FABP2 Ala54Thr genotype is associated with glucoregulatory function and lipid oxidation after a high-fat meal in sedentary nondiabetic men and women

Edward P Weiss, Josef Brandauer, Onanong Kulaputana, Ioana A Ghiu, Christopher R Wohn, Dana A Phares, Alan R Shuldiner, and James M Hagberg

ABSTRACT

Background: A common functional missense mutation [Ala54Thr of the fatty acid–binding protein 2 gene (FABP2)] has previously been studied for associations with glucoregulation, postprandial lipemia, and lipid oxidation rates. However, most of those studies have not accounted for the interactive and potentially confounding effects of habitual physical activity and diet.

Objective: We tested the hypothesis that, in sedentary nondiabetic subjects following a low-fat diet, Thr54 FABP2 carriers have lower glucoregulatory function, greater postprandial lipemia, and greater lipid oxidation rates than do their Ala54 FABP2–homozygous counterparts.

Design: Men and women (n = 122) aged 50–75 y who were following a low-fat diet were genotyped and underwent oral-glucose-tolerance tests. A subgroup (n = 36) also underwent postprandial lipemia tests with lipid oxidation rate measurements.

Results: Thr54 carriers were less likely to have normal glucose tolerance (P = 0.05) and had higher fasting glucose concentrations (P = 0.003) than did Ala54 homozygotes. In Thr54 carriers, the insulin sensitivity index was lower (P = 0.02), and the fasting insulin and the oral-glucose-tolerance test insulin area under the curve were higher (P = 0.05 and 0.03, respectively) than in Ala54 homozygotes. FABP2 genotype was not associated with fasting or postprandial lipemia test triacylglycerol or free fatty acids (P ≥ 0.22 for all), but postprandial lipid oxidation rates were higher (P = 0.01), which suggests that fat absorption is higher in Thr54 carriers than in Ala54 homozygotes.

Conclusions: In sedentary nondiabetic persons following a low-fat diet, FABP2 Thr54 carriers have lower glucose tolerance and lower insulin action than do Ala54-homozygous persons. Furthermore, FABP Thr54 carriers have higher lipid oxidation rates, which may be the mechanism of glucoregulatory dysfunction.

KEY WORDS  Postprandial lipemia, fatty acid–binding protein, insulin action, glucose tolerance, genotype, lipid oxidation

INTRODUCTION

The common missense variation Ala54Thr in the intestinal fatty acid (FA)–binding protein 2 gene (FABP2) has been extensively studied as a risk factor for impaired insulin action and type 2 diabetes and for associations with postprandial lipemia (1, 2). In light of evidence that the Thr54 variant of FABP2 results in functional consequences at the molecular (3, 4), cellular (5), and organ (6) levels, it was previously suggested that this variant increases the lipemic response to food ingestion and that chronic exposure to postprandial hyperlipidemia (ie, triacylglycerol, free FAs, or both) may ultimately impair insulin action, cause glucose intolerance, and increase diabetes risk (2, 4). Although many studies have found associations between the FABP2 Thr54 allele and postprandial lipemia (7–10), others (11, 12) have not. Likewise, many but not all studies have identified relations between FABP2 Thr54 carrier genotypes and insulin action or diabetes risk, as reviewed by Weiss et al (2). Because physical activity levels, diet composition, or both were generally not accounted for in most of the previous studies, it is possible that some of these conflicting findings resulted from confounding effects of variations in those factors. Therefore, the purpose of the current study was to determine whether FABP2 Ala54Thr genotype is associated with postprandial lipemia and insulin action, at the same time that experimental control for habitual physical activity levels and diet composition is in place. The subjects studied were specifically selected to be sedentary, and all subjects were following a low-fat diet for ≥2 wk before testing. We hypothesized that, in these sedentary, middle-aged to older men and women, Thr54 carriers would have lower insulin action, poorer glucose tolerance, and greater postprandial lipemia than would their Ala54-homozygous counterparts. Furthermore, in light of previous findings that FABP2 Ala54Thr genotype was associated with fasting lipid oxidation rates (4, 12), we hypothesized that FABP Thr54 carriers would also have higher fasting and postprandial lipid oxidation rates.

