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RESEARCH ARTICLE

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Effects of prebiotic consumption on serum intestinal fatty acid-binding protein levels in patients with diabetes: A case-control study

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a condition involving several molecular mechanisms related to the intestinal microbiota for its development. Intestinal fatty acid-binding protein (I-FABP) is a sensitive marker to study enterocyte damage. A prebiotic is a non-digestible food ingredient that improves host health by selectively stimulating the growth and/or activities of bacteria in the colon. We aimed to clarify the currently described effects of prebiotics in the prevention and management of T2DM.

Methods: In this case-control study, we chose 68 participants with T2DM and 52 healthy participants. Both groups were further divided based on consumption of prebiotics. Forty participants with T2DM consumed prebiotics, and 28 did not; 30 healthy volunteers consumed prebiotics, and 22 did not. We used the analysis of variance to compare the inflammation levels between the case and control groups. Multiple linear regression was performed for the significantly correlated groups to estimate the influence of prebiotics on inflammation level.

Results: Age was a significant factor for difference in I-FABP levels (standardized coefficient: 0.06; $P = .047$). The analysis of eating habits showed that vegetarian diets produced lower I-FABP levels than non-vegetarian diets (standardized coefficient: −2.55; $P = .022$). Results showed that patients with T2DM who consumed prebiotics expressed lower I-FABP levels, reflecting an improvement in inflammation level, than the healthy volunteers who did not consume prebiotics (standardized coefficient: −3.20; $P = .019$).

Conclusions: For patients with T2DM, prebiotics supplemented produced no significant impact on serum I-FABP levels.

Abbreviations: BMI(s), body mass index (es); DF, diabetes patients with fructooligosaccharides consumption; DO, diabetes patients without fructooligosaccharides consumption; FOS, fructooligosaccharides; HbA1c, hemoglobinA1c; HF, health participants consume fructooligosaccharides; HO, health participants did not consume fructooligosaccharides; I-FABP, fatty acid-binding protein; IL-6, interleukin-6; LBS, lipopolysaccharide-binding protein; LDL, low-density lipoprotein; LPS, lipopolysaccharide; Mets, metabolic syndrome; T2DM, type 2 diabetes mellitus; TNFa, tumor necrosis factor alpha; VLDL, very low-density lipoprotein.

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KEYWORDS
diabetes mellitus, fructooligosaccharides, intestinal fatty acid-binding protein, prebiotics, synbiotics

1 | INTRODUCTION

Diabetes is a chronic condition associated with abnormally high levels of sugar (glucose) in the blood. The diagnostic criteria of diabetes, established by the World Health Organization (WHO), are fasting plasma glucose ≥7.0 mmol/L, 2-hour post-load plasma glucose ≥11.1 mmol/L, orHbA1c ≥48 mmol/mol.[1] Though the origin of diabetes is considered complex and multifactorial, the disease is currently highly prevalent, accounting for 3.5% of the mortality cases due to non-communicable chronic diseases.[2] According to WHO, one in 10 people have diabetes worldwide, reaching up to one in three in some regions.[3]

Probiotics are microorganisms used as food supplements that are beneficial for the host.[4] Prebiotics are designed to selectively stimulate beneficial microbiota, which has been shown to improve the health of the host.[5] The most widely accepted prebiotics are the fermentable oligosaccharides inulin, fructooligosaccharides (FOS), galactooligosaccharides (GOS), and lactulose. Probiotics and relevant supportive prebiotics can be administered simultaneously to increase survivability and enhance the beneficial effects in the intestinal tract.[6] Such combinations of probiotics and prebiotics that aim to improve gut health are called synbiotics.[5,7]

Fructooligosaccharides is found in a variety of edible plants,[8] with onions and leeks being the most common ingredients in the Western diet.[9] A previous study showed that FOS are non-digestible oligosaccharides; for healthy individuals, FOS would survive the small intestine and eventually be fully metabolized by the colonic microbiota[10] which generated many results regarding its effects on human health. Similar to the fermentation of dietary fibers, consumption of FOS leads to an increase in breath hydrogen concentration.[10-12] The short-chain fatty acids produced during the fermentation of FOS, such as acetate, propionate, and butyrate, are absorbed by the colonic mucosa.[13-15] Acetate and propionate absorbed through the portal vein influence systemic carbohydrate and lipid metabolism,[14] glucose metabolism,[16-18] and serum lipids metabolism.[18,19] By studying FOS fermentation, researchers hope to predict their metabolic effects.

