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The effect of prebiotic supplementation on serum levels of tryptophan and kynurenine in obese women with major depressive disorder: a double-blinded placebo-controlled randomized clinical trial

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Abstract

Objective The objective of the present study was to examine the effect of calorie restricted diet (CRD) plus inulin supplementation on serum levels of tryptophan (Trp), kynurenine (Kyn) and Trp/Kyn ratio in obese women with major depressive disorder (MDD).

Results In this double-blind placebo-controlled randomized clinical trial, 51 obese women (BMI = 30–40 kg/m^2) with mild MDD were assessed for depression level using Hamilton depression rating scale (HDRS). The patients were randomly allocated into either "*Prebiotic group*" (received 10 g/day inulin) or "*Placebo group*" (received 10 g/day maltodextrin). All participants also received individualized CRD. Fasting serum levels of Trp, Kyn, and Trp/Kyn ratio were assessed at baseline and after 8 weeks. Results showed slightly greater increases in serum levels of Trp and Trp/Kyn ratio as well as reductions in serum level of Kyn and HDRS score in prebiotic group than placebo group. However, between group differences in these parameters as well as HDRS score were not statistically significant after adjusting for baseline variables at the end of the trial. Results indicates that CRD accompanied by inulin supplementation (10 g/day) did not influence serum levels of Trp, Kyn and Trp/Kyn ratio as well as HDRS score after 8 weeks.

Trial registration: The trial was registered in the Iranian registry of clinical trials at 2018-08-02 (https://www.irct.ir/; registration number: IRCT20100209003320N15).

Keywords Major depressive disorder (MDD), Obesity, Prebiotics, Tryptophan (Trp), Kynurenine (Kyn), Inulin

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Introduction

Major depressive disorder (MDD)—as a prevalent psychiatry disease- affects around 4.4% of adults worldwide [1]. It is characterized by depressed mood, diminished interests, impaired cognitive function and disturbed sleep or appetite [2]. MDD is more prevalent in women than men and is categorized as "mild", "moderate", or "severe" based on the severity of symptoms.

There is evidence indicating the association between depression and obesity, particularly in women [1, 3, 4].

Obese adults are more likely to be depressed compared to non-obese adults [5]. By increasing obesity, the global prevalence of depression has increased by 29% [6]. Non-genetic factors, medications, psychological inputs, and obesity-related metabolic conditions could contribute in depression-obesity relationship. Antidepressants, mood-stabilizing, or antipsychotic medications may contribute in weight gain through suppressing satiety, decreasing physical activity, or increasing consumption of calorie-rich foods. However, studies have shown that long-term weight loss diets could increase the risk of depression development. Indeed, impaired self-esteem, social isolation, and chronic unemployment could lead to depression in obese patients. Metabolic consequences of obesity e.g. insulin resistance usually results in impaired serotonin, a brain neurotransmitter which involves in mood and satiety control of both mood and satiety [7]. Apart from underlying mechanisms for both obesity and depression- i.e. Hypothalamic–Pituitary–Adrenal (HPA) axis dysregulation, activation of inflammatory processes, and intestinal microbiota dysbiosis, inflammation plays a pivotal role in depression by activating enzymes involving in tryptophan (Trp) metabolism. The enzymes degrade Trp into kynurenine (Kyn) metabolites, which act as N-methyl-D-aspartate (NMDA) receptor agonists and increase susceptibility to MDD [8, 9].

