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Original Article

Melatonin supplementation improves glycemic hemostasis, lipid profile, and adipokine concentrations of obese women: A double-blind randomized clinical trial

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Summary

Introduction: Obesity and related diseases are an important universal public issue that harms man's well-being. Recently, growing attention has been paid to the anti-obesity effect of melatonin. This study aims to assess melatonin's impact on obesity-related factors including glycemic status, adipokines levels, lipid, and anthropometric indices in women who are obese and undergoing a calorie-restricted diet.

Methods: In this double-blind placebo-controlled randomized clinical trial (RCT) study, 46 obese women were randomly assigned into either melatonin (6 g/d) or placebo (6 g/d) group and calorie-restricted diets for 40 days. Serum concentrations of fasting blood sugar (FBS), insulin, leptin, adiponectin, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), low-density lipoprotein cholesterol (LDL-c), insulin resistance as well as anthropometric indices were evaluated at the beginning and end of the intervention.

Findings: Melatonin consumption grave rise a marked diminish in insulin ($P=0.006$) and HOMA-IR ($P=0.001$), which the between-group comparisons were substantial only for HOMA-IR ($P=0.020$) after adjusting for confounders. Adiponectin levels improved remarkably relative to the placebo ($P=0.010$). Lipid measures including TG, LDL-c, and HDL-c declined remarkably in the melatonin group post-intervention, whereas among-group percent changes were notable in HDL-c after adjusting for confounders ($P=0.040$). Notable variations were not observed in anthropometric indices in the melatonin group, compared to the placebo at the final.

Conclusion: the present study, revealed that melatonin supplementation markedly improved glycemic indices, adiponectin, and lipid profile related to obesity.

Trial Registration: Identifier: IRCT2012122411867N1; https://irct.behdasht.gov.ir/.

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Introduction

It is known that; fatness is a challenging universal public health issue. It is estimated that almost 2.5 billion people are overweight and obese which includes one-third of the whole world population.[1] In adults, the fatness rate was nearly 18.5% and 14% among women and men respectively in 2022.[2] Obesity results in multiple complications, like type 2 diabetes mellitus (T2DM), cancers, lipid dysregulations, fatty liver disorder, and cardiovascular disorders which all of them cause complexity in obesity management.[3]

The augmented increment in obesity is to some extent explained by an imbalance between calorie intake and increased sedentary lifestyle, inappropriate food choices, low quality of sleep, and epigenetic susceptibility.[4-6] White adipose tissue (WAT) as a critical endocrine organ discharges bioactive molecules including the adipokines regulate lipid metabolism, energy balance, insulin sensitivity, angiogenesis immunity, and inflammation.[7,8]

Melatonin (N-acetyl-5-methoxytryptamine) as an internal indoleamine hormone takes part in different physiologic procedures and is regulated through the hypothalamic suprachiasmatic nucleus (SCN). It is rhythmically produced in the pineal gland and does its role by melatonin receptor 1 (MT1) and melatonin receptor 2 (MT2), G-protein-coupled membrane receptors.[9] Furthermore, melatonin has prominent impacts on the circadian rhythm, immunity, energy metabolism, and endocrine system.[5,10]

Numerous metabolic pathways in adipose tissue, like the induction and discouragement of adipokines, are controlled by circadian rhythm that is partly regulated by melatonin, which may act on WAT through MT1 and MT2 or using the sympathetic nervous system.[3,11,12]

Different animal studies emphasize the beneficial effects of melatonin in the obesity management.[13-17] The investigations about melatonin's effect on obesity in humans are scarce.[18-20] The aims of this study are the evaluation of melatonin's effect on the glycemic variables, adipokines level mediated in the regulation of energy, lipid profiles, and anthropometric indices of obese women

under the low-calorie diet.

Methods

Study design and subjects

Obese subjects referred from outpatient clinics of Tabriz University of Medical Sciences, Tabriz, Iran were employed in the present double-blind placebo-controlled randomized clinical trial (RCT), carried out from February to July 2023. Eligible subjects were adults with body mass index (BMI) ≥ 30 kg/m^2 and between 20 to 50 years, stable body weight within the past 6 months. Subjects were eliminated if they were pregnant or lactation period, menopause phase, smoking, consuming alcohol, hypertension, diabetes mellitus, consuming medicine that may affect lipid and glucose function like glucose-lowering, lipid-modifying drugs or kidney disorders, mental disease, using tranquilizers, contraceptives, anti-inflammatory drugs, taking any antioxidant supplements, anti-obesity drugs, multivitamins, in the last 3 months. Moreover, patients were excluded if less than 90% of their intervention were consumed. Patients completed the written informed consent at baseline. Personal features like demographic data were taken from all participants.

