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Research Article

Effects of probiotic yogurt consumption on inflammatory biomarkers in patients with type 2 diabetes

Majid Mohamadshahi[1], Masoud Veissi[2], Fatemeh Haidari[2], Hajieh Shahbazian[3], Gholam-Abas Kaydani[4], Fatemeh Mohammadi[3*]

[1] Hyperlipidemia Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[2] Nutrition and Metabolic Diseases Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[3] Diabetes Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[4] Department of Laboratory Sciences, School of Para-medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran

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Abstract

Introduction: The role of inflammatory cytokines in diabetes and its complications has been shown in some studies. The purpose of this study was to compare the effect of probiotic and conventional yogurt on inflammatory markers in patients with type 2 diabetes.
Methods: Forty-four patients with type 2 diabetes were participated in this randomized, double-blind controlled clinical trial and assigned to two intervention and control groups. The subjects in the intervention group consumed 300 g/d probiotic yogurt and subjects in the control group consumed 300 g/d conventional yogurt for 8 weeks. Anthropometric indices, dietary intakes, and serum levels of glucose, HbA1c, IL-6, TNF-α and hs-CRP were evaluated at the beginning and end of the intervention.
Results: For anthropometric indices and dietary intakes, no significant differences were seen within and between groups post intervention ($p > 0.05$). The consumption of probiotic yogurt caused significant decrease in HbA1c and TNF-α levels ($p = 0.032$ and $p = 0.040$, respectively) in the intervention group.
Conclusion: It is suggested that probiotic yogurt may be used as an alternative prevention approach and treatment method to control diabetic complications.

Introduction

Type 2 diabetes mellitus (T2DM) is one of the common metabolic disorders across the world.[1] It is an established major independent risk factor for several chronic diseases such as coronary artery disease (CAD).[1,2] The role of inflammatory cytokines in diabetes and its complications has been shown in some studies.[3,4] Moreover, hyperglycemia in insulin resistance can lead to increase of AGEs (Advanced glycation end-products) density. These products may directly increase the synthesis of TNF-α, IL-6 and IL-1 cytokines by activating the macrophages and increasing the oxidative stress.[5] It seems that inflammatory intermediates may cause the destruction of β-cells and their functions and consequently insulin resistance in patients with T2DM.[6,7] Regarding the central role of inflammation in the pathogenesis of T2DM complications, decreasing of inflammatory cytokines would be effective to prevent complications of diabetes.[8] Recently, several treatments including consumption of herbal medicines,[9] multivitamin[10] and w-3 fatty acid[11] supplements have been suggested to improve inflammatory status in diabetic patients. It is suggested that consumption of probiotics would be also a novel approach to reduce pro- inflammatory factors in humans.[12,13] Probiotics are kinds of living microorganisms which have beneficial health effects on their host, when enter the intestine with an adequate amount.[14] Some of these health effects include reducing inflammation,[15] lowering hypercholesterolemia,[16] prevention or management of diarrhea, constipation, lactose intolerance, inflammatory bowel disease, diabetes mellitus,[17] and colon cancer.[18] Two main groups of probiotic bacteria which are most commonly used, involve Lactobacilli and bifidibacteria.[19,20] Some studies indicated that consumption of probiotics may be able to make modifications to the inflammatory responses by decreasing density of pathogenic gram negative bacteria in the intestine, which consequently prevent and reduce the inflammation.[21] However, available evidence about the effects of probiotic bacteria on inflammatory markers is controversial.[22-24] Therefore, the aim of this study was to evaluate the effects of probiotic yogurt on inflammatory factors and glycosylated

***Corresponding author:** Fatemeh Mohammadi, Email: fatemehmohammadi58@gmail.com

hemoglobin in patients with T2DM. It is important to note that conventional yogurt is usually consumed in Iran; so if probiotic yogurt can affect inflammation status in diabetes, it may be suggested as a potential agent in medical nutrition therapy for patients with T2DM.