Recently, a systematic review investigated the association between metabolic endotoxemia and diabetes mellitus. This review found that most of the studies observed high lipopolysaccharide (LPS) or LPS-binding protein (LBP) concentrations in diabetic subjects compared with healthy controls.[20] Scientific evidence suggests that intestinal microbiota interacts with environmental factors and susceptible genetic factors, which contribute to the development of diabetes.[21] Previous studies have shown no significant effect of consuming FOS on fasting plasma glucose and serum total cholesterol concentrations in individuals with type 2 diabetes mellitus (T2DM).[5,22] Yamashita et al[23] administered 8 g FOS supplementation per day for 2 weeks to T2DM patients with elevated blood glucose and serum lipid concentrations.

Several experiments in rats have shown that FOS lowers total, LDL, and VLDL cholesterol and serum triacylglycerol.[24,25] Luo et al[22] studied the effect of consuming 20 g of FOS daily on humans. Although no effect from consuming FOS was found in T2DM individuals, they found increased basal hepatic glucose production in the healthy subjects. Pedersen et al[26] found no significant changes in either total, HDL, and LDL cholesterol, or triacylglycerol in healthy females with a daily intake of 14 g inulin. To put these studies into context, the mean daily consumption of prebiotics such as inulin and oligofructose from natural foods ranges from 1 to 4 g in the United States.[6] However, though there have been studies on the effects of FOS, very few were placebo-controlled and double-blind clinical experiments performed to examine specific health outcomes.

Considering the association between T2DM and intestinal fatty acid-binding protein (I-FABP),[27] we expected that prebiotics could improve I-FABP levels in patients with T2DM. In addition, we examined the relationship between I-FABP levels and prebiotic effects to assess the underlying mechanisms. This case-control study aimed to clarify the currently described effects of prebiotics in the prevention and management of T2DM by screening biomarkers of blood or urine samples in patients with T2DM.

2 | METHODS

2.1 | Patient and report

All patients and healthy volunteers signed an informed consent form. The inclusion and exclusion criteria were followed during the recruitment of participants. We recruited patients ≥18 years old who had been diagnosed with diabetes (based on the WHO diagnostic criteria[17]). The study was approved by the Research Ethics Committee of the Buddhist Taipei Tzu Chi General Hospital. The protocol of this study was reviewed and approved by the Research Ethics Committee of the Buddhist Taipei Tzu Chi General Hospital. The study was registered in the Chinese Clinical Trial Registry on August 2, 2018, ChiCTR1800017529, and retrospectively registered on the Registry website as http://www.chictr.org.cn/historyversionpuben.aspx?regno=ChiCTR1800017529.

The participants in this study had no history of gastrointestinal disease and had not been treated with antibiotics or laxatives within 3 months before the experiment; patients with diabetes mellitus all received dietary advice to control and treat diabetes.

