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Randomized Control Trials

Clinical and metabolic response to probiotic administration in people with Parkinson's disease: A randomized, double-blind, placebo-controlled trial

Omid Reza Tamtaji [a], Mohsen Taghizadeh [b], Reza Daneshvar Kakhaki [c], Ebrahim Kouchaki [a, c], Fereshteh Bahmani [b], Shokoofeh Borzabadi [d], Shahrbanoo Oryan [d], Alireza Mafi [b], Zatollah Asemi [b, *]

[a] Physiology Research Center, Kashan University of Medical Sciences, Kashan, Iran
[b] Research Center for Biochemistry and Nutrition in Metabolic Diseases, Kashan University of Medical Sciences, Kashan, Iran
[c] Department of Neurology, School of Medicine, Kashan University of Medical Sciences, Kashan, Iran
[d] Department of Biology, Science and Research Branch, Islamic Azad University, Tehran, Iran

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SUMMARY

Background & aims: The investigation was done to assess the impacts of probiotic supplementation on movement and metabolic parameters in individuals with Parkinson's disease (PD).

Methods: The study is randomized, double-blind, placebo-controlled clinical trial, which was done in sixty people with PD. Individuals were randomly divided into two groups in order to take either 8×10^9 CFU/day probiotic or placebo (n = 30 each group) that lasted 12 weeks. The Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) was recorded at pre- and post-intervention.

Results: Compared with the placebo, consuming probiotic decreased MDS-UPDRS (−4.8 ± 12.5 vs. +3.8 ± 13.0, P = 0.01). Probiotic supplementation also reduced high-sensitivity C-reactive protein (−1.6 ± 2.5 vs. +0.1 ± 0.3 mg/L, P < 0.001) and malondialdehyde (−0.2 ± 0.3 vs. +0.1 ± 0.3 μmol/L, P = 0.006), and enhanced glutathione levels (+40.1 ± 81.5 vs. −12.1 ± 41.7 μmol/L, P = 0.03) in comparison with the placebo. Additionally, probiotic consumption resulted in a statistically significant reduction in insulin levels (−2.1 ± 3.4 vs. +1.5 ± 5.1 μIU/mL, P = 0.002) and insulin resistance (−0.5 ± 0.9 vs. +0.4 ± 1.2, P = 0.002), and a statistically significant rise in insulin sensitivity (+0.01 ± 0.02 vs. −0.006 ± 0.02, P = 0.01) in comparison with the placebo. Probiotic intake had no any significant impact on other metabolic profiles.

Conclusions: Our study evidenced that 12 weeks of probiotic consumption by individuals with PD had useful impacts on MDS-UPDRS and few metabolic profiles. Registered under ClinicalTrials.gov Identifier no. http://www.irct.ir: IRCT2017082434497N4.

1. Introduction

Parkinson's disease (PD) is a neuropsychiatric disturbance that influences up to two percent of people older [1] and reported a prevalence of 14 per 100,000 subjects [2]. Approximately, 40% of PD people present cognitive disorders [3]. Various factors such as increased production of free radicals and oxidative damage, mitochondrial dysfunction, excitotoxicity, increased inflammatory cytokines, genetic factors, environmental factors, and apoptosis in neuronal degeneration of PD have been proposed [4]. In addition, data from epidemiological studies reported that more than 50% of people with PD have impaired carbohydrate metabolism [5], however data from prospective studies suggest the association is more modest with type 2 diabetes mellitus subjects having approximately a 40% elevated risk of developing PD [6].

Animal studies have reported a disturbed gut microbiota (GM) in a number of central nervous system disturbances, such as PD and multiple sclerosis (MS); data from human studies is little and

* Corresponding author.
E-mail address: asemi_r@yahoo.com (Z. Asemi).

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controversial [7]. Multiple factors including aging, gut barrier, and functions related to blood–brain barrier may be associated with neurodegenerative disorders [8]. GM can affect various neurological outcomes, such as cognition, learning, and memory [9]. Earlier, some researchers have exhibited that probiotics are benefit on clinical and metabolic parameters in neurodegenerative disorders. The authors have previously demonstrated that 12 weeks of probiotic consumption by individuals with MS had beneficial impacts on clinical signs, mental health, insulin resistance and markers of cardio-metabolic risk [10]. The intake of synbiotic milk was benefit in improving constipation in people with PD [11]. Moreover, a meta-analysis study supported probiotic intake is effective in reducing lipid values and factors related to cardiovascular disease [12].