Sample size calculation

The mean ± standard deviation (SD) of high-density lipoprotein cholesterol (HDL-c)[21] was applied for sample size computation. Considering the confidence interval (CI) of 95% and power of 90%, 21 subjects were calculated for each group. Supposing a 10% drop-out rate, the sample size for each group is considered 23.

Randomization, blinding, and intervention

The randomized block approach was used to allocate the obese subjects through Random Allocation Software (RAS) to melatonin and/or placebo arms (1:1) by research staff who were not involved in the procedure of the study. Randomization was conducted by block of size 2 for age and BMI. The assistant supplied the supplement and placebo tablets with a code consisting of three digits for any treatment. All the participants and research staff were blinded relative to the study arms.

The assignments of participants to each group were concealed from the research experts before the randomization.

Melatonin supplemented group (n = 23) took two melatonin tablets, (3 mg each; Nature Made, USA) once a day 2h before bedtime together with a calorie-restricted diet, while the placebo group (n = 23) took 2 placebo tablets, 3 mg each which resembled the melatonin tablets (encompass cellulose and starch) once a day 2 hours preceding bedtime for 40 days. Calorie-restricted diets were planned for subjects by an expert dietitian, based on the specific features of the subjects, considering a daily caloric limitation (500 kcal below the total energy expenditure measured by Mifflin Eq). Participants were controlled 3 times throughout the study for evaluation of any adverb effects of supplementation.

The supplement and placebo were provided every 2 weeks. Participants must return their unconsumed supplements and placebo every two weeks so the compliance rate can be calculated. Dietary recommendations were explained to the participants, and weight variations were evaluated every 2 weeks. It was requested by the participants to keep their ordinary lifestyles and follow the dietary suggestions.

Evaluation of anthropometric indices

Anthropometric measures were evaluated before and after intervention. Weight and height were assessed with minimal clothing and without shoes through a stadiometer to the nearest 100 g and 0.5 cm, respectively. Then, BMI was estimated as weight (kg) divided by height squared (m^2). Waist circumference (WC) and hip circumference (HC) were determined using a measuring tape to the nearest 0.1 kg.

Laboratory measurements

After the 8–12 hour overnight fasting state, blood samples were gathered. The serum was detached and stocked at −80 °C until measurements. Fasting blood sugar (FBS), total cholesterol (TC), HDL-c, and TG through the colorimetric-enzymatic procedure by commercial kits (Pars-Azmoon Co, Tehran, Iran). Low-density lipoprotein cholesterol (LDL-c) was determined by Friedewald formula.[22]

Insulin was measured by the enzyme-linked immunosorbent assay (ELISA) procedure with the commercial kits (Crystal Day, Shanghai, China). The homeostatic model assessment for IR (HOMA-IR) was used as follows[23]: HOMA-IR = [fasting insulin (μIU/mL) × fasting glucose (mg/dL)] /405.

Study outcomes

The main outcomes of the study were glycemic indices, adipokines levels, and lipid profile variations. The secondary outcomes were anthropometric indices variations.

Statistical analysis

Data entry and analysis were done by SPSS Statistics software (IBM SPSS Statistics, Armonk, USA, version 26). The Kolmogorov–Smirnov examinations were applied to measure the distribution of continuous variables. The mean ± SD was used for numerical data and frequency (percentage) for categorical data. Between-group and within-group changes were computed by independent samples t-test and paired samples t-test respectively. Percentage changes were determined by the following equation:

[(after intervention measures – before intervention

measures)/ before intervention measures] × 100 calculated and among-group variations were evaluated by the analysis of covariance (ANCOVA) exam which is adjusted for the confounding factors (i.e., baseline measures, energy intake, and BMI. The significance level was defined at a *P* value lower than 0.05.