Materials and methods

Subjects

Forty-four patients with T2DM were participated in this double-blind, randomized controlled clinical trial. All subjects were overweight or obese (BMI≥25). Exclusion criteria included insulin injection, any changes in using medication, use of corticosteroids, immunosuppressive and non-steroidal anti inflammatory drugs (NSAID), smoking, lactose intolerance, thyroid dysfunction, chronic inflammatory diseases, cardio-vascular disease, renal dysfunction, pregnancy, breast feeding, and having any weight loss or weight gain regimes. Subjects presenting probiotic yogurt consumption or nutritional supplements within the previous 2 months of testing were also excluded. The study was approved by and performed under the guidelines of the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Iran, and a written consent was obtained from all subjects.

Study design

All subjects were divided into two groups (intervention and control) by blocked randomization (n=22). Subjects in the intervention group were provided with 300 g probiotic yogurt which was to be consumed every day for 8 weeks. On the other hand, the control group received 300 g/d conventional yogurt for 8 weeks. The probiotic and conventional yogurts contained *Lactobacillus delbrueckii* subsp. *bulgaricus* and *Streptococcus thermophilus*. The probiotic yogurt was also enriched with *Bifidobacterium animalis* subsp. *lactis* Bb12 (DSM 10140) and *Lactobacillus acidophilus* strain La5 (Chr. Hansen, Hoersholm, Denmark) as Direct Vat Set cultures. The yogurts were produced weekly and distributed to the participants. Microbial analysis of the probiotic yogurt showed that average colony contained 3.7×10^6 cfu/g of both *L. acidophilus* (La5) and *B. lactic* (Bb12). Table 1 describes the mean of components of probiotic and conventional yogurts per 100 g. The yogurts had a similar taste and appearance, and were specially prepared for this study by Pegah Dairy Industries Co. (Ahvaz, Iran).

At home, subjects were instructed to maintain their normal lifestyle and dietary habits and avoid consuming other probiotic and fermented products during the study. They also were asked to keep yogurts in the refrigerator at a temperature of below 4 °C. Anthropometric indices and dietary intakes were evaluated at the beginning and end of the intervention.

Biochemical analysis

TNF-α, hs-CRP and IL-6 were determined by the ELISA technique using commercially available kits (Orgenuim Laboratories Business Unit, Finland) in accordance with the manufactures' instructions. HbA1c was measured in the whole blood by Nycocard HbA1C kit, Norway.

Table 1. Components of probiotic and conventional yogurt

Components	Probiotic yogurt	Conventional yogurt
Calories (kcal)	48.8	46.0
Carbohydrate (g)	7.5	4.9
Fat (g)	1.5	1.5
Protein (g)	2.4	2.8
Sodium (mg)	40	50
Potassium (mg)	110	156
Phosphorus (mg)	53	120
Calcium (mg)	100	100
PH	4.3	4.3

Statistical analysis

Statistical analyses were carried out using SPSS version 17.00. All data were expressed as mean ± SD. Independent sample t-test was used for comparing the differences in variables between two groups. Differences in inflammatory markers and glycemic indices between two groups were also compared by ANCOVA in the adjusted models, which were adjusted for WHR and energy intake changes. The end values of each variable were also compared with the baseline values of it using paired sample t-test. *The* $p < 0.05$ was considered significant.

Results

Forty-two patients (10 male and 32 female) attended for two visits and two recruited patients were withdrawn during the study. Patients did not report any serious adverse effect during the study related to yogurt consumption. Some demographic and anthropometric data pre- and post-intervention were shown in Table 2.

There were no significant differences in baseline features of the patients (age, weight, BMI, waist circumference, hip circumference, waist to hip ratio, and body fat percentage) within and between groups. Furthermore, for anthropometric indices, no significant differences were seen within and between groups post intervention ($p > 0.05$).

Regarding the dietary intake analysis, the differences in mean energy and nutrient intake were not significant between two groups at baseline ($p > 0.05$). Calcium intake was increased in both groups after conventional and probiotic yogurt consumption, but not significantly ($p = 0.061$ and $p = 0.057$, respectively). Protein intake was significantly ($p = 0.008$) elevated in control group at the end of study. However, the intakes of other nutrients did not significantly change from baseline to the post intervention in both groups (Table 3).