Blood or urine samples were collected at baseline and at 1, 3, and 6 months. Each patient kept a specific diary where they recorded the time of supplement consumption, possible diseases or discomfort, medications used, and deviations in usual lifestyle behavior (including eating and drinking). Complaints of flatulence were rated on a 4-point scale (none, mild, moderate, or severe). All patients consumed FOS (15-20 g/d) for 1-2 months. Regarding food intake and supplementation, the patients were instructed to maintain their usual lifestyle. However, instructions emphasized that the patients were not allowed to eat probiotics and other prebiotic dairy products, specifically ones that contained microorganisms that survive the passage through the upper gastrointestinal tract, or food products, such as onions and leeks, which are known to contain large amounts of FOS naturally. A list of these probiotic, prebiotic, and high FOS-containing foods was provided to all patients. In the diary, patients recorded their 3-day habitual dietary intakes in each treatment period. The FOS were isoenergetic (30-40 kcal/d) and were mixed with a self-prepared beverage; the FOS dose was gradually increased 5 g/d during the first 3 days to prevent adverse gastrointestinal side effects. Initially, we recruited 80 patients with T2DM and 80 healthy volunteers. However, of the total participants, only 68 patients with T2DM and 52 healthy volunteers were included in this study. Forty participants with T2DM consumed prebiotics and 28 did not consume prebiotics. Moreover, 30 healthy volunteers consumed prebiotics and 22 did not consume prebiotics.

2.2 | Measurement of cytokines

We collected the patients' blood, centrifuged it, and refrigerated it at −70°C until testing. The cytokines interleukin-6 (IL-6) and tumor necrosis factor-alpha (TNFa), as well as I-FABP, in the serum were measured using an enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems), according to the manufacturer's instructions.

2.3 | Statistical analysis

The demographic and clinical characteristics of the study population were compared using analysis of variance (ANOVA) for continuous variables and chi-square test for categorical variables. We also performed post hoc analysis when continuous variables showed significant differences. A multivariate linear regression analysis was performed to confirm the relationship between inflammation level and prebiotics after adjusting for other factors. All statistical analyses were performed using SAS 9.3 software. A *P*-value of <.05 was considered significant in all tests.

3 | RESULTS

3.1 | Participants' demographic data

We recruited 68 patients with T2DM and 52 healthy participants (Figure 1). Forty diabetes patients consumed FOS (DF), and 28 diabetes patients did not consume FOS (DO). A total of 30 healthy participants consumed FOS (HF), and 22 healthy participants did not consume FOS (HO). The mean ages of the DF, DO, HF, and HO groups were 59.88 ± 12.24, 53.25 ± 13.65, 38.03 ± 15.99, and 41.41 ± 19.81 years, respectively. Patients in the DF and DO groups were older than those in the other groups. Seventy-three (60.83%) female patients and 47 (39.17%) male patients were enrolled in this study. The DF, DO, HF, and HO groups had body mass indexes (BMIs) of 27.10 ± 4.69, 26.57 ± 6.33, 20.00 ± 2.46, and 22.60 ± 3.60, respectively. Patients with T2DM had higher BMIs than the healthy volunteers. Participants in the DF, DO, HF, and HO groups weighed 71.77 ± 16.40 kg, 68.36 ± 16.84 kg, 52.01 ± 8.73 kg, and 58.45 ± 8.65 kg, respectively. The weight measurements of patients with T2DM were consistent with their BMI results. The height measurements of the participants in the DF, DO, HF, and HO groups were 162.38 ± 9.60, 160.38 ± 8.33, 160.96 ± 8.72, and 161.11 ± 7.15 cm, respectively. Their systolic blood pressure measurements were 135.61 ± 17.02, 128.04 ± 15.51, 114.21 ± 13.31, and

