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Effect of Zinc Supplementation on Physical and Psychological Symptoms, Biomarkers of Inflammation, Oxidative Stress, and Brain-Derived Neurotrophic Factor in Young Women with Premenstrual Syndrome: a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract
Zinc is known to have multiple beneficial effects including anti-inflammatory and antioxidant and anti-depressant actions. Data on the effects of zinc supplementation on biomarkers of inflammation, oxidative stress, and antidepressant-like effect among young women with premenstrual syndrome (PMS) are scarce. This study was a randomized, double-blind, placebo-controlled trial. Sixty women (18–30 years) with premenstrual syndrome diagnosed according to 30-item questionnaire were randomly assigned to receive either 30-mg zinc gluconate (group 1; $n = 30$) and/or placebo (group 2; $n = 30$) for 12 weeks. Premenstrual syndrome symptoms, total antioxidant capacity, high sensitivity reactive protein, and brain-derived neurotrophic factor were measured at study baseline and after 12-week intervention. After 12 weeks of intervention, PMS physical symptoms ($P = 0.03$) and psychological symptoms ($P = 0.006$) significantly decreased in zinc group compared to placebo group. We observed a significant increase in brain-derived neurotrophic factor ($P = 0.01$) and total antioxidant capacity ($P < 0.001$) after 12 weeks of intervention with zinc compared to placebo. We failed to find any significant effect of zinc supplementation on high sensitivity reactive protein. Overall, zinc supplementation for 12 weeks among women with premenstrual syndrome had beneficial effects on physical and psychological symptoms of premenstrual syndrome, total antioxidant capacity, and brain-derived neurotrophic factor.

Keywords Zinc · Supplementation · Premenstrual syndrome · Inflammation · Oxidative stress · Brain-derived neurotrophic factor

Introduction

Premenstrual syndrome (PMS) is a wide range of cyclic physical and psychological symptoms that many women experience during their reproductive age throughout the world [1]. Women who suffer from PMS reported more than 200 symptoms and more common psychological symptoms include mood swing, irritability, anxiety, difficulty in concentration, and depression [1, 2]. The symptoms usually occur during the luteal phase and subside shortly after the beginning of the next follicular phase [3]. There is not any specific laboratory or physical indicators to identify PMS [1]. Based on DSM V, at least 5 of 11 symptoms that disturb work, education, and social relationships should be present in luteal phase of menstrual cycle and diminish within the first days of commencement of menses [4]. Worldwide estimations of PMS prevalence differ in the range of 10–98% [5]. Up to 80% of women around the world experience at least one symptom of PMS [3]. In 2010, World Health Organization (WHO) estimated that 199 million women suffer from PMS globally [6]. PMS can affect many aspects of women's life including health-related quality of life, occupational productivity, quality of sleep, and interpersonal relationships [7]. The fundamental mechanisms of this syndrome are complex and are not fully understood [8].

It is suggested that some minerals deficiency may play a role in PMS; however, this role has not been fully recognized

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[9]. Serum zinc concentrations change during the menstrual cycle. In women who suffer from PMS, serum zinc level is significantly lower than the normal women [10–12]. Zinc deficiency can reduce the zinc serum concentrations and consequently may cause the glucocorticoid's production irregularity leading to some neuropsychological symptoms such as irritability, depression, and emotional instability [13, 14]. Some studies show decreased total antioxidant capacity (TAC) in PMS patients [12, 15]. Considering the antioxidant role of zinc [16], supplementation may increase TAC in these patients. Brain-derived neurotrophic factor (BDNF) that engages in neurogenesis and neuronal plasticity has a role in women's sex hormones actions on the brain, and it may play a part in pathogenesis of PMS. Cubeddu et al. claimed that serum BDNF levels in PMS patients in luteal phase were lower than women without PMS [17]. Zinc has antidepressant activity, and this function might be due to its participation in increasing BDNF gene expression [18]. It was also observed that inflammatory markers are significantly associated with menstrual symptoms severity in women [19]; since zinc functions as anti-inflammatory agent [16], it may affect inflammatory markers such as high sensitivity C-reactive protein (hs-CRP) [20] and, therefore, alleviate PMS symptoms as well.

Except the case-control studies that support the idea of supplementation with zinc in PMS [10, 12, 21], there has been only one study published on the effect of zinc supplementation on quality of life of PMS patients and their symptoms, indicating positive effect of zinc supplementation in PMS [9].

Accordingly, we aimed to explore the effects of zinc supplement on PMS patients' symptoms and serum levels of BDNF, hs-CRP, and TAC in these women.