After adjusting for WHR and energy intake, the effects of probiotic and conventional yogurt consumption on glucose, HbA1c and inflammatory markers in patients with T2DM have been shown in Table 4. There were no

Table 2. Anthropometric characteristics of subjects at baseline and post intervention

	Baseline		Post intervention					
	Conventional (Mean ± SD)	Probiotic (Mean ± SD)	Conventional (Mean ± SD)	Probiotic (Mean ± SD)	P_a	P_b	P_c	P_d
Age (years)	49.00±7.08	53.00 ±5.9	-	-	0.101	-	-	-
Weight (kg)	79.33 ± 10.15	74.66 ± 11.11	78.61±9.04	74.33±10.89	0.163	0.173	0.543	0.516
BMI	29.22±3.20	28.36±4.14	29.18±3.57	28.24±4.10	0.464	0.434	0.949	0.525
Waist circumference (cm)	107.66±14.28	101.90±10.06	108.00±14.51	102.04±10.24	0.139	0.133	0.495	0.480
Hip circumference (cm)	115.42±12.55	111.00±9.59	115.61±12.55	110.85±9.72	0.206	0.177	0.329	0.186
WHR	0.93±0.06	0.91±0.03	0.93±0.64	0.92±0.03	0.412	0.448	0.776	0.202
Body fat (%)	37.10±8.25	36.15±9.40	37.12±8.00	35.99±8.16	0.733	0.654	0.948	0.846

Data are the mean ± SD. P_a indicates *p* value between probiotic and conventional yogurt groups at baseline(Independent-sample t-test); P_b indicates *p* value between probiotic and conventional yogurt groups after 8 weeks of intervention (Independent-sample t-test); P_c indicates *p* value within conventional yogurt groups before and after intervention(Paired sample t-test); P_d indicates *p* value within probiotic yogurt groups before and after intervention (Paired sample t-test).

Table 3. Dietary intakes of subjects at baseline and post intervention

	Baseline		Post intervention					
	Conventional (Mean ± SD)	Probiotic (Mean ± SD)	Conventional (Mean ± SD)	Probiotic (Mean ± SD)	P_a	P_b	P_c	P_d
Energy (Kcal)	2401.14±516.07	2439.85 ± 454.37	2655.61 ± 491.30	2265.33± 737.45	0.798	0.060	0.080	0.327
Protein (g)	136.79 ± 22.82	136.38 ± 22.36	158.02 ± 26.42	144.64 ± 26.15	0.957	0.107	0.008	0.301
Fat (g)	75.60 ± 11.59	77.18 ± 9.63	81.64 ± 12.15	74.43 ± 12.23	0.634	0.062	0.149	0.395
Pufa(g)	10.35± 0.88	10.39±1.00	10.25±0.65	10.33±0.78	0.87	0.73	0.69	0.81
Mufa (g)	11.32±0.60	11.39±0.64	11.06±0.65	11.10±0.66	0.71	0.53	0.19	0.33
Vitamin D (μg)	2.65 ± 1.12	2.42 ± 0.91	3.05 ± 1.76	2.76 ± 1.18	0.469	0.531	0.353	0.305
Vitamin K (μg)	53.6 ± 17.2	50.69 ± 8.29	62.45 ± 34.22	56.27 ± 23.04	0.489	0.497	0.299	0.300
Dietary fiber (g)	13.05 ± 3.06	13.09 ± 2.56	13.29 ± 3.16	12.58 ± 2.97	0.728	0.647	0.698	0.664
Zinc (mg)	13.05 ± 3.06	13.06 ± 2.56	13.29 ± 3.16	12.58 ± 2.97	0.965	0.459	0.773	0.573
Copper (mg)	1.57 ± 0.43	1.54 ± 0.37	1.5 ± 0.49	1.73 ± 0.47	0.781	0.145	0.645	0.132

Data are the mean ± SD. P_a indicates *p* value between probiotic and conventional yogurt groups at baseline (Independent-sample t-test); P_b indicates *p* value between probiotic and conventional yogurt groups after 8 weeks of intervention (Independent-sample t-test); P_c indicates *p* value within conventional yogurt groups before and after intervention (Paired sample t-test); P_d indicates *p* value within probiotic yogurt groups before and after intervention (Paired sample t-test).

significant differences between two groups regarding the glucose and HbA1c concentrations at baseline ($p > 0.05$). HbA1c levels were significantly reduced in the intervention group compared with the control group at the end of study ($p = 0.038$). However, no significant differences were observed in glucose levels between two groups at the end of study ($p > 0.05$). HbA1c levels were decreased in subjects in the intervention group post probiotic consumption ($p = 0.032$).

