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The Effect of Zinc Supplementation on Glycemic, Weight, and Blood Pressure Control in Patients With Type 2 Diabetes Mellitus: A Double-Blind Randomized Controlled Trial

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ABSTRACT

Backgrounds and Aims: Type 2 diabetes and its complications are assumed to be major public health problems globally. Zinc is one of the elements that play a part in insulin secretion and signaling. Therefore, this study seeks the answer to the following question: "What are the effects of 220 mg zinc sulfate supplementation on the weight, blood pressure, and glycemic control of patients with Type 2 diabetes?".

Methods: In this randomized controlled double-blind trial, 79 patients with Type 2 diabetes were allocated into two groups through permuted block randomization method. The study group received two capsules of 220 mg of zinc sulfate containing 50 mg of zinc, and the control group received two capsules of 220 mg of placebo ingredient per week for 12 weeks. At the start and end of the treatment period, the fasting blood glucose (FBG), glycated hemoglobin (HbA1c), zinc level, weight, waist circumference (WC), and blood pressure were measured.

Results: After 12 weeks of follow-up, 72 patients completed the study. There were no significant differences before and after the intervention in the FBG, HbA1c, zinc levels, and WC between the two groups. Intragroup analysis showed that weight and body mass index increased in the intervention group; however, these changes were not significant in comparison to the control group. Also, diastolic blood pressure significantly increased in the control group; however, changes in systolic blood pressure were not significant in both groups.

Conclusion: Taking 220 mg of zinc sulfate supplement twice a week did not show significant benefit for weight, blood pressure, and glycemic control in patients with Type 2 diabetes.

Trial Registration: This trial was registered on the Iranian Registry of Clinical Trials (IRCT) website with code number 29627 on September 18, 2018.

1 | Introduction

Type 2 diabetes is one of the concerning issues in public health, affecting nearly 462 million people all around the world. In 2017, more than one million fatalities were attributed to Type 2 diabetes [1]. The number of pre-diabetic and diabetic patients has been an incremental trend during the past three decades all over the world, with more rapid growth in low- and middle-income countries due to sedentary lifestyles, unhealthy diets, and obesity [2]. The goal behind diabetes management is to improve the quality of life and prevent the common complications of the disease through a comprehensive person-centered treatment plan, including glycemic control, weight management, risk assessment, and management of complications and comorbidities [3].

Type 2 diabetes is characterized by impaired insulin secretion and insulin resistance in peripheral tissues such as skeletal muscle, liver, and adipose tissue, resulting in glucose and lipid metabolism dysregulation [4]. Studies have indicated a higher likelihood of zinc deficiency in individuals with diabetes [5]. Zinc plays a crucial role in insulin production by stabilizing insulin hexamers and supporting their storage in the pancreas [6, 7]. Additionally, zinc is involved in enhancing glucose uptake in target tissues by promoting the phosphorylation of insulin substrate-1 and protein kinase B, key components of the insulin signaling pathway [8, 9]. Furthermore, oxidative stress is a significant factor in the development and complications of diabetes, with zinc being essential for the synthesis of antioxidant enzymes. Therefore, a deficiency in zinc can disrupt the production of antioxidant enzymes and lead to increased oxidative stress [10, 11].

Due to the major role of zinc in diabetes, several studies have investigated the effect of zinc supplementation among diabetic patients. Some of them found that zinc supplementation improved the glycemic indices, whereas some of them found no significant effect [12]. Also, studies used different dosages of zinc supplementation, and most of them used daily intake of the supplement [12]. Furthermore, patients with Type 2 diabetes often take multiple pills every day, and adding to the pills decreases compliance. Therefore, this study aimed to explore the following research question: "What are the effects of taking 220 mg zinc sulfate supplementation twice a week on glycemic indices, blood pressure, and obesity in patients with Type 2 diabetes?" The CONSORT (Consolidated Standards of Reporting Trials) guidelines [13] were followed for reporting this randomized controlled trial.

2 | Materials and Methods

2.1 | Study Design and Population

This randomized, double-blind, one-center, placebo-controlled, parallel study was conducted at the Diabetes clinic of Shiraz, Iran from July 2019 to January 2020. The study was designed to evaluate the effect of zinc supplementation on glycemic control, blood pressure, and obesity in patients with Type 2 diabetes. The study was conducted on 79 eligible participants who were gathered through advertisements or personal invitations from the care providers.

