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The Effects of Probiotic Honey Consumption on Metabolic Status in Patients with Diabetic Nephropathy: a Randomized, Double-Blind, Controlled Trial

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Abstract

To the best of our knowledge, this study is the first evaluating the effects of probiotic honey intake on glycemic control, lipid profiles, biomarkers of inflammation, and oxidative stress in patients with diabetic nephropathy (DN). This investigation was conducted to evaluate the effects of probiotic honey intake on metabolic status in patients with DN. This randomized, double-blind, controlled clinical trial was performed among 60 patients with DN. Patients were randomly allocated into two groups to receive either 25 g/day probiotic honey containing a viable and heat-resistant probiotic *Bacillus coagulans* T11 (IBRC-M10791) (10^8 CFU/g) or 25 g/day control honey ($n = 30$ each group) for 12 weeks. Fasting blood samples were taken at baseline and 12 weeks after supplementation to quantify glycemic status, lipid concentrations, biomarkers of inflammation, and oxidative stress. After 12 weeks of intervention, patients who received probiotic honey compared with the control honey had significantly decreased serum insulin levels (-1.2 ± 1.8 vs. -0.1 ± 1.3 μIU/mL, $P = 0.004$) and homeostasis model of assessment-estimated insulin resistance (-0.5 ± 0.6 vs. 0.003 ± 0.4, $P = 0.002$) and significantly improved quantitative insulin sensitivity check index ($+0.005 \pm 0.009$ vs. -0.0007 ± 0.005, $P = 0.004$). Additionally, compared with the control honey, probiotic honey intake has resulted in a significant reduction in total-/HDL-cholesterol (-0.2 ± 0.5 vs. $+0.1 \pm 0.1$, $P = 0.04$). Probiotic honey intake significantly reduced serum high-sensitivity C-reactive protein (hs-CRP) (-1.9 ± 2.4 vs. -0.2 ± 2.7 mg/L, $P = 0.01$) and plasma malondialdehyde (MDA) levels (-0.1 ± 0.6 vs. $+0.6 \pm 1.0$ μmol/L, $P = 0.002$) compared with the control honey. Probiotic honey intake had no significant effects on other metabolic profiles compared with the control honey. Overall, findings from the current study demonstrated that probiotic honey consumption for 12 weeks among DN patients had beneficial effects on insulin metabolism, total-/HDL-cholesterol, serum hs-CRP, and plasma MDA levels, but did not affect other metabolic profiles. http://www.irct.ir: IRCT201705035623N115.

Keywords Probiotic · Honey · Supplementation · Diabetic nephropathy · Metabolic status

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Introduction

Diabetic kidney disease (DKD) is one of the most complications of diabetes mellitus and is the main cause of end-stage kidney disease in the worldwide [1]. Diabetic patients suffered from classical diabetic nephropathy (DN), which starts with glomerular hyperfiltration, followed by multiple complications such as microalbuminuria, macroalbuminuria, and nephrotic-range proteinuria [2]. DKD is a serious complication that influences 20% to 40% of all diabetics [3]. Hyperglycemia and insulin resistance are well-known risk factors for DKD and it recognized that intensive glycemic control decreases the risk of DKD [4]. In addition, several studies have reported relations between systemic markers of inflammation and oxidative stress and the progress of DN [5, 6].

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It has been documented that the progressive loss of kidney function significantly contributes to worsen the intestinal dysbiosis found in patients with DN [7]. Different mechanisms including hypervolemia and intestinal ischemia caused by aggressive ultrafiltration volumes or intradialytic hypotension are involved due to derangement of the intestinal barrier and modifications of microbiota composition [8]. Few studies have reported the beneficial effects of probiotics on kidney function and metabolic status in patients with DKD. *Bacillus coagulans* is a lactic acid producing bacterial species, which is catalase positive, spore forming, motile, and a facultative anaerobe [9]. Spores of *Bacillus coagulans* have strong resistance, resurrection, and stability, can be activated in the acidic environment of the stomach, and begin germinating and proliferating in the gut [10, 11]. Few studies have reported the beneficial effects of *Bacillus coagulans* intake on metabolic profiles and biomarkers of inflammation and oxidative stress in patients without DN [12, 13]. In addition, in a study by Abbasi et al. [14], consuming probiotic soy milk for 8 weeks by patients with DN significantly improved indexes of kidney function. In addition, we have previously demonstrated that probiotic supplementation for 12 weeks to diabetic hemodialysis people had beneficial effects on glycemic control, and some biomarkers of inflammation and oxidative stress, but did not affect lipid profiles [15]. Moreover, in a meta-analysis conducted by Yao et al. [16], probiotics supplementation was correlated with significant improvement in HbA1c, fasting insulin, and insulin resistance in people with type 2 diabetes mellitus (T2DM), but did not influence fasting glucose and lipid profiles.