Results

Of 46 obese patients, 44 subjects (22 subjects in each group) fulfilled the investigation. In the melatonin-supplemented group, one person used below 90% of the supplements, since using the tranquilizers as required medicine was eliminated. In the placebo arm, one person was eliminated since did not follow the weight loss diet program properly (Figure 1). The mean age of participants was 33.86 ± 6.94 years old in the melatonin arm and 34.86 ± 7.29 years old in the placebo arm. No remarkable variations were observed in demographic, and anthropometric variables of the study participants at baseline ($P \geq 0.05$). Indeed, melatonin supplementation for forty days resulted in a −3% decrement in BMI, while it declined to −2.5% in the placebo group relative to baseline values, which comparisons of percent changes between groups declare that there are no marked variations between studied arms ($P = 0.130$). Furthermore, the among-group comparison for weight, waist, and hip circumference changes declares that there is no marked discrepancy among groups for the mentioned anthropometric indices ($P \geq 0.05$).

As presented in Table 1, no marked variations related to glucose-related factors were observed among groups at the beginning of the study($P > 0.05$). Melatonin supplementation declined the insulin levels ($P = 0.006$) and HOMA-IR ($P = 0.001$) significantly, while there were no remarkable variations in the placebo group following intervention in mentioned variables. The discrepancy in percentage changes of glucose-related variables among groups was notable just in HOMA-IR (18.24% vs 4.57% decrement in intervention and placebo arms respectively, $P = 0.020$) considering the role of the potential confounders (Figure 2A)

There were no variations between groups in leptin and adiponectin concentrations at baseline($P > 0.05$). However, after 40 days, adiponectin increased remarkably in the melatonin arm ($P < 0.001$), while it did not alter in the placebo arm. Leptin levels did not change significantly after 40 days relative to baseline values in both groups

