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ORIGINAL RESEARCH

Effects of polymorphism in *FABP2* Ala54Thr on serum lipids and glycemic control in low glycemic index diets are associated with gender among Han Chinese with type 2 diabetes mellitus

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Background/aims: Low glycemic index (GI) diets may have beneficial effects on glycemic control and serum lipid levels in patients with type 2 diabetes, but whether its effect is affected by polymorphisms of genes associated with lipid metabolism remains unclear. This study investigated whether the effects of a low-GI diet on serum lipids and glycemic control in patients with diabetes are associated with polymorphisms of *FABP2* Ala54Thr (rs1799883).

Methods: A retrospective study was conducted involving 165 patients with type 2 diabetes mellitus (T2DM) who participated in two completed trials. Parameters reflecting the glycemic control, inflammatory factors, and fasting plasma lipids before and after intervention were measured, and the polymorphism of rs1799883 for each participant was genotyped using a MassARRAY. Differences between the genotypes of rs1799883 before or after the intervention were compared, and changes in the lipid profiles, glycemic control, inflammatory profiles, and dietary intake from baseline were analyzed using an analysis of covariance (generalized linear model).

Results: When the data were analyzed as a whole, after 4–5 weeks of similar low-GI diet intervention, we found that the decrease of triglycerides (TG) in the homozygous Ala54 carriers was more significant than that in the Thr54 allele carriers ([−0.58±1.24] vs [−0.14±1.08], P=0.015) with the adjustment for potential confounding factors; furthermore, compared with the Thr54 carriers, there was a significant trend in the decrease of total cholesterol (TC) in the homozygous Ala54 carriers (P=0.057). Subgroup analysis revealed that in women the homozygous Ala54 carriers exhibited a significant decrease of serum TG, TC, fasting blood glucose, and glycated albumin in women, but this was not noted in men.

Conclusion: The effect of *FABP2* Ala54Thr polymorphism on response to blood lipids and glycemic control in low-GI diets is associated with gender among Han Chinese patients with T2DM.

Keywords: type 2 diabetes mellitus, plasma lipids, fatty acid-binding protein 2, single-nucleotide polymorphism, low glycemic index diet

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Introduction

Plasma lipids, including low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides (TG), and total cholesterol (TC), are heritable and modifiable risk factors for coronary artery disease,[1] which is a leading cause of death.[2] To manage and prevent heart disease, numerous human genetic studies of lipid levels have been performed to identify targets for therapies that treat dyslipidemia,[1] with hundreds of genes proposed as candidates. Among them, the fatty

acid-binding protein 2 (*FABP2*) gene, a member of the FABP superfamily, is located on the long arm of chromosome 4; it encodes for the intestinal fatty acid-binding protein, thus it plays a key role in the absorption and intracellular transport of long-chain fatty acids in the diet.[3,4] An in vivo study proposed that, in the absence of confounding factors such as environmental and genetic variables, *FABP2* polymorphism specifically influences small-intestinal lipid absorption without modifying glucose uptake or metabolism.[5] The association between Ala54Thr polymorphism of *FABP2* and several chronic diseases has been extensively studied. Thr54 carriers of *FABP2* have been shown to be associated with higher body mass index (BMI), insulin resistance, metabolic syndrome, type 2 diabetes mellitus (T2DM), and both fasting and postprandial hyperlipidemia.[4,6–11] Several studies have suggested that this variant of *FABP2* increases the lipemic response to food ingestion and chronically exposes its carriers to postprandial hyperlipidemia.[8,13] Furthermore, it was reported that Thr54 carriers have higher lipid oxidation rates than Ala54-homozygous persons do.[13] All of the aforementioned factors may contribute to impaired insulin action, cause glucose intolerance, and increase diabetes risk.[8,13,14] Individuals with T2DM, in addition to frequently exhibiting increased serum fasting TG and decreased HDL-c, may also exhibit elevated postprandial serum TG.[15] Several studies have suggested the association of Ala54Thr polymorphism with increased serum fasting and postprandial TG,[8,13] and Almeida et al[12] found that the Thr54Thr genotype of *FABP2* in patients with T2DM increased fatty acids absorption, and they suggested that this might increase susceptibility to the effects of dietary lipids.[13] In addition, Ala54Thr *FABP2* polymorphism has been reported to play a distinct role in T2DM among different populations and sexes.[10,16] However, data on fat metabolism and glycemic response associated with this polymorphism in Han Chinese patients with T2DM are scarce.

