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The effects of synbiotic supplementation along with non-surgical periodontal therapy in improving the metabolic status and inflammatory markers in type 2 diabetes mellitus patients with periodontal disease: A double-blind randomized clinical trial

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Abstract:

BACKGROUND: Diabetes mellitus and periodontitis are two common chronic diseases with bidirectional relationship. Considering the role of oxidative stress in the pathogenesis of these two diseases, the use of nutritional supplements with antioxidant properties can be useful. The purpose of this study was to determine the effectiveness of daily synbiotic supplement in the management of patients with type 2 diabetes mellitus (T2DM) and periodontal disease (PD) under non-surgical periodontal therapy (NSPT).

MATERIALS AND METHODS: In this randomized double-blind placebo controlled clinical trial, 50 patients suffering from T2DM and periodontal disease were recruited and randomly assigned to two groups: intervention group (n = 25), where one capsule of multi-species probiotic plus 100 mg fructo-oligosaccharide supplement (500 mg in each capsule) every day is given, and control group (n = 25), which received one placebo capsule containing 500 mg wheat flour for 8 weeks. At the beginning and end of the study, the serum levels of fasting blood glucose (FBG), glycosylated hemoglobin (HbA1c), the lipid profile including total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C) and inflammatory markers such as tumor necrosis factor alpha (TNF-α), interleukin 6 (IL-6), and high-sensitivity C-reactive protein (hs-CRP) were measured. All subjects received NSPT including oral health education, scaling, and root planning at the beginning of study. One month after the intervention, the second NSPT was performed. The paired-sample test was used to identify within-group differences. The independent sample *t*-test (crude model) and the analysis of covariance or ANCOVA (adjusted model) were used to compare the results between the two groups.

RESULTS: Synbiotic supplement with NSPT significantly decreased serum levels of FBG, HbA1c, TNF-α, and IL-6 compared with the baseline values (all $P < 0.05$). Furthermore, LDL-C levels significantly decreased compared with the baseline value in both groups (all $P < 0.05$). Also, the mean changes of IL-6 were significantly lower in the intervention group compared with the control group after the adjustment of confounding factors ($P = 0.01$).

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CONCLUSIONS: Synbiotic supplementation with NSPT may be beneficial in improving glycemic control and inflammation and decreasing LDL-C in patients with T2DM and PD.

Keywords:

Glycemic control, inflammation, lipid profile, periodontal disease, synbiotic, type 2 diabetes mellitus

Introduction

During the past few decades, type 2 diabetes mellitus (T2DM) and periodontal disease prevalence has rapidly increased in the world.[1,2] Periodontal or gum disease is a pathological inflammatory condition of the gum and bone support (periodontal tissues) surrounding the teeth and characterized by gingival bleeding, pocket formation, alveolar bone destruction, connective tissue degradation, and tooth loss.[3] Experimental and clinical evidence has suggested that periodontal disease plays a major role in the pathogenesis and progression of diabetes and its complications and vice versa.[4] Therefore, a complex two-way relationship between DM and periodontitis would suggest a vicious circle that exacerbates both diseases when present in the same individual.[5] Both periodontal diseases and DM have major inflammatory components, which may have both local (periodontal destruction) and systemic (impaired glycemic control) effects.[6] Based on studies, insulin resistance, inflammatory markers such as C-reactive protein, interleukin-1 beta (IL-1β), tumor necrosis factor-alpha (TNF-α), and interleukin-6 (IL-6) are higher in periodontitis than in patients with diabetes without periodontitis, which lead to disturb blood glucose management and lipid metabolism.[7,8] So, the successful management of periodontal infection in patients with diabetes may reduce local signs and symptoms and may lead to better control of non-insulin-dependent DM and metabolism.[9] Recently, the use of probiotics to decrease metabolic profiles,[10] periodontal status,[11] inflammatory factors,[12] and biomarkers of oxidative stress[13] has received great attention. According to the World Health Organization, probiotics are defined as viable microorganisms that confer a health benefit when administered in sufficient doses. Studies show that probiotics can influence metabolic profiles by enzymatic deconjugation of bile acids, conversion of cholesterol into coprostanol in the gut,[14] and improving insulin sensitivity.[15] Probiotics also can scavenge superoxide and hydroxyl radicals,[16] increase glutathione (GSH) levels,[17] decrease expression of IL-6 in adipocytes, and decrease adiposity,[18] which lead to decrease inflammation and oxidative stress. The hypothesis of the present study was that the consumption of synbiotic supplement with non-surgical periodontal therapy (NSPT) is effective in improvement of periodontitis, metabolic factors, and biomarkers of oxidative stress against the lack of effect. There are no studies that target the effects of multi-species probiotic supplement in adjunct with NSPT in T2DM patients with PD. So, the aim of the current study was to investigate the effectiveness of daily consumption of synbiotic supplement in conjunction with NSPT on FBG, HbA1c, lipid profiles, and inflammatory markers in T2D patients with PD.