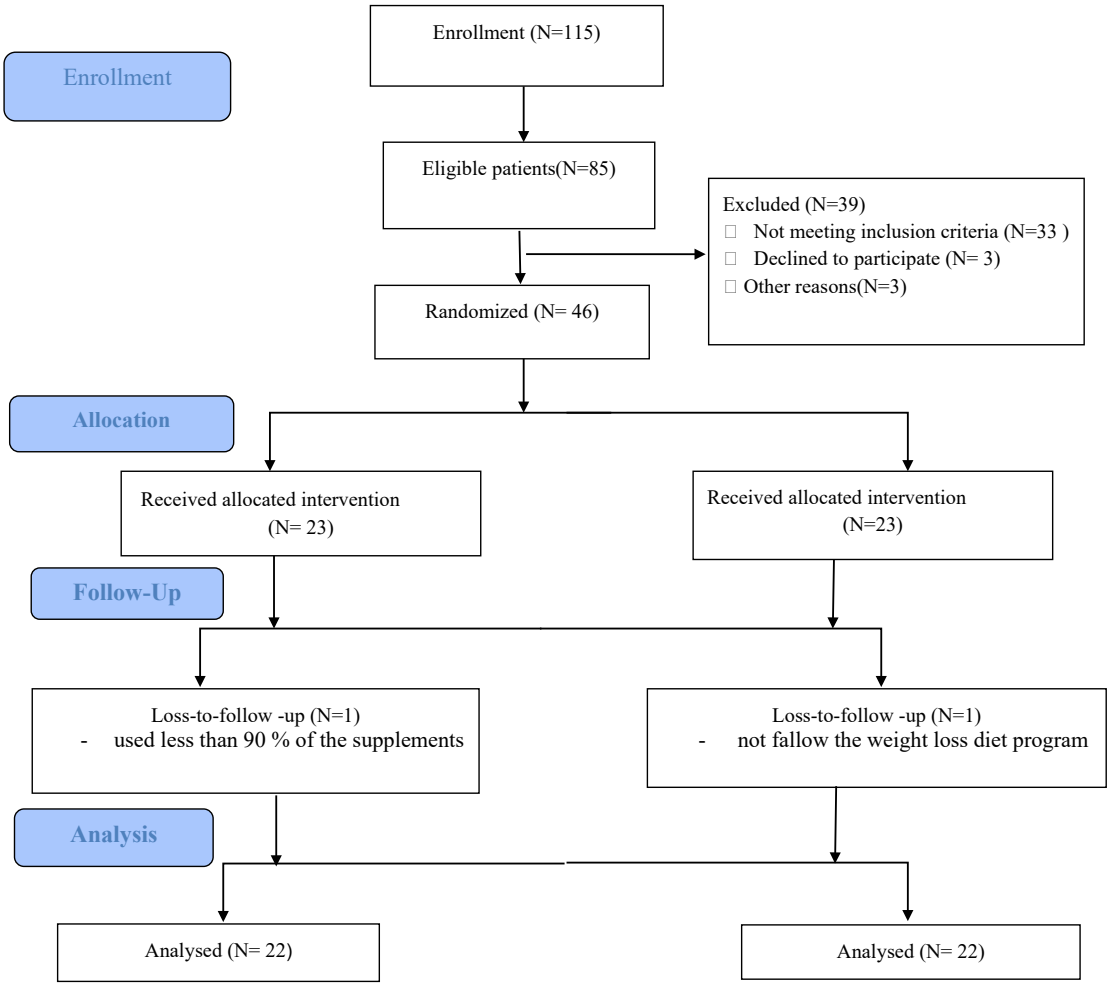

Figure 1. Study flow diagram

(Table 1). Indeed, following adjustments for confounders were done, adiponectin levels meliorated markedly in the melatonin arm relative to the placebo arm (+19.17% vs -7.66%, $P=0.010$) whereas leptin did not vary significantly between the two groups (Figure 2B).

Table 2 presents the evaluation of lipid profiles between the two studied groups. At baseline, there was no striking discrepancy between the studied arms considering the lipid profile ($P>0.05$). Following the intervention, melatonin resulted in a marked decrement of serum LDL-c ($P=0.042$) and TC ($P=0.040$), meanwhile, the TG and HDL-c concentrations did not vary remarkably. Regarding the placebo arm, no remarkable alterations were noticed in lipid profile levels. Figure 2C shows

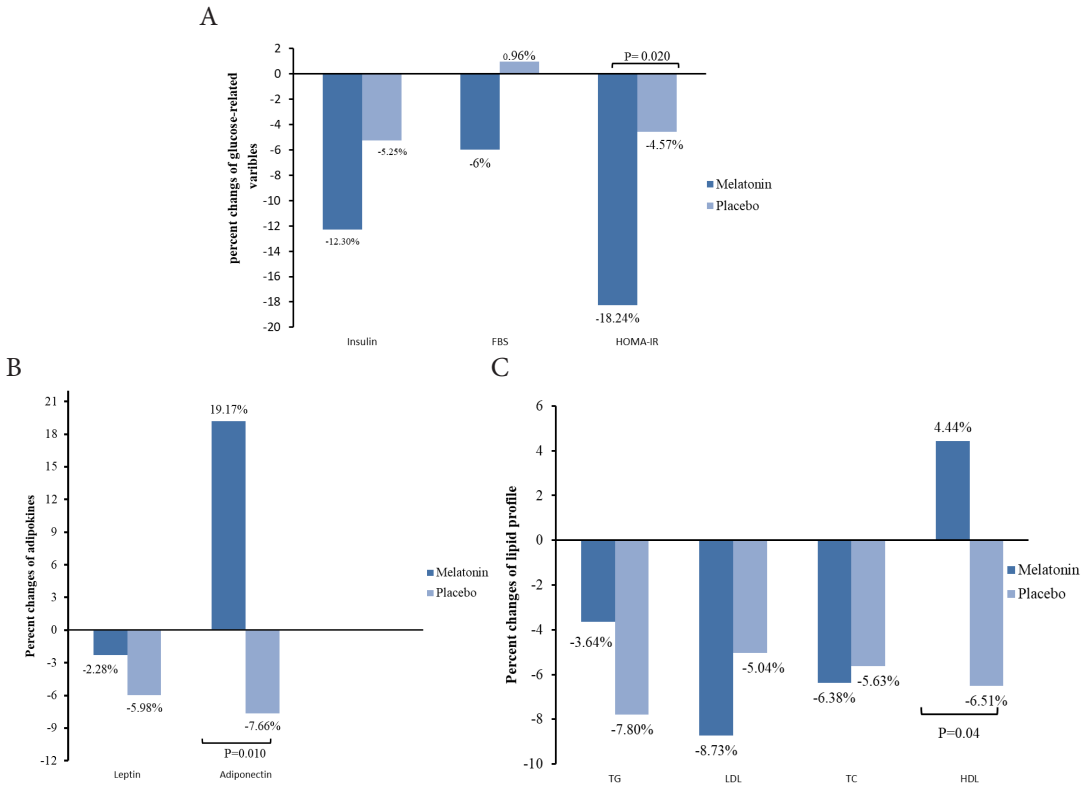

Figure 2. Comparison of percentage changes of glucose related parameters(A), adipokines(B) and lipid profiles (C) between the two study groups. $P<0.05$, by independent samples *t*-test