Although specific medications are considered as the first line treatment for depression, there are many side effects [10]. It seems strategies such as calorie-restricted diets (CRDs), adjuvant to the medications could help to combat both obesity and depression treatment because CRDs are non-invasive and could increase neuronal signaling as well as apply positive effects on molecular systems supporting neuronal function [11]. A number of clinical trials provide beneficial effects of CRDs in depression. For example, results of a recent clinical trial revealed that following CRDs (by decreasing 25% of energy requirement) for two years improved mood in both genders [12]. Furthermore, Fuller et al. [3] reported a significant decrease in Beck Depression Inventory-II (BDI-II) score after three months weight loss. Moreover, there is evidence that prebiotics- substrates selectively utilized by microorganisms with health benefits appear to affect Trp metabolism pathway and improve gut microbiota and consequently, obesity and depression [13, 14]. Studies have shown that prebiotics supplementation may save Trp for serotonin production rather than the unfavorable Kyn pathway [13]. Indeed, the administration of inulin-type fructans for 12 weeks in overweight and obese adults led to reductions in body fat, hunger, desire to eat and prospective food consumption [15]. Moreover, inulin supplementation (10 g/kg/day) for 10 weeks could accelerate body weight loss in obese mice by regulating gut microbiota and serum metabolites [16]. Furthermore, daily supplementation with 10 g resistant dextrin for 8 weeks in women with type 2 diabetes led to a significant decrease in serum levels of Kyn, Kyn/Trp ratio as well as interferon gamma (IFNγ), Interleukin (IL)-12, IFNγ/IL-10 ratio, and lipopolysaccharide (LPS) and a significant increase in serum levels of IL-10 and IL-4 [17]. Nevertheless, in patients with MDD, galacto-oligosaccharide supplementation for 8 weeks failed to reveal any significant effect on BDI score and Kyn/Trp ratio [18]. Therefore, the current clinical trial was aimed to examine the effect of CRD plus inulin supplementation on serum levels of Trp, Kyn and Trp/Kyn ratio in obese women with MDD.

Methods

Study participants

In this double-blind placebo-controlled randomized clinical trial, 51 obese premenopausal women aged 20–50 years (BMI: 30–40 kg/m^2) with MDD were studied. MDD was diagnosed according to the Diagnostic and Statistical manual of Mental disorders, 5th Edition (DSM-5) criteria, and those with mild depression (a score between 8 and 16 based on the 17-item Hamilton Depression Rating Scale (HDRS) were studied. Indeed, characteristic attitudes and symptoms of depression were assessed according to a self-reported BDI-II questionnaire. Both psychological questionnaires were completed for each patient before and after the trial.

The study protocol was approved by the ethic committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1398.813) and also registered in the Iranian registry of clinical trials at 2018-08-02 (https://www.irct.ir/; registration number: IRCT20100209003320N15). The reporting of this manuscript adheres to CONSORT guidelines. A written informed consent form before initiating the clinical trial was signed after offering a complete description of the research process to the patients.

Inclusion and exclusion criteria

Women aged 20–50 years with BMI ranged from 30 kg/m^{2}to 40 kg/m^2 suffered from MDD were included in the trial. Those who were pregnant, lactating, cigarette smoker, substance abuser or addicted to opiates, those with history of other psychiatric or neurological disorders as reported by the psychiatrist, thyroid dysfunction, following specific diet, taking chemical or herbal medications for weight loss (during the last year), anti-depressants (at least 6 months prior to the study), fiber supplements or consuming more than 25 gr/day of dietary fiber, consuming pre- or probiotic supplements/products or antibiotics (during two months prior to study) were excluded. Indeed, the patients who

underwent serious events affecting their mental health (e.g. loss of near relative, major accidents, major financial problems etc.), taking nutritional supplements and changed medication protocol during the trial were excluded during the study.

Sample size

The sample size was estimated based on the reported mean (SD) of Kyn reported by Abbasalizad-Farhangi, et al. [17] Given a = 0.05 and power = 80%, the number of samples for each group was determined to be 12. However, this number was increased to 17 for a possible dropout rate of 45%.

Intervention

An individualized CRD was prescribed for the patients by estimating total energy expenditure of each participant according to RMR, physical activity level, and thermic effect of food and assuming 25% weight loss over the trial. The proportion of carbohydrate, protein and fat from energy was considered 55%, 30%, and 15%, respectively to plan the CRD diet. Then, the participants were randomly assigned (1:1) into either "*Prebiotic group*" [received individualized CRD plus one sachet including 10 g/day inulin (Sensus Co., the Netherlands) dissolved in a glass of water and drunk after lunch] or "*Placebo group*" [received individualized CRD plus one sachet including 10 g/day maltodextrin (FIC Co., China) dissolved in a glass of water and drunk after lunch]. Randomization was performed using RAS software by a person who was not involved in the study after stratifying by depression severity and BMI (i.e. < 35 kg/m^2 and ≥ 35 kg/m^2). A 3-digit code was assigned to each of the treatments by the same person. The psychologist, assessors and participants were blinded to the allocation. Color, odor, weight and other aspects of the supplements and placebo sachets were completely similar. The patients were visited fortnightly for delivering supplement and consuming ≥ 80% of the supplements by counting unused sachets was determined as compliance.