Materials and Methods

Study design and setting

In this double-blind (participants and investigator) randomized clinical trial, 50 patients with T2DM with periodontal diseases (30–60 years old) were selected from Ahvaz Jundishapur University of Medical Sciences. The sample size was determined based on the primary information obtained from the study by Mafi *et al*.[19] for TG (triglyceride) as a primary outcome (α value equal to 0.05, a confidence level of 95%, and a power of 90%; the sample size was computed using this formula $n = \frac{\left(z_1 - \frac{\alpha}{2} + z_1 - \beta\right)^2 \left(\delta_1^2 + \delta_2^2\right)}{(\mu_1 - \mu_2)^2}$ (α = 0.05 and β = 0.1) as 23 subjects per group. Considering the loss of 10%, 50 T2DM patients (30–60 y) with chronic adult periodontal disease were recruited from the Endocrinology clinic of Golestan Hospital in Ahvaz city, Iran. For evaluation of periodontal status, pocket depth (PD) and clinical attachment loss (CAL) were measured by a single clinical examiner (periodontologist). The method of measuring periodontal indices including PD, CAL, plaque index, and bleeding on probing (BOP) is stated in our previous article.[20]

In the present study, the inclusion criteria included males or females aged between 30 and 60 years old, confirmed T2DM (no more than 5 years since diagnosis), mild and moderate periodontal disease diagnosed by a periodontologist based on a pocket depth ≥4 mm and CAL = 1–4 mm in at least one site in three quarters of the mouth and radiographic photos,[21] and a body mass index (BMI) range between 18.5 and 30 kg/m^2. Subjects were excluded if they had the following criteria: subjects were hospitalized due to any complications of diabetes; any diseases affecting levels of glycosylated hemoglobin such as anemia, hemodialysis, hemoglobinopathies, uremia, pregnancy, and lactation; travel more than 2 weeks; smoking; other serious systemic diseases; noticeable change in diet in the past 6 months; noticeable change in consumption of medications and treatment

of diabetes; having periodontal treatment for at least 6 months; receiving immunosuppressive drugs or any dietary supplements including antioxidant supplements; using antibiotics; patients with severe periodontitis; and probiotic products.

Study participants and sampling

Of the 90 patients, 40 patients were excluded from study (due to disapproval to participate in the study (n = 17) and lack of inclusion criteria (n = 23)], and according to inclusion and exclusion criteria, 50 patients were selected to participate in the study. Then subjects were randomly allocated to intervention and control groups consisting of 25 subjects in each by another investigator [Figure 1] using a random permuted block procedure (block design) based on the combined analysis. Participants and the investigator were not informed about which group was allocated to "A" and which one was allocated to B. The person performing the laboratory tests did not know the type of study.

In this study, subjects in the intervention group consumed one capsule/day synbiotic supplement (500 mg) (Zist Takhmir Co., Tehran, Iran) [contained seven viable and freeze-dried strains of naturally occurring beneficial bacteria: *Lactobacillus acidophilus* (strain number ZT-Lac. 51) (2×10^9 CFU), *L. casei* (strain number ZT-Lca. 106) (7×10^9 CFU), *L. rhamnosus* (strain number Zt-Lrh. 54) (1.5×10^9 CFU), *L. bulgaricus* (strain number ZT-LBU.90) (2×10^8 CFU), *Bifidobacterium breve* (strain number ZT-Bbr. 22) (2×10^{10} CFU), *B. longum* (strain number ZT: Blo. 105) (7×10^9 CFU), *Streptococcus thermophilus* (strain number ZT-Sth. 20) (1.5×10^9 CFU), and 100 mg fructo-oligosaccharide],[22] and those in the control group received one capsule/day placebo (500 mg) in the same packing like synbiotic supplement that contained the same substance without bacteria and prebiotic. All subjects received NSPT including oral health education, scaling, and root planning at the beginning of study. One month after the intervention, the second NSPT was performed. The patients were instructed to avoid