Table 1. Glucose related and adipokines variables of the study participants throughout the study

Variables	Melatonin group (n=22)		*P* value*	Placebo group (n=22)		*P* value*
	Before	After		Before	After	
FBS (mg/dL)	98.17±63.91	59.9±13.86	141.0	74.24±50.98	99.25±45.99	592.0
Insulin (μU/mL)	70.4±99.19	77.4±53.17	006.0	89.5±27.18	95.4±31.17	091.0
HOMA-IR	56.1±55.4	06.1±72.3	001.0	54.1±37.4	40.1±17.4	120.0
Adiponectin (ng/mL)	45.1±40.7	2.3±59.9	001.0>	2.67±.599	41.2±71.8	0.341
Leptin (ng/mL)	18.97±94.46	16.18±42.58	282.0	82.20±66.48	40.15±59.36	0.571

Mean (SD) are presented for data presentation.
*P value for paired t test.

Table 2. Lipid profiles of the study participants throughout the study

Variables	Melatonin group (n=22)		*P* value*	Placebo group (n=22)		*P* value*
	Before	After		Before	After	
TG (mg/dL)	57.62±45.175	37.61±05.169	461.0	57.56±41.130	32.56±23.120	0.110
LDL-c (mg/dL)	09.28±05.113	45.27±18.103	042.0	29.23±65.124	.5425±36.118	0.051
TC (mg/dL)	04.34±95.194	68.34±50.182	040.0	74.45±55.202	.3743±14.191	0.310
HDL-c (mg/dL)	68.8±86.39	49.9±63.41	153.0	46.8±90.43	8.87±.0441	0.20

Mean (SD) are presented for data presentation.
*P value for paired t test.

the evaluations of percentage changes in lipid profile in two studied arms. Following adjustments were done for confounders, melatonin contributed to HDL-c levels augmentation in comparison to placebo ($P = 0.040$), while the percent changes in other lipid-related parameters were not significant between the two studied groups.

Discussion

Obesity, the pandemic health problem, is associated with complicated chronic disease. Although

modern clinical approaches to obesity management have evolved, the therapeutic challenge continues. Among numerous supplements already examined, the last investigations proposed that melatonin consumption might be an effective therapeutic perspective in obesity control.

This clinical trial assessed melatonin supplementation impacts on anthropometric indices, the glycemic, adipokines, and lipid profile of obese women undergoing a calorie-restricted diet. This investigation observed that melatonin administration in obese women for 40 days led to a noticeable promotion in cardiometabolic risk factors including HDL-c, insulin resistance, adiponectin, and insulin levels, with no remarkable effects on anthropometric indices like weight and BMI after adjusting for the confounders.

Increasing evidence suggests the promoting effects of melatonin consumption on insulin resistance and glucose-related factors. Our results showed a remarkable decrement in insulin concentrations and HOMA-IR, but no notable following adjustments were done for confounders which are consistent with former animal[9,11,24] and clinical research.[25]

A late systematic review and meta-analysis of RCTs evaluated the melatonin supplementation impact and brought about a marked drop in FBS, insulin, and HOMA-IR.[26] Furthermore, A recent RCT observed that melatonin supplementation during 12 weeks in patients with T2DM and coronary heart disease remarkably declined FBS, and serum insulin, and promoted the HOMA-IR[20] The underlying mechanism of melatonin in amelioration of insulin sensitivity encompasses induction of β -cell regeneration, hepatic glycogen synthesis promotion which reduce hyperglycemia in an animal model.[13,27,28] Furthermore, melatonin prevents insulin resistance by activating the cyclic adenosine monophosphate (cAMP)-response element binding protein (CREB)-peroxisome proliferator-activated receptor gamma coactivator 1-(PGC-1α) pathway.[9] It also provokes the IRS1-PI3K-PKC route to improve glucose absorption in skeletal muscle.[24]