These discrepancies may be due to the variation in the population studied, type, and different dosages of probiotic used, duration of intervention, underlying levels of metabolic profiles. Despite these findings, there is still limited evidence suggesting whether or how *Bacillus coagulans* could affect glycemic control, lipid profiles, biomarkers of inflammation, and oxidative stress in DN patients. The current trial was to investigate the effects of probiotic honey intake on metabolic status in DN patients.

Materials and Methods

Participants and Ethics Statements

This randomized, double-blind, controlled clinical trial, in the Iranian website for registration of clinical trials (no: IRCT201705035623N115), was conducted among participants with DN with a proteinuria level > 0.3 g/24 h, aged 45–85 years old referred to Akhavan Clinic in Kashan, Iran from April 2017 to December 2017. We defined DN as diabetic renal disease with proteinuria, with or without elevation of serum creatinine levels [17]. The exclusion criteria were as

follows: history of active infection within 3 months, the intake of probiotic and/or synbiotic supplements within 3 months, and malignancy and/or liver cirrhosis. To determine sample size, we used the standard formula suggested for parallel clinical trials by considering type 1 error (α) of 0.05 and type 2 error (β) of 0.20 (power = 80%). Based on a previous study [18], we used 1.86 as SD and 1.50 as the difference in mean (d) of the homeostasis model of assessment-insulin resistance (HOMA-IR) as key variable. Based on this, we needed 25 participants in each group. Considering five dropouts in each group, the final sample size was determined to be 30 participants per group. This investigation was conducted in accordance with the Declaration of Helsinki. The informed written consent was taken from all enrolled patients, with ethical clearance for the study obtained from the ethics committee of Kashan University of Medical Sciences (KAUMS).

Study Design

Initially, 60 patients with DN were randomly divided into two groups to receive either 25 g/day probiotic honey containing a viable and heat-resistant probiotic *Bacillus coagulans* T4 (IBRC-N10791) (10^8 CFU/g) or 25 g/day control honey ($n = 30$ each group) for 12 weeks. Probiotic and control honey were produced by Gaz Sekkeh Company (Isfahan, Iran). Due to viability against the high temperature, acidity of the stomach, bile acids, and growth at physiological conditions as well as beneficial effects on the intestinal environment, stool frequency, and characteristics [19], we selected *Bacillus coagulans* than other probiotic species. The viability of *Bacillus coagulans* was assessed in the laboratory of Food and Drug Administration in Tehran, Iran and in the laboratory of Gaz Sekkeh Company (Isfahan, Iran). Also, the viability of *Bacillus coagulans* was re-assessed by the first investigator (NM) in the laboratory of Food and Drug Administration in Kashan, Iran, at weeks 6 and 12 of the intervention. Randomization was done using a random number table by one of the investigators who had no clinical involvement in the study. Compliance to the intake of probiotic and control honey was evaluated through receiving short messages on cell phones by patients. All patients completed 3-day food records and three physical activity records at weeks 0, 4, 9, and 12 of the intervention. Macro- and micronutrient intake was analyzed by nutritionist IV software (First Databank, San Bruno, CA). Anthropometric measurements were quantified in an overnight fasting status using a digital scale (Seca, Hamburg, Germany) at baseline and after the 12-week intervention. Body mass index (BMI) was calculated by weight and height measurements (weight (kg)/height (m^2)).

