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Original Article

Effect of melatonin on oxidative stress and inflammation in obese women: A randomized double-blind clinical trail

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Summary

Introduction: Obesity and its associated disorders pose a significant global public health challenge affecting overall human well-being. Supplementation with melatonin has been proposed as a potential strategy to mitigate the negative health impacts of obesity. This study aimed to investigate the influence of melatonin intake on markers of inflammation and oxidative stress in obese female participants.

Methods: The research was conducted as a randomized, double-blind, placebo-controlled clinical trial. In total, 46 obese women were randomly allocated to receive either melatonin at a dosage of 6 mg per day or a matching placebo, alongside calorie-restricted diets, for a duration of 40 days. Key serum biomarkers including superoxide dismutase (SOD), glutathione peroxidase (GPx), soluble receptor for advanced glycation end-products (s-RAGE), catalase, and 8-iso-prostaglandin F2 alpha (8-iso-PGF2α) were measured at baseline and post-intervention.

Findings: After adjusting for baseline measurements and confounding variables, participants in the melatonin group showed significant increases in SOD (217.08 U/mg Hb, $P=0.010$) and catalase levels (15.89 U/mg Hb, $P=0.001$) compared to placebo. No notable changes were observed in GPx concentrations. Additionally, s-RAGE levels were significantly reduced (-9.07 pg/mL, $P=0.021$) between the groups, while 8-iso-PGF2α levels remained unchanged.

Conclusion: The findings suggest that melatonin supplementation may exert beneficial effects on inflammatory and oxidative stress factors in obese women, potentially aiding in the management of obesity-related complications. Further research is warranted to confirm these preliminary results.

Trial Registration: http://www.irct.ir, Identifier: IRCT2012122411867N1.

Keywords: Inflammation, Melatonin, Obesity, Oxidative stress

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Introduction

Obesity is recognized as a major global public health challenge. Nearly 2.5 billion individuals worldwide are classified as overweight or obese, accounting for about one-third of the global population.[1] In 2022, the prevalence of obesity among adults was approximately 18.5% in women and 14% in men.[2] This condition is linked to various serious health issues such as type 2 diabetes mellitus (T2DM), different types of cancers, lipid metabolism disorders, fatty liver disease, and cardiovascular problems, all of which complicate the management of obesity.[3]

The rising prevalence of obesity can partly be attributed to a mismatch between calorie intake and energy expenditure, sedentary lifestyles, poor dietary choices, inadequate sleep quality, and genetic factors influencing susceptibility.[4-6] White adipose tissue (WAT), functioning as a vital endocrine organ, secretes bioactive substances such as adipokines which regulate lipid metabolism, energy homeostasis, insulin sensitivity, angiogenesis, immunity, and inflammation.[7,8]

Adipose tissue releases several proinflammatory cytokines including tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), and adipokines like leptin and adiponectin, which promote the generation of reactive oxygen species (ROS), leading to oxidative stress (OS).[5] Consequently, individuals with obesity exhibit elevated oxidative biomarkers.[6] Furthermore, evidence suggests that an increase in adipose tissue mass is associated with a significant reduction in antioxidant enzyme activities and overall antioxidant capacity.[7] Given these complexities, exploring additional therapeutic approaches beyond current strategies such as diet modification, behavioral changes, and lifestyle interventions may be beneficial to ameliorate the metabolic consequences linked to obesity.[8,9] Emerging research highlights the positive effects of melatonin supplementation in weight regulation.[10,11]

Melatonin (N-acetyl-5-methoxytryptamine) is an endogenous indoleamine hormone involved in various physiological processes, controlled by the hypothalamic suprachiasmatic nucleus (SCN). It is secreted rhythmically by the pineal gland and exerts its effects mainly via melatonin receptors MT1 and MT2, which are G-protein-coupled receptors.[9] Additionally, melatonin plays a critical role in regulating circadian rhythms, immune function,

energy metabolism, and the endocrine system.[5,10]

Studies on melatonin's role in obesity have mainly been conducted in animal models of diet-induced obesity. These studies demonstrate that melatonin supplementation may reduce body weight, enhance energy expenditure, regulate fat mass, modulate insulin secretion, and improve glucose and lipid metabolism.[12-14] Mechanistic insights further confirm melatonin's potent anti-inflammatory and antioxidant properties.

