

Postprandial Lipemic Response Is Modified by the Polymorphism at Codon 54 of the Fatty Acid–Binding Protein 2 Gene

Jyrki J. Ågren, Raisa Valve, Helvi Vidgren, Markku Laakso, Matti Uusitupa

Abstract—Polymorphism of the fatty acid–binding protein 2 (FABP2) gene has been shown to affect the affinity of intestinal FABP for fatty acids. This could cause changes in postprandial triglyceride metabolism. In the present study, postprandial lipemia was studied in normotriglyceridemic subjects with genetic variation in the FABP2 gene. Oral fat-loading tests were performed in 8 subjects homozygous for the Thr-encoding allele at codon 54 of the FABP2 gene and in 7 subjects homozygous for the Ala-encoding allele (wild type). There were no significant differences between these 2 groups in age, body mass index, fasting plasma triglyceride and cholesterol levels, or fasting glucose and insulin levels. The increase of plasma triglyceride concentration after the fat test meal was significantly greater in subjects who were homozygous for the Thr-54 allele (area under the response curve, 4.27 ± 1.31 versus 2.49 ± 1.18 mmol/L · h⁻¹, $P=0.04$). The difference was seen in both chylomicron (2.51 ± 0.98 versus 1.41 ± 0.74 mmol/L · h⁻¹, $P=0.03$) and very low-density lipoprotein triglycerides (1.57 ± 0.77 versus 0.99 ± 0.40 mmol/L · h⁻¹, $P=0.04$). Postprandial triglyceride response correlated with fasting triglycerides in the Ala-54 homozygotes ($r=0.79$, $P=0.05$) but not in the Thr-54 homozygotes ($r=0.09$), who showed a strong correlation between triglyceride and insulin responses ($r=0.83$, $P=0.02$). With reservations related to a small number of subjects studied, these results indicate that the Thr-encoding allele of the FABP2 gene is associated with increased postprandial lipemia. The lipemic response was associated with postprandial insulin response, suggesting that in the Thr-54 homozygotes, altered postprandial lipemia may also modify insulin action or vice versa. (*Arterioscler Thromb Vasc Biol.* 1998;18:1606-1610.)

Key Words: postprandial lipemia ■ fatty acid–binding protein ■ triglycerides ■ insulin

Fatty acid–binding proteins (FABPs) are intracellular proteins found in many tissues. They are involved in fatty acid transfer and metabolism, but their exact functions are not well known.^{1,2} The FABP2 gene encodes intestinal FABP (I-FABP), which is expressed only in intestinal enterocytes.² Polymorphism at codon 54 of the FABP2 gene causes production of Ala-containing (wild-type) or Thr-containing (mutated-type) I-FABP. Thr-containing protein has been shown to have 2-fold greater affinity for long-chain fatty acids than does Ala-containing protein.³ This greater affinity has been suggested to cause increased absorption and processing of fatty acids. This could, in turn, be responsible for the increased fat oxidation rate and impaired insulin action found in Pima Indians with the Thr-54 allele.³

If the FABP2 gene polymorphism modifies the absorption of fatty acids, it could also alter the postprandial triglyceride response. A strong correlation between the magnitude of triglyceride response and fasting triglyceride levels has been found in several studies.⁴ However, it has been reported that there are also high responders with normal fasting triglyceride but high insulin levels.⁵ In addition, postprandial lipemia

has been shown to correlate with insulin resistance in nondiabetic subjects.⁶ Thus, it is possible that insulin action can modify the postprandial triglyceride response or that a hypertriglyceridemic response can lead to impaired insulin action. In an earlier study of obese Finnish subjects,⁷ the frequencies of the Thr-encoding allele (28%) and Thr-54 homozygotes (5% of population) were found to be similar to those in Pima Indians (29% and 4%, respectively).³ Polymorphism of the FABP2 gene was not associated with changes in fasting insulin levels, basal metabolic rate,⁷ or fatty acid composition of serum lipids⁸ in obese Finns, but a nonsignificant trend to higher fasting triglyceride levels was found in those with the Thr-encoding allele. This finding prompted us to investigate whether there are differences in postprandial responses between normotriglyceridemic subjects who are homozygous for the Thr- or Ala-encoding allele of the FABP2 gene.