Considering the antioxidant and anti-inflammatory effects of probiotic, we assumed that probiotic might be useful in patients with PD. Therefore, this investigation was done to define the impacts of probiotic supplementation on clinical and biochemical profiles in people with PD.

2. Subjects and methods

2.1. Trial design and participants

This study was a 12-week randomized, double-blinded, placebo-controlled clinical trial, which was registered with the website for registration of clinical trials in Iran (http://www.irct.ir: IRCT2017082434497N4). Sixty individuals with PD, aged 50–90 years, which were diagnosed in accordance with the UK PD Society Brain Bank clinical diagnostic criteria [13] were included in this trial. The study was carried out from August to December 2017 and study protocol was confirmed by the Kashan University of Medical Sciences (KAUMS) Research Ethics Committee. Signed informed consent was taken from all patients. The exclusion criteria were as follows: taking antioxidants supplements and anti-inflammatory medications, depression and severe psychosis, hypo- and hyperthyroidism, and smoking.

2.2. Study design

First, all patients were randomized into two treatment groups to intake probiotic containing *Lactobacillus acidophilus, Bifidobacterium bifidum, Lactobacillus reuteri,* and *Lactobacillus fermentum* (each 2×10^9 CFU/g) (n = 30) or placebo (n = 30) for 12 weeks. Probiotics and its placebos were produced by Lactocare Zisttakhmir Company (Tehran, Iran) and Barij Essence Pharmaceutical Company (Kashan, Iran), respectively. Capsules had similar packaging. Randomization assignment was done using computer-generated random numbers as blindness by a trained staff at the neurology clinic. Patients, investigators, clinical site staff and laboratory staff were all masked to treatment assignment throughout the study. Compliance rate was assessed counting the remaining supplements.

2.3. Assessment of outcomes

In this study, Movement Disorders Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) and high-sensitivity C-reactive protein (hs-CRP) were considered as the primary measurement and other metabolic profiles were considered as the secondary measurements.

2.4. Clinical evaluation

To evaluate clinical signs, UPDRS total score as well as 4 subscores were used [14].

2.5. Laboratory procedures

Fasting blood samples (10 mL) were collected at weeks 0 and 12 at Kashan Reference Laboratory, Kashan, Iran. Hs-CRP (LDN, Nordhorn, Germany) and insulin (Monobind, California, USA) levels were measured using an ELISA kit. Plasma total antioxidant capacity (TAC) using the method of Benzie and Strain [15], GSH by the method of Beutler et al. [16] and malondialdehyde (MDA) levels using the spectrophotometric method were evaluated. In order to determine fasting plasma glucose (FPG) and lipid profiles, we used available kits (Pars Azmun, Tehran, Iran) Homeostasis model of assessment-estimated insulin resistance (HOMA-IR) and the quantitative insulin sensitivity check index (QUICKI) were calculated according to suggested formulas. Inter- and intra-assay coefficient variances (CVs) for metabolic profiles were lower than 5%.

2.6. Sample size

In order to have the power of study at 80%, type one (α) and type two errors (β) were considered to be 0.05, and 0.20. We used 2.8 mg/L as mean difference (d) for hs-CRP and 3.5 mg/L as the SD, using a similar study published by Kouchaki et al. [10]. Thereupon, 25 subjects should be recruited in each treatment group. Considering 20% dropouts in each group; the final sample size was calculated to be 30 participants in each group.

2.7. Statistical methods

The normality tests were conducted using Kolmogorov–Smirnov test. Anthropometric indices and dietary intakes (macro- and micronutrients) were compared between intervention groups, using independent samples *t*-test. One-way repeated measures analysis of variance was applied to determine the effects of probiotic supplementation on clinical signs of the disease and patients' metabolic profiles. Differences in baseline values, including age and BMI, were adjusted using analysis of covariance (ANCOVA). Significant levels were defined as P-values <0.05.