The inclusion criteria included individuals aged 30 to 60 years diagnosed with Type 2 diabetes mellitus according to the American Diabetes Association (ADA) [14] criteria with medical records at the diabetes clinic. The exclusion criteria encompassed individuals with Type 1 diabetes, other chronic conditions (e.g., renal, cardiac, pulmonary diseases), diabetes-related complications (e.g., nephropathy, retinopathy, diabetic ulcer), pregnancy, lactation, smoking, history of blood transfusion, anemia, and use of supplements like antioxidants and omega-3.

Participants with diabetes were randomly assigned to either the intervention group ($n = 40$) or the control group ($n = 39$). The intervention group received two capsules of 220 mg zinc sulfate (containing 50 mg of zinc) weekly for 12 weeks, while the control group received two capsules of 220 mg placebo designed to resemble the zinc sulfate capsules in color and shape. The placebo contained avesil as an inactive substance. Laboratory experiments measured FBG, HbA1c, and serum zinc levels before and after the 12-week intervention period.

2.2 | Sample Size Calculation

According to the objectives and type of study, taking into account the assumptions: 5% error, 80% power, and 60% effect size by $n = \frac{\frac{1+r}{r}s^2(z_{1-\alpha/2} + z_{1-\beta})^2}{(\partial)^2}$ Formula, 33 patients were estimated in each group. Due to the longitudinal nature of the study and repeated measurements using the $n' = n \times \frac{1}{1-p}$ formula, and a drop-off rate of 20%, the final sample size is 40 in each group. Therefore, a total of 80 patients was needed. In the above formula, the values of z are fixed and equal to the 97.5 percentile and the 80th percentile of the standard normal distribution and r is the ratio of people in two groups. We used Cohen's effect size (d) and we considered a relative effect size. In this study, 60% have been considered a relative effect size from a clinical point of view [15, 16].

2.3 | Randomization and Blinding

The study involved 79 patients diagnosed with Type 2 diabetes mellitus who were referred to a diabetes clinic and met the study's criteria. These individuals were randomly divided into two groups, namely the intervention and control groups, using Permuted Block Randomization with block sizes of four. The random assignment resulted in six conditions: AABB, ABAB, ABBA, BAAB, BABA, and BBAA. The allocation of interventions (A or B) was determined by a statistical expert, and a randomized list was generated by a statistician. A person not involved in the study assigned codes to each patient based on this list. The capsules used in the study were identical in color and shape for both groups, ensuring the blinding of participants, caregivers, assessors, and analysts regarding the group assignments and capsule contents.

2.4 | Measurements

Demographic features including sex (male/female), age (years) [modeled as a continuous variable], educational attainment

[modeled as an ordinal variable], family history of diabetes (yes/no), duration of diabetes (years) [modeled as a continuous variable], and medications [modeled as a categorized variable] were based on the medical records of participants. Height (cm), weight (kg) [modeled as a continuous variable], and waist circumference (WC) (cm) [modeled as a continuous variable] were measured by standard techniques at the baseline and after 12 weeks of intervention. Body mass index (BMI) was calculated as weight (Kg)/(height)^2 (m^2) [modeled as a continuous variable].

Venous blood samples were drawn in the fasting state (at least 8 h overnight) at baseline and after 12 weeks in the treatment period. Blood samples were centrifuged and analyzed immediately. The blood pressure (mmHg) [modeled as a continuous variable] of participants was measured based on the International Society of Hypertension (ISH) guideline [17] in a sitting position after 5 min of rest. HbA1c [modeled as a continuous variable] was measured by the colorimetric method (Pishtaz Teb, Iran). Fasting blood glucose (FBG) (mg/dL) [modeled as a continuous variable] levels were measured by the enzymatic method (Delta Darman Part, Iran). The serum zinc level [modeled as a continuous variable] was measured by the colorimetric method (Persian Tajhiz System, Iran).

2.5 | Statistical Methods

The normality of the variables was checked by the Shopiro–Wilk test. Continuous and categorical variables were presented by mean ± SD and number (%), respectively. Data were analyzed using χ^2, paired, and independent sample *t*-test. The mean changes in both groups were considered and analyzed with an independent sample *t*-test in the differences analysis. All statistical tests were performed by SPSS for Windows, Version 16.0. Chicago, SPSS Inc. A *p*-value lower than 0.05 was considered as significant.