Methods

Subjects

Subjects were selected from participants of a weight reduction program⁹ and from the nondiabetic control subjects of an earlier

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TABLE 1. Subject Characteristics

	Ala-54 Homozygotes (n=7)	Thr-54 Homozygotes (n=8)
Sex (F/M)	2/5	5/3
Age, y	58.7±10.1	56.4±9.1
BMI, kg/m ²	29.7±6.0	32.8±4.2
Waist-to-hip ratio	0.99±0.06	0.98±0.11
Fasting glucose, mmol/L	5.8±0.6	5.6±0.6
Fasting insulin, mU/L	11.6±4.7	13.9±5.4
Serum lipids, mmol/L		
Total cholesterol	5.93±0.98	6.17±1.17
VLDL cholesterol	0.36±0.09	0.50±0.20
LDL cholesterol	4.07±0.76	4.45±0.95
HDL cholesterol	1.50±0.31	1.22±0.25
Triglycerides	1.08±0.31	1.36±0.39
Free fatty acids	0.72±0.18	0.59±0.18

Values are mean±SD.

study^{10,11} conducted by the Departments of Clinical Nutrition and Medicine, University of Kuopio. Ten subjects homozygous for the Thr-54 allele were identified from these groups. They and 12 subjects homozygous for the Ala-54 allele, selected on the basis of

sex, age, body mass index (BMI), and triglyceride levels determined in the previous studies,^{9,11} were asked to participate. Five subjects with high fasting plasma triglyceride levels (>2.0 mmol/L), 1 who had apolipoprotein E phenotype E2/3, and 1 who did not follow study instructions were excluded from the study. The final study group consisted of 8 subjects homozygous for the Thr-54 allele and 7 subjects homozygous for the Ala-54 allele of the FABP2 gene. The study was approved by the Ethics Committee of the University of Kuopio, and all subjects gave written consent.

Dietary Data

Subjects kept food records for 3 days, using household measures, before undergoing an oral fat-loading test. Nutrient intake from food records was calculated using the Micro-Nutrica dietary analysis program, which is based on the database of the Finnish Social Insurance Institute.¹²

Oral Fat-Loading Test

The oral fat-loading test started at 7:30–8:30 AM after a 12-hour fast. Subjects were advised not to drink alcohol and to avoid strenuous exercise for 3 days before the test. After fasting blood samples were collected, subjects ate a small rice cake (7.6 g) with a piece of cheese (10 g, 2.3 g fat/70 kg body weight). Five minutes after eating the cake, they drank a cream mixture (100 mL, 27.4 g fat/70 kg body weight) and fish oil (20 mL, 18.6 g fat/70 kg body weight). The cream mixture had a fatty acid profile resembling that of the average Finnish diet. In addition, it contained heptadecanoic acid (4 g/70 kg body weight). The total amount of fat given was 0.75 g/kg body