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2 Supported by the National Institutes of Health (grants T32 AG00268, K24 DK02673, R01 DK54261, R01 AG17474, and R01 AG15389); the American Diabetes Association; the Baltimore VA Geriatric Research, Education, and Clinical Center; and the Royal Thai Government Scholarship.

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Received April 19, 2006.

Accepted for publication August 23, 2006.
SUBJECTS AND METHODS

Subjects

Sedentary nonsmoking men (n = 50) and postmenopausal women (n = 72), all of whom were 50–75 y old, were included in the study. “Sedentary” was defined as not having performed regular vigorous exercise for ≥20 min/d 2 times/wk during the 6 mo before screening. All subjects were free of clinical cardiovascular disease as determined by medical history, physical examination, and diagnostic exercise stress test. None of the subjects had diabetes, according to their medical history and a standard clinical oral-glucose-tolerance test [OGTT (13)] performed at screening. None of the subjects were taking hypoglycemic agents, fibrates, or niacin. Lactose intolerance, gall bladder dysfunction, chronic gastritis, diverticulosis, diverticulitis, ulcers, or other gastrointestinal conditions were exclusionary for postprandial lipemia tests (PPLTs). Further details about subject recruitment and screening were published previously (14). The PPLT was added to the study protocol later in the study; therefore, of the 122 subjects who underwent the OGTT, only a subset (n = 36) also underwent PPLTs.

All subjects gave written informed consent. The study protocol was approved by the Institutional Review Board of the University of Maryland at College Park.

Dietary control

The subjects attended twice-weekly classes for the 6 wk before testing, in which they were instructed by a registered dietitian to consume a low-fat diet that was consistent with the American Heart Association’s Dietary Recommendations for the General Population (15). Subjects were advised to maintain this diet during the 2 wk before testing. The study dietitian monitored compliance with the dietary recommendations by quantitatively assessing 7-d food records. In addition, a computerized nutrient analysis using NUTRITIONIST IV software (version 4.0; N-Squared Computing, Salem Park, OR) was performed on food records from a subset of the subjects (n = 80) to determine whether dietary patterns that may affect glucose tolerance (ie, daily intakes of energy, fiber, and sugar and the percentage of energy from fat) were different between genotype groups.

FABP2 genotype

DNA was extracted from blood leukocytes by using published methods (16) and evaluated for FABP2 Ala54Thr genotype with the use of HhaI restriction endonuclease digest analysis as described by Baier et al (4). Study technicians involved in collecting outcome data were blinded to the genotype status of the subjects until the collection of the data was complete.

Oral-glucose-tolerance tests

OGTTs were begun between 0630 and 0900 and after a 12–24-h fast. For 3 d before the OGTT, subjects consumed ≥250 g carbohydrate/d. Before and 30, 60, 90, and 120 min after a 75-g oral glucose load, venous blood was drawn into tubes containing 15% potassium EDTA. Samples were stored on ice for later isolation of plasma by centrifugation (4 °C and 1800 × g for 20 min) and subsequent storage at −80 °C. Plasma was later analyzed for glucose and insulin by using the glucose oxidoase method (model 2300 Stat Plus; YSI Inc, Yellow Springs, OH) and radioimmunoassay (kit HI-14K; Linco Research Inc, St Charles, MO), respectively. Glucose and insulin total area under the curve (AUC) values were calculated with the use of the trapezoidal method (17). Insulin sensitivity index was calculated as described by Matsuda and DeFronzo (18). Glucose tolerance was considered clinically normal if fasting glucose was <5.6 mmol/L (100 mg/dL) and 2-h glucose was <7.8 mmol/L (140 mg/dL) (13). Furthermore, although subjects with diabetes were screened out before enrollment, 2 of the enrolled subjects had fasting plasma glucose concentrations ≥7.0 mmol/L (≥126 mg/dL) or 2-h OGTT glucose concentrations ≥11.1 mmol/L (≥200 mg/dL); they were deemed provisionally diabetic and were included in the study (13).