As presented in Table 4, there were no significant differences between two groups regarding serum inflammatory factors at baseline. Post intervention, the levels of TNF-α were significantly lowered in the intervention group compared with the control group ($p = 0.047$). Serum levels of IL-6 and hs-CRP were also reduced in the intervention group compared with the control group, but not significantly ($p > 0.05$). TNF-α levels were significantly decreased in subjects in the intervention group post probiotic yogurt consumption ($p = 0.040$).

Discussion

T2DM is a metabolic disorder that is characterized by hyperglycemia and associated with elevated levels of inflammatory cytokines like IL-6, IL-1 and TNF-α.[5,25,26] It is speculated that improvement of inflammatory status could be contributed to diabetes control.[27,28] Some studies have suggested that using of probiotics may inhibit production of pro-inflammatory cytokines.[21] Therefore,

Table 4. Effects of probiotic and conventional yogurt consumption on glucose, HbA1c and inflammatory markers in patients with type 2 diabetes

Variables		Conventional	Probiotic	P_a	P_b
FBS (mg/dl)	Baseline	187.42 ± 55.13	175.24±46.63	0.451	0.497
	Post intervention	185.19 ± 63.60	157.28±43.63	0.105	0.135
	P_c	0.874	0.353	-	-
HbA_1C (%)	Baseline	8.33 ± 1.46	8.24±1.68	0.851	0.832
	Post intervention	8.09 ± 1.58	7.09±1.23	0.029	0.038
	P_c	0.593	0.032	-	-
hs-CRP (mg/l)	Baseline	3.08±1.54	3.26±1.36	0.697	0.465
	Post intervention	3.29±1.72	2.80±1.48	0.334	0.327
	P_c	0.612	0.305	-	-
IL-6 (pg/ml)	Baseline	23.64 ± 3.31	22.60±2.81	0.281	0.197
	Post intervention	24.19 ± 2.86	22.18±2.56	0.021	0.401
	P_c	0.787	0.623	-	-
TNF-α (pg/ml)	Baseline	4.07 ± 1.53	4.36±1.9	0.596	0.682
	Post intervention	3.76 ± 1.30	2.92±1.16	0.033	0.047
	P_c	0.444	0.040	-	-

Data are the means ± SD. P_a indicates *p* value between probiotic and conventional yogurt groups at baseline and post intervention (Independent sample t-test); P_b indicates *p* value between probiotic and conventional yogurt groups after adjusted for WHR change and energy intake change at baseline and post intervention (ANCOVA); P_c indicates *p* value within conventional and probiotic yogurt groups at baseline and after intervention (Pairedsample t-test).

the present study was conducted to evaluate the effects of probiotic yogurt consumption in comparison with conventional yogurt consumption on inflammatory factors in patients with T2DM.

No significant differences were observed in dietary intake and anthropometric indices between probiotic and conventional consumers during the study. Thus, it is suggested that unchanged anthropometric indices and dietary intake did not affect the results of other parameters in this study.

In current study it was shown that consumption of probiotic yogurt significantly reduced HbA1c levels and diminished serum levels of glucose. The findings support previous reports on the anti-diabetic property of probiotics. Ejtahed *et al.* in a similar study investigated the hypoglycemic and anti-oxidative effects of probiotic yogurt in T2DM patients and found that consumption of probiotic yogurt for 6 weeks significantly decreased serum concentrations of glucose and HbA1c.[29] Harisa *et al.* reported a significant decrease in fasting blood sugar and HbA1c by using *L. acidophilus* alone or in combination with acarbose.[30] In a study by Matsuzaki *et al.,* it was indicated that using *Lactobacillus casei* significantly decreased plasma levels of glucose and pro-inflammatory cytokines (such as IL-2 and IFN-γ) in none-insulin-dependent diabetic mice after 16 weeks.[31] The exact mechanism involved in the hypoglycemic effects of probiotics is unclear. These effects may be partly due to the colonization of lactic acid bacteria in intestinal epithelium, using of glucose by them and consequently reduced glucose absorption from the intestine.[32] Inhibitory effect of Lactic acid bacteria on production of cytokines which are responsible for destruction of pancreatic cells may be another mechanism.[30,33]