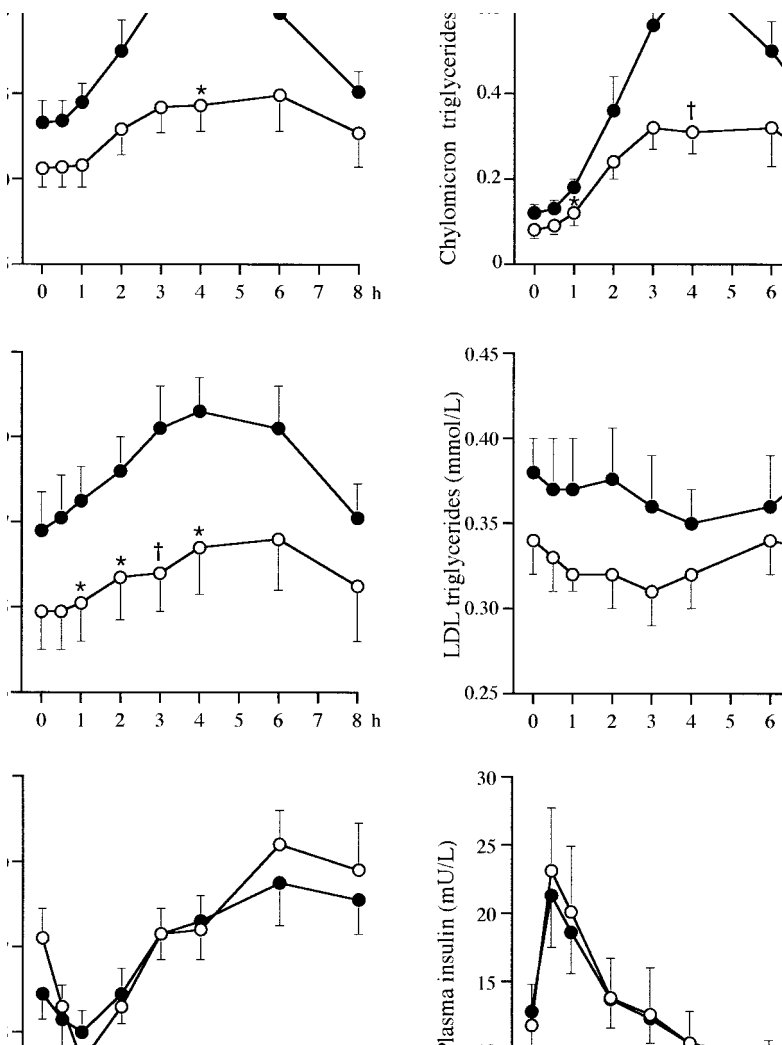


Figure 1. Responses of plasma total, chylomicron, VLDL, and LDL triglycerides and serum free fatty acids and plasma insulin to an oral fat load in subjects with the Ala54Ala genotype (○) and in subjects with the Thr54Thr genotype (●) of the FABP2 gene. Bars depict SEM. Significant difference between groups: **P*<0.05; †*P*<0.01. Area under the response curves are significantly different in plasma (*P*=0.04), chylomicron (*P*=0.03), and VLDL (*P*=0.04) triglycerides.

TABLE 2. Area Under the Response Curves of Triglycerides and Cholesterol After the Fat Test Meal

	Ala-54 Homozygotes (n=7)	Thr-54 Homozygotes (n=8)	<i>P</i>
Triglycerides, mmol/L · h ⁻¹			
Total	2.49±1.18	4.27±1.31	0.04
Chylomicron	1.41±0.74	2.51±0.98	0.03
VLDL	0.99±0.40	1.57±0.77	0.04
Cholesterol, mmol/L · h ⁻¹			
Chylomicron	0.11±0.07	0.26±0.11	0.01
VLDL	0.35±0.22	0.51±0.49	NS

Values are mean±SD.

weight (51% saturated, 28% monounsaturated, and 21% polyunsaturated). Blood samples were collected 0.5, 1, 2, 3, 4, 6, and 8 hours after the test meal.

Laboratory Measurements

To separate chylomicrons, plasma (1.8 mL) was overlaid with 1.6 mL of sodium chloride solution ($d=1.006$ g/mL) and ultracentrifuged with a TFT 45.6 rotor (Kontron Instruments) (18 000 rpm, 30 minutes). The top milliliter was aspirated to remove the chylomicron fraction. The infranate was overlaid again with sodium chloride solution, and samples were ultracentrifuged to separate VLDL (37 000 rpm, 16 hours). After aspiration of VLDLs, the density of the infranate was adjusted to 1.063 g/mL to separate LDL (37 000 rpm, 23 hours). Lipoproteins were separated from fasting serum samples by ultracentrifugation ($d=1.006$ g/mL) to remove VLDL and by precipitation of LDL. Cholesterol and triglyceride concentrations in plasma or serum and in separated lipoprotein fractions were determined by enzymatic colorimetric methods using commercial kits (Boehringer Mannheim) and serum free fatty acids with a turbidometric method using an automated instrument (Specific Clinical Analyser, Kone Ltd). Plasma insulin was measured with a radioimmunoassay method (Phadeseph Insulin RIA 100, Pharmacia Diagnostics). Plasma glucose was analyzed by using a glucose oxidase method (Glucose Auto&Stat, model GA-110, Daiichi). The Ala-54 allele for Thr substitution of the FABP2 gene was determined as previously described.⁷

Statistics

Nonparametric methods were used, and analyses were performed with the StatView™ program (BrainPower Inc). The Mann-Whitney *U* test was used for comparisons of groups, and Spearman's correlation coefficient was used for correlation analyses. Areas under the response curves were calculated by the trapezoidal rule using the Canvas™ program (Deneba Software Inc) for drawing and calculations.

Results

Characteristics of subjects are presented in Table 1. There were no significant differences between the Ala-54 and Thr-54 homozygotes in age, anthropometric measurements, fasting plasma glucose and insulin levels, and serum lipid levels. On the basis of the 3-day food records, there were no differences in nutrient intake values between the groups (data not shown).