3. Results

Six participants dropped during follow-up, due to personal reasons, four in the supplemented and 2 in the placebo groups (Fig. 1). However, using ITT analyses, all sixty individuals were included in the final analysis. Above 90% of capsules were used during intervention in case and control groups leading to high compliance rate in this study. Probiotic supplementation in PD patients did not result in any reported side effects.

Mean age and anthropometric indices at baseline and end of trial were not statistically different between the case and control groups (Table 1).

We didn't find significant change in mean dietary intakes between the case and control groups throughout the trial (Data not shown).

Consuming probiotic decreased MDS-UPDRS (-4.8 ± 12.5 vs. $+3.8 \pm 13.0$, P = 0.01) (Table 2). Probiotic consumption also reduced hs-CRP (-1.6 ± 2.5 vs. $+0.1 \pm 0.3$ mg/L, P < 0.001) and MDA (-0.2 ± 0.3 vs. $+0.1 \pm 0.3$ μmol/L, P = 0.006), and increased GSH levels ($+40.1 \pm 81.5$ vs. -12.1 ± 41.7 μmol/L, P = 0.03) in comparison with the placebo. Additionally, probiotic intake decreased insulin levels (-2.1 ± 3.4 vs. $+1.5 \pm 5.1$ μIU/mL, P = 0.002) and HOMA-IR (-0.5 ± 0.9 vs. $+0.4 \pm 1.2$, P = 0.002), and elevated QUICKI ($+0.01 \pm 0.02$ vs. -0.006 ± 0.02, P = 0.01). In addition, a trend toward a greater decrease in triglycerides (-19.7 ± 53.5 vs. $+0.4 \pm 21.5$, P = 0.06) and VLDL-cholesterol levels (-3.9 ± 10.7 vs. $+0.1 \pm 4.3$, P = 0.06) was observed after probiotic intake.

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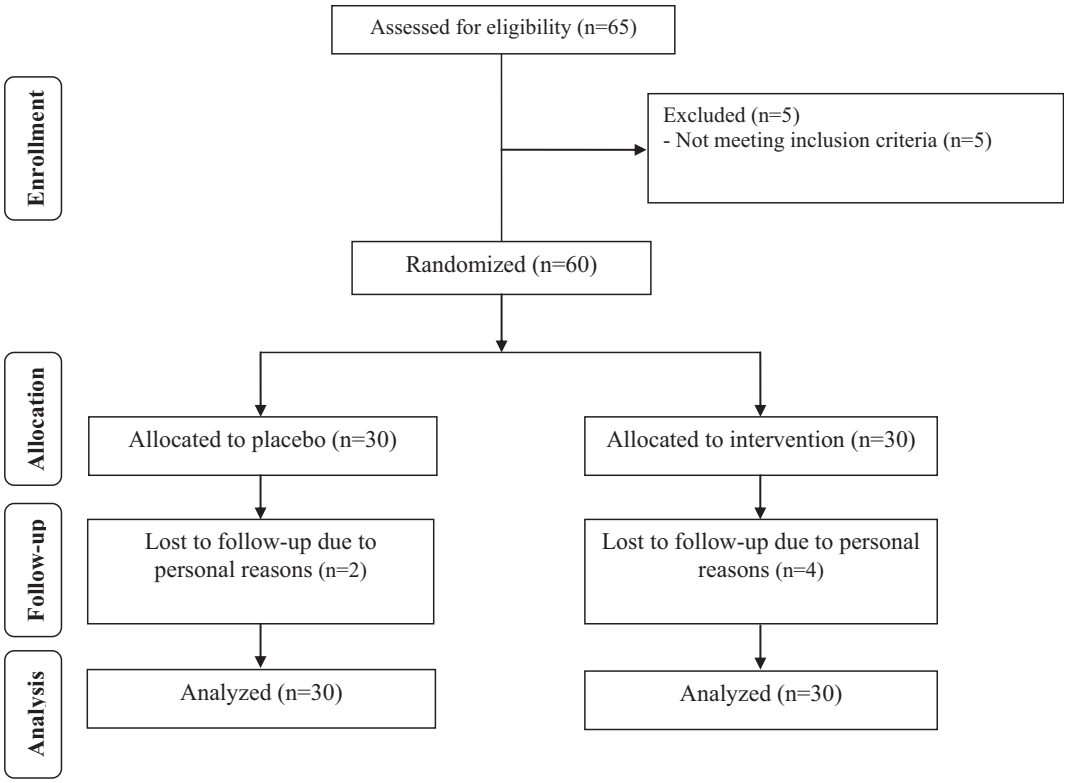

Fig. 1. Summary of patient flow.