Subjects and Methods

Participants

This parallel double-blind, randomized, placebo-controlled clinical trial was carried out on 60 young university students residing at dormitories, Isfahan University of Medical Sciences, between June 2017 and June 2018 who met the following inclusion criteria: healthy single young women with regular menstrual cycle of 21–35 days, aged 18–30 years old, BMI between 18.5–24.9, not taking any oral contraceptives or any medications, not exercising regularly, not taking zinc supplement in past 3 months, not being depressed or having anxiety. Exclusion criteria were the following: not filling out the daily record questionnaire, taking less than 80% of the zinc or placebo pills, getting married, and not willing to continue the study. To calculate the sample size, we used the standard formula used for parallel clinical trials considering the type I error (α) of 0.05 and type II error (β) of 0.20 (power = 80%). Based on previous study [22], we used 17.2 pg/mL as SD and 183.2 pg/mL as the difference in mean (d) of serum BDNF levels as key variable. Based on this assumption and considering the dropouts, we reached to 30 patients in each group.

Study Design

This study had two phases. In the first phase, 200 young women residing at girls' dormitories that met the inclusion criteria and had been interviewed were asked to fill out the 30-item checklist consisting of PMS symptoms to temporary diagnosis of the PMS. Participants that experienced 5 of 30 symptoms that interfered with their daily life, 7 days prior to the menses till maximum 4 days after their menses start, were asked to complete the Beck's depression and anxiety inventory (BDI). Participants whose Beck's scores for depression and anxiety were below 4 and 15, respectively, were eligible to participate in the trial.

In the second phase of the study, aims and method of the study were fully explained to the participants, and they were informed that they could leave the study whenever they want. All subjects gave the written informed consent. They also completed food frequency questionnaire (FFQ) with the help of a trained nutritionist. To find nutrient intake, we used Nutritionist 4 software (N-Squared inc., San Bruno, CA, USA). All eligible women recorded their symptoms with daily record questionnaire consisted of 30 symptoms of PMS based on DSM-VI [23], for two consecutive menstrual cycles prior to the intervention. After two cycles, participants who were definitely diagnosed with PMS were allocated into two groups of 30 participants; one group consumed zinc gluconate (containing 30-mg elemental zinc) and the other group consumed placebo. Both zinc supplements and placebo tablets were provided by Dine Iran Pharmaceutical Company (Tehran, Iran) in identical appearance. Subjects were advised not to change their diet or physical activity and not to take any other supplements during the 12 weeks of intervention and pre-intervention. Compliance to supplements and placebos was checked by giving one package of 30 tablets every month and taking back the empty package and following up by sending short message service every day. Along with the second package of tablets, subjects were provided with the same daily record questionnaire as before to record their symptoms during the next two menstrual cycles.

The study protocol was approved by the Medical Ethics Committee at the Isfahan University of Medical Sciences, and it was registered in the Iranian website for registration of clinical trials (http://www.irct.ir) under the number IRCT20180215038738N1.

Randomization and Blinding

Participant allocation and block size were obtained using random number tables. To ensure the double-blind design,

supplement and placebo packages were coded by a third person. The participants and researchers were blind to the coding until the end of the study.

Assessment of Anthropometric Measure

All participants were assessed 1 week before menses (the luteal phase) pre- and post-intervention. Anthropometric indices included measurements of weight and height (using Seca scale, Hamburg, Germany) and body mass index (BMI). Subject's waist circumference was determined at the minimum circumference between the iliac crest and the last rib.

Biochemical Assessment

To avoid diurnal variation, blood samples were collected after an overnight fasting from cubital vein of each subject. The samples were then centrifuged at 5000 rpm for 15 min and serums were removed and stored at − 80 °C until further measurements. Serum zinc levels were measured with a colorimeter using 5-BR-PAPS method. Available auto analyzer kits (Biosystems S.A., Barcelona, Spain) were applied to determine serum zinc using this method. Results obtained from this technique are correlated well with those by atomic absorption spectrophotometry [24, 25].Serum BDNF values were measured using ELISA kits (Zellbio, Veltlinerweg, Germany). Serum hs-CRP was quantified by latex-high sensitivity kits (Biosystems S.A., Barcelona, Spain) by an auto analyzer device. Serum CRP causes agglutination of the latex particles coated with anti-human C-reactive protein. The agglutination of the latex particles is proportional to the CRP concentration and can be measured by an auto analyzer device. The serum TAC concentrations were determined by the use of the ferric reducing antioxidant power (FRAP) method developed by Benzie and Strain [26].