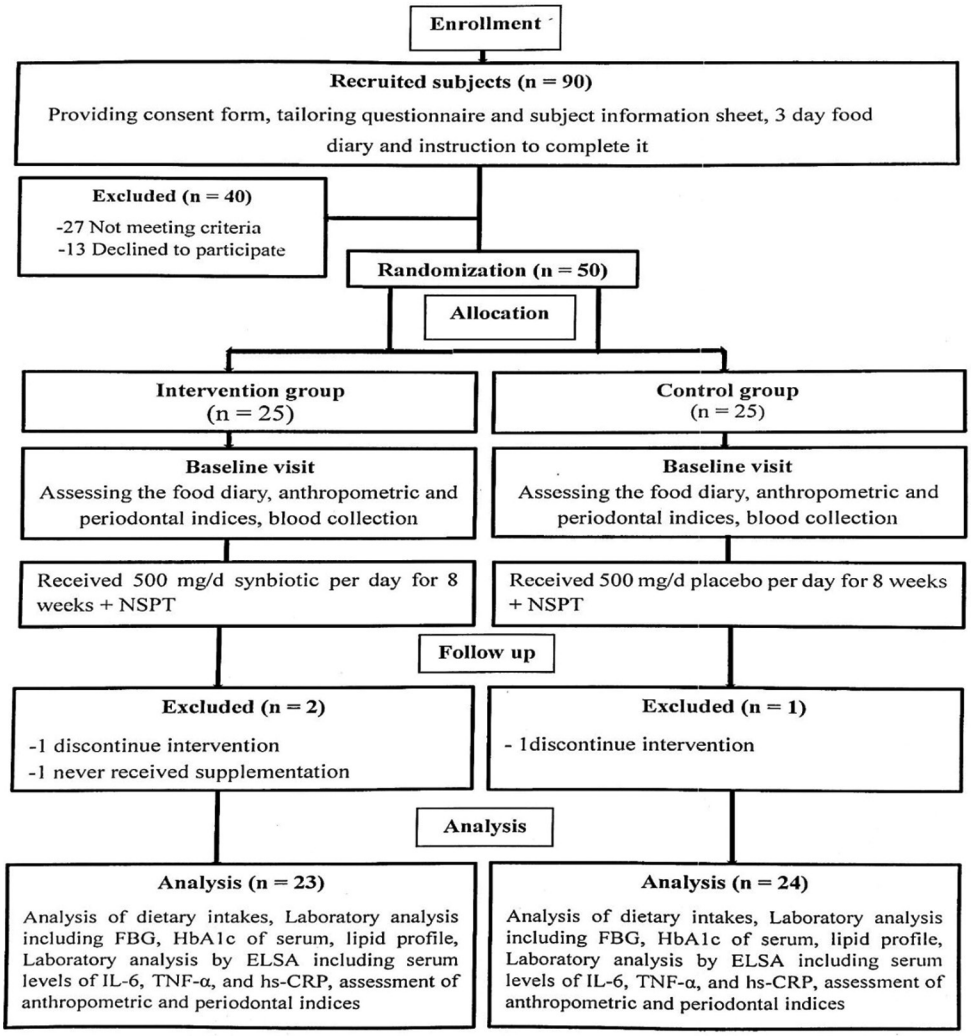

Figure 1: Flow diagram of the study

consuming any other probiotic products; maintain their usual dietary habits, lifestyle, and physical activity during the study; and avoid any changes in medication if possible.

Data collection tool and technique

Anthropometric indices and three-day food intake were measured by a trained interviewer (nutritionist) at the beginning and at the end of the study. Body weight was measured in an overnight fasting status, without shoes and in minimal clothing, using an analog scale (Seca, Germany) with 0.1 kg accuracy, and height was measured using a stadiometer (Seca) with 0.5 cm accuracy without shoes. BMI was calculated as the weight in kilogram divided by the height in meters squared.[23] Waist (widest area between the edge of lower rib and iliac corset) and hip circumferences (WC and HC) were measured using a tape measure with an accuracy of 0.5 cm at baseline and post intervention.