Probiotic consumption did not have any significant impact on other metabolic profiles.

After controlling for potential confounders, the difference in changes in MDA ($P = 0.12$) between the two groups became non-significant, while difference in changes in triglycerides ($P = 0.04$) and VLDL-cholesterol ($P = 0.04$) (Table 3).

4. Discussion

In this investigation, we determined the effect of consuming probiotic on movement and metabolic parameters in people with PD. We realized that taking probiotic for 12 weeks by people with PD had favorable impacts on MDS-UPDRS, hs-CRP, GSH, MDA and insulin metabolism, but did not affect other metabolic parameters. This investigation is the first report of the impacts of probiotic consumption on movement and metabolic parameters in people with PD.

4.1. Effects on clinical signs and inflammation and oxidative stress

We demonstrated that taking probiotic reduced MDS-UPDRS, hs-CRP and MDA, and elevated GSH levels, although unchanged TAC. There is growing evidence that probiotic supplementation can considerably modulate gut microbiota, therefore representing important assets in the management of oxidative damage. Earlier, we have demonstrated that probiotic consumption for 12 weeks to Alzheimer's disease subjects was benefit in improving cognitive function, hs-CRP, MDA, but unaltered TAC and GSH [17]. In addition, supplementation with probiotic for 48 weeks to human immunodeficiency virus-infected people significantly decreased CRP levels [18]. In another study, synbiotic administration to obese children for 4 weeks improved cardio-metabolic risk [19]. It has confirmed that increased oxidative damage and the inflammatory response occur in the severity of PD and these factors contribute to and/or intensify the nigro-striatal degeneration [4]. Probiotics are highly capable of producing potential antioxidants and bioactive molecules, thus are capable to decrease free radicals and oxidative stress [9]. In addition, probiotics can produce gamma-aminobutyric acid, noradrenaline, serotonin and acetylcholine, which in turn affect central neurochemistry and behavior [20]. Probiotics intake may improve clinical signs via the inhibiting indoleamine 2,3-dioxygenase and inflammatory factors such as interferon gamma and interleukin-6 (IL-6) [21]. Also, probiotics might improve hs-CRP and oxidative stress through the increased production of short chain fatty acids (SCFA) in the gut [22]. SCFA may decrease hs-CRP values through suppressing the enzymatic synthesis of hepatic CRP [23]. Hegazy et al. [24] demonstrated that taking probiotic by people with ulcerative colitis for 8 weeks decreased inflammation by reducing levels of IL-6, and gene expression of tumor necrosis factor-alpha and nuclear factor kappa B.

4.2. Effects on insulin metabolism and lipid profiles

This study confirmed that probiotic supplementation reduced insulin concentrations, HOMA-IR and QUICKI, however, unchanged

Table 1
General characteristics of study participants.

	Placebo group (n = 30)	Probiotic group (n = 30)	P[a]
Age (y)	67.7 ± 10.2	68.2 ± 7.8	0.83
Height (cm)	164.8 ± 6.0	164.2 ± 5.3	0.69
Weight at study baseline (kg)	70.0 ± 10.0	71.6 ± 8.6	0.49
Weight at end-of-trial (kg)	69.9 ± 9.0	72.0 ± 8.5	0.37
Weight change (kg)	−0.1 ± 0.8	0.4 ± 1.1	0.07
BMI at study baseline (kg/m^2)	25.8 ± 3.5	26.6 ± 3.2	0.36
BMI at end-of-trial (kg/m^2)	25.7 ± 3.5	26.7 ± 3.1	0.26
BMI change (kg/m^2)	−0.1 ± 0.3	0.1 ± 0.4	0.07

Data are means ± SDs.
[a] Obtained from independent *t*-test.