While animal studies consistently support melatonin's benefits in managing obesity, investigations in human subjects remain limited. This study aims to evaluate the effects of melatonin supplementation on oxidative stress and inflammatory markers in obese women following a calorie-restricted diet.

Methods

Study design and subjects

Obese participants were recruited from outpatient clinics affiliated with Tabriz University of Medical Sciences in Tabriz, Iran. This double-blind, placebo-controlled randomized clinical trial was conducted between February and July 2014. Eligible participants were adults aged 20 to 50 years with a body mass index (BMI) ≥ 30 kg/m^2 who had maintained a stable body weight over the preceding six months. Exclusion criteria included pregnancy or lactation, menopausal status, smoking, alcohol consumption, hypertension, diabetes mellitus, use of medications affecting lipid or glucose metabolism (such as lipid-lowering or glucose-lowering drugs), kidney disorders, psychiatric conditions, tranquilizer use, contraceptive or anti-inflammatory drug intake, antioxidant supplementation, anti-obesity drugs, and multivitamins within the past three months. Additionally, subjects who consumed less than 90% of the prescribed intervention were excluded. Written informed consent was obtained at baseline from all participants. Demographic and personal data were collected. The study protocol received ethical approval from the Research Ethics Committee of Tabriz University of Medical Sciences (Ethics Code: IR.TBZMED.REC: 924) and adhered to the principles of the Declaration of Helsinki. This trial was registered at the Iranian Registry of Clinical Trials (Registration Number: IRCT2012122411867N1).

Sample size

Sample size estimation was based on the mean and standard deviation of HDL cholesterol levels from previous study[15]. With a 95% confidence interval and 90% statistical power, 21 subjects per group were calculated; accounting for an anticipated 10% dropout, 23 participants were recruited per group.

Randomization and intervention

Randomization employed a block design using Random Allocation Software (RAS), stratified by age and BMI, with a block size of two. A research assistant not involved in the study assigned participants equally (1:1) to the melatonin or placebo groups using a coded three-digit system. Both participants and study personnel were blinded to group assignment.

The melatonin group (n = 23) received 6 mg of melatonin daily (two 3-mg tablets, Nature Made, USA) taken two hours before bedtime, alongside a calorie-restricted diet. The placebo group (n = 23) received identical placebo tablets containing cellulose and starch at the same dosing schedule and accompanying diet. Calorie restriction was prescribed by a dietitian based on individual requirements, with a daily energy intake set 500 kcal below total energy expenditure calculated via the Mifflin equation. Participants were monitored at three intervals during the study to assess adverse effects.

Supplements and placebos were dispensed biweekly. Participants were instructed to return unused tablets to verify adherence. Nutritional counseling was provided, and body weight was recorded every two weeks. Participants were asked to maintain their usual lifestyle habits while following dietary guidelines.

Dietary intake was assessed using a three-day food record (two weekdays and one weekend day) at baseline and post-intervention. Data were analyzed using Nutritionist 4 software (First Databank Inc., San Bruno, CA, USA).

Measurements of biochemical parameters

Following an overnight fast of 8–12 hours, blood samples were collected. Serum was separated and stored at −80 °C until analysis. Activities of glutathione peroxidase (GPx) and superoxide dismutase (SOD) were quantified via colorimetric assays using an automated analyzer (RANSEL and RANSOD kits; RANDOX Laboratory, UK). Serum soluble receptor for advanced glycation end-products (s-RAGE) was measured by ELISA. Catalase activity was determined following Aebi's method.

Statistical analysis

Statistical analyses were performed using SPSS version 26 (IBM, Armonk, NY, USA). Normality of continuous variables was evaluated by Kolmogorov–Smirnov tests. Data were expressed as mean ± standard deviation for continuous variables and frequencies (percentages) for categorical variables. Between-group and within-group comparisons used independent and paired samples t-tests, respectively. Percentage change was calculated as [(post-intervention minus pre-intervention) / pre-intervention] × 100 and analyzed between groups using ANCOVA adjusted for confounders. Statistical significance was set at $P < 0.05$.