3 | Results

Among 79 diabetic participants who enrolled in this clinical trial, 40 participants were allocated to the intervention group and 39 participants were allocated to the control group. During the follow-up period, seven participants from the control group were lost to follow-up (Figure 1.).

Table 1. summarizes the demographic characteristics and disease records of the control and intervention groups. There were no significant differences between the groups in case of sex, age, marital status, educational attainment, and type of medications for

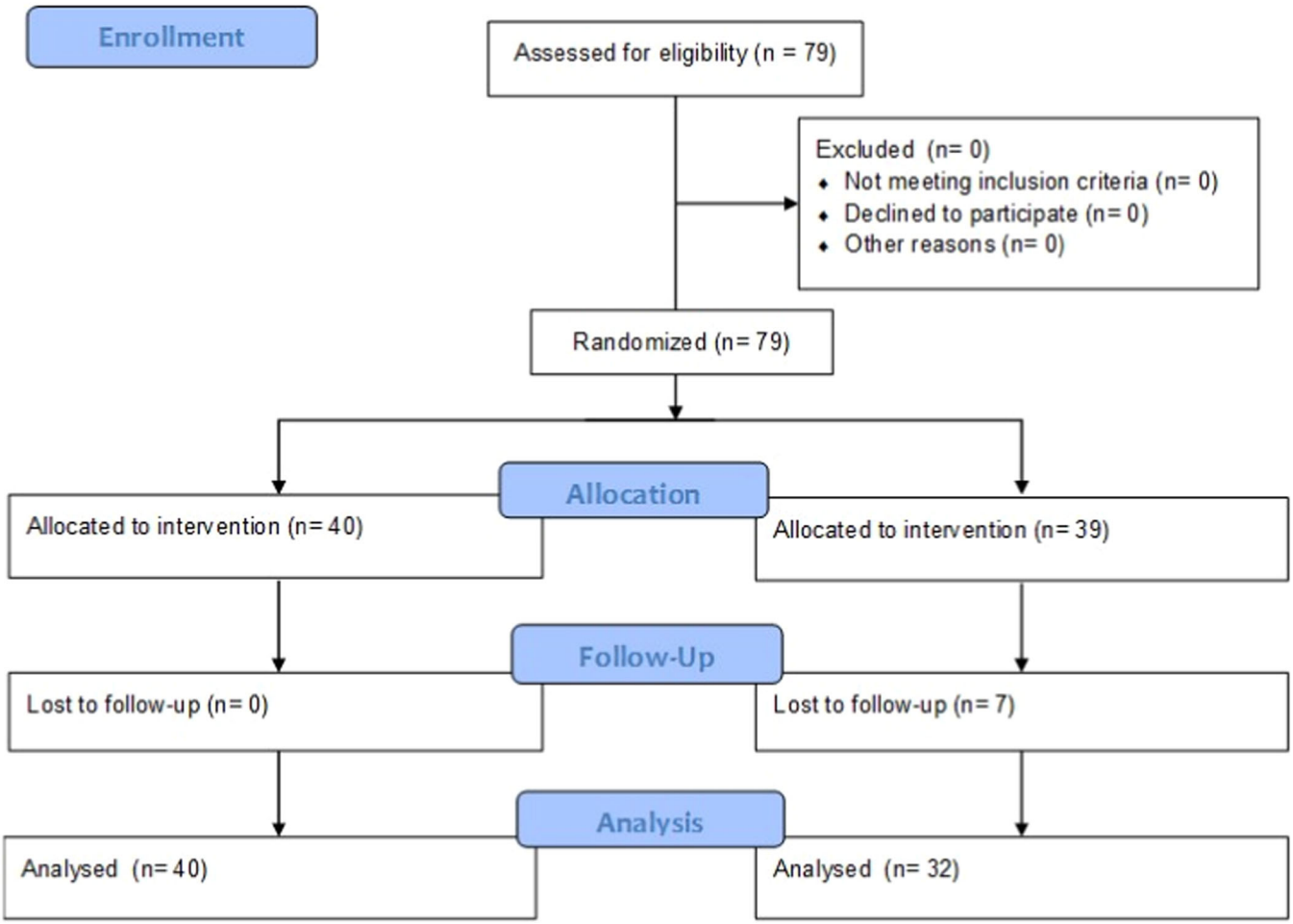

FIGURE 1 | CONSORT flow diagram of the study.