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Table 2
Unified Parkinson's disease rating stage, biomarkers of inflammation and oxidative stress, and metabolic profiles at baseline and after the 12-week intervention in people with Parkinson's disease that received either probiotic or placebo.

	Placebo group (n = 30)			Probiotic group (n = 30)			P[1]
	Baseline	End-of-trial	Change	Baseline	End-of-trial	Change	
MDS-UPDRS total (0–195)	60.0 ± 37.5	63.8 ± 35.4	3.8 ± 13.0	76.2 ± 37.2	71.5 ± 35.3	−4.8 ± 12.5	0.01
hs-CRP (mg/L)	4.4 ± 2.5	4.5 ± 2.4	0.1 ± 0.3	5.3 ± 3.0	3.7 ± 1.4	−1.6 ± 2.5	<0.001
TAC (mmol/L)	818.8 ± 216.5	823.4 ± 213.5	4.5 ± 26.7	826.3 ± 88.7	842.6 ± 79.1	16.3 ± 49.6	0.25
GSH (μmol/L)	566.6 ± 120.9	554.5 ± 107.1	−12.1 ± 41.7	493.6 ± 85.4	533.7 ± 89.9	40.1 ± 81.5	0.03
MDA (μmol/L)	2.4 ± 0.4	2.5 ± 0.4	0.1 ± 0.3	2.7 ± 0.3	2.5 ± 0.2	−0.2 ± 0.3	0.006
FPG (mg/dL)	98.5 ± 19.2	96.4 ± 23.9	−2.0 ± 12.7	105.3 ± 16.4	98.5 ± 16.9	−6.8 ± 12.1	0.14
Insulin (μIU/mL)	11.0 ± 4.8	12.6 ± 4.5	1.5 ± 5.1	12.3 ± 5.9	10.2 ± 5.1	−2.1 ± 3.4	0.002
HOMA-IR	2.7 ± 1.4	3.1 ± 1.3	0.4 ± 1.2	3.2 ± 1.7	2.7 ± 1.4	−0.5 ± 0.9	0.002
QUICKI	0.33 ± 0.02	0.33 ± 0.03	−0.006 ± 0.02	0.33 ± 0.03	0.34 ± 0.04	0.01 ± 0.02	0.01
Triglycerides (mg/dL)	138.1 ± 52.9	138.5 ± 58.1	0.4 ± 21.5	140.5 ± 50.0	120.8 ± 41.2	−19.7 ± 53.5	0.06
VLDL-cholesterol (mg/dL)	27.6 ± 10.6	27.7 ± 11.6	0.1 ± 4.3	28.1 ± 10.0	24.1 ± 8.2	−3.9 ± 10.7	0.06
Total cholesterol (mg/dL)	180.9 ± 39.3	178.8 ± 41.3	−2.1 ± 26.0	183.3 ± 39.1	182.2 ± 45.1	−1.1 ± 43.5	0.90
LDL-cholesterol (mg/dL)	109.5 ± 30.3	106.7 ± 32.6	−2.8 ± 23.9	106.9 ± 34.2	109.2 ± 38.1	2.3 ± 40.4	0.55
HDL-cholesterol (mg/dL)	43.8 ± 11.5	44.4 ± 11.6	0.6 ± 4.6	48.2 ± 10.1	48.7 ± 9.5	0.5 ± 7.9	0.98

Data are means ± SDs.
[1]P values represent the time × group interaction (computed by analysis of the one-way repeated measures ANOVA).
FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MDS-UPDRS, Movement Disorders Society-Unified Parkinson's Disease Rating Scale; MDA, malondialdehyde; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity; UPDRS, unified Parkinson's disease rating stage.