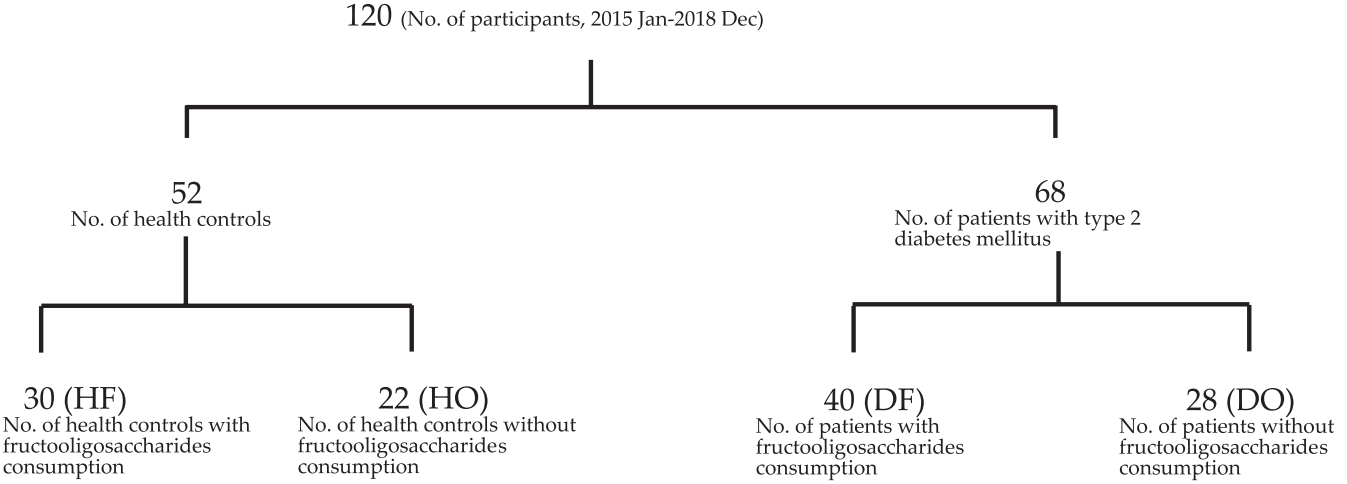

FIGURE 1 Flow chart of this study

TABLE 1 Demographic data of patients with type 2 diabetes mellitus

	DF (N = 40)			DO (N = 28)			HF (N = 30)			HO (N = 22)				
		Mean	SD		Mean	SD		Mean	SD		Mean	SD	*P*-value	Post hoc
Age	40	59.88	±12.24	28	53.25	±13.65	30	38.03	±15.99	22	41.41	±19.81	<.0001*	DF > HF, HO; DO > HF
BMI	38	27.10	±4.69	28	26.57	±6.33	27	20.00	±2.46	22	22.60	±3.60	<.0001*	DF, DO > HF, HO
Body weight	38	71.77	±16.40	28	68.36	±16.84	27	52.01	±8.73	22	58.45	±8.65	<.0001*	DF > HF, HO; DO > HF
Body height	38	162.38	±9.60	28	160.38	±8.33	27	160.96	±8.72	22	161.11	±7.15	.8106	
Systolic blood pressure	33	135.61	±17.02	26	128.04	±15.51	24	114.21	±13.31	17	117.29	±12.97	<.0001*	DF > HF, HO; DO > HF
Diastolic blood pressure	31	84.10	±13.75	26	81.81	±14.02	23	72.39	±8.95	17	73.59	±11.05	.0017*	DF > HF
I-FABP (difference)	30	0.43	±3.70	16	−1.27	±3.75	22	0.62	±1.46	21	1.42	±6.52	.2891	
TNFa (difference)	23	0.04	±0.38	17	0.01	±0.37	18	−0.18	±0.43	12	−0.13	±0.27	.2137	
IL-6 (difference)	23	0.14	±0.55	18	0.10	±0.38	17	0.02	±0.30	12	2.75	±10.07	.2581	
Eating habits	39			26			27			22				
Non-vegetarian		33	84.62		22	84.62		20	74.07		13	59.09	.0988	
Vegetarian		6	15.38		4	15.38		7	25.93		9	40.91		
HbA1C (baseline)	39	6.81	±1.32	27	8.08	±2.13	28	5.28	±0.37	22	5.37	±0.29	<.0001*	DO > DF > HF, HO
HbA1C (follow up)	31	6.73	±1.35	19	7.81	±2.20	23	5.28	±0.33	20	5.38	±0.26	<.0001*	DO > DF > HF, HO
HbA1C (difference)	31	−0.14	±0.52	18	−0.13	±0.95	23	0.01	±0.20	20	−0.02	±0.22	.6800	

Note: Difference of I-FABP, TNFa, IL-6, and HbA1C means improvement of measurements between before and after prebiotic consumption for 6 wk.