Postprandial lipemic responses for both groups are shown in Figure 1 and Table 2. The postprandial increase of triglycerides, cholesterol, and insulin was calculated as an area under the response curve above the baseline. This area for triglycerides was greater in the Thr-54 homozygotes than

in the Ala-54 homozygotes with respect to total plasma, chylomicrons, and VLDL. A small increase of triglycerides in HDL of the Thr-54 group ($0.11±0.17$ mmol/L · h⁻¹) was also seen, whereas no increase could be seen in the Ala-54 homozygotes. In LDL triglyceride response, there was a difference between the groups at 6 hours: in Thr-54 homozygotes, triglycerides increased significantly from 6 to 8 hours (change, $0.04±0.03$ mmol/L, $P=0.01$, compared with the Ala-54 group), whereas there was no change in Ala-54 homozygotes ($0.00±0.02$ mmol/L). Chylomicron cholesterol response followed the same pattern as triglyceride response (ie, it was greater in the Thr-54 homozygotes). A similar trend was seen in VLDL cholesterol, but the difference was not statistically significant (Table 2).

Responses of free fatty acids and insulin were similar in both groups (Figure 1). The areas under the response curves of insulin were $21.2±15.1$ and $19.7±9.5$ mU/L · h⁻¹ in Ala-54 and Thr-54 homozygotes, respectively.

Fasting triglyceride levels correlated with triglyceride response in the Ala-54 homozygotes but not in Thr-54 homozygotes (Table 3 and Figure 2). On the other hand, triglyceride response in the Thr-54 homozygotes correlated strongly with insulin response ($r=0.83$, $P=0.02$), whereas no correlation was found in the Ala-54 homozygotes ($r=-0.40$). Fasting insulin and glucose levels also correlated in the Thr-54 homozygotes ($r=0.83$, $P=0.02$) but not in the Ala-54 homozygotes ($r=0.07$).

Among the 294 subjects screened for the Thr-54 allele, fasting triglycerides were $1.60±0.91$ mmol/L in Ala-54 homozygotes ($n=147$), $1.74±1.72$ mmol/L in Thr-54/Ala-54 heterozygotes ($n=131$), and $1.80±1.34$ mmol/L in Thr-54 homozygotes ($n=16$) ($P=0.82$ after adjustment for BMI and age).

TABLE 3. Correlation of BMI, Triglycerides, and Triglyceride Response With Lipids, Lipoproteins, Insulin, and Age in Subjects Who Were Homozygous for the Ala- or Thr-encoding Allele at Codon 54 of FABP2 Gene

	Ala-54 Homozygotes (n=7)		Thr-54 Homozygotes (n=8)	
	<i>r</i>	<i>P</i>	<i>r</i>	<i>P</i>
BMI and				
Triglycerides	0.93	0.01	0.07	NS
VLDL cholesterol	0.78	0.06	0.29	NS
LDL cholesterol	-0.39	NS	-0.26	NS
HDL cholesterol	-0.72	0.10	-0.14	NS
Insulin	0.68	NS	0.05	NS
Triglycerides and				
HDL cholesterol	-0.75	0.08	0.43	NS
Triglyceride response	0.79	0.05	0.09	NS
Triglyceride response and				
Insulin	0.21	NS	0.52	NS
Insulin response	-0.40	NS	0.83	0.02
Age	-0.27	NS	-0.72	0.06
BMI	0.57	NS	0.23	NS

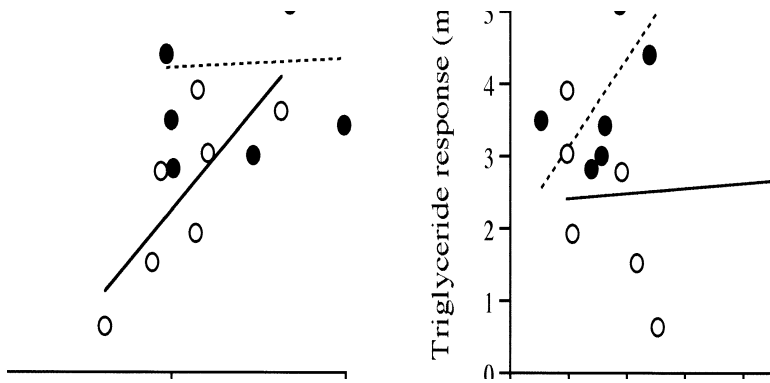


Figure 2. Correlations of postprandial triglyceride response with fasting triglycerides (A) and insulin response (B) in subjects with the Ala54Ala genotype (○) and in subjects with the Thr54Thr genotype (●) of FABP2 gene.

Discussion

The novel finding of this study was that the polymorphism at codon 54 of the FABP2 gene is associated with postprandial lipemic response. Significantly greater postprandial triglyceride response, in both the chylomicron and VLDL fractions, was seen in subjects homozygous for the Thr-54 allele than in the subjects homozygous for Ala-54. Fasting insulin levels and insulin responses did not differ between the 2 groups. However, the strong correlation between triglyceride and insulin responses in the Thr-54 homozygotes suggests an association between postprandial triglyceridemia and insulin action in these subjects.