Statistical Methods

To calculate the sample size, we used the standard formula used for parallel clinical trials considering the type I error (α) of 0.05 and type II error (β) of 0.20 (power = 80%). Based on previous study [22], we also use 17.2 pg/mL as SD and 183.2 pg/mL as the difference in mean (d) of BDNF levels as key variable. Based on this assumption and considering the dropouts, 30 patients in each group were yielded.

The Kolmogorov-Smirnov test was applied to control the normal distribution of variables. To detect differences in anthropometric measures, zinc intakes, PMS family history, age at menarche, anxiety and depression Beck score, duration of cycle, duration of menstruation, and between the two groups, we used independent t test. Multivariate analysis of covariance (MANCOVA) test was applied to determine the effects of zinc supplementation on physical and psychological symptoms average score, TAC, hs-CRP, and BDNF with adjustment for changes in baseline values of biochemical parameters. The P value of < 0.05 was considered statistically significant. To perform statistical analyses, Statistical Package for Social Science version 16 (SPSS Inc., Chicago, IL, USA) was used.

Results

In the current study, from 200 participants who met the inclusion criteria, those with Beck's scores for depression and anxiety were below 4 and 15, respectively, and also recorded their symptoms through daily record questionnaire for two consecutive menstrual cycles; 60 participants were diagnosed with PMS and allocated into two groups of 30 (Fig. 1). During the intervention phase, three participants in the intervention group were excluded due to personal reasons. On average, the rate of compliance in our study was high, such that higher than 90% of tablets were taken throughout the study in both groups. No side effects were reported following the supplementation of zinc in patients with PMS throughout the study. Participants' management, height, weight, body mass index, age at menarche, duration of cycle, duration of menstruation, depression beak score, and anxiety Beck score

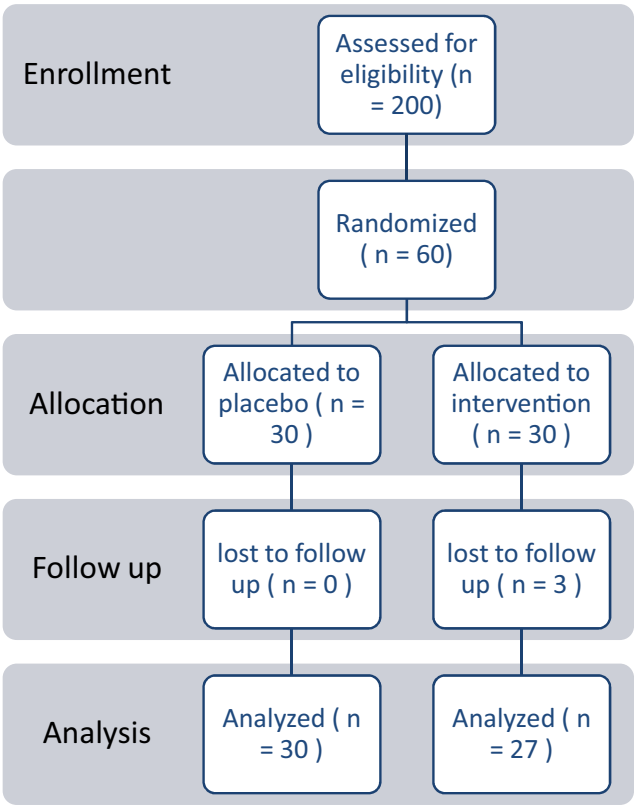

Fig. 1 Summary of patient flow diagram

Table 1 Basic characteristics of study subjects

	Placebo group ($n = 30$)	Zinc supplementation group ($n = 30$)	P^1
Age (year)	22.53 ± 1.85	23.04 ± 2.97	0.063
Weight at study baseline (kg)	56.50 ± 5.81	57.05 ± 7.28	0.748
BMI at study baseline (kg/m^2)	21.03 ± 1.90	21.39 ± 2.00	0.668
Age at menarche (year)	12.26 ± 1.36	12.10 ± 1.21	0.133
Duration of cycle (days)	27.56 ± 2.92	27.73 ± 2.53	0.814
Duration of menstruation (days)	6.23 ± 1.19	6.56 ± 0.77	0.205
Zinc intake (mg/day)	8.00 ± 0.96	7.8 ± 1.16	0.56
Depression Beck's score	2.53 ± 1.77	3.03 ± 1.60	0.25
Anxiety Beck's score	8.23 ± 3.43	7.86 ± 4.03	0.70
Family history of PMS (%)	11 (36.7%)	10 (33.3%)	0.787
Drink coffee more than 2 cups a day (%)	0 (0%)	1 (3.3%)	0.313
Habit of adding salt	4 (13.3%)	7 (23.3%)	0.317

Data are mean ± SDs

[1] Obtained from independent-sample *t* test

at the baseline and end of trial were not statistically different between the two groups (Table 1). Also, based on the FFQ obtained at the baseline, we found no significant difference in dietary intakes of zinc between the two groups. After the 12-week intervention, zinc supplementation significantly increased serum zinc levels ($P < 0.001$). Women who received zinc supplementation showed increased TAC ($P < 0.001$), BDNF ($P = 0.01$), and decreased physical symptoms average score ($P = 0.03$) and psychological symptoms average score ($P = 0.006$) compared to placebo group (Table 2). Serum hs-CRP levels remained unchanged.