TABLE 1 | Comparison of baseline characteristics among participants in the intervention and control group.

Baseline characteristics	Study group	Control group	Statistic	*p*-value
Age (years)	51.2 ± 6.49	53.8 ± 4.8	1.990	0.051
Gender				
Male	9 (22.5%)	5 (12.8%)	1.269	0.260
Female	31 (77.5%)	34 (87.2%)		
Marital status				
Married	37 (92.5%)	34 (87.2%)	0.614	0.342
Single	3 (7.5%)	5 (12.8%)		
Education Level				
Illiterate or Primary school	6 (15%)	13 (33.3%)		
Secondary school	12 (30%)	11(28.2%)		
Diploma	13 (32.5%)	13 (33.3%)	7.070	0.132
University degree	9 (22.5%)	2 (5.1%)		
Diabetes mellitus duration (years)	**8.07 ± 5.48**	**11.20 ± 7.75**	**2.06**	**0.043**
Family history of diabetes	29 (72.5%)	26 (66.7%)	0.318	0.573
Oral agents consumption	36 (90%)	34 (87.2%)	0.156	0.693
Insulin consumption	11 (27.5%)	9 (23.1%)	0.204	0.651
Oral agents and insulin consumption	9 (22.5%)	7 (17.9%)	0.253	0.615

Note: Bold values indicate statistically significance $p < 0.05$.

diabetes. However, the duration of the disease in the intervention group was significantly less than the control group ($p = 0.043$).

Our findings showed that taking zinc supplement does not improve weight and blood pressure management significantly (Table 2). There were no differences between the control and intervention groups in terms of obesity and blood pressure at the baseline. Also, no differences were observed between the two groups in weight, BMI, WC, and systolic blood pressure (SBP) after intervention. However, the control group had a significantly higher diastolic blood pressure (DBP) after the treatment period, compared to the intervention group ($p = 0.018$). Also, the intragroup analysis showed that zinc supplementation significantly increased the weight and BMI of the intervention group ($p < 0.001$). However, these incremental changes in BMI and weight were not significantly higher than the control group. DBP was significantly increased among participants in the control group ($p = 0.021$).

Our findings failed to show statically significant benefit from taking zinc supplement for glycemic control among patients with Type 2 diabetes (Table 3). There were no significant differences in FBG, HbA1c, and zinc levels between the two groups. Also, the intragroup analysis revealed no significant changes in each of the two groups after the treatment period.

4 | Discussion

Our findings showed that consuming 220 mg of zinc sulfate supplement twice a week alongside the standard diabetes medications did not improve the weight, glycemic, or blood pressure control in patients with Type 2 diabetes. It is worth noting that, despite the previous studies finding that diabetic patients had lower zinc levels than the normal population [18], the mean serum zinc level in our study was within the normal range. Therefore, the participants had sufficient zinc for insulin activity and glucose uptake. Furthermore, the zinc level did not increase significantly after taking zinc supplementation, which explains that this dosage of zinc supplementation could not interrupt the zinc hemostasis. The control group had a longer duration of diabetes which may affect the results as it is associated with altered glucose metabolism and increased diabetes complications [19].

Our study indicated that zinc supplementation was not beneficial for decreasing HbA1c and FBG levels. Compatible with our findings, Afkhami-Ardekani et al. [20] in 2008 found that daily consuming 660 mg of zinc sulfate for 6 weeks does not change HbA1c and FBG levels. In comparison to our study, this study had fewer participants (40 participants), a shorter treatment period, and a higher dose of zinc sulfate. Also, another study by Asghari et al. [21] on 60 patients with Type 2 diabetes found that using 30 mg zinc gluconate every day for 12 weeks did not improve FBG and HbA1c levels significantly. In contrast, a study in 2019 by Nazem and colleagues [22] on 70 obese Type 2 diabetic patients showed that using 50 mg zinc gluconate per day for 8 weeks decreased HbA1c and FBG levels. The dosage of zinc supplementation in this study was higher than in our study (50 mg daily vs. 50 mg of elemental zinc twice a week). A recent systematic review and meta-analysis indicated that zinc supplementation decreased FBG by 27.68 mg/dL in patients with Type 2 diabetes. However, the changes in HbA1c and insulin resistance were not significant [23]. Another meta-analysis in 2021 found that low-dose zinc (lower than 25 mg/day) supplementation significantly decreased FBG, but

TABLE 2 | Anthropometric characteristics of the patients with Type 2 diabetes.