The glycemic index (GI) is a classification of carbohydrate-containing foods according to the glycemic response that they evoke,[17] and a low-GI diet is effective in glycemic control and in improving various markers of cardiovascular risk in people with diabetes.[18] The utility of low-GI diets in the management of T2DM has been demonstrated by two systematic reviews, in which low-GI diets led to a 5% reduction in hemoglobin A1c (HbA1c).[19,20] The effect of low-GI diets on plasma lipid profiles has also been the focus of considerable attention. However, the results of studies on the subject have shown inconsistent findings.[18,21,22] Whether the effects of low-GI diets on serum lipid levels, glycemic control, and inflammatory factors are affected by polymorphisms of genes related to lipid metabolism is not yet clear; therefore, this study investigated whether the effects of low-GI diets on blood lipids, glycemic control, and inflammatory factors in patients with diabetes are affected by polymorphisms of *FABP2* Ala54Thr (rs1799883).

Materials and methods

This was a retrospective study involving 165 individuals who had previously been recruited in our two completed trials, in which 114 people received intervention diets (daily substitution of either extruded adzuki bean convenience food or black-grained wheat for a partial staple food) and 51 people (as a co-control group of the two trials) received a traditional diabetic diet, with both diets being low-GI diets.[23,24] The participants (aged between 30 and 80 years) were recruited from Pinggu Hospital of Traditional Chinese Medicine (Beijing, People's Republic of China) in 2016, and they were all diagnosed with T2DM according to the American Diabetes Association Diagnosis Criteria.[25] They all presented with at least one of the following: 1) latest lab-testing fasting glucose ≥6.1 mmol or 2) HbA1c >6.5%, as in the previous studies (Trial registration: NCT02999867 at www.ClinicalTrials.gov).[23,24] The study protocol was approved by the Ethics Committee of Peking Union Medical College Hospital of the Chinese Academy of Medical Science (Unique Protocol ID: PUMCH-ZS-1048). This study was conducted in accordance with both the Declaration of Helsinki of 1975, as revised in 1983, and the guidelines of the center's institutional review board. All the participants were informed of the details of the study, and every participant provided written informed consent. All participants received intensive nutritional education, mainly related to dietary nutrition and T2DM management every week during follow-up in the test period. Systematic dietary programs were designed according to the Dietary Guidelines for the Chinese Residents 2013 and the China Medical Nutrition Therapy Guidelines for Diabetes 2010.[23,24] The participant's medications and/or other clinical interventions needed to remain unchanged during the intervention period.

Dietary assessment

The dietary intake of each participant was assessed through 3-day food records that included 2 days from Monday to Friday and 1 day on the weekend. Before the intervention, the participants received a dietitian's instructions regarding how to record their own diet diary, and they were given templates for diaries. After reviewing the diet records, the data were analyzed by using the Nutrition Clinic Consultation

Management System (Zhending Health Technology Co. Ltd., Shanghai, People's Republic of China).

Anthropometric measurement

Anthropometric measurements of individuals wearing light clothing and without shoes were conducted by well-trained examiners. Height was measured to the nearest 0.1 cm with a portable stadiometer. Weight was measured in an upright position to the nearest 0.1 kg with a calibrated scale. BMI was calculated according to the formula BMI = weight (kg)/height^2 (m^2), and waist circumference measurements were taken at the end of normal expiration to the nearest 0.1 cm, measuring from midway between the lower borders of the rib cage and the iliac crest.

