**Research Article**

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

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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. It is an established major independent risk factor for several chronic diseases such as coronary artery disease (CAD). The role of inflammatory cytokines in diabetes and its complications has been shown in some studies. 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. It seems that inflammatory intermediates may cause the destruction of β-cells and their functions and consequently insulin resistance in patients with T2DM. Regarding the central role of inflammation in the pathogenesis of T2DM complications, decreasing of inflammatory cytokines would be effective to prevent complications of diabetes. Recently, several treatments including consumption of herbal medicines, multivitamin and w-3 fatty acid 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. Probiotics are kinds of living microorganisms which have beneficial health effects on their host, when enter the intestine with an adequate amount. Some of these health effects include reducing inflammation, lowering hypercholesterolemia, prevention or management of diarrhea, constipation, lactose intolerance, inflammatory bowel disease, diabetes mellitus, and colon cancer. Two main groups of probiotic bacteria which are most commonly used, involve Lactobacilli and bifidobacteria. 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. However, available evidence about the effects of probiotic bacteria on inflammatory markers is controversial. Therefore, the aim of this study was to evaluate the effects of probiotic yogurt on inflammatory factors and glycosylated hemoglobin.
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 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 \(3.7 \times 10^6\) cfu/g of both L. acidophilus (La5) and B. lactis (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 (Mean ± SD) | Baseline (Mean ± SD) | Conventional (Mean ± SD) | Conventional (Mean ± SD) | Probiotic (Mean ± SD) | Probiotic (Mean ± SD) | P_a | P_b | P_c | P_d |
|--------------------|----------------------|----------------------|--------------------------|--------------------------|-----------------------|-----------------------|-----|-----|-----|-----|
| Age (years)        | 49.00 ± 7.00         | 53.00 ± 5.9          | -                        | -                        | -                     | -                     | 0.101|     |     |     |
| Weight (kg)        | 79.33 ± 10.15        | 74.66 ± 11.11        | 78.61 ± 9.09             | 74.33 ± 10.89            | 0.163                 | 0.173                 | 0.543| 0.516|     |     |
| BMI                | 29.22 ± 3.20         | 28.36 ± 14.4         | 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 (Mean ± SD) | Baseline (Mean ± SD) | Conventional (Mean ± SD) | Conventional (Mean ± SD) | Probiotic (Mean ± SD) | Probiotic (Mean ± SD) | P_a | P_b | P_c | P_d |
|--------------------|----------------------|----------------------|--------------------------|--------------------------|-----------------------|-----------------------|-----|-----|-----|-----|
| Energy (Kcal)      | 2401.14 ± 16.07      | 2439.85 ± 45.34      | 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. It is speculated that improvement of inflammatory status could be contributed to diabetes control. Some studies have suggested that using of probiotics may inhibit production of pro-inflammatory cytokines. Therefore,
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. Harisa et al. reported a significant decrease in fasting blood sugar and HbA1c by using *L. acidophilus* alone or in combination with acarbose. 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. 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. Inhibitory effect of Lactic acid bacteria on production of cytokines which are responsible for destruction of pancreatic cells may be another mechanism.

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. 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. 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. 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. The imbalance of microflora in the gastrointestinal tract has been reported in T2DM. It seems that probiotics may be useful in improving intestinal micro-flora imbalance by enriching gram-positive bacteria. 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. 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. Probiotic bacteria like *Bifidobacterium longum* by suppressing NF-Kβ activation of lamina propria mono nuclear cells down regulates TNF-α production.
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.36-43 It is indicated that different bacterial species may have different abilities to affect inflammatory markers.36 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.

**References**

1. Azimi-Nezhad M, Ghayour-Mobarhan M, Parizadeh MR, Safarian M, Esmaeili H, Parizadeh SM, et al. Prevalence of type 2 diabetes mellitus in Iran and its relationship with gender, urbanisation, education, marital status and occupation. *Singapore Med J* 2008; 49: 571-576.

2. Pearson TA. New tools for coronary risk assessment: what are their advantages and limitations? *Circulation* 2002; 105: 886-892.

3. Goldberg RB. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalance coagulation in development of diabetes and its complications. *J Clin Endocrinol Metab* 2009; 94: 3171-82.

4. Bertoni AG, Burke GL, Owusu JA, Carnethon MR, Vaidya D, Barr RG, et al. Inflammation and the incidence of type 2 diabetes: the Multi-Ethnic Study of Atherosclerosis (MESA). *Diabetes Care* 2010; 33: 804-810.

5. Coppola G, Corrado E, Muratori I, Tantillo R, Vitale G, Lo Coco L, et al. Increased levels of C-reactive protein and fibrinogen influence the risk of vascular events in patients with NIDDM. *Int J Cardiol* 2006; 106: 16-20.

6. Hayashi-Okano R, Yamasaki Y, Katakami N, Ohtoshi K, Gorogawa S, Kuroda A, et al. Elevated c-reactive protein associates with early-stage carotid atherosclerosis in young subjects with type 1 diabetes. *Diabetes Care* 2002; 25: 1432-1438.