Measurements

Demographic information and physical activity level were obtained using personal questionnaire and the international physical activity questionnaire-short form (IPAQ-SF) through face to face interview. Height and weight were measured with light cloths and without shoes using stadiometer (Seca, Germany) to the nearest 0.5 cm and 0.1 kg and then, BMI was calculated by dividing body weight (kg) by height square (m^2). Indirect calorimetry (Fitmate Pro, Rome, Italy) was used for RMR measurement by a trained nutritionist according to the device instructions in fasting state, without caffeine consumption and without moderate or vigorous physical activity during the past day [19]. Habitual dietary intake was assessed using a 3-day food record questionnaire (two week days and one weekend) for adherence to the dietary plans given to the patients before and after the trial. Nutritionist IV software (First Databank, San Bruno, CA, USA) modified for Iranian foods was used to assess dietary intake of energy, protein, fat and fiber.

Physical activity was assessed using the validated Persian version of IPAQ-SF for the last week and presented as Metabolic Equivalents per week (METs/week). Physical activity level was categorized as follow: "*High*" (MET-minutes/week of ≥ 3000),"*Moderate*" (MET-minutes/week of 600–3000), or"*Low*" (MET-minutes/week of < 600) physical activity [20].

To determine serum Trp and Kyn, 12-h fasting blood samples were taken, centrifuged at 3500 rpm for 10 min, serum was transferred into microtubes and stored at -80°C until analysis. The concentration of serum Trp and Kyn were measured by enzyme-linked immune-sorbent assay (ELISA) kits (Mybiosource Inc., USA). All measurements were done before and after 8-week intervention.

Statistical analysis

The Statistical Package for Social Science (SPSS) software version 17 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. The Kolmogorov–Smirnov test was used for assessing the normality of data distribution. Mean (standard deviation, SD) and median (interquartiles) were used for symmetric and asymmetric quantitative variables, respectively. Qualitative variables were presented as frequency (percentage). Independent sample t-test was applied to assess between-group differences, whereas within-group differences were done using paired t-test. To compare differences in nominal qualitative variables between the groups, Chi-square test was applied. At the end of the study, analysis of covariance (ANCOVA) was applied to analyze between-group differences by adjusting for baseline values. Mean percent of changes in depression scores was calculated as follows:

$$\begin{aligned}&\text{Mean percent of change}\\&= (\text{Mean score}_{\text{end}} - \text{Mean score}_{\text{baseline}})\\&\quad /\text{Mean score}_{\text{baseline}}) * 100\end{aligned}$$

P-values < 0.05 were set as statistically significant level.

Results

Of total 51 patients enrolled in the study, 34 patients (17 in each group) completed the trial. Seventeen subjects (8 in prebiotic group and 9 in placebo group) were lost to follow because of the following reasons: did not follow the study protocol (7 patients) and the CRD (9 patients)

and pregnancy (one patient). Hence, at the end of the trial, mean compliance rate in the prebiotic and placebo group was 92.25% and 91.17%, respectively. No adverse events were reported, apart from gastrointestinal discomfort (flatulence and soft stool in three participants in the prebiotic group) ameliorated after two weeks.

Mean age was 38.53 ± 5.91 years and 39.88 ± 6.99 years in prebiotic and placebo group, respectively (p = 0.542). The depression duration was 3.70 ± 1.68 years in prebiotic group and 4.94 ± 2.92 years in placebo group (p = 0.146). Table 1 shows baseline characteristics of the patients. There were not found any differences in baseline characteristic between the groups at the beginning of the trial.