Measurements of blood sample

All participants underwent venous blood collection in the morning after fasting for at least 8 hours to determine levels of fasting blood glucose (FBG), glycosylated HbA1c, glycated albumin (GA), tumor necrosis factor alpha (TNF-α), and IL-6 before and after intervention. In addition, concentrations of TC, TG, HDL-c, and LDL-c were measured from previously collected blood samples. FBG, TC, TG, HDL-c, and LDL-c concentrations were measured by an automatic analyzer (Olympus AU5400; Olympus, Tokyo, Japan) using commercial kits from Wako Pure Chemical Industries Ltd. (Tokyo, Japan). The level of HbA1c was analyzed using a glycosylated glucose meter (Bio-Rad Laboratories Inc., Hercules, CA, USA) based on HPLC. GA was tested through enzymology using the Japan Lucina GA-L kit from Asahi Kasei Corporation (Tokyo, Japan). Detection of hs-CRP using the immune transmission ratio was conducted using a Beckman Coulter LX-20 automatic biochemical analyzer (Beckman Coulter Inc., Brea, CA, USA). TNF-α and IL-6 levels were detected by ELISA using a Siemens Immulite 1000 (Siemens AG, Munich, Germany).

DNA extraction

DNA was extracted from the blood leukocytes using a TIANamp Blood DNA Maxi Kit DP349-02 (Tiangen Biotech Co, Ltd., Beijing, People's Republic of China) according to the instruction manual. The polymorphisms of rs1799883 were genotyped using MassARRAY in this study. Extension probes were designed so that 25 different SNP assays could be amplified and analyzed in a PCR cocktail. The assay mix including forward, reverse, and extension primers and 10–20 ng of genomic DNA was heated for 2 minutes at 50°C, denatured at 95°C for 5 minutes, and cycled at 95°C for 15 seconds and 60°C for 1 minute for a total of 30 cycles. After purification, objective fragments were detected using a matrix-assisted laser desorption/ionization–time-of-flight mass spectrometer (Agena Bioscience, San Diego, CA, USA) and analyzed using the manufacturer's software.

Statistical analysis

Statistical analysis was conducted using SPSS 16.0 software. The genotype distribution was assessed for the Hardy–Weinberg equilibrium and subsequently analyzed using the chi-squared test. First, regardless of gender, the participants were divided into two groups according to their genotypes, including the homozygous Ala54 group and the Thr54 group (Ala54/Thr54 and Thr54/Thr54). Then, considering possible gender differences in the effect of *FABP2* on fat metabolism,[9] the data were analyzed separately by gender. Categorical variables were represented by frequency or percentage and examined, whereas quantitative variables were presented as mean ± SD. Differences in age, course of disease, BMI, waist circumference, ratio of men, types of low-GI diet, and use of lipid-lowering agents between the groups at baseline were analyzed using chi-square or Student's *t*-tests when appropriate. An analysis of covariance (generalized linear model) was performed to assess the differences in lipid profiles, inflammatory factors, glycemic control variables, nutrient intakes before and after intervention, as well as changes in lipid profiles, glycemic control, inflammatory profiles, and dietary intakes from baseline; $P<0.05$ was considered statistically significant.

Results

Basic characteristics of the study population

In our study, 165 individuals with T2DM were evaluated. A total of 80 (48.5%) had the homozygous Ala54 genotype, and 85 (51.5%) had the variant genotype (18 Thr54Thr and 67 Ala54Thr). According to the Hardy–Weinberg equilibrium, no significant difference was found between the observed value and expected value of genotype distribution ($P>0.05$). No significant differences were noted in age, course of disease, BMI, waist circumference, ratio of men, types of low-GI diet, and use of lipid-lowering agents between the two groups (Table 1).