Table 2 Metabolic profiles at baseline and after the 12-week intervention in subjects with premenstrual syndrome

	Group	Baseline	Week 12	Change	*P* value
Serum zinc (μg/dL)	Intervention	75.50 ± 11.72	110.42 ± 17.14	34.56 ± 17.17	< 0.001*
	Placebo	85.55 ± 26.75	88.69 ± 14.45	3.13 ± 23.36	0.46
	P value	0.065	< 0.001*[2]	< 0.001*	
Physical symptoms average score	Intervention	0.66 ± 0.62	0.32 ± 0.29	2.25 ± 9.91	0.006*
	Placebo	0.47 ± 0.31	0.45 ± 0.3	0.02 ± 0.09	0.20
	P value	0.140	0.035*[2]	0.222	
Psychological symptoms average score	Intervention	0.62 ± 0.43	0.31 ± 0.36	0.32 ± 0.27	< 0.001*
	Placebo	0.47 ± 0.29	0.48 ± 0.4	0.01 ± 0.27	0.77
	P value	0.116	0.006*[2]	< 0.001*	
TAC (mmol/L)	Intervention	769.63 ± 197.93	1053.46 ± 68.41	281.49 ± 233.6	< 0.001*
	Placebo	828.65 ± 139.41	850.13 ± 130.68	21.48 ± 81.87	0.161
	P value	0.187	< 0.001*[2]	< 0.001*	
hs-CRP (mg/L)	Intervention	1.76 ± 1.31	1.44 ± 1.28	0.36 ± 1.01	0.074
	Placebo	1.41 ± 1.65	1.47 ± 1.84	0.06 ± 1.53	0.823
	P value	0.372	0.728[2]	0.226	
BDNF (ng/mL)	Intervention	0.87 ± 0.04	1.1 ± 0.42	0.23 ± 0.18	< 0.001*
	Placebo	1.17 ± 0.68	1.09 ± 0.60	0.07 ± 0.39	0.411
	P value	0.086	0.019*[2]	0.002*	

All values are means ± SDs

TAC total antioxidant capacity, *hs-CRP* high-sensitivity C-reactive protein, *BDNF* brain-derived neurotrophic factor