A venous blood sample (5 ml) was collected from subjects after an overnight fasting at the baseline and end of the study. 2 ml of whole blood was collected into a tube containing ethylene-diamine-tetra acetic acid in order to measure the blood levels of glycosylated hemoglobin A1C. HbA1c was measured by an enzymatic method using a Nycocard A1C kit (Norway). Serum glucose was measured by the standard enzymatic methods using a Pars Azmoon kit (Karaj, Iran). Serum total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-C) and serum low-density lipoprotein cholesterol (LDL-C) were measured by the standard enzymatic methods using Pars Azmoon kits. TG and TC were assayed using enzymatic colorimetric tests with laboratory kits of Pars Azmoon (Tehran, Iran). We assessed serum hs-CRP using a commercial cytokine-specific enzyme linked immunosorbent assay (ELISA) kit (LDN Labor Diagnostika Nord GmbH and Co KG, Nordhorn, Germany) and serum IL-6 and TNF-α using a commercial cytokine-specific enzyme linked immunosorbent assay (ELISA) kit [Human IL-6 and Human TNF-α Elisa kit (Ebioscience, Germany)].

Ethical consideration

At the beginning of the study, a written informed consent was obtained from patients. This parallel intervention study conformed to the ethical guidelines of the 1975 Declaration of Helsinki and was approved by the Ethics Committee of Ahvaz Jundishapur University of Medical Sciences (Ethical Code: AJUMS. REC.1395.452 and registration code of Iran clinical trials: IRCT2016110430694N1).

Statistical analysis

All statistical analyses were performed using SPSS (version 23; SPSS Inc., Chicago, IL). All results were expressed as means ± standard deviations (SD) for quantitative variables or number and frequency for qualitative variables. To ensure a normal distribution of variables, Kolmogorov–Smirnoff test was used. The paired-sample test was used to identify within-group differences (before and after the intervention). We used independent sample *t*-test to compare the results between the two groups (placebo and synbiotic supplement). The analysis of covariance (ANCOVA) was used to identify any differences between two groups at the end of study after adjusting for baseline values and covariates. To compare the qualitative variables in the two groups, the Chi-square test was used. Results with $P < 0.05$ were considered statistically significant.

Results

General characteristics, anthropometric status and energy, and the dietary intake

Fifty subjects randomly allocated to the control group (n = 25) and intervention group (n = 25) received interventions for 8 weeks completed the study. Two patients in the intervention group (discontinued intervention and never received supplementation) and one patient in the control group (discontinued intervention) were excluded from the study. Finally, 47 patients completed the study [Figure 1]. Thirty-three subjects (45%) were male, and 14 subjects (30%) were female. No serious adverse effect or symptoms were reported during the study related to synbiotic supplement consumption. Table 1 shows general and demographic characteristics of the participants in the intervention and control groups. Weight, BMI, WC, HC, and waist to hip ratio values [Table 1] and energy and nutrient intakes (data have been reported in a previous study)[20] were not significantly different within or between groups at the beginning and at the end of the study ($p \geq 0.05$).

Effects of intervention on FBG and HbA1C

FBG (150.52 ± 17.05 *vs* 156.82 ± 19.13; $P = 0.008$) and HbA1C (7.95 ± 1.23 *vs* 8.22 ± 1.14; $P = 0.004$) levels were

Table 1: Baseline characteristics of study participants

Variable	Control group (*n*=24)	Intervention group (*n*=23)	*P**
Age (years)	50.1±3.6	48.6±5.8	0.28
Men/women	16/8	17/6	0.59[a]
Weight (kg)	69±6.1	68±8.9	0.96
BMI (kg/m^2)	25.5±2.7	24±3.6	0.12
WC (cm)	103.3±7.9	106.9±6.7	0.10
HC (cm)	107.8±8.2	108.4±8.1	0.81
WHR	0.96±0.07	1±0.09	0.11
Disease duration (years)	6.66±1.57	7.26±2.17	0.28

P<0.05 was considered as significant. The results are described as mean±SD for quantitative data and number for qualitative data. **P*<0.05 was considered as significant using independent *t*-test between the two groups at baseline. a. *P*<0.05 was considered as significant using Chi-square test. BMI: body mass index, WHR: waist–hip ratio, WC: waist circumference. HC: hip circumference

significantly decreased in the intervention group post intervention compared to the baseline. In addition, the serum levels of FBG and HbA1C were also reduced but not significantly in the control group that had received placebo and NSPT ($p \geq 0.05$). The mean changes of FBG and HbA1C were not statistically significant between the two groups of intervention and control after adjusting for confounding factors ($p \geq 0.05$) [Table 2].