Results

Out of the initial forty-six obese participants, forty-four

(with 22 individuals in each group) completed the study. In the melatonin group, one participant was excluded for consuming less than 90% of the supplements, and in the placebo group, one participant was removed due to non-adherence to the prescribed weight loss diet (see Figure 1). The average age of participants was 33.86 ± 6.94 years in the melatonin group and 34.86 ± 7.29 years in the placebo group. There were no significant differences in baseline demographic or anthropometric characteristics between the groups ($P \geq 0.05$). Melatonin supplementation over the 40-day period led to a 3% reduction in BMI, compared to a 2.5% decrease in the placebo group relative to baseline; however, the percent change between groups was not statistically significant ($P = 0.130$). Similarly, no significant differences were observed between groups concerning changes in weight, waist circumference, or hip circumference ($P \geq 0.05$). As presented in Table 1, no marked variations related to dietary intakes were observed among groups at the beginning of the study($P > 0.05$). After 40 days of intervention energy intake and all macronutrient intake were decreased significantly in placebo and melatonin group. Between group comparisons showed that after adjusting for baseline values and potential confounders, only carbohydrate changes were significant ($P = 0.030$).

Figure 2 shows the evaluations of percentage changes of dietary intake in two studied arms. Following adjustments were done for confounders, melatonin contributed to decrement of carbohydrate in comparison to placebo ($P = 0.040$), while the percent changes of energy intake, protein and fat intake were not significant between the two studied groups.

There were no variations between groups in SOD, GPx, s-RAGE, catalase and 8-iso-PGF2α concentrations at baseline ($P > 0.05$). However, after 40 days, SOD, GPx and catalase concentrations increased remarkably in the melatonin arm ($P = 0.028$, $P = 0.007$, $P = 0.025$ respectively), while they did not change in the placebo arm. S-RAGE and 8-iso-PGF2α decreased remarkably after 40 days relative to baseline values in melatonin group (Table 2). Following adjustments for confounders were done, SOD (217.08 U/mg Hb, $P = 0.010$) and catalase (15.89 U/mg Hb, $P = 0.001$) markedly increased in the melatonin arm relative to the placebo arm, while GPx levels did not change significantly. Moreover, s-RAGE levels decreased remarkably (-9.07 pg/mL, $P = 0.021$) in between group comparisons, while 8-iso-PGF2α did not change significantly.

