intervention in patients with polycystic ovary syndrome that received either carnitine or placebo[a].

	Placebo group ($n=30$)				Carnitine group ($n=30$)				
	Baseline	End-of-trial	Change	p^b	Baseline	End-of-trial	Change	p^b	p^c
BDI total scores	14.0 ± 5.9	13.8 ± 6.0	−0.2 ± 0.7	0.07	13.6 ± 8.8	10.9 ± 7.8	−2.7 ± 2.3	<0.001	<0.001
GHQ scores	47.9 ± 14.3	47.0 ± 14.7	−0.9 ± 1.5	0.002	48.7 ± 7.1	41.8 ± 7.1	−6.9 ± 4.9	<0.001	<0.001
DASS scores	89.3 ± 15.7	88.1 ± 16.1	−1.2 ± 2.9	0.02	93.8 ± 23.0	85.1 ± 20.3	−8.7 ± 5.9	<0.001	0.001
TAC (mmol/L)	896.3 ± 163.4	900.9 ± 173.4	4.6 ± 64.5	0.69	957.2 ± 209.5	1041.3 ± 229.4	84.1 ± 151.8	0.005	0.01
GSH (μmol/L)	480.5 ± 84.1	507.3 ± 121.2	26.8 ± 110.5	0.19	550.5 ± 150.1	603.2 ± 136.0	52.6 ± 138.5	0.04	0.42
MDA (μmol/L)	2.8 ± 1.0	3.3 ± 1.3	0.5 ± 1.5	0.08	3.1 ± 1.1	2.7 ± 1.0	−0.4 ± 1.0	0.04	0.01
MDA/TAC ratio	0.0032 ± 0.0013	0.0039 ± 0.0019	0.0006 ± 0.0019	0.08	0.0032 ± 0.0010	0.0026 ± 0.0008	−0.0005 ± 0.0010	0.004	0.003

[a]Data are means ± SDs.
[b]Obtained from paired-samples *t*-tests.
[c]*p* values represent the time × group interaction (computed by analysis of the one-way repeated measures ANOVA).
BDI: Beck Depression Inventory; DASS: Depression Anxiety and Stress Scale; GHQ: General Health Questionnaire; GSH: total glutathione; MDA: malondialdehyde; TAC: total antioxidant capacity.

antioxidant activity, stabilization of membranes, protein and gene expression modulation and enhancement of cholinergic neurotransmission [11]. Furthermore, the effects in behavioral activities of carnitine could be due to changes in brain metabolism such as mental flexibility, the recovery of neuropsychological activities related to attention/concentration, language short-term memory, attention, and computing ability [41]. In animal models, behavioral effects of carnitine were also attributed to its modulatory effect on dopamine in the mesolimbic cortex pathway [42].

Findings of the current study demonstrated that carnitine administration among patients with PCOS for 12 weeks was associated with a significant increase in plasma TAC and a significant decrease in plasma MDA compared with the placebo, but unchanged GSH levels. Carnitine is a dietary supplement with known antioxidant properties and has been suggested to have favorable effects in metabolic diseases. In line with our findings, Cao et al. [43] demonstrated that liquid carnitine administration (2.0 g) as a single dose in healthy subjects resulted in a significant increase in plasma TAC levels. In addition, a 2-week daily oral supplementation of L-carnitine (2 capsules containing totally 2000 mg L-carnitine) increased TAC and decreased MDA concentrations in active healthy young men [44]. Similar findings were observed following the supplementation with 2 g/day L-carnitine for 3 months in patients with T2DM [14] and 20 mg/kg body weight L-carnitine as intravenous therapy for 8 weeks in patients undergoing hemodialysis [45]. However, 750 mg/day L-carnitine supplementation among women with knee osteoarthritis for 8 weeks did not influence biomarkers of oxidative stress [16]. Previous studies have shown that NADPH oxidase is the major enzymatic source of free radicals in PCOS, which in turn result in increased production of superoxide radicals in response to both hyperglycemia and increased levels of free fatty acids [46]. The increase of these components in PCOS is strongly associated with atherosclerosis and hypertension [6]. Carnitine intake may decrease oxidative stress due to its effect on stabilization of various membranes [47], increased concentrations of antioxidant enzymes [48], inhibition of microsomal peroxidation [49] as well as prevention of fatty acid membrane peroxidation [50].

The present study had few limitations. In the present study, due to funding limitations, we did not evaluate the effect of carnitine administration on serum carnitine levels. Another limitation was that we did not assess the beneficial effects of carnitine supplementation on gene expression related to biomarkers of oxidative stress.

Overall, the current study demonstrated that carnitine supplementation for 12 weeks among patients with PCOS had favorable effects on parameters of mental health and biomarkers of oxidative stress.

Declaration of interest

None.

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