Anthropometric measures and serum concentrations of Trp, Kyn and Trp/Kyn ratio in both groups before and after the intervention are presents in Table 2. There were not found any differences in weight and BMI at baseline, however, significant reductions in weight and BMI were observed in both groups (p < 0.001). Mean weight loss was 2.94 kg and 2.45 kg in prebiotic and placebo group, respectively and average weight reduction in all patients was 2.6 kg over 8 weeks which was found in 44.1% of women who complete the trial (i.e. 7 patients in the prebiotic group, and 8 patients in the placebo group). At the end of the intervention, no significant differences in anthropometric measures were observed after adjusting for baseline values while there was found a significant reduction in Kyn concentration in both groups (p < 0.05).

Table 1 Baseline characteristics of the patients

	Prebiotic (N = 17) N (%)	Placebo (N = 17) N (%)	P*
Marital status			
Married	16 (94.1)	17 (100)	1.000**
Divorced or widow	1 (5.9)	0 (0)	
Educational level			
Diploma and lower	13 (76.5)	12 (70.6)	0.705**
Bachelors and higher	4 (23.5)	5 (29.4)	
Occupation			
Housewife	14 (82.4)	16 (94.1)	0.603**
Employee	3 (17.7)	1 (5.9)	
Medication			
Sertraline	4 (23.5)	8 (48.1)	0.607**
Citalopram	2 (11.8)	1 (5.9)	
Fluoxetine	11 (64.7)	8 (47.1)	
Physical activity level			
Low	7 (41.2)	8 (47.1)	1.000**
Moderate	8 (47.1)	8 (47.1)	
High	2 (11.8)	1 (5.9)	

* P-value based on Chi-square test

However, at the end of the intervention, inter- group changes in the mentioned biochemical parameters were not statistically significant, after adjusting for baseline values.

Comparing changes in depression status in the patients at beginning and end of the trial reveal that only HDRS score decreased significantly in both groups compared to baseline, i.e. greater mean reduction in prebiotic group *vs* placebo group [MD (95% CI) − 3.00(− 4.40, − 1.60) compared with MD (95% CI) − 1.94(− 3.55, − 0.33), respectively]. However, no significant differences were found in HDRS changes between the group at the end of the intervention, after adjusting for baseline values (Table 2).

Figure 1 also demonstrates mean percent of change in the study outcomes in the two groups and indicates that there were greater changes in Trp/Kyn ratio and HDRS score (82.92% and − 24.39%, respectively) in the prebiotic group *vs* the placebo group (54.60% and − 14.82%, respectively). However, there were no statistically significant differences in mean percent of changes in the studied outcomes between the groups, after adjusting for the baseline values.

Discussion

The results of the present trial revealed that, supplementing obese depressed women with 10 g/day of inulin in combination with CRD had no significant effects on serum Trp, Kyn level, Trp/Kyn ratio and HDRS score. Although there is evidence that prebiotics may improve mental health via shifting Trp metabolism from Kyn production to serotonin synthesis [21], we previously reported that 25% CRD plus prebiotic supplementation (10 g/day Inulin) failed to change HDRS and BDI-II score after 8 weeks [22]. Possible factors which may explain the differences in the findings are study duration, prebiotic dose and depression severity.

The results of present study indicated that inulin supplementation associated with CRD did not make significant differences in serum Trp and Kyn level as well as their ratio, which was in agreement with those of previous studies. Earlier studies have often reported similar results and only few studies could show that prebiotics improved serum Trp and Kyn level. For example, Abbasalizad-Farhangi et al. [17] showed that supplementation with 10 g/day resistant dextrin in patients with type 2 diabetes mellitus could not change Trp and Kyn level, while Kyn/Trp ratio decreased significantly in the intervention group. Moreover, Kazemi et al. [18] reported that Trp/Kyn ratio did not change significantly after 6 weeks of prebiotic supplementation in patients with MDD.