Abbreviations: BMI, body mass index; DF, diabetes patients with fructooligosaccharides consumption; DO, diabetes patients without fructooligosaccharides consumption; HbAIc, haemoglobinA1c; HF, health participants consume fructooligosaccharides; HO, health participants did not consume fructooligosaccharides; I-FABP, fatty acid-binding protein; IL-6, interleukin-6.

*$P < .05$.

117.29 ± 12.97 mm Hg, respectively. Their diastolic blood pressure measurements were 84.10 ± 13.75, 81.81 ± 14.02, 72.39 ± 8.95, and 73.59 ± 11.05 mm Hg, respectively. The blood pressure measurements of patients with T2DM were higher than those of the healthy volunteers. The baseline haemoglobinA1c (HbA1c) levels of participants in DF, DO, HF, and HO groups were 6.81 ± 1.32, 8.08 ± 2.13, 5.28 ± 0.37, and 5.37 ± 0.29, respectively (Table 1). Results of the post hoc analysis are presented in Table 2. We found that DF was higher than other groups in age, BMI, body weight, systolic blood pressure, and diastolic blood pressure. We found that DO was higher than other groups inHbA1C (baseline and follow-up).

3.2 | Linear regression results

The improvements between the inflammation variables at baseline and follow-up were denoted as I-FABP (difference), TNFa (difference), and IL-6 (difference). A multiple linear regression model was used to estimate the possible influence of prebiotics on the inflammation variables. We set I-FABP (difference) as the dependent variable in the regression model. In Table 2, the results showed that age is significant at different I-FABP levels (standardized coefficient: 0.06; $P = .047$). Analysis of eating habits showed that vegetarian diets produced lower I-FABP levels than the non-vegetarian diets(standardized coefficient: −2.55; $P = .022$). In the comparison between groups, the DF group expressed lower I-FABP levels than the HO group (standardized coefficient: −3.20; $P = .019$). In addition, the DO group showed lower I-FABP levels than the HO group (standardized coefficient: −4.06; $P = .005$). Table 2 shows that patients who received education courses had lower I-FABP levels (standardized coefficient: −3.19; $P = .004$).

TABLE 2 Linear regression analysis of the age, eating habits, and I-FABP of patients with type 2 diabetes mellitus

	Full model	
	Coefficient	*P*-value
Age	0.06	.047*
Eating habits		
Vegetarian vs non-vegetarian	−2.55	.022*
Education		
Yes vs no	−3.19	.004*
Group		
DF vs HO	−3.20	.019*
DO vs HO	−4.06	.005*
HF vs HO	−0.84	.495

Abbreviations: DF, diabetes patients with fructooligosaccharides consumption; DO, diabetes patients without fructooligosaccharides consumption; HF, health participants consume fructooligosaccharides; HO, health participants did not consume fructooligosaccharides.
*$P < .05$.

4 | DISCUSSION

Prebiotics are food ingredients that induce the growth or activity of beneficial microorganisms (eg, bacteria and fungi).[28] FOS is among the most common prebiotics. A previous study showed the significance of the correlation between age and I-FABP levels.[29] I-FABP is a new biomarker for intestinal diseases and is released into the circulation immediately after the small intestinal mucosal tissue is injured[30]; I-FABP is significantly higher in patients with T2DM.[31] According to previous published studies, the association of FABP2 Ala54Thr polymorphism with T2DM, obesity, and metabolic syndrome (MetS) is controversial. To this concern, in global populations, a meta-analysis conducted to show associations between the FABP2 Ala54Thr polymorphism and T2DM and MetS.[32]

In daily diet, people consume prebiotics from inulin and oligofructose as natural ingredients.[6] Prebiotics are beneficial to the host, especially on human gastrointestinal health.[1-4]