Characteristics		Group ($n = 72$)			
		Study ($n = 40$)	Placebo ($n = 32$)	*p*-value	95% CI
WC (cm)	Before	11.9 ± 98.3	13.5 ± 98.7	0.877	−6.1, 5.25
	After	12 ± 98.8	10.9 ± 99.3	0.848	−5.45, 5.24
Change		0.55 ± 4.2	0.60 ± 11.7	0.977	−3.79, 3.68
p-value		0.416	0.196	—	
Weight (m)	Before	14 ± 75.85	14.8 ± 75	0.803	−5.64, 7.26
	After	14.5 ± 77.2	11 ± 75.6	0.587	−4.20, 7.38
Change		1.35 ± 1.85	0.57 ± 9	0.530	−2.12, 3.67
p-value		**< 0.001**	0.693	—	
BMI (kg/m^2)	Before	5.1 ± 29	5.6 ± 29.4	0.771	−2.76, 2.05
	After	5.3 ± 29.6	4.5 ± 29.6	0.971	−2.24, 2.16
Change		0.52 ± 0.73	0.2 ± 3.6	0.585	−0.83, 1.45
p-value		**< 0.001**	0.721	—	
SBP (mmHg)	Before	7.7 ± 127.8	20 ± 126.5	0.705	−5.47, 8.05
	After	6.7 ± 128.3	14 ± 133.2	0.066	−10.21, 0.34
Change		0.5 ± 10.8	23.3 ± 6.3	0.098	−14.33, 1.88
p-value		0.772	0.079	—	
DBP (mmHg)	Beforer	5.3 ± 80.3	5.7 ± 81.3	0.407	−3.49, 1.43
	After	5.5 ± 80.5	12.1 ± 85.7	***0.018***	**−9.46, −0.99**
Change		0.23 ± 7.3	11.4 ± 4.4	***0.049***	**−8.15, −0.12**
p-value		0.830	**0.021**	—	

Note: Bold values indicate statistically significance $p < 0.05$.
Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; SBP, systolic blood pressure; WC, waist circumference.

TABLE 3 | Effect of zinc supplementation on glycemic control in patients with Type 2 diabetes.

Characteristics		Group ($n = 72$)			
		Study ($n = 40$)	Placebo ($n = 32$)	*p*-value	95% CI
FBG (mg/dL)	Before	48.81 ± 149.8	76.99 ± 158.76	0.540	−37.77, 19.83
	After	43.59 ± 154.02	88.61 ± 170.72	0.294	−47.86, 14.46
Change		4.23 ± 42.62	101.82 ± 11.95	0.660	−42.54, 27.08
p-value		0.538	0.468	—	
HbA1C (%)	Before	1.65 ± 7.89	2.21 ± 8.35	0.301	−1.33, 0.41
	After	11.53 ± 9.41	8.65 ± 10.26	0.711	−5.42, 3.72
Change		1.52 ± 11.77	1.91 ± 8.47	0.866	−4.99, 4.21
p-value		0.419	0.167	—	
Zinc (μg/dL)	Before	10.32 ± 104.37	12.27 ± 100.3	0.115	−1.01, 9.14
	After	58.31 ± 106.79	41.58 ± 105.93	0.943	−21.92, 23.55
Change		2.42 ± 60.25	5.67 ± 41.26	0.781	−26.44, 19.93
p-value		0.801	0.396		

Abbreviations: FBG, fasting blood glucose; HbA1C, hemoglobin glycosylate.

not HbA1c. Also, using zinc supplementation for 12 weeks or more showed similar results [12].

Our study showed no significant change in weight, BMI, and WC after receiving zinc supplement for 12 weeks. In line with our findings, the study of Afkhami-Ardekani and colleagues [20] found that using 660 mg/day zinc sulfate for 6 weeks did not change BMI and weight significantly. Also, a randomized controlled trial in Iraq on 50 Type 2 diabetic patients found no significant change in BMI after receiving 50 mg/day zinc gluconate

for 6 weeks [24]. In contrast, the study by Nazem et al. [22] found that using the same dose of zinc supplement for 8 weeks decreased weight and BMI significantly. A systematic review and meta-analysis in 2020 revealed that consuming zinc supplements did not change body weight, WC, and BMI significantly. Also, subgroup analysis of participants with Insulin resistance–related disorders like Type 2 diabetes showed the same results [25].