Dietary intake

The dietary intake of each participant was assessed according to the dietary diaries recorded by the participant by using the Nutrition Clinic Consultation Management System

Table 1 Basic characteristics of the two groups

Characteristics	Ala54Ala carriers (n=80)	Thr54 carriers (n=85)	*P*-value
Men, n	37	34	0.436
Age, years	57.0±9.4	58.8±10.1	0.238
Course of disease, years	8.2±6.4	7.4±6.1	0.427
BMI, kg/m^2	26.5±3.4	26.7±3.4	0.687
Normal weight, n	17	13	NS
Overweight, n	39	48	NS
Obesity, n	24	24	NS
Waist circumference, cm	92.2±9.2	91.6±8.4	0.656
Types of low-GI diet			0.806
Intervention diets, n	56	58	
A traditional diabetic diet, n	24	27	
Lipid-lowering agents, n	10	12	0.805

Abbreviations: BMI, body mass index; GI, glycemic index; NS, not significant.

(Zhending Health Technology Co. Ltd.), and the nutrient intakes were calculated automatically based on the Chinese Food Composition Table (2009).[26] With the adjustment for age, sex, BMI, and course of disease, no significant differences ($P>0.05$ for all) were revealed in energy and nutrient intake between the Ala54Ala and Thr54 carriers before and after intervention (Table 2) or in both sex groups (data not shown).

Differences in variables between the two groups at baseline and after intervention and changes in variables from baseline

When the participants were divided into two groups according to the genotype rs1799883, TG levels were greater in the homozygous Ala54 carriers than they were in the variant genotype carriers at baseline ([2.17±1.87] vs [1.80±1.29], $P=0.001$), and no significant differences existed in FBG, HbA1c, GA, inflammatory factors, TC, HDL-c, and LDL-c at baseline and after intervention between the two groups ($P>0.05$ for all). When comparing changes of the aforementioned variables from baseline in the two groups with adjustment for age, sex, BMI, and disease course, we found that the decrease of TG in the homozygous Ala54 carriers was more significant than that in the variant genotype carriers ([−0.58±1.24] vs [−0.14±1.08], $P=0.015$). Furthermore, compared with the variant genotype carriers, a significant trend was found in the decrease of TC in the homozygous Ala54 carriers ($P=0.057$), and no significant differences were seen in the changes of FBG, HbA1c, GA, inflammatory factors, HDL-c, and LDL-c from baseline in the two groups (Table 3).

Table 2 Daily energy and nutrient intakes of the participants at baseline and after a 4-week dietary intervention

Variables	Ala54Ala carriers	Thr54 carriers	*P*-value
Energy, kcal			
Baseline	1,556.2±396.2	1,489.4±358.9	0.255
After intervention	1,581.5±228.2	1,538.5±304.4	0.737
Change from baseline	25.3±254.6	36.9±331.5	0.217
Protein, g			
Baseline	55.3±16.8	54.4±15.3	0.731
After intervention	65.7±10.2	65.3±15.9	0.809
Change from baseline	10.4±15.4	10.3±14.8	0.842
Fat, g			
Baseline	44.9±16.6	42.4±15.2	0.303
After intervention	43.0±11.1	39.2±11.5	0.412
Change from baseline	−1.9±12.6	−2.5±13.2	0.693
Carbohydrate, g			
Baseline	239.5±66.5	234.5±66.2	0.330
After intervention	234.9±61.3	232.5±59.4	0.389
Change from baseline	−4.6±64.3	−2.0±61.5	0.189
Dietary fiber, g			
Baseline	12.5±5.9	12.1±4.0	0.636
After intervention	13.8±4.9	15.3±6.1	0.225
Change from baseline	1.3±5.3	3.2±5.4	0.228
Cholesterol, mg			
Baseline	353.0±107.6	341.9±121.5	0.532
After intervention	294.2±163.6	280.4±178.7	0.606
Change from baseline	−58.8±128.9	−61.5±137.6	0.713

Notes: Data at baseline and after intervention are expressed as mean ± SD. Differences in variables between groups and changes from baseline were analyzed using the ANCOVA (generalized linear model) test with adjustments for sex, age, BMI, and course of disease.
Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index.