The reason for increased postprandial lipemia in the Thr-54 homozygotes could be expected to be found in enterocytes providing that the polymorphism of the FABP2 gene affects the functional properties of I-FABP. It could be speculated that the greater affinity of Thr-containing I-FABP for fatty acids increases the absorption of fatty acids or modifies triglyceride synthesis in enterocytes. Fatty acid transport and triglyceride secretion have been shown to be greater in Caco-2 cells with Thr-containing I-FABP compared with Ala-containing I-FABP.¹³ Altered postprandial lipid metabolism could cause an increased lipid oxidation rate, which has been found in both Thr-54 homozygotes with³ and without¹⁴ insulin resistance and the Thr-54/Ala-54 heterozygous Pima Indians.³ Increased lipid oxidation could block glucose oxidation in muscle and liver¹⁵ and thus contribute to insulin resistance.

The increased postprandial triglyceride response in Thr-54 homozygotes could also be a secondary phenomenon. Insulin deficiency or insulin resistance are known to increase postprandial lipemia, probably by modifying lipoprotein lipase activity in different tissues and by increasing competition between chylomicrons and VLDL as a result of increased VLDL levels.¹⁶ Thus, increased postprandial lipemia in the Thr-54 homozygotes may be caused, or at least potentiated, by impaired insulin action. It is possible that the Ala-to-Thr shift in I-FABP causes slightly increased postprandial response, alters the amount of absorbed or endogenous fatty acids transported by the portal route to the liver, or causes some other modification of postprandial metabolism not revealed by plasma triglyceride responses. These mechanisms could also alter postprandial glucose metabolism and thereby predispose individuals to the development of insulin resistance over the long term. This notion is consistent with the

variability of postprandial lipemia, correlating with insulin response, seen in the Thr-54 homozygotes in the present study and also the variable results obtained in other studies of FABP2 polymorphism and insulin action.^{3,7,14,17}

The results of the current study support the hypothesis that polymorphism of the FABP2 gene alters postprandial lipid metabolism and has a relationship with insulin response. However, the frequency of Thr-54 homozygotes has been only few percent in populations studied.^{3,7} In our study, the number of Thr-54 homozygotes was low, so the results should be confirmed by studies with more subjects. It also remains to be determined whether Thr-54/Ala-54 heterozygotes, which represent ~45% of the population, differ from Ala-54 homozygotes in their postprandial response.

The magnitude of triglyceride response has been reported to be modified by gender, age, apolipoprotein E phenotype, and fasting triglyceride and insulin levels.⁴ There were no differences between our study groups in age or BMI, and all subjects had apolipoprotein E phenotypes E3/3 or 3/4. Women have been reported to have lower postprandial responses in some studies, but their fasting triglyceride levels have also been lower.^{18,19} In the present study, there were more women in the Thr-54 homozygotes group than in the Ala-54 homozygotes group. However, there were no significant differences in postprandial responses between women and men within groups. If the postprandial responses in women were really lower, independently of fasting triglyceride level, the observed difference between groups would decrease rather than increase. A strong correlation between fasting triglyceride levels and postprandial lipemia has been found in several studies.⁴ Although fasting triglyceride levels did not differ significantly between groups in this study, the difference of 0.3 mmol/L in mean values could explain part of the difference in postprandial responses. However, in the Thr-54 homozygotes, there was no correlation between fasting and postprandial triglyceride levels.

Increased LDL and HDL triglycerides have been found in subjects with familial combined hyperlipidemia who have the Thr-54 allele.¹⁴ In the current study, fasting lipid levels did not differ between the groups. However, in the Ala-54 homozygotes, BMI correlated strongly with triglyceride levels and slightly less with VLDL cholesterol levels. HDL cholesterol level tended to correlate inversely with BMI and triglyceride level (Table 3). In Thr-54 homozygotes, these correlations were not found. These differences suggest that

fasting lipid levels may also be affected by the codon 54 polymorphism of the FABP2 gene.

In conclusion, the results of this study show that the codon 54 polymorphism of the FABP2 gene is associated with the postprandial triglyceride response. These results are important because postprandial lipemia increases the risk of atherosclerotic vascular disease.^{20,21} It remains to be determined whether increased postprandial triglyceridemia is the primary change and thus responsible for increased lipid oxidation and impaired insulin action associated with the Thr-encoding allele at codon 54 of the FABP2 gene or whether it is a result of some other alteration caused by this mutation.

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