Our findings revealed that zinc supplementation did not affect blood pressure significantly. In line with our findings, a randomized controlled trial in Singapore indicated that using 240 mg of zinc gluconate per day did not change either SBP or DBP [26]. Also, the study by Afkhami-Ardekani et al. [20] found that taking zinc supplements significantly decreased SBP but not DBP in diabetic patients. A systematic review and meta-analysis revealed that the consumption of zinc supplements significantly reduced SBP, but did not have a significant impact on DBP. Sub-analyses conducted on patients with insulin-resistant disorders indicated that zinc supplementation resulted in significant reductions in both SBP and DBP. However, when analyzing the effects of different types of zinc supplements, it was found that zinc sulfate supplementation significantly lowered DBP, but did not have a significant effect on SBP [27].

Previous studies indicated that zinc modulates glucose hemostasis with different mechanisms like decreasing insulin resistance, increasing GLUT4, increasing insulin secretion, and α-glucosidase inhibition. It is worth noting that two zinc ions bind the hexameric structure of insulin to complete the maturation process in pancreatic β cells. Also, zinc transporter proteins play crucial roles in transporting insulin hormone into secretory granules and, finally, insulin secretion. Furthermore, zinc increases insulin sensitivity in peripheral tissues like muscles and adipose tissue. Also, this mineral plays a part in the transcription of insulin receptor genes through zinc finger proteins. Zinc promotes the phosphorylation of insulin receptors and activates Akt to facilitate the GLUT4 translocation, which eventuates into glucose uptake by cells [28–30]. Moreover, Zinc-α2-glycoprotein provokes AMP-activated protein kinase (AMPKα) in muscles and adipose tissue, leading to increased GLUT4 concentration in the cytoplasm. Besides, at a certain concentration, zinc could inhibit glucose uptake in intestinal epithelial cells by binding to α-glucosidase [31]. Last but not least, zinc is a well-known antioxidant, decreasing oxidative stress, which is an established common pathway for the pathogenesis of many diseases including diabetes, metabolic syndrome, obesity, and hypertension [32].

Although the experimental studies support the idea that zinc enhances glycemic control in diabetic patients, our study indicated that low-dose zinc supplementation did not have a significant effect on the weight, blood pressure, and glycemic control of diabetic patients. First things first, the study population did not have zinc deficiency. So, they had enough amounts of zinc to maintain routine hormonal activities. Also, low-dose zinc could not increase the zinc level. Therefore, a higher dose of zinc supplementation could be effective, especially in those with zinc deficiency.

Our study had some limitations. One limitation was the small sample size, which decreased the generalizability. However, previous studies had approximately the same sample size [23]. Therefore, further research with larger sample sizes is required. Additionally, the limited sample size restricted our ability to conduct sub-analysis (e.g., for diabetes medications) in this study.

In conclusion, our study showed that consuming 220 mg zinc sulfate supplement twice a week did not improve the glycemic indices, weight control, and blood pressure significantly in patients with Type 2 diabetes. Further studies are needed to determine the effect of zinc supplementation and its optimal dosage for diabetic patients.

Author Contributions

Mehrab Sayadi: conceptualization, methodology, formal analysis. **Sara Javadpour Nowbandegani:** conceptualization, resources, data curation, investigation. **Fatemeh Balaghi Inalou:** data curation, resources, investigation. **Bahman Nazemzadegan:** data curation, resources, investigation. **Shirzad Javidi Alsaadi:** investigation. **Mohammadreza Eskandari:** methodology, validation. **Matin Sepehrinia:** writing–review and editing, writing–original draft.

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Ethics Statement

The study protocol received approval from the ethics committee at Shiraz University of Medical Sciences under reference number IR.SUMS.REC.1391.S6398.

Consent

An informed consent was provided for every participant to be aware of the purposes, risks, and benefits of this study. Also, the Helsinki statement was followed throughout the study.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Transparency Statement

The lead author Matin Sepehrinia affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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