Differences between carriers of different genotypes in both sex groups at baseline and after intervention and changes in variables from baseline

To determine possible gender differences in the effects of *FABP2* on metabolism, the data were analyzed separately by gender. Overall, no significant differences were found in age, BMI, waist circumference, and course of disease as well as the parameters of glycemic control, inflammation, and lipid profiles between the carriers of different genotypes in both sex groups at baseline and after intervention ($P>0.05$ for all). When comparing the changes of the aforementioned parameters from baseline in both sex groups with adjustments for age, BMI, and course of disease, we found that the decreases of FBG, TC, TG, and GA in the female homozygous Ala54 carriers were more significant than those in the variant genotype carriers. Moreover, in women, compared with variant genotype carriers, a significant trend was revealed

Table 3 Differences in variables between the two groups at baseline and after intervention and changes in variables from baseline

Variables	Ala54Ala carriers	Thr54 carriers	*P*-value
Fasting blood glucose			
Baseline	9.0±2.9	8.5±2.4	0.160
After intervention	8.4±2.2	8.1±2.2	0.402
Change from baseline	–0.6±1.8	–0.3±1.5	0.263
TC			
Baseline	4.91±1.13	4.79±1.06	0.099
After intervention	4.61±0.93	4.71±1.06	0.495
Change from baseline	–0.31±0.82	–0.08±0.75	0.057
Triglycerides			
Baseline	2.17±1.87	1.80±1.29	0.001
After intervention	1.59±0.97	1.66±1.12	0.658
Change from baseline	–0.58±1.24	–0.14±1.08	0.015
HDL-c			
Baseline	1.20±0.29	1.21±0.32	0.842
After intervention	1.18±0.26	1.21±0.32	0.463
Change from baseline	–0.03±0.18	0.00±0.16	0.358
LDL-c			
Baseline	2.85±0.94	2.80±0.84	0.733
After intervention	2.74±0.80	2.82±0.81	0.496
Change from baseline	–0.11±0.65	0.02±0.57	0.163
HbA1c			
Baseline	7.2±1.5	7.0±1.2	0.340
After intervention	6.9±1.0	6.9±1.4	0.670
Change from baseline	–0.4±1.5	0.1±1.4	0.218
GA			
Baseline	18.4±4.8	17.9±4.3	0.438
After intervention	16.9±3.9	16.8±3.9	0.953
Change from baseline	–1.6±2.4	–1.1±1.8	0.116
IL-6			
Baseline	2.82±2.73	2.64±3.08	0.680
After intervention	3.00±2.60	3.02±3.53	0.831
Change from baseline	0.18±2.19	0.38±1.35	0.416
TNF-α			
Baseline	7.4±2.5	7.5±2.2	0.743
After intervention	10.0±8.4	9.5±4.5	0.658
Change from baseline	2.6±8.4	2.0±4.4	0.453

Notes: Data at baseline and after intervention are expressed as mean ± SD. Differences in variables between groups and changes from baseline were analyzed using the ANCOVA (generalized linear model) test with adjustments for sex, age, BMI, and course of disease.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; GA, glycated albumin; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor alpha.

in the decrease of LDL-c in the homozygous Ala54 carriers (*P*=0.051). In men, no significant differences were noted between carriers of different genotypes in the changes of parameters regarding glycemic control, inflammation, and lipid profiles (Table 4).

Discussion

The present study was a retrospective analysis of data from 165 patients with T2DM from our two previous completed trials. We observed the association between polymorphism of *FABP2* Ala54Thr (rs1799883) with the response of glycemic control, lipid profiles, and inflammatory markers in an intervention featuring a low-GI diet for 4–5 weeks among Han Chinese patients with T2DM. In general, polymorphism of *FABP2* Ala54Thr may affect the response of serum lipids to a low-GI diet. However, our subgroup analysis indicated that the effect of polymorphism of *FABP2* Ala54Thr on glycemic control and serum lipids is more significant in women than in men.