Outcomes

Primary outcomes were parameters of insulin metabolism in the current study. Secondary outcome variables were fasting

plasma glucose (FPG), lipid profiles, biomarkers of inflammation, and oxidative stress, serum creatinine, blood urea nitrogen (BUN) concentrations. Before the onset and after the end of the intervention, 10-mL fasting blood samples were obtained from each patient at Kashan reference laboratory. Available commercial kits were used to determine FPG, lipid profiles, creatinine, and BUN concentrations (Pars Azmun, Tehran, Iran) with inter- and intra-assay coefficient variances (CVs) for FPG, lipid concentrations, creatinine, and BUN that were less than 5%. Serum insulin levels were assessed using an ELISA kit (Monobind, California, USA) with the intra- and inter-assay CVs lower than 6%. To determine the HOMA-IR and the quantitative insulin sensitivity check index (QUICKI), we used from suggested formulas [20]. Serum hs-CRP concentrations were quantified by an ELISA kit (LDN, Nordhorn, Germany) with the intra- and inter-assay CVs lower than 7%. The plasma NO concentrations by the use of Griess method [21], plasma TAC levels using ferric reducing antioxidant power (FRAP) developed by Benzie and Strain [22], total glutathione (GSH) using Beutler et al. [23] and malondialdehyde (MDA) concentrations by the use of the thiobarbituric acid reactive substances (TBARs) spectrophotometric test [24] were assessed with the intra- and inter-assay CVs lower than 4%.

Statistical Methods

We applied the Kolmogrov-Smirnov test to evaluate the normal distribution of variables. The analyses were carried out based on intention-to-treat (ITT) principle. To detect differences in anthropometric measures and dietary intakes between the two groups, we applied independent t test. To determine the effects of probiotic honey intake on metabolic profiles, we used one-way repeated measures analysis of variance. P values < 0.05 were considered statistically significant. All statistical analyses were done by the use of the Statistical Package for Social Science version 18 (SPSS Inc., Chicago, Illinois, USA).

Results

Among patients in the probiotic honey group, two patients [withdrawn ($n = 2$)] and in the control honey group, one person [withdrawn ($n = 1$)] were excluded (Fig. 1). Finally, 57 participants [probiotic honey ($n = 28$) and control honey ($n = 29$)] completed the trial. However, as the analysis was done based on ITT principle, all 60 participants (30 in each group) were included in the final analysis.

Mean age, height, baseline weight, and BMI of study participants were not statistically different between the two groups (Table 1).

Based on the 3-day dietary records obtained throughout the trial, we found no significant change in dietary macro- and micro-nutrient intakes (data not shown).

After 12 weeks of intervention, patients who received probiotic honey compared with the control honey had significantly decreased serum insulin levels (-1.2 ± 1.8 vs. -0.1 ± 1.3 μIU/mL, $P = 0.004$) and HOMA-IR (-0.5 ± 0.6 vs. 0.003 ± 0.4, $P = 0.002$) and significantly improved QUICKI ($+0.005 \pm 0.009$ vs. -0.0007 ± 0.005, $P = 0.004$) (Table 2). Additionally, compared with the control honey, probiotic honey intake has resulted in a significant reduction in total-/HDL-cholesterol (-0.2 ± 0.5 vs. $+0.1 \pm 0.1$, $P = 0.04$). Probiotic honey intake significantly reduced serum hs-CRP (-1.9 ± 2.4 vs. -0.2 ± 2.7 mg/L, $P = 0.01$) and plasma MDA levels (-0.1 ± 0.6 vs. $+0.6 \pm 1.0$ μmol/L, $P = 0.002$) compared with the control honey. Probiotic honey intake had no significant effects on other metabolic profiles compared with the control honey.

Discussion

In the current investigation, we evaluated the effects of probiotic honey intake on glucose homeostasis parameters, lipid profiles, biomarkers of inflammation, and oxidative stress among patients with DN. We found that probiotic honey consumption for 12 weeks among DN patients had beneficial effects on insulin metabolism, total-/HDL-cholesterol, serum hs-CRP, and plasma MDA levels, but did not affect other metabolic profiles. To the best of our knowledge, this study is the first indicating the effects of probiotic honey intake on glycemic control, lipid concentrations, biomarkers of inflammation, and oxidative stress in patients with DN.