A recent systematic review concluded that inulin ingestion has potential impact on human gut microbiota composition and increasing *Bifidobacterium*

Table 2 Changes in BMI, biochemical parameters and depression scores over the trial

	Prebiotic (N = 17)	Placebo (N = 17)	P
BMI (kg/m^2)			
Baseline	34.84 (99.3)	32.31 (3.23)	0.051**
End	33.64 (3.69)	31.36 (3.16)	0.909***
MD (95% CI), P*	− 1.2 (− 1.73, − 0.67), < **0.001**	− 0.95 (− 1.38, − 0.51), < **0.001**	
Tryptophan (µmol/L)			
Baseline	65.89 (9.74)	63.46 (11.05)	0.503**
End	69.31 (7.95)	66.61 (10.12)	0.500***
MD (95% CI), P*	3.42 (1.65, 5.19), **0.001**	3.15 (1.36, 4.92), **0.002**	
Kynurenine (µmol/L)			
Baseline	2.09 (0.55)	1.86 (0.62)	0.275**
End	1.62 (0.84)	1.35 (0.42)	0.472***
MD (95% CI), P*	− 0.47 (− 0.84, − 0.09), **0.018**	− 0.51 (− 0.81, − 0.21), **0.002**	
TRP/KYN ratio			
Baseline	32.76 (6.04)	36.65 (9.66)	0.170**
End	57.57 (36.67)	53.39 (15.67)	0.689***
MD (95% CI), P*	24.81(5.40, 44.20), **0.015**	16.74 (7.78, 25.69), **0.001**	
HDRS			
Baseline	11.41 (3.80)	11.65 (3.46)	0.836
End	8.41 (2.78)	9.70 (3.58)	0.248
MD (95% CI), P*	− 3.0 (− 4.40, − 1.60); < **0.001**	− 1.94 (− 3.55, − 0.33); **0.021**	
BDI-II			
Baseline	16.06 (8.26)	19.18 (7.82)	0.267
End	14.0 (7.73)	16.06 (7.23)	0.429
MD (95% CI), P*	− 2.06 (− 5.67, 1.55); 0.245	− 3.12 (− 7.66, 1.43); 0.165	

Bold indicates $p < 0.05$ is statically significant

MD: Mean difference; CI: Confidence interval; BMI: Body Mass Index; TRP/KYN, Tryptophan to Kynurenine; HDRS, Hamilton Depression Rating Scale; BDI-II, Beck Depression Inventory

* P based on Paired sample t-test

** P based on Independent sample t-test

*** P based on ANCOVA adjusted for baseline values

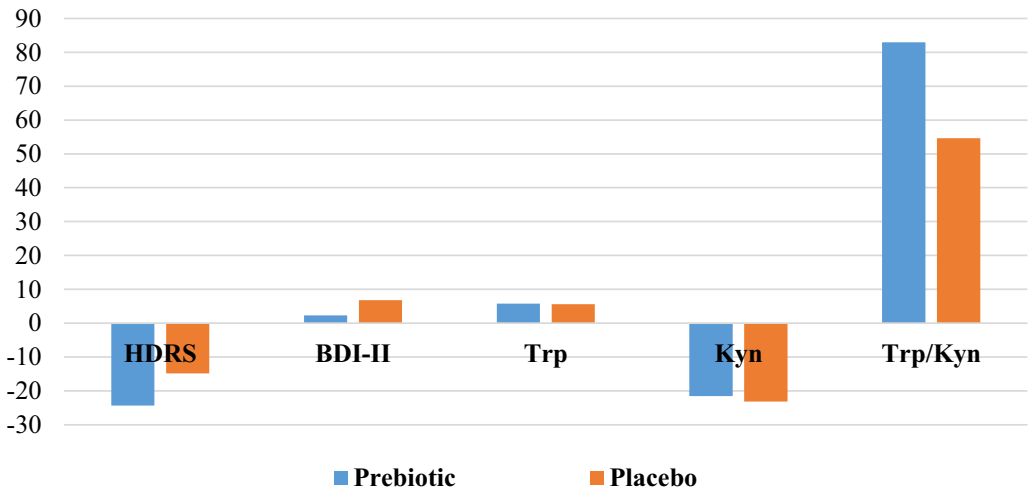

Fig. 1 Mean percent of changes of depression scores, serum levels of Trp and Kyn, and Trp/Kyn ratio. HDRS: Hamilton Depression Rating Scale; BDI-II: Beck Depression Inventory-II; Trp: tryptophan; Kyn: kynurenine; Trp/Kyn: Tryptophan/Kynurenine ratio

resulting in alleviating depressive behaviors via increasing in 5- hydroxytryptophan secretion [23, 24]. Nevertheless, some studies reported that achieving gut microbiota modification using such dietary supplements need enough time (>8 weeks), particularly when KYN metabolite are assessed [13]. Although previous studies have shown that prebiotics may alleviate depression only through decreasing gut permeability and inflammation, our previous results showed that no significant positive effects on inflammation and intestinal permeability were observed [22, 25].