Often, patients with T2DM exhibit increased serum fasting TG as well as elevated postprandial serum TG.[15] For better glycemic control, a low-GI diet is often recommended to patients with T2DM due to its role in reducing HbA1c demonstrated by two systematic reviews.[19,20] However, the effects of a low-GI diet on serum lipids have shown inconsistent findings.[18,21,22] Fleming and Godwin reported that a low-GI diet may help lower total and LDL-c and had no significant effects on HDL-c and TG in their systematic review and meta-analysis.[21] However, in the same year, another systematic review showed that low-GI diets were effective in increasing HDL-c but had no significant effects on LDL-c and TG in the management of individuals with T2DM.[18] Notably, a more recent systematic review using the Cochrane Database concluded that no convincing evidence exists that low-GI diets have a clear beneficial effect on plasma lipids.[22] Because plasma lipid levels are determined by a multifactorial process that involves both environmental and genetic factors, these inconsistent results are possibly associated with variables such as polymorphisms of genes related to lipid metabolism, different study populations, and differences in definitions of low-GI diets. Therefore, in addition to environmental factors, numerous studies have explored the effects of polymorphisms of genes associated with plasma lipid levels. Recently, genome-wide association studies revealed more than a 100 single-nucleotide polymorphisms that are associated with lipid levels and explain 35%–40% of the genetic variability in plasma lipid phenotypes.[1,27,28] In addition to environmental factors including high-fat or high-carbohydrate diets, association of the Ala54Thr polymorphism with increased fasting and postprandial TG has been suggested,[8,13] and the potential mechanism might be that the Thr54 genotype of *FABP2* in patients with diabetes increases fatty acids absorption, which leads to an increased

Table 4 Differences between carriers of different genotypes in both sex groups at baseline and after intervention and changes in variables from baseline

	Women			Men		
Variables	**Ala54Ala carriers (n=43)**	**Thr54 carriers (n=50)**	***P*-value**	**Ala54Ala carriers (n=37)**	**Thr54 carriers (n=35)**	***P*-value**
Age (years)[a]	57.6±9.0	58.4±9.2	0.680	56.3±10.0	59.4±11.4	0.221
BMI (kg/m^2)[a]	26.4±3.2	26.8±3.3	0.513	26.7±3.6	26.6±3.5	0.913
Waist circumference (cm)[a]	91.0±9.7	90.6±8.6	0.776	93.4±8.6	93.0±7.9	0.846
Course of disease (years)[a]	7.7±5.5	7.4±5.4	0.762	8.8±7.3	7.6±7.0	0.465
Types of low-GI diet (control)[a]	14	12		15	10	
Lipid-lowering agents (n)[a]	5	8		5	4	
Fasting blood glucose (mmol/L)						
Baseline	9.3±3.3	8.3±2.3	0.095	8.7±2.4	8.6±2.5	0.873
After intervention	8.5±2.5	8.1±2.3	0.524	8.3±1.9	8.1±2.1	0.572
Change from baseline	–0.8±1.7	–0.2	0.035	–0.4±2.0	–0.5±1.7	0.695
TC (mmol/L)						
Baseline	5.07±1.29	4.88±1.18	0.476	4.74±0.90	4.65±0.85	0.655
After intervention	4.71±1.02	4.90±1.08	0.384	4.48±0.82	4.43±0.98	0.802
Change from baseline	–0.36±0.79	0.02±0.78	0.024	–0.26±0.87	–0.22±0.68	0.832
TG (mmol/L)						
Baseline	2.03±1.51	1.71±1.20	0.250	2.33±2.23	2.00±1.41	0.458
After intervention	1.47±0.77	1.70±1.00	0.207	1.73±1.15	1.60±1.27	0.660
Change from baseline	–0.56±1.21	–0.01±1.01	0.016	–0.6±1.29	–0.4±1.15	0.381
HDL-c (mmol/L)						
Baseline	1.22±0.26	1.28±0.35	0.385	1.18±0.32	1.11±0.25	0.317
After intervention	1.20±0.25	1.27±0.34	0.229	1.15±0.28	1.11±0.27	0.583
Change from baseline	–0.02±0.17	0.00±0.14	0.585	–0.03±0.18	0.00±0.18	0.456
LDL-c (mmol/L)						
Baseline	3.00±1.02	2.86±0.92	0.480	2.67±0.82	2.71±0.71	0.814
After intervention	2.83±0.87	2.91±0.84	0.615	2.63±0.70	2.68±0.75	0.771
Change from baseline	–0.17±0.57	0.05±0.56	0.051	–0.04±0.73	–0.03±0.58	0.964
HbA1c (%)						
Baseline	7.5±1.7	7.1±1.1	0.195	6.9±1.2	6.9±1.3	0.922
After intervention	7.0±1.1	7.1±1.4	0.731	6.6±0.9	6.6±1.2	0.996
Change from baseline	–0.5±2.0	0.0±1.7	0.219	–0.3±0.7	–0.3±0.8	0.873
GA (%)						
Baseline	19.4±5.4	18.0±4.5	0.177	17.4±3.9	17.8±4.1	0.683
After intervention	17.6±4.4	17.1±4.0	0.523	15.9±2.8	16.4±3.7	0.538
Change from baseline	–1.8±2.4	–0.9±1.5	0.032	–1.5±2.7	–1.4±2.1	0.870
IL-6						
Baseline	3.19±3.58	2.36±0.85	0.111	2.40±1.00	3.04±4.75	0.422
After intervention	3.28±3.26	2.81±1.41	0.875	2.68±1.49	3.54±5.32	0.347
Change from baseline	0.09±2.54	0.45±1.31	0.378	0.28±1.73	0.49±1.42	0.566
TNF-α						
Baseline	6.9±2.0	7.6±2.5	0.157	8.0±2.9	7.4±1.6	0.326
After intervention	9.0±5.5	9.0±5.5	0.958	10.5±8.9	9.7±5.6	0.273
Change from baseline	2.1±5.6	1.4±5.1	0.525	2.5±8.8	2.3±3.9	0.767