Adiponectin a hormone that is secreted from subcutaneous and visceral WAT depots involved in the regulation of lipid and glucose metabolism, ameliorates insulin sensitivity, modulates appetite and energy expenditure, and demonstrates anti-inflammatory and antiproliferative functions.[8] Our results also showed the beneficial effects of 6 g/d of melatonin for 40 days on adiponectin levels without any significant changes in leptin after adjustment for potential confounders. Different animal models and clinical studies approved the melatonin's effect on the treatment of circulating adiponectin.[19,29,30] The underlying mechanism of melatonin action on adiponectin includes the effects of indoleamine function on adiponectin signaling pathways, the antioxidant and anti-inflammatory features of melatonin, progression in mitochondrial action, and effects on other adipokine concentrations.[7] Melatonin administration decreases the circulating leptin levels in most animal models,[29,30] however, the results are inconsistent in human studies.[19,31] Leptin amount did not vary after a 40-day melatonin supplementation in the present study.

The present results also found that melatonin supplementation for 40 days declined TC and LDL-c levels while improving HDL-c. However, after confiders adjustments only improvements of HDL-c were significant. Experimental studies report the lowering properties of melatonin on serum TC concentrations prohibition of the absorption and biosynthesis of cholesterol and also increasing its catabolism.[16,32] In agreement with our results, a new systematic review and meta-analysis of RCTs demonstrated the beneficial impacts of melatonin consumption on lipids at doses greater than 8 mg/d and long durations of more than 8 weeks including a notable reduction in TG, TC, and a small reduction in LDL-c and HDL-c.[33] The lipid-promoting effects of melatonin arise from the promotion of innate cholesterol release through the production of bilirubin acid and the prevention of low-density lipoprotein receptor function. Moreover, enhancement of irisin levels and improvement fecal cholesterol repulsion are some pathways that melatonin acts.[16,34,35]

Growing evidence showed that melatonin supplementation decreased weight in animals.[17,36-38] However, the clinical evidence reveals melatonin supplements did not have striking effects on weight and the results of various doses and times on weight are inconsistent.[39-42] It was reported that melatonin is effective in weight reduction in those subjects with mental disease and consumed drugs led to adverse effects like weight variations. More research with various doses and lengths of study is requisite to approve this effect. The suggested mechanism for the obesity-modifying feature of melatonin is induction of lipolysis in adipocytes by up-regulation of the expression of hormone-sensitive lipase, adipocyte triglyceride lipase, and perilipin 1 via MT2, increasing cellular respiratory capacity through upregulation of the PGC-1, and transcription factor A mitochondrial expression and induction of the expression of thermogenic genes in adipocytes, as carnitine palmitoyl transferase and UCP3, which cause diffractions to beige phenotype formation.[10,12,14]

Strengths and limitations of the study

An important strength of the present work was the small omission rate, and great admission rate of the subjects to the supplements in both arms, considering possible confounders and using individualized dietary plans for weight reduction as an approved method in obesity combat. However, the restricted number of participants, the low study period, and the small melatonin dose were this investigation's limitations.

Conclusion

Melatonin shows beneficial impacts on the improvement of adiponectin, lipid-related factors, insulin resistance, and obesity-related complications. The interactive mechanism of action of melatonin including the regulation of adipose tissue metabolism, and insulin resistance, may be involved in obesity management. Most importantly, more investigation with great supplement dose, prolonged study duration, and more extensive methods are needed to unravel the path in which melatonin takes part in the fatness procedure.

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Authors' Contribution

Conceptualization: Naimeh Mesri Alamdari.
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Visualization: Naimeh Mesri Alamdari, Farzad Najafipour.
Writing–original draft: Naimeh Mesri Alamdari.
Writing–review & editing: Arvin Namazi Shabestari, Farzad Najafipour, Amirali Mirmazhari.

Competing Interests

The authors declare no conflict of interest.

Ethical Approval

The Ethics Committee of Tabriz University of Medical Sciences reviewed and approved the protocol (Ethical code: IR.TBZMED.REC: 924). Moreover, the investigation was carried out in accordance with the Helsinki Declaration of 1964, and its later amendments. All participants filled out the informed consent in the study. Additionally, it was registered in the Iranian Registry of Clinical Trials (identifier: IRCT2012122411867N1; http://www.irct.ir).

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