Effects of intervention on lipid profiles (LDL-C, HDL-C, TC, and TG)

No significant differences were seen between two groups in terms of TG, TC, LDL-c, and HDL-c levels at baseline. LDL-C was significantly decreased in both intervention (111.21 ± 21.67 *vs* 126.34 ± 28.42; $P = 0.044$) and control (114.08 ± 30.57 *vs* 127.08 ± 23.25; $P = 0.042$) groups post intervention compared to the baseline. There was no significant difference in other lipid biochemical measures ($p \geq 0.05$). Also, the results showed the mean changes of lipid profile (LDL-C, HDL-C, TC, TG) were not statistically significant between the two groups of intervention and control after adjusting for confounding factors ($p \geq 0.05$) [Table 2].

Effects of intervention on TNF-α, IL-6, and hs-CRP

As shown in Table 3, there were no significant differences in serum mean of TNF-α, IL-6, and hs-CRP at baseline ($p \geq 0.05$). However, at the end of the study, a significant difference in serum levels of TNF-α was observed between the two groups ($P = 0.001$). Moreover, serum TNF-α (8.99 ± 1.75 *vs* 10.65 ± 4.08; $P = 0.03$) and IL-6 (2.93 ± 0.79 vs 3.28 ± 0.98; $P = 0.01$) were significantly decreased in the intervention group compared with their baseline. But there was no significant change in mean of serum levels of hs-CRP in both groups ($p \geq 0.05$). The finding of this study suggested that the mean changes of TNF-α and hs-CRP were similar between the groups after adjusting for confounding factors ($P = 0.14$ and $P = 0.91$, respectively). Nevertheless, the mean changes of IL-6 were significantly lower in the intervention group

Table 2: Serum levels of FBG, HbA1C, and lipid profile of subjects at baseline and post-intervention

Variables	Control group (*n*=24)	Intervention group (*n*=23)	*P*	*P*[d]	*P*[e]
FBG (mg/dl)					
Baseline	161.12±31.47	156.82±19.13	0.57[a]		
After intervention	157.37±34.78	150.52±17.05	0.39[b]		
P[c]	0.37	0.008			
Difference	-3.75±20.18	-6.30±10.40		0.59	0.35
HbA1C (%)					
Baseline	8.20±0.95	8.22±1.14	0.94[a]		
After intervention	8.02±0.97	7.95±1.23	0.84[b]		
P[c]	0.067	0.004			
Difference	-0.17±0.45	-0.26±0.39		0.49	0.90
TC (mg/dl)					
Baseline	168.79±23.91	167.26±20.86	0.81[a]		
After intervention	165.62±23.45	159.69±30.64	0.45[b]		
P[c]	0.46	0.20			
Difference	-3.16±20.84	-7.56±27.88		0.54	0.33
LDL-C (mg/dl)					
Baseline	127.08±23.25	126.34±28.42	0.92[a]		
After intervention	114.08±30.57	111.21±21.67	0.71[b]		
P[c]	0.042	0.044			
Difference	-13±29.52	-15.13±33.94		0.81	0.92
HDL-C (mg/dl)					
Baseline	45.66±8.55	42.78±9.64	0.28[a]		
After intervention	44.04±9.08	45.26±8.50	0.63[b]		
P[c]	0.28	0.67			
Difference	-1.62±2.06	2.48±7.89		0.02	0.08
TG (mg/dl)					
Baseline	140.54±38.92	149.13±35.07	0.43[a]		
After intervention	138.33±44.94	145.73±40.81	0.55[b]		
P[c]	0.68	0.59			
Difference	-2.20±26.50	-3.39±30.29		0.88	0.47