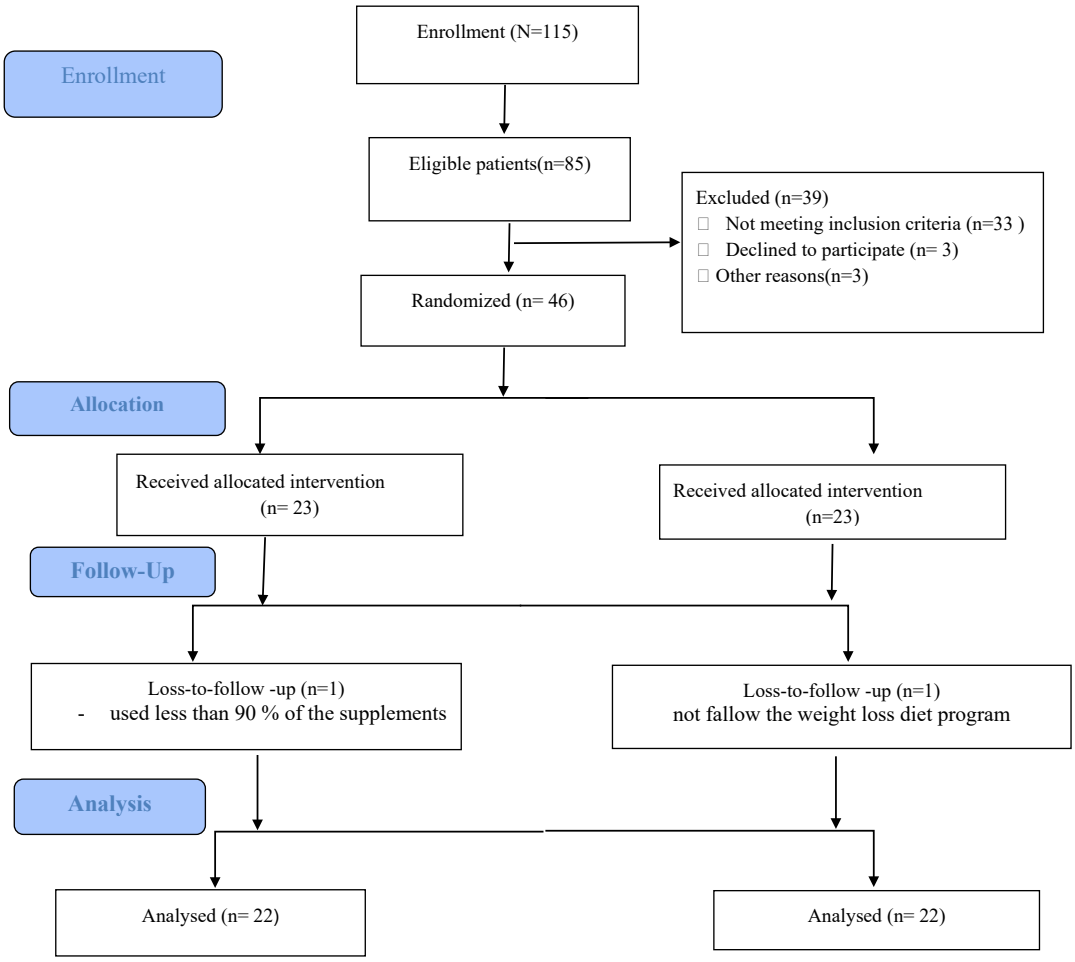

Figure 1. Study Flow Diagram

Table 1. Dietary intakes of participants at baseline and at the end of the study

Variables	Period	Placebo (n = 22)	Melatonin (n = 22)	*P-value
Energy (kcal/day)	Initial	219 ± 2503.21	2870 ± 226.41	0.421
	End	2000 ± 220.47	105 ± 2218.34	0.130
P**		0.030	0.040	
Protein (g/d)	Initial	7 ± 101	7 ± 105	0.143
	End	7 ± 86	8 ± 89	0.251
P**		0.040	0.020	
Carbohydrate (g/d)	Initial	33 ± 393	394 ± 31	0.214
	End	± 32135	17 ± 282	0.030
P**		0.020	0.030	
Fat (g/d)	Initial	8 ± 86	9 ± 94	0.741
	End	7 ± 70	6 ± 79	0.149
P**		< 0.001	< 0.001	

Data are presented as mean (SD).
* *P* value from student t- test for Pre-intervention and ANCOVA for Post-intervention after adjusting for baseline values and potential confounders including baseline values, age and BMI.
** *P* value for paired t-test.

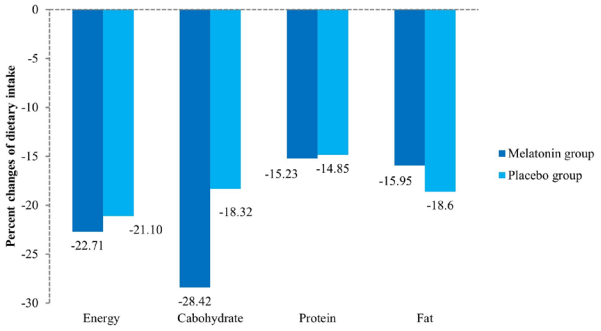

Figure 2. Comparison of Percentage Changes of dietary intake Between Two Study groups. $P<0.05$, By Independent Sample t-Test

Discussion

Obesity, a widespread global health concern, is linked to various complex chronic conditions. Despite advances in clinical management strategies, effective treatment remains challenging. Recent research highlights the potential of melatonin supplementation as a promising therapeutic approach to obesity management.[12,16,17]

This clinical trial evaluated the effects of melatonin supplementation on oxidative stress and inflammatory markers in obese women following a calorie-restricted diet. Our findings indicate that a 40-day course of melatonin significantly improved antioxidant and inflammatory parameters without substantially altering dietary intake after controlling for confounding variables.

Obesity-induced lipotoxicity and glucotoxicity lead to elevated reactive oxygen species (ROS) production, which activates proinflammatory pathways and exacerbates tissue damage[18]. The chronic low-grade inflammation in obesity results from altered secretion of proinflammatory mediators, such as TNF-α, IL-6, and CRP, primarily originating from white adipose tissue, along with enhanced oxidative injury.[19,20] Over the past decade, multiple studies have underscored the health benefits of melatonin, including its antioxidant, anti-inflammatory, immunomodulatory properties, and its roles in regulating body fat and weight.[13,15,21]

To our knowledge, no prior studies have assessed the combined effect of melatonin supplementation and a low-calorie diet on inflammatory and oxidative stress markers specifically in obese women. Hence, this trial was conducted in healthy subjects without any major medical conditions.