Notes: Data at baseline and after intervention are expressed as mean ± SD. [a]Differences between groups were analyzed using Student's *t*-test, and differences in the other parameters between groups and changes from baseline were analyzed using the ANCOVA (generalized linear model) test with adjustments for sex, age, BMI, and course of disease.

Abbreviations: ANCOVA, analysis of covariance; BMI, body mass index; GA, glycated albumin; HbA1c, hemoglobin A1c; HDL-c, high-density lipoprotein cholesterol; LDL-c, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; TNF-α, tumor necrosis factor alpha.

conversion to triacylglycerols,[8] and increases susceptibility to the effects of dietary lipids.[13] Furthermore, Nakanishi et al reported that the effects of *FABP2* polymorphism on TG and LDL-c were associated with long-term gender differences.[10] Therefore, we analyzed not only the data of the participants as a whole but also the data of men and women separately.

In our study, according to the previous dietary records of the participants, no significant differences were found in energy and nutrient intakes between the homozygous Ala54 carriers and variant genotype carriers. After 4–5 weeks of the low-GI diet interventions, the decrease of TG levels from baseline in the homozygous Ala54 carriers was generally more significant than that in the variant genotype carriers, although the TG level in the homozygous Ala54 carriers was higher than in the variant carriers at baseline. In addition, compared with the variant genotype group, a significant trend was found in the decrease of TC in the homozygous Ala54 group. Furthermore, we separately analyzed the data for men and women. Compared with Thr54 carriers, we found that the homozygous Ala54 carriers exhibited significant decreases in TG and TC as well as a decrease of LDL-c in women, but not in men. Based on the findings of our present study, an association exists between polymorphisms of *FABP2* Ala54Thr (rs1799883) and the effects of low-GI diets on plasma lipid levels in female Han Chinese individuals with T2DM, but not in men. However, the reason for this finding remains unclear.