It appears that higher dosage or higher duration of prebiotics supplementation is needed to modify the assumed gut microbiota dysbiosis in MDD. In addition, factors such as prebiotic type, characteristics of study population and prescribing CRD associated with inulin supplementation could be attributed in different results [26].

In the present study, when the data were reanalyzed based on stratifying by minimum weight loss of 2.6 kg, again no changes were found in serum Trp, Kyn, Trp/Kyn ratio as well as HDRS score, i. e. woman who lost more than 2.6 kg weight had insignificantly greater reduction in HDRS score and increase in Trp level at the end of the study. Strasser et al. [27] showed that CRD (1200 kcal/day) reduced significantly plasma Trp and Kyn levels after 2 weeks but did not affect Trp/Kyn ratio. Stefańska et al. [28] also demonstrated that a six-month weight loss diet (daily calorie intake between 1200 and 1500 kcal) among women with major depression, did not alter HDRS score significantly. Few studies have also reported that caloric restriction may induce antidepressant-like effects, which was in contrast with the results of the present study [11, 29].

Conclusion

Inulin supplementation (10 g/day) among obese women with depression for 8 weeks resulted in no significant changes in serum Trp, Kyn, Trp/Kyn ratio and HDRS score. Long-term well-designed clinical trials are required to assess the effect of using various types and dosage of prebiotics on patients with depression.

Limitations

Our trial has the following limitations. Other important biomarkers in MDD such as serotonin, gut and fecal microbial composition were not assessed in the present study, due to financial limitations. Indeed, the study duration was relatively short to find possibly significant changes in the outcomes. Moreover, we could not distinguish if the observed effects were related to prebiotic supplementation or CRDs. However, it seems this study is the first clinical trial to investigate the effects of prebiotics accompanied by CRD on Trp, Kyn, Trp/Kyn ratio as important biomarkers of MDD and HDRS score. Furthermore, dietary plans were individually administered according to each patient's measured RMR and dietary preferences.

Abbreviations

ANCOVA	Analysis of covariance
BDI-II	Beck Depression Inventory-II
BMI	Body mass index
CRDs	Calorie-restricted diets
CI	Confidence interval
DSM-5	Diagnostic and Statistical manual of Mental disorders, 5th Edition
ELISA	Enzyme-linked immune-sorbent assay
$GABA_B$	Gamma-Amino Butyric Acid class B
HDRS	Hamilton depression rating scale
HPA	Hypothalamic–Pituitary–Adrenal
IDO	Indoleamine 2 and 3 dioxygenase
IL-12	Interleukin-12
IPAQ-SF	International physical activity questionnaire-short form
ISAP	International Scientific association for probiotics and prebiotics
Kyn	Kynurenine
LPS	Lipopolysaccharide
MDD	Major depressive disorder
METs/week	Metabolic Equivalents per week
MUFAs	Monounsaturated fatty acids
NMDA	N-methyl-D-aspartate
PA	Physical activity
PUFAs	Polyunsaturated fatty acids
RAS	Random allocation software
RMR	Resting metabolic rate
SD	Standard deviation
SFAs	Saturated fatty acids
SNRIs	Serotonin-norepinephrine reuptake inhibitor
SPSS	Statistical package for social science
SSRIs	Selective serotonin reuptake inhibitors
TEE	Total energy expenditure
TEF	Thermal effect of food
Trp	Tryptophan
Trp/Kyn	Tryptophan to kynorenine ratio

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Author contributions

The authors' responsibilities were as follows: F.K. wrote the paper draft; E.V.M. and M.E.M. contributed to the conception of the article; H.T. and M.E.M. contributed to the statistical analysis as well as the final revision of the manuscript. All authors read and approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

All procedures performed in this study were in accordance with the ethical standards of the Ethics Committee of Tabriz University of Medical Science. The study protocol obtained approval from the Ethics Committee of Tabriz

University of Medical Science (IR.TBZMED.REC.1398.813). Informed written consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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