Our results demonstrated a significant reduction in energy and macronutrient intake following 40 days of melatonin supplementation combined with calorie restriction ($P<0.05$). The placebo group, which also adhered to a low-calorie diet, similarly exhibited reductions in energy, carbohydrate, protein, and fat intake at the end of study. Although decreases in energy, carbohydrate, and protein consumption were greater in the melatonin group, between-group differences were not statistically significant.

This study is, to the best of our knowledge, the first clinical trial investigating melatonin's impact on energy and macronutrient intake during weight loss in obese women. Due to the lack of comparable human data, references are made to relevant animal studies. For example, administering melatonin at 30 mg/kg for three weeks in high-fat diet-induced obese rats did not affect food consumption.[22] Similarly, Wolden-Hanson et al. reported no significant change in food intake after 12 weeks of melatonin supplementation (0.4 μg/mL) in aged, normal-weight rats fed ad libitum.[23] Conversely, Hussein Mahmud R and colleagues observed a non-significant decrease in food intake following daily subcutaneous melatonin injections (1 mg/kg) for four weeks in obese rabbits.[24]

The anti-obesity effects of melatonin are thought to derive from its ability to regulate the balance between energy intake and expenditure, influencing overall energy metabolism.[25,26] It also modulates insulin intracellular signaling pathways, thereby reducing insulin resistance and glucose intolerance, which collectively contribute to weight loss and fat reduction.[27]

Given that both melatonin supplementation and calorie restriction were utilized in this study, the observed weight loss and decreased energy intake in both groups are primarily attributed to the low-calorie diet, with melatonin's specific involvement in these outcomes appearing limited.

Consistent with previous research, melatonin supplementation improved antioxidant status in our

Table 2. Comparisons of oxidative stress biomarkers in study groups before and after the intervention

Variables	Placebo (n=22)	Melatonin(n=22)	MD (95% CI) between groups	*P* value**
SOD (U/mg Hb)				
Initial	1423.24 (104.38)	1526.14 (213.09)	102.9 (47.27 to 136.0)	0.127
End	1476.17 (163.78)	1693.25 (215.04)	217.08 (18.4 to 241.01)	0.010
MD (95% CI) within groups	-52.93 (-85.94 to 12.10)	167.11 (15.52 to 209.90)		
P value*	0.144	0.028		
GPx (U/mg Hb)				
Initial	43.16 (3.50)	46.12 (2.96)	2.96 (-1.24 to 9.17)	0.420
End	49.74(6.16)	54.25 (4.27)	4.51 (-0.11 to 6.17)	0.240
MD (95% CI) within groups	6.58 (-1.78 to14.27)	8.13 (0.71 to 11.55)		
P value*	0.251	0.007		
s-RAGE (pg/mL)				
Initial	617.31 (101.91)	628.50 (142.15)	11.19 (-14.1 to 26.5)	0.218
End	603.17 (122.11)	594.10 (121. 51)	-9.07 (-11.05 to 13.48)	0.021
MD (95% CI) within groups	-14.14 (-21.60 to -24.10)	-34.40 (-12.19 to -43.19)		
P value*	0.217	0.043		
Catalase (U/g Hb)				
Initial	61.17 (14.23)	63.70 (18.50)	2.53 (-3.42 to 10.20)	0.136
End	63.23 (15.47)	79.12 (24.71)	15.89 (-2.12 to 18.9)	0.001
MD (95% CI) within groups	2.06 (-1.02 to 7.14)	15.42 (-3.16 to 25.30)		
P value*	0.898	0.025		
8-iso-PGF2α				
Initial	152.14 (27.28)	147.34 (21.42)	-4.8 (-7.5 to 10.7)	0.632
End	148.51 (24.32)	141.15 (19.69)	-7.36 (-18.0 to 3.8)	0.105
MD (95% CI) within groups	-3.63 (-8.17 to 10.68)	-6.19 (-10.14 to -2.43)		
P value*	0.528	0.014		

CI, confidence interval; sRAGE, soluble receptor for AGE; SOD, superoxide dismutase; GPx, glutathione peroxidase; PGF-2α, 8-iso prostaglandin F2alpha. Data are presented as mean (SD)

* *P* value was based on within-group comparisons by paired t-test.