Effects of Glycemic Control and Lipid Profiles

DN is correlated with multiple metabolic disturbances, such as impaired glucose and lipid metabolism, and increased biomarkers of inflammation and oxidative [25]. The current study demonstrated that probiotic honey intake for 12 weeks among patients with DN resulted in a significant reduction in serum insulin, HOMA-IR and total-/HDL-cholesterol, and a significant increase in QUICKI score compared with the control honey, but did not affect other lipid profiles. Earlier, the beneficial effects of probiotics on glycemic control and lipid profiles have reported. In a meta-analysis conducted by Yao et al. [16], probiotics supplementation resulted in a significant improvement in HbA1c and fasting insulin in patients with T2DM, but did not affect FPG, HOMA-IR, and lipid profiles. In addition, two previous meta-analyses with smaller numbers of studies have documented that probiotics significantly improved insulin resistance and significantly decreased glycated hemoglobin levels [26, 27]. A most recent meta-analysis, with 11 RCTs and 614 patients, also reported similar results [28]. In

Fig. 1 Summary of patient flow diagram
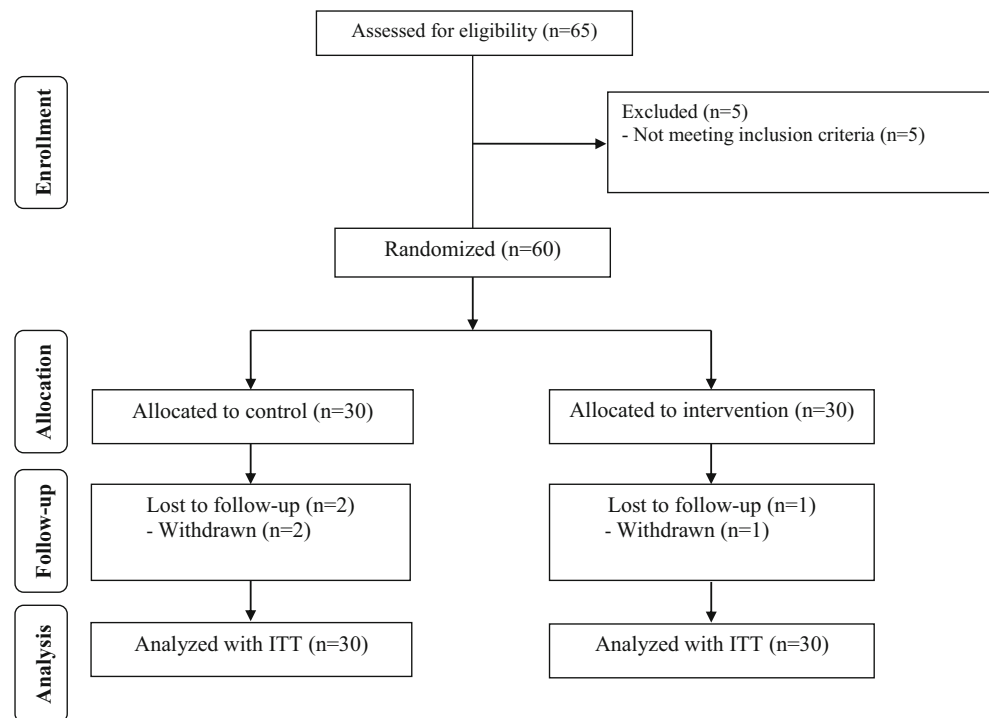
another meta-analysis conducted by He et al. [29], probiotic supplementation to patients with T2DM significantly decreased triglycerides, total- and LDL-cholesterol levels, but did not influence other lipid profiles. Furthermore, consumption of a synbiotic food containing *Bacillus coagulans* and inulin for 9 weeks by pregnant women significantly reduced insulin and HOMA-IR and significantly increased QUICKI score [18]. In another study, oral spore-based probiotic supplementation containing *Bacillus coagulans*, *Bacillus licheniformis*, and *Bacillus clausii* to healthy subjects for 30 days significantly decreased triglycerides and interleukin 12 levels [30]. Administering of a probiotic/prebiotic blend containing 4.5 billion live cells of *Bacillus coagulans* and galactomannans (300 mg) to obese patients for 3 months reduced triglycerides and LDL-cholesterol levels [12]. Discrepancies in these findings may be due to differences in study design, characteristics of study populations, and dosage of probiotic used, kind of bacteria used, and duration of the intervention. Insulin resistance and dyslipidemia are two major risk factors for T2DM and cardiovascular disease (CVD) [31]. Accumulating studies demonstrate that restoration of impaired function of the diabetic macro- and microvasculature may ameliorate a range of CVD states and diabetes-associated complications [32]. Therefore, *Bacillus coagulans* due to their beneficial effects on markers of insulin metabolism may be useful to reduce complications related to diabetes. Improved glycemic control and lipid profiles following the consumption of probiotics by patients with DN may be related to decreasing cytokines and suppressing the nuclear factor-κB pathway [33], the effect on gene expression related to insulin and lipid metabolism [34] and gut microbiota-short chain fatty acid (SCFA)-hormone axis [35].