The present study also indicated a significant decrease in TNF-α level in the intervention group compared with the control group after 8 weeks. These results concur with other studies. Decreased serum levels of TNF-α by Lactobacillus HY 7801 have been also reported by Konishi *et al.*[34] In another study, Twetman *et al.* showed that chewing gums containing two strains of *Lactobacillus ruteri* significantly reduced TNF-α level, but did not impact IL-6 level in healthy adults.[35]

However, there are some other studies in contrast with our study regarding the above-mentioned results. Hatakka *et al.* indicated that intake of *Lactobacillus rhamnosus* LC705 did not change IL-6 and TNF-α level in rheumatoid arthritis patients.[36] Asemi *et al.* showed that eating probiotic yogurt for 9 weeks in pregnant women did not decrease TNF-α concentration but significantly reduced serum levels of hs-CRP.[37]

The imbalance of microflora in the gastrointestinal tract has been reported in T2DM.[38] It seems that probiotics may be useful in improving intestinal micro-flora imbalance by enriching gram-positive bacteria.[39] Lee *et al.* demonstrated that decline in TNF-α concentration by probiotic bacteria like *Lactobacillus HY* may result from inhibition of tri-nitrobenzene sulfonic acid and consequently inhibition of TNF-α gene expression.[40] It is also confirmed that NF-Kβ plays a crucial role in expression of inflammatory mediators. NF-Kβ regulates transcriptional activity of inflammatory agents. Activating anti-apoptic genes such as TNF-α receptor-related genes and suppressing the apoptosis of some inflammatory cells such as neutrophils and activated macrophage are another function of NF-Kβ.[41] Probiotic bacteria like *Bifidobacterium longum* by suppressing NF-Kβ activation of lamina propria mono nuclear cells down regulates TNF-α production.[42] In

addition, Lactobacillus species may be able to produce soluble molecules that suppress production of TNF-α in activated macrophages. Soluble protein factors that are produced by intestinal Lactobacilli may bind to cell surface receptors and prevent synthesis or secretion of TNF-α, independent of pro-apoptotic effectors or cell necrosis.[43]
In the present study, serum levels of IL-6 and hs-CRP did not decrease significantly after consumption of probiotic yogurt. This finding is in agreement with Hatakka *et al.* findings which showed that use of *Lactobacillus rhamnosus* LC705 did not decrease serum level of IL-6 in patients with arthritis rheumatoid.[36] Furthermore, consumption of *L. plantarum* in critically ill patients had no effects on CRP concentration in McNaught *et al.* study.[44] In contrast, reduced serum hs-CRP levels have been also displayed in patients suffering from chronic kidney disease by probiotic.[45]
As discussed previously, there are several possible mechanisms suggested about the effects of probiotic bacteria on inflammatory biomarkers.[39-43] It is indicated that different bacterial species may have different abilities to affect inflammatory markers.[37] The findings of this study suggested that probiotic yogurt consumption might not affect the serum IL-6 and hs-CRP levels in patients with T2DM due to some possibilities such as the type of microorganism used and some limitations of study like the number of subjects and short period of intervention in this study.

Conclusion

In conclusion, the findings indicated that consuming probiotic yogurt can reduce HbA1c and some inflammatory markers in patients with type 2 diabetes mellitus. Therefore it is suggested that eating probiotic yogurt may be used as an alternative preventive approach and treatment method to control diabetic complications. Further studies with larger sample size, longer period of intervention and various types of probiotic are needed to confirm these effects.

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Ethical issues

The study was approved by and performed under the guidelines of the Research Ethics Committee of Ahvaz Jundishapur University of Medical Sciences, Iran and a written consent was obtained from all subjects.

Competing interests

The authors declare no conflict of interests**.**

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