FPG and lipid profiles. Multiple researches have previously investigated the impacts of the supplementation of probiotic on glycemic status and lipid fractions in people with metabolic diseases. Earlier, we showed that probiotic supplementation for 12 weeks to people with diabetic foot ulcer was benefit on glycemic status and total cholesterol levels, but unaltered lipid profiles [25]. Also, 12 weeks of probiotic administration by people with non-alcoholic fatty liver disease showed a beneficial impact on insulin metabolism, but did not influence fasting glucose [26]. In a meta-analysis investigation, receiving probiotic by women with gestational diabetes significantly reduced HOMA-IR, although unchanged fasting glucose and LDL-cholesterol levels [27]. Changes in glucose homeostasis parameters correlated with loss of dopaminergic function might happen in people with PD, which may result in increased comorbidity and mortality [6]. Therefore, PD treatment by probiotic might modulate diabetes risk and decrease complications related to PD. This difference in the results of various studies could be correlated with the differences in the kind of studied diseases, composition of the basal microbiota population, type of probiotic supplements and dosage of probiotic used, basic concentrations of glycemic and lipid parameters and duration of the intervention. Probiotic may benefit in improving the insulin resistance through reducing the concentration of endotoxin, increasing fecal PH and increasing production of SCFA in the gut, and decreasing the production and absorption of intestinal toxins [28]. In addition, probiotics may increase glucagon-like peptide 1 production from enteroendocrine L-cells to ameliorate carbohydrate metabolism, reduce glucotoxicity, and decrease insulin resistance in target cells [29]. Probiotic intake also influences the structure of the gut flora, which might reclaim the integrity of the intestinal epithelium, weaken the immune responses, and decrease the Toll-like receptor 4 pathways [30], which in turn reduces pro-inflammatory signaling and increases insulin sensitivity.

Table 3
Adjusted changes in unified Parkinson's disease rating stage, biomarkers of inflammation and oxidative stress, and metabolic profiles in patients with Parkinson's disease that received either probiotic or placebo[a].

	Placebo group (n = 30)	Probiotic group (n = 30)	P[b]
MDS-UPDRS total (0–195)	3.1 ± 2.2	−4.1 ± 2.2	0.03
hs-CRP (mg/L)	−0.03 ± 0.2	−1.4 ± 0.2	<0.001
TAC (mmol/L)	4.4 ± 7.3	16.5 ± 7.3	0.24
GSH (μmol/L)	−3.5 ± 10.8	31.5 ± 10.8	0.03
MDA (μmol/L)	−0.02 ± 0.04	−0.1 ± 0.04	0.12
FPG (mg/dL)	−2.2 ± 2.3	−6.6 ± 2.3	0.19
Insulin (μIU/mL)	1.3 ± 0.7	−1.8 ± 0.7	0.003
HOMA-IR	1.3 ± 0.7	−1.8 ± 0.7	0.003
QUICKI	−0.006 ± 0.005	0.01 ± 0.005	0.01
Triglycerides (mg/dL)	0.3 ± 6.8	−19.6 ± 6.8	0.04
VLDL-cholesterol (mg/dL)	0.1 ± 1.4	−3.9 ± 1.4	0.04
Total cholesterol (mg/dL)	−2.0 ± 6.3	−1.3 ± 6.3	0.93
LDL-cholesterol (mg/dL)	−1.6 ± 5.6	1.1 ± 5.6	0.73
HDL-cholesterol (mg/dL)	0.1 ± 1.1	1.0 ± 1.1	0.58

[a] All values are means ± SEs.
[b] Obtained from analysis of ANCOVA adjusted for baseline values + age and baseline BMI. FPG, fasting plasma glucose; GSH, total glutathione; HOMA-IR, homeostasis model of assessment-estimated insulin resistance; hs-CRP, high-sensitivity C-reactive protein; MDA, malondialdehyde; QUICKI, quantitative insulin sensitivity check index; TAC, total antioxidant capacity; UPDRS, unified Parkinson's disease rating stage.

This investigation had a few limitations. In this study, fecal bacteria loads were not determined after taking probiotic. Also, the determination of gene expression related to biochemical profiles to find possible mechanisms is interesting.

Overall, our study proved that probiotic supplementation for 12 weeks by people with PD had useful impact on MDS-UPDRS, hs-CRP, GSH, MDA, insulin metabolism, but unchanged other metabolic profiles.

Conflicts of interest

None.

Author contributions

ZA and MT contributed in conception, design, statistical analysis and drafting of the manuscript. O-RT, RD-K, EK, FB, SB, SO and AM contributed in conception, data collection and manuscript drafting.

Clinical registration

http://www.irct.ir: IRCT2017082434497N4.

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Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.clnu.2018.05.018.

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