Table 1 General characteristics of study participants

	Control honey ($n = 30$)	Probiotic honey ($n = 30$)	P^a
Age (year)	60.3 ± 8.5	62.7 ± 9.1	0.29
Height (cm)	159.6 ± 9.5	162.2 ± 8.9	0.14
Weight at study baseline (kg)	78.0 ± 12.5	79.6 ± 15.0	0.64
Weight at end-of-trial (kg)	77.9 ± 12.9	79.3 ± 15.4	0.70
Weight change (kg)	-0.1 ± 1.1	-0.3 ± 1.4	0.41
BMI at study baseline (kg/m^2)	31.1 ± 4.6	30.3 ± 5.6	0.56
BMI at end-of-trial (kg/m^2)	31.0 ± 4.8	30.2 ± 5.8	0.53
BMI change (kg/m^2)	-0.1 ± 0.4	-0.1 ± 0.5	0.48

Data are means ± SDs

[a] Obtained from independent t test

Table 2 Metabolic profiles, biomarkers of inflammation, and oxidative stress at study baseline and after 3-month intervention in patients with diabetic nephropathy that received either probiotic or control honey

	Control honey ($n = 30$)			Probiotic honey ($n = 30$)			P^a
	Wk0	Wk12	Change	Wk0	Wk12	Change	
FPG (mg/dL)	122.7 ± 35.1	124.3 ± 31.0	1.6 ± 18.2	132.8 ± 37.9	127.1 ± 34.9	− 5.7 ± 20.3	0.14
Insulin (μIU/mL)	16.1 ± 4.5	16.0 ± 4.6	− 0.1 ± 1.3	16.7 ± 5.9	15.5 ± 6.0	− 1.2 ± 1.8	0.004
HOMA-IR	4.9 ± 2.1	4.9 ± 2.2	0.003 ± 0.4	5.5 ± 2.2	5.0 ± 2.2	− 0.5 ± 0.6	0.002
QUICKI	0.30 ± 0.01	0.30 ± 0.01	− 0.0007 ± 0.005	0.30 ± 0.02	0.30 ± 0.02	0.005 ± 0.009	0.004
Triglycerides (mg/dL)	137.8 ± 44.5	138.2 ± 41.5	0.3 ± 27.2	124.4 ± 34.7	122.1 ± 34.7	− 2.3 ± 25.2	0.70
VLDL-cholesterol (mg/dL)	27.6 ± 8.9	27.7 ± 8.3	0.1 ± 5.4	24.9 ± 6.9	24.4 ± 6.9	− 0.5 ± 5.0	0.70
Total cholesterol (mg/dL)	164.7 ± 29.9	167.1 ± 28.8	2.4 ± 18.9	159.7 ± 38.7	154.5 ± 35.9	− 5.2 ± 22.9	0.16
LDL-cholesterol (mg/dL)	92.2 ± 28.8	95.2 ± 27.1	3.0 ± 17.9	90.2 ± 35.3	84.8 ± 33.2	− 5.5 ± 22.9	0.11
HDL-cholesterol (mg/dL)	44.9 ± 7.3	44.3 ± 5.9	− 0.7 ± 3.1	44.6 ± 9.2	45.3 ± 9.3	0.7 ± 2.7	0.07
Total-/HDL-cholesterol ratio	3.7 ± 0.7	3.8 ± 0.6	0.1 ± 0.4	3.6 ± 0.7	3.4 ± 0.6	− 0.2 ± 0.5	0.04
hs-CRP (mg/L)	5.6 ± 3.4	5.4 ± 3.9	− 0.2 ± 2.7	6.9 ± 2.6	5.0 ± 3.5	− 1.9 ± 2.4	0.01
NO (μmol/L)	30.3 ± 4.0	30.6 ± 4.0	0.3 ± 2.3	30.0 ± 1.4	29.8 ± 1.8	− 0.2 ± 1.3	0.25
TAC (mmol/L)	1035.5 ± 151.8	1064.8 ± 162.3	29.3 ± 72.9	989.1 ± 80.9	1065.1 ± 213.3	75.9 ± 214.3	0.26
GSH (μmol/L)	406.7 ± 83.4	417.3 ± 63.8	10.6 ± 55.0	351.6 ± 82.4	391.6 ± 99.2	39.9 ± 106.9	0.18
MDA (μmol/L)	2.5 ± 0.4	3.1 ± 0.8	0.6 ± 1.0	2.7 ± 0.3	2.6 ± 0.5	− 0.1 ± 0.6	0.002
BUN (mg/dL)	19.6 ± 6.2	19.9 ± 7.3	0.3 ± 4.3	19.6 ± 7.1	19.3 ± 6.8	− 0.3 ± 2.1	0.54
Creatinine (mg/dL)	1.3 ± 0.5	1.5 ± 0.8	0.2 ± 0.7	1.6 ± 0.6	1.5 ± 0.5	− 0.1 ± 0.5	0.09