7. Wang C, Guan Y, Yang J. Cytokines in the progression of pancreatic β-cell dysfunction. *Int J Endocrinol* 2010; 2010: 515136.

8. Badawi A, Klip A, Haddad P, Cole DE, Bailo BG, El-Sohemy A, et al. Type 2 diabetes mellitus and inflammation: Prospects for biomarkers of risk and nutritional intervention. *Diabetes Metab Syndr Obes* 2010; 3: 173-186.

9. Omar EA, Kam A, Alqhtani A, Li KM, Razmovski-Naumovski V, Nammì S, et al. Herbal medicines and nutraceuticals for diabetic vascular complications: mechanisms of action and bioactive phytochemicals. *Curr Pharm Des* 2010; 16: 3776-3807.

10. Song Y, Xu Q, Park Y, Hollenbeck A, Schatzkin A, Chen H. Multivitamins, individual vitamin and mineral supplements, and risk of diabetes among older U.S. adults. *Diabetes Care* 2011; 34: 108-114.

11. Wall R, Ross RP, Fitzgerald GF, Stanton C. Fatty acids from fish: the anti-inflammatory potential of long-chain omega-3 fatty acids. *Nutr Rev* 2010; 68: 280-289.

12. Imaoka A, Shimia T, Kato K, Mizuno S, Uehara T, Matsumoto S, et al. Anti-inflammatory activity of probiotic Bifidobacterium: enhancement of IL-10 production in peripheral blood mononuclear cells from ulcerative colitis patients and inhibition of IL-8 secretion in HT-29 cells. *World J Gastroenterol* 2008; 14: 2511-2516.

13. Wallace TD, Bradley S, Buckley ND, Green-Johnson JM. Interactions of lactic acid bacteria with human intestinal epithelial cells: effects on cytokine production. *J Food Prot* 2003; 66: 466-472.

14. Verna EC, Lucak S. Use of probiotics in gastrointestinal disorders: what to recommend? *Therap Adv Gastroenterol* 2010; 3: 307-319.

15. Bansal T, Alanzir RC, Wood TK, Jayaraman A. The bacterial signal indole increases epithelial-cell tight-junction resistance and attenuates indicators of inflammation. *Proc Natl Acad Sci USA* 2010; 107: 228-233.

16. Baroutkoub A, Mehdi RZ, Beglarian R, Julayi H, Sohrabi Z, Eskandari M, et al. Effects of probiotic yoghurt consumption on the serum cholesterol levels in hypercholesteromic cases.
in Shiraz, Southern Iran. Sci Res Essays 2010; 5: 2206-2209.

17. Kaur IP, Kuhad A, Garg A, Chopra K. Probiotics: delineation of prophylactic and therapeutic benefits. J Med Food 2009; 12: 219-235.

18. Kumar M, Kumar A, Nagpal R, Mohania D, Behare P, Verma V, et al. Cancer-preventing attributes of probiotics: an update. Int J Food Sci Nutr 2010; 61: 473-496.

19. Srividy A, Rishnuvarthan VY. Probiotic: a rational approach to use Probiotic as medicine. Int J Pharmaceutic Front Res 2011; 1: 126-134.

20. Iannitti T, Palmieri B. Therapeutic use of probiotic formulations in clinical practice. Clin Nutr 2010; 29: 701-725.

21. Lyne HS, Kuan CY, Ewe JA, Fung WY, Liong MT. The improvement of hypertension by probiotics: effects on cholesterol, diabetes, renin, and phytoestrogens. Int J Mol Sci 2009; 10: 3755-3775.

22. Andreasen AS, Larsen N, Pedersen-Skovgaard T, Berg RM, Møller K, Svendsen KD, et al. Effects of Lactobacillus acidophilus NCFM on insulin sensitivity and the systemic inflammatory response in human subjects. Br J Nutr 2010; 104: 1831-1838.

23. Zhang JW, Du P, Gao J, Yang BR, Fang WJ, Ying CM. Preoperative probiotics decrease postoperative infectious complications of colorectal cancer. Am J Med Sci 2012; 343: 199-205.

24. Marschan E, Kuhtinen M, Kukkonen K, Poussa T, Sarnesto A, Haatelta T, et al. Probiotics in infancy induce protective immune profiles that are characteristic for chronic low-grade inflammation. Clin Exp Allergy 2008; 38: 611-618.

25. Yeo ES, Hwang JY, Park JE, Choi YJ, Huh KB, Kim WY. Tumor necrosis factor (TNF-alpha) and C-reactive protein (CRP) are positively associated with the risk of chronic kidney disease in patients with type 2 diabetes. Yonsei Med J 2010; 51: 519-525.

26. Goldfine AB, Fonseca V, Shoeelson SE. Therapeutic approaches to target inflammation in type 2 diabetes. Clin Chem 2011; 57: 162-167.