FBG: fasting blood glucose, HbA1C: glycated hemoglobin A1C, LDL: low-density lipoprotein, HDL: high-density lipoprotein, TC: total cholesterol, TG: triglyceride. $P<0.05$ was considered significant. The results are described as mean±SD. [a]Difference between groups at baseline, *P* value is reported based on independent *t*-test. [b]Difference between groups post intervention, *P* value is reported based on ANCOVA. [c]Within group difference, *P* value is reported based on paired *t*-test. [d]$P<0.05$ was considered as a significant difference using independent *t*-test between the two groups post intervention. [e]$P<0.05$ was considered as a significant difference using ANCOVA between the two groups post intervention after adjusting for confounding factors

Table 3: Inflammatory markers at baseline and post-intervention

Variables	Control group (*n*=24)	Intervention group (*n*=23)	*P*	*P*[d]	*P*[e]
TNF-α (pg/mL)					
Baseline	11.62±3.79	10.65±4.08	0.40[a]		
After intervention	12.10±3.87	8.99±1.75	0.001[b]		
P[c]	0.37	0.03			
Difference	0.47±2.61	-1.66±3.53		0.02	0.14
IL-6 (pg/mL)					
Baseline	3.19±0.83	3.28±0.98	0.74[a]		
After intervention	3.20±0.84	2.93±0.79	0.26[b]		
P[c]	0.92	0.01			
Difference	0.01±0.54	-0.34±0.61		0.04	0.01
hc-CRP (mg/L)					
Baseline	3.22±1.00	3.51±0.77	0.74[a]		
After intervention	3.10±0.97	3.29±0.70	0.26[b]		
P[c]	0.56	0.24			
Difference	-0.11±0.98	-0.22±0.91		0.69	0.91

TNFα: tumor necrosis factor-α, IL-6: interleukin 6, hc-CRP: high-sensitivity C-reactive protein. The results are described as mean±SD. $P<0.05$ was considered significant. [a]Difference between groups at baseline, *P* value is reported based on independent *t*-test. [b]Difference between groups post intervention, *P* value is reported based on ANCOVA. [c]Within group difference, *P* value is reported based on paired *t*-test. [d]$P<0.05$ was considered as a significant difference using independent *t*-test between the two groups post intervention. [e]$P<0.05$ was considered as a significant difference using ANCOVA between the two groups post intervention after adjusting for confounding factors

compared with the control group without adjustment and after the adjustment of confounding factors ($P = 0.04$ and $P = 0.01$, respectively) [Table 3].

Effects of intervention on periodontal status: PD, CAL, plaque index, and BOP

The useful effects of synbiotic supplementation with NSPT on periodontal status have been previously described in our study.[20]

Discussion

There is a complex two-way relationship between DM and periodontitis. It is speculated that controlling of diabetes could be contributed to improvement of periodontal status and vice versa. Hyperglycemia caused by diabetes can lead to an abnormal increase in polymorphonuclear leukocytes (PMNLs), the first line of defense in the mouth, through protein glycosylation and the polyol pathway,[24] deposit advanced glycation end products (AGEs) within periodontal tissues and subsequently induce oxidative stress in the gingiva, alter the phenotype of macrophages and induce production of inflammatory mediators, stimulate bone resorption, and increase collagen breakdown.[25]

Using probiotics may improve periodontal status and glycemic control.[26] To our knowledge, this was the first study that evaluated the effects of synbiotic supplement in adjunct with NSPT in patients with diabetes and periodontal disease. The present study results showed that synbiotic supplement decreased FBG and HbA1C levels compared to the baseline. These findings were in agreement with the results of previous 4 to 12 weeks studies that showed probiotic products may decrease glycemic status and HbA1C and improve insulin and insulin sensitivity in humans[27,28] and animals.[29,30] In addition, in the present study, the levels of inflammatory markers including TNF-α and IL-6 decreased in the intervention group compared with the baseline. Therefore, the risk of periodontal disease may be reduced by effective control of metabolic status in patients with diabetes and also the treatment of periodontal disease, which may be accompanied by the reduction of inflammatory markers and may improve the metabolic status in patients with diabetes and periodontal disease.