** *P* value was based on between-group comparison by student t-test for Pre-intervention and ANCOVA for post-intervention after adjusting for baseline values and potential confounders.

participants. For instance, Hussein et al. reported increased total antioxidant capacity (TAC) in obese rabbits receiving daily melatonin (1 mg/kg subcutaneously for 4 weeks).[24] She et al demonstrated reductions in malondialdehyde levels and enhanced superoxide dismutase (SOD-1) activity following melatonin treatment in obese rats (4 mg/kg intraperitoneally for 8 weeks).[28] Clinical studies further support these findings; supplementation with 5 mg/d melatonin for durations ranging from 30 days to two months significantly increased SOD-1 and catalase activities while reducing lipid peroxidation markers in patients with metabolic syndrome, type 2 diabetes, and primary hypertension.[29,30]

Extensive evidence positions melatonin as a powerful scavenger of oxygen- and nitrogen-based reactive species.[31] It enhances intracellular antioxidant enzyme activities, including SOD and glutathione peroxidase, and stimulates glutathione synthesis.[32] Moreover, melatonin exerts genomic effects by regulating the expression of antioxidant enzymes such as SOD and GPx, impacting both enzyme activity and gene expression.[33]

In the current study, 6 mg/d melatonin supplementation significantly decreased inflammatory responses in obese women, as evidenced by reductions in s-RAGE. Previous in vivo studies corroborate melatonin's anti-inflammatory actions, showing inhibition of proinflammatory cytokines (TNF-α, IL-6, IL-1β) and inducible nitric oxide synthase (iNOS) expression.[34] Jung et al. demonstrated that melatonin administration (50 mg/kg) suppressed mRNA levels of these mediators in rats,[35] while Veneroso et al found similar effects at a lower dose (1 mg/kg).[36] Clinical data also report that melatonin treatment (5 mg/d for one month) significantly lowered TNF-α and IL-6 levels in patients with steatohepatitis.[32] Melatonin likely reduces proinflammatory cytokine release and iNOS production by inhibiting nuclear factor-κB (NF-κB) expression or activation. Receptors for advanced glycation end-products (RAGEs), as members of the immunoglobulin superfamily. The binding of AGEs to RAGE stimulates the intracellular formation of ROS by activating

Nicotinamide adenine dinucleotide phosphate (NADPH) oxidases, which in turn leads to the activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) target genes transcription, insulin resistance, platelet activation, endothelial dysfunction, and low-grade inflammation.[37] It seem that melatonin may serve as receptor ligands of RAGEs.

A notable strength of this study was the high compliance and low dropout rates in both groups, use of individualized dietary plans, and control of potential confounders. Limitations include the relatively small sample size, short duration, and modest melatonin dosage.

Conclusion

Melatonin supplementation positively influences oxidative stress and inflammation, key contributors to obesity-related complications. Further studies with larger sample sizes, longer intervention periods, and higher doses of melatonin are warranted to elucidate its precise role in obesity management.

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Author's Contribution

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Formal analysis: Majid Mobasseri, Farzad Najafipour.
Funding acquisition: Naimeh Mesri Alamdari.
Investigation: Majid Mobasseri, Farzad Najafipour.
Methodology: Hossein Darabi, Farzad Najafipour.
Project administration: Naimeh Mesri Alamdari.
Resources: Naimeh Mesri Alamdari.
Supervision: Naimeh Mesri Alamdari.
Validation: Majid Mobasseri.
Visualization: Naimeh Mesri Alamdari.
Writing—original draft: Farzad Najafipour.
Writing—review & editing: Majid Mobasseri.

Competing Interests

The authors declare no conflicts of interest.

Ethical Approval

The study protocol was approved by the Ethics Committee of Tabriz University of Medical Sciences (Ethical code: IR.TBZMED.REC: 924) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

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Intelligence Use Disclosure

This article has not utilized artificial intelligence (AI) tools for research and manuscript development, as per the GAMER reporting guideline.

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