27. Arumugam VA, Mubarak M, Natarajan D, Ramalingam S, Tajuddin NB, Jayaraman G, et al. Clinical significance of hyperlipidemia, diabetes and inflammation, as predictor of cardiovascular disease. Int J Biol Med Res 2011; 2: 369-373.

28. Garcia-Bailo E, Sohemy A, Haddad PS, Arora P, Benzaied F, Karmali M, et al. Vitamins D, C, and E in the prevention of type 2 diabetes mellitus: modulation of inflammation and oxidative stress. Biologies 2011; 5: 7-19.

29. Ejtahed HS, Mohtadi-Nia J, Homayouni-Rad A, Niafar M, Aghari-Jafarabadi M, Mofid V. Probiotic yogurt improves antioxidant status in type 2 diabetic patients. Nutrition 2012; 28: 539-543.

30. Harisa GI, Taha EI, Khalil AF, Salem MM. Oral administration of lactobacillus acidophilus restores nitric oxide level in diabetic rats. Aust J Basic Appl Sci 2009; 3: 2963-2969.

31. Matsuzaki T, Yamazaki R, Hashimoto S, Yokokura T. Antidiabetic effects of an oral administration of Lactobacillus casei in a non-insulin-dependent diabetes mellitus (NIDDM) model using KK-Ay mice. Endocr J 1997; 44: 357-365.

32. Yadav H, Jain S, Sinha PR. Antidiabetic effect of probiotic dahi containing Lactobacillus acidophilus and Lactobacillus casei in high fructose fed rats. Nutrition 2007; 23: 62-68.

33. Zhang JW, Du P, Chen DW, Cui L, Ying CM. Effect of viable bifidobacterium supplement on the immune status and inflammatory response in patients undergoing resection for colorectal cancer. Zhonghua Wei Chang Wai Ke Za Zhi 2010; 13: 40-43.

34. Konishi N, Miki C, Yoshida T, Tanaka K, Toiyama Y, Kusunoki M. Interleukin-1 receptor antagonist inhibits the expression of vascular endothelial growth factor in colorectal carcinoma. Oncology 2005; 68: 138-145.

35. Tvetemt S, Derawi B, Keller M, Ekstrand K, Yuel-Lindberg T, Steckens-Blicks C. Short-term effect of chewing gums containing probiotic Lactobacillus reuteri on the levels of inflammatory mediators in gingival crevicular fluid. Acta Odontol Scand 2009; 67: 19-24.

36. Hatakkka K, Martio J, Korppela M, Herranen M, Poussa T, Laasonen T, et al. Effects of probiotic therapy on the activity and activation of mild rheumatoid arthritis--a pilot study. Scand J Rheumatol 2003; 32: 211-215.

37. Asemi Z, Jazayeri S, Najafi M, Samimi M, Mofid V, Shidfar F, et al. Effects of daily consumption of probiotic yoghurt on inflammatory factors in pregnant women: a randomized controlled trial. Pak J Biol Sci 2011; 14: 476-482.

38. Tayebi-Khosroshahi H, Kalantar-Zadeh K, Tabrizi A. Long-term substitution of intestinal microflora with health bacteria may play a role in preventing certain diabetic complications. Med Hypotheses Res 2010; 6: 37-42.

39. Larsen N, Vogensen FK, Van den Berg FW, Nielsen DS, Andreasen AS, Pedersen BK, et al. Gut microbiota in human adults with type 2 diabetes differs from non-diabetic adults. PLoS One 2010; 5: e9085.

40. Lee JH, Lee B, Lee HS, Bae EA, Lee H, Ahn YT, et al. Lactobacillus suntoryeus inhibits pro-inflammatory cytokine expression and TLR-4-linked NF-kappaB activation in experimental colitis. Int J Colorectal Dis 2009; 24: 231-237.

41. Hegazy SK, El-Bedewy MM. Effect of probiotics on pro-inflammatory cytokines and NF-kappaB activation in ulcerative colitis. World J Gastroenterol 2010; 16: 4145-4151.

42. Shi XZ, Lindholm PF, Sarna SK. NF-kappa B activation by oxidative stress and inflammation suppresses contractility in colonic circular smooth muscle cells. Gastroenterology 2003; 124: 1369-1380.

43. Peña JA, Versalovic J. Lactobacillus rhamnosus GG decreases TNF-alpha production in lipopolysaccharide-activated murine macrophages by a contact-independent mechanism. Cell Microbiol 2003; 5: 277-285.

44. McNaught CE, Woodcock NR, Anderson AD, MacFie J. A prospective randomized trial of probiotics in critically ill patients. Clin Nutr 2005; 24: 211-219.

45. Ranganathan N, Friedman EA, Tam P, Rao V, Ranganathan P, Dheer R. Probiotic dietary supplementation in patients with stage 3 and 4 chronic kidney disease: a 6-month pilot scale trial in Canada. Curr Med Res Opin 2009; 25: 1919-1930.