According to previous studies, a lack of short-chain fatty acids (especially butyrate) may cause metabolic and intestinal dysfunction.[7,10,11,27,30] Diabetes mellitus is associated with gut microbiota, probiotics, FABP2, and LPS or LBP.[18,20,30,32] Based on previous studies, T2DM may be an operable intestinal disease characterized by a component of intestinal dysfunction.[33] To our knowledge, I-FABP was correlated with LPS among all participants with human immunodeficiency virus. According to previous studies and our results, we may assume that improvement of I-FABP levels was correlated with LPS in T2DM patients with intake of prebiotics. There is no relevant literature discussing the relationship between I-FABP and metabolic endotoxemia. However, epidermal-type FABP (E-FABP) is specifically involved in the LPS-induced cytokine production of mast cells and could play a role in the host defense against bacterial infection, possibly through regulation of TNFa production.[34] In addition, I-FABP is a cytoplasmic protein that is specifically expressed in the epithelium of intestinal mucosa, and the serum concentration may be increased when intestinal barrier dysfunction occurs. However, the relationship between I-FABP and endotoxemia has not been well explored. We believe endotoxemia may cause gut barrier dysfunction and the relevant biomarker, serum I-FABP, may be increased.

No relevant studies have investigated the effects of prebiotic consumption on serum I-FABP levels in patients with T2DM. This study found that the intake of prebiotics may reduce I-FABP levels in patients with T2DM. To our knowledge, this is the first study to evaluate the association between prebiotics and I-FABP levels. We suggest that T2DM patients treated with FOS can recover from small intestinal mucosal tissue injury. Our study provides clinical novelty to investigate the effect of FOS on I-FABP levels compared with previous studies.[5,28,30] However, other inflammation indices, including TNFa and IL-6, showed no significant association with prebiotics. TNFa and IL-6 are proinflammatory cytokines. Moreover, prebiotics did not trigger an increase in the HbA1c level. Therefore, intake of prebiotics might control I-FABP levels in patients with T2DM.

In our study, the education course for patients with T2DM was important to control the level of inflammation (Table 2). In addition,

the improvement of I-FABP levels in the DO group was larger than that in the DF group. This is probably because the baseline HbA1c of the DO group was higher than that of the DF group (Table 1). For eating habits, we use Chi-square test to analysis count data of eating habits of patients with type 2 diabetes mellitus and healthy controls listed in Table S1. The result showed distribution of eating habits was not different between patients and health controls ($P > .05$).

This study had several limitations. First, the baseline HbA1c among patients with T2DM varied due to participants' willingness. According to experiences, the sweet taste of FOS decreased the willingness to participate of patients with T2DM who had higher HbA1c levels. Moreover, the differences between patients and controls' ages may affect the results. The lack of random allocation might limit the interpretations of our results. Second, this study had a relatively small sample size, which might have biased our results. Third, the lack of quantitative assessment of the patients' compliance to FOS consumption might limit the interpretations of our results. A further study with more patients and fewer confounding factors might be warranted in the future. Fourth, we conducted a cross-sectional study, which might make it difficult to measure predictions, associations, and any causal relationships. Finally, we found that I-FABP levels were not significantly different between the DF and DO groups. In our clinical viewpoint, the HO group is a pure control against the DO group.

5 | CONCLUSIONS

In conclusion, diets supplemented with prebiotics may result in improvements in serum I-FABP levels for patients with T2DM than healthy controls. Among T2DM patients, prebiotics consumption produced no significant impact on I-FABP levels.

AUTHORS' CONTRIBUTIONS

YCH, IST, and CYK created the research idea, performed the analysis, wrote the results and discussion, and contributed to the literature review. CWL provided clinical suggestions and helped revise the manuscript. CFC performed the literature review. YYL performed the laboratory analysis. THH performed the analyses. JHW supported protocol preparation. IST prepared the manuscript for submission. All authors read and approved the final manuscript.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

We confirm that all methods were performed in accordance with the relevant guidelines. This study was approved by the Institutional Review Board of Taipei Tzu Chi Hospital, Buddhist Tzu Chi Medical Foundation, and New Taipei City, Taiwan (IRB 03-XD28-059).

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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