In addition to abnormal lipid levels, elevation of inflammatory factors is considered a risk factor for cardiovascular disease. Only a few studies have examined the relationship between genetic polymorphisms of rs1799883 and inflammatory factors. A study from de Luis et al found that nondiabetic obese individuals carrying the Thr/Ala54 or Thr/Thr54 phenotype had higher levels of C-reactive protein and IL-6 compared with Ala54/Ala54 carriers.[29] However, we found no significant differences in IL-6 or in TNF-α at baseline and after intervention between Ala54 homozygotes carriers and Thr54 carriers. Moreover, we noted no significant differences in changes of inflammatory factors from baseline between the two groups in both sexes. Similarly, another study reported that both Ala54Ala carriers and Thr54 carriers exhibited no statistically significant differences in changes of TNF-α and IL-6 after 3 months of a lifestyle modification program.[30]

The effects of Thr54 polymorphism in the FABP2 protein on glycemic control response to low-GI diets were also observed in our study. Previously, several studies have showed that Thr54 carriers of *FABP2* are associated with higher BMIs, insulin resistance, and metabolic syndrome,[6–8,31] and a review suggested that *FABP2* (rs1799883) Ala54Thr polymorphisms are associated with increased susceptibility to T2DM among Asians.[4] In addition, Weiss et al reported that *FABP2* Thr54 carriers had lower glucose tolerances and lower levels of insulin action than do Ala54-homozygous carriers in sedentary nondiabetic individuals following a low-fat diet, and they also suggested that the increased lipid oxidation rates in *FABP2* Thr54 carriers might be due to glucoregulatory dysfunction.[14] Interestingly, although we found no significant effect of *FABP2* (rs1799883) Ala54Thr polymorphisms on glycemic control overall in patients with diabetes receiving low-GI diets, through subgroup analysis, we found that Ala54Ala carriers had a significant decrease of FBG and GA 4–5 weeks after low-GI diet intervention in women but not in men. Because we did not measure immediate postprandial lipid changes and fat oxidation rates, we could not reasonably explain these results in the present study. Therefore, further prospective studies are necessary.

To the best of our knowledge, this is the only study that analyzes the effects of Thr54 polymorphism in the FABP2 protein on plasma lipids, glycemic control, and inflammatory factors among patients with T2DM on similar low-GI diets. All participants received intensive nutritional education, mainly related to dietary nutrition and T2DM management every week during follow-up in the test period, and the dietary assessment was based on an average of three food records. Moreover, unlike other studies, both groups in our study received similar low-GI diets, which minimized the impact of environmental factors and more clearly illustrated the effect of the genetic polymorphisms of rs1799883 on plasma lipid levels. However, our study had several limitations that should be noted. First, we only made short-term retrospective observations on the effects of the *FABP2* Ala54Thr genotype on metabolic and inflammatory changes to low-GI diets, but we did not examine the immediate and long-term effects that may help us to further understand the consequences for patients with T2DM. Second, similar to previous studies, the sample size of this study was relatively small, and our study was a single-center study, which may limit the generalizability of the findings. Third, in our study, we did not measure the concentrations of adiponectin and leptin whose imbalances may be important mediators of the elevated risk of developing T2DM and cardiovascular disease linked closely to dyslipidemia.[32] Furthermore, we did not investigate the relationship between polymorphism of *FABP2* Ala54Thr and adiponectin and leptin as well as the associations between lipid response to low-GI diets and adiponectin and leptin. These are all areas we can further explore through future studies.

Conclusion

From the results of the present study, we conclude that the effects of polymorphism in *FABP2* Ala54Thr on serum lipids and glycemic control are associated with gender among

patients with T2DM receiving a short-term low-GI diet. The immediate effects of a low-GI diet on postprandial plasma lipids and its long-term regulatory effect on plasma lipids must be further explored in studies with higher population sizes to improve interpretations of the function of the FABP2 protein.

Data sharing statements

We do not intend to share any further data at present.

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Author contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

The authors have no conflicts of interest to report in this work. The authors alone are responsible for the content and writing of this paper.

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