*Significant result

[2] Computed by multivariate analysis of covariance MANCOVA

Discussion

Results of the present study revealed significant decrease in physical and psychological symptoms average scores of PMS and an increase in serum levels of TAC and BDNF following zinc supplementation. According to several studies, patients with PMS are susceptible to decreased levels of TAC, BDNF, and increased average scores of physical and psychological symptoms and hs-CRP [12, 15, 17, 19, 27]. Our study showed that, 12-week supplementation with 30 mg/day of zinc significantly lowered the average scores of physical and psychological symptoms in these patients. There are scarce data about the effect of zinc supplementation on physical and psychological symptoms of PMS. It has been documented that the hippocampus in the brain has the highest zinc concentration. Zinc deficiency might lead to decreased zinc concentration in hippocampus that results in abnormal secretion of glucocorticoids and causes feeling of isolation and depression [28]. Consistent with our findings, 12-week supplementation with 220 mg of zinc sulfate in PMS improved PMS symptoms and health-related quality of life [9]. The usual symptoms of PMS include adverse changes in mood and behavioral and physical symptoms [29]. In line with our study, 6 to 12 weeks of supplementation with 25 mg/day of zinc, significantly reduced Hamilton scores in depressed subjects [30]. Similarly, it has been documented that 12 weeks of supplementation with zinc improved depressive symptoms in patients with unipolar major depression [31]. Moreover, in a study by Siwek et al., all depressive symptom scores, in those who were previously resistant to antidepressant treatment, were decreased following zinc supplementation [32]. Although the etiology of PMS is not fully recognized, but it has been documented that premenstrual symptoms occur due to abnormal response to gonadal hormones and not because of the altered levels of hormones [33]. Allopregnanolone is the major metabolite of progesterone. This metabolite binds to GABA-A receptors and increases the sensitivity of these receptors, that leads to anxiety in reaction to stressors [34]. It has been suggested that zn2+ has inhibitory role of at neurosteroid sensitive extra synaptic GABA-A receptors [35]. Thus, zinc might have a relieving role in PMS through this mechanism. Cubbeddu et al. claimed that serum levels of BDNF in luteal phase of PMS women are significantly lower than healthy women so that decreased serum BDNF might play a role in the pathogenesis of PMS [17]. Our findings demonstrated that taking zinc supplements for 12 weeks in women with PMS resulted in significant increase in BDNF compared with the placebo. There has been no other study that assessed the effect of zinc supplementation on serum levels of BDNF in PMS subjects. Though, there are some animal studies done on the effect of zinc administration on BDNF gene expression. Sowa-Kuc'ma et al. found that zinc increases the BDNF mRNA and protein in the hippocampus [13]. Also Cies'lik et al. revealed that zinc therapy with or without imipramine improved the BDNF mRNA levels in the rats' hippocampus [36]. Corona et al. reported an increase in cerebral BDNF levels of Alzheimer's disease mouse models [37]. Consistent with our study, Solati et al. found that along with the improvement in BDI score, BDNF levels elevated as well [38]. However, Ranjbar.et al. did not see any rise in BDNF levels in depressed subjects [30]. Zinc applies its antidepressant-like action through several ways. One of these mechanisms is through elevating synthesis of BDNF in the brain especially in hippocampus [18]. Zinc induces the matrix metalloproteinase that activates tropomyosin-related kinase proteinase, and this leads to release of pro-BDNF from cells and then converts to BDNF [39]. BDNF supports the survival and differentiation of serotonin neurons [40]. Serotonin plays an important role in the management of mood, sleep, learning, memory, and sexual behavior [41]. It has also been reported that serotonin may have role in etiology of PMS [22]. We observed that supplementation with 30 mg/day for 12 weeks, significantly improved TAC in PMS subjects. Similar to our study, Mazani. et al. showed 8-week supplementation with 100 mg/day, elevated circulating TAC levels in hemodialysis patients [42]. Furthermore, in a study done by Ebrahimi.et al., zinc supplementation of 50 mg/day in PCOS patients for 12 weeks increased serum level of TAC [43]. In an animal study on diabetic model rats, zinc therapy reduces oxidative stress [44]. In accordance with our results, Momen-Heravi.et al. demonstrated that taking 50 mg/day supplement as zinc sulfate for 12 weeks on patients with diabetic foot ulcer, could improve TAC levels [45]. However, Jamilian et al. did not observe any significant difference in TAC levels after 8-week supplementation with 50 mg of elemental zinc in PCOS women [46]. Zinc as an antagonist of redox-active transition metals, such as iron and copper, compete for the binding sites on the cell membrane, thus, can inhibit lipid peroxidase. Another way in which zinc works as an antioxidant is increased production of some ultimate antioxidants such as metallothioneins [47, 48]. In addition, zinc is believed to inhibit NADPH oxidase, leading to neutralize the excess ROS in the body [49].

Our study demonstrated that zinc supplementation did not influence plasma hs-CR levels. Supporting our results, Dias et al. noticed that administration of rosuvastatin with or without supplementation with 30 mg/day zinc for4 months in subjects with atherosclerosis did not affect hs-CRP levels [50]. Furthermore, no significant change in hs-CRP levels was observed following the administration of 50 mg/day zinc supplementation for 8 weeks compared with the placebo in a study by Jamilian et al. [46]. On the other hand, Kelishadi et al. observed that hs-CRP levels significantly decreased after receiving supplemental zinc (20 mg/day) for 8 weeks among obese Iranian children with metabolic syndrome [51]. Our discrepant findings with other studies might be due to different

study designs, different dosage and form of zinc administration, as well as duration of the study.

Our study had some limitations. One of the limitations was the lack of measurement of sex hormones to confirm the menstrual cycle phases.

To conclude, our study demonstrated that zinc supplementation for 12 weeks on PMS women had beneficial effects on physical and psychological symptoms average scores and also serum levels of TAC and BDNF. This suggests that zinc supplementation may exert practical aspect in the management of PMS. As we mentioned earlier, PMS has a high prevalence rate of 10–98% [5]. It is known as a prevalent disorder that results in impaired quality of life, similar to major depressive disorder, and responsible for 14.5 million disability adjusted life-years in the USA [7]. There is a high demand for effective and inexpensive approaches that can alleviate the symptoms and make life easier for women all around the world. We found that zinc as an inexpensive and available agent can positively affect women with premenstrual syndrome and probably make their life better in various ways. Further research with longer duration is needed to verify the safety of such supplementation approach.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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