Data are means ± SDs

[a] Obtained from repeated measures ANOVA test

BUN blood urea nitrogen, *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, *NO* nitric oxide, *QUICKI* quantitative insulin sensitivity check index, *TAC* total antioxidant capacity

Effects on Biomarkers of Inflammation and Oxidative Stress

Findings from the present study documented that taking probiotic honey for 12 weeks by patients with DN was associated with a significant decrease in serum hs-CRP and MDA levels compared with the control honey, but did not influence other biomarkers of inflammation and oxidative stress. CRP is a key inflammatory marker for diabetes progression and complications [36]. We have previously shown that probiotic supplementation for 9 weeks to pregnant women improved biomarkers of inflammation and oxidative stress [37]. In addition, probiotic supplementation for 8 weeks to women with rheumatoid arthritis improved inflammatory cytokines [38]. In an animal study, supplementing *Bacillus coagulans* had beneficial effects on promoting nutrients' metabolism, maintaining intestinal integrity, and alleviating oxidative stress [39]. Moreover, cell walls from the live *Bacillus coagulans* GBI-30 and 6086 strain have demonstrated immune modulating and anti-inflammatory effects in vitro [40]. Daily consumption of *Bacillus coagulans* BC30 by adults aged 65–80 years for 28 days could potentially increase production of anti-inflammatory cytokines [13]. Results from a recent clinical trial suggested that the consumption of *Bacillus coagulans* BC30 in combination with protein by male subjects for 2 weeks tended to reduce indices of muscle oxidative damage [41]. However, a previous meta-analysis presented non-significant effects of probiotics on CRP concentrations [26]. These results suggest that probiotics may have an important role in intestinal immunological modulation [42]. With inflammatory markers and signaling pathways as key mediators, targeting inflammation may be a useful approach to new avenue for treating diabetic events [31]. In addition, oxidative stress has been documented to play important role in the pathogenesis of DN [43]. Probiotic intake might improve inflammatory markers and oxidative stress through the increasing production of short chain fatty acids (SCFA) in the gut [44]. SCFA may decrease inflammation and oxidative stress through blocking the enzymatic synthesis of hepatic CRP [45].

Limitations of our study include the absence of fecal sample data to demonstrate transit of the specific probiotic through the gastrointestinal tracts of study subjects in the intervention group. Moreover, we did not assess gene expression related to insulin and lipid metabolism. We believe that yeast compared with bacilli better tolerates in the high sugar content. This should be considered in the interpretation of our findings.

Conclusions

Overall, findings from the current study demonstrated that probiotic honey consumption for 12 weeks among DN patients had beneficial effects on insulin metabolism, total-/HDL-cholesterol, serum hs-CRP, and plasma MDA levels, but did not affect other metabolic profiles.

Author's Contributions NM-A and ZA contributed in conception, data collection, and manuscript drafting. ZE-D, HT, RS-C, and AS contributed in conception, data collection, and manuscript drafting. All authors read and approved the final version of the paper.

Compliance with Ethical Standards

This investigation was conducted in accordance with the Declaration of Helsinki. The informed written consent was taken from all enrolled patients, with ethical clearance for the study obtained from the ethics committee of Kashan University of Medical Sciences (KAUMS).

Conflicts of Interest The authors declare that they have no conflict of interest.

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