Diabetes mellitus and periodontal diseases resulted in metabolic dysregulation of lipid metabolism through a mechanism involving insulin resistance and inflammatory markers.[7,31] Elevated levels of certain blood lipids have been reported to be the principal cause of cardiovascular disease and other disabilities in developed countries. Various approaches have been used to alleviate this issue, including the use of probiotics, especially *Bifidobacterium spp*. and *Lactobacillus spp*., which confer health benefits on the host when administered in adequate amounts. In the present study, LDL-C levels significantly decreased in both study groups. This result showed the beneficial effect of periodontal treatment on controlling of some plasma lipids that may be through a decrease in the inflammatory markers and glycemic profile of patients with diabetes and periodontal diseases, as observed in the present study. Tawfig *et al.* in a study that investigated the effect of NSPT on patients with diabetes showed a significant decrease in LDL due to NSPT, which is consistent with the results of our study.[32] There is a need for more clinical trial to investigate the effect of probiotics on LDL-C levels. In a study conducted by Asemi *et al*., probiotic

supplementation did not significantly improve lipid profiles in patients with diabetes.[33] Our results about HDL-C, TG and, TC levels were in disagreement with the results of some studies,[34-37] which may be due to the differences in probiotic organism, doses of probiotic, the kind of carriers (supplement or enriched food products with probiotic), study samples, participants, duration of study, and their blood lipid levels in the beginning of the study, because except for LDL-C levels, serum levels of other lipid parameters in the present study were in the normal range.

The findings of the present study were in agreement with the results of some previous studies that showed probiotic products may decrease inflammatory markers in humans.[38,39] The proposed mechanism of action of probiotics on inflammatory factors can be inhibition of nuclear factor-kappa beta (NF-κB) and consequently reduction of TNF-α production. In addition, *lactobacillus* species may be able to produce soluble molecules that suppress the production of TNF-α in active macrophages. The soluble protein markers produced by *lactobacilli* in the intestines can also be connected to the receptors at the cell surface to prevent TNF-α production.[40] While the results of the present study and many other studies in other inflammatory conditions have indicated that probiotics are effective on serum TNF-α, some studies have reported the inability of probiotics to effect on serum levels of this pro-inflammatory marker.[41,42] The difference in the results obtained in various studies may be due to the differences in target groups, study duration, probiotic organism, doses of probiotic, study sample size, and also different methods of periodontal treatment, monitoring, and the length of the measurement period. As summary, the main mechanism of the effect of probiotics is indirectly through modification of intestinal microflora. In addition, some probiotics have direct effects on the host, including antioxidative effects,[28] stabilization of the gut mucosal barrier,[24] increasing the IL-10 and interferon gamma (IFNγ) expression, increased immunoglobulin A (IgA) secretion, and anti-inflammatory effects.[21]

Limitations and recommendations

The limitations of this study included its short duration and the absence of a group that only consumed synbiotic supplement and also a control group that received no synbiotic supplement and NSPT. Moreover, many exclusion criteria in this study could limit the generalizability of the results. Therefore, further studies with a longer duration and two additional groups, that is, a group that consumed only synbiotic supplement and a control group that received no synbiotic supplement and NSPT, and a larger trial with some form of stratification are needed to confirm the positive effect of synbiotic supplementation in adjunct with NSPT in the management of T2DM and PD.

Conclusion

Based on findings, it seems that 8-week synbiotic supplementation in conjunction with NSPT may improve glycemic control and decrease lipid profiles and inflammation in patients with T2DM and PD. These findings need further investigation in larger trials with more precise design to determine the optimal dose and study duration and subject characteristics.

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Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Authors' contributions

MY: all steps of research and writing the manuscript, A-ZJ: corresponding author, supervision and all steps of research and writing the manuscript, HB: corresponding author, supervision and all steps of research and writing the manuscript, HA-Y, EG, and TN: clinical supervision and conception or design, MH-HZ: acquisition, analysis, or interpretation of data and statistical analysis.

Abbreviations

T2DM; type 2 diabetes mellitus, CP; chronic periodontitis, TNF-α; tumor necrosis factor-alpha, IL-6; interleukin-6, Hs-CRP; hs-C-reactive protein, CAL; clinical attachment loss, BOP; bleeding on probing, PD; pocket depth, NSPT; non-surgical periodontal therapy, WC; waist circumference, HC; hip circumference, WHR; waist to hip ratio, ELISA; enzyme-linked immunosorbent assay.

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Conflicts of interest

There are no conflicts of interest.

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