Postprandial lipemia tests

Subject preparation for the PPLTs was the same as for the OGTTs except that the subjects were also advised to refrain from alcohol consumption for 24-h before the OGTT and were not advised about pretest carbohydrate consumption. The PPLT protocol was based on that of Patsch et al (19) except that we used a shorter postmeal follow-up period (ie, 4 h) because it reduced the subject burden and because peak lipemia typically occurs by ~4 h after meal ingestion. The size of the fat meal was based on body size (386 g meal/2 m² body surface area) (20). The meal contained heavy whipping cream, sugar, chocolate syrup, and nonfat powdered milk. A 386-g serving of the high-fat meal provided 1362 kcal, 84% of which are from fat (19). In the current study, one subject experienced nausea and vomiting after the meal. Her test was discontinued, and her PPLT data were excluded from all analyses. The fat meal was well tolerated by all other subjects, which is consistent with previously published reports (19, 21).

Venous blood was drawn before and every 30 min for 4 h after consumption of the fat meal for subsequent isolation of serum and plasma by standard methods. Glycerol-blanked triacylglycerol concentrations were measured with the use of a 2-step colorometric assay (kit 337-B; Sigma Diagnostics Inc, St Louis, MO). Serum concentrations of free FAs were measured with the use of a colorometric assay (kit NEFA C; Wako Chemicals USA Inc, Richmond, VA). AUCs for triacylglycerols and FAs were calculated with the use of the trapezoidal rule (17).

Fasting and postprandial substrate utilization

Expired respiratory gas was collected for 20 min on 3 occasions during the PPLT, during the fasting baseline, and just before the 120- and 240-min postprandial time points. The samples were collected with the use of a nonrebreathing valve (model 2700; Hans Rudolph, Kansas City, MO) and the Douglas Bag system (5-way distribution valve and 100-g nondiffusing balloons; Kaysam Worldwide, Inc, Totowa, NJ) while the participant was quietly seated in an armchair. The samples were immediately analyzed for respiratory exchange ratio, total energy expenditure, and lipid oxidation rate by using indirect calorimetry with a medical gas analyzer (model 1100; Perkin-Elmer Inc, Danbury, CT), 120-L gasometer (Collins Inc, Boston, MA), and published equations (22). Lipid oxidation rates are expressed as a percentage of total energy expenditure to account for differences in metabolically active cell mass between persons (22).

Maximal oxygen uptake

Maximal oxygen uptake was measured by using indirect calorimetry during a graded treadmill exercise test to exhaustion as described previously (23).
TABLE 1

Subject characteristics

<table>
<thead>
<tr>
<th>FABP2 genotype</th>
<th>Ala54Ala</th>
<th>Ala54Thr</th>
<th>Thr54Thr</th>
<th>P for Ala54Ala compared with Thr54 carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subjects with OGTT data (n = 122)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>58</td>
<td>59</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>62</td>
<td>54</td>
<td>80</td>
<td>0.51</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58 ± 6</td>
<td>57 ± 5</td>
<td>57 ± 7</td>
<td>0.41</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>79.4 ± 15.4</td>
<td>83.7 ± 14.9</td>
<td>81.9 ± 17.7</td>
<td>0.14</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.1 ± 4.1</td>
<td>29.2 ± 4.7</td>
<td>29.9 ± 2.8</td>
<td>0.15</td>
</tr>
<tr>
<td>Percentage body fat (%)</td>
<td>37.1 ± 9.5</td>
<td>36.3 ± 9.3</td>
<td>42.3 ± 7.5</td>
<td>0.85</td>
</tr>
<tr>
<td>VO₂max (L/min)</td>
<td>1.94 ± 0.44</td>
<td>2.03 ± 0.51</td>
<td>2.03 ± 0.95</td>
<td>0.34</td>
</tr>
<tr>
<td>VO₂max (mL · kg⁻¹ · min⁻¹)</td>
<td>24.6 ± 4.3</td>
<td>24.4 ± 5.0</td>
<td>23.9 ± 5.8</td>
<td>0.73</td>
</tr>
<tr>
<td>Subjects with OGTT and PPLT data (n = 36)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n</td>
<td>12</td>
<td>22</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>Female (%)</td>
<td>58</td>
<td>45</td>
<td>100</td>
<td>0.64</td>
</tr>
<tr>
<td>Age (y)</td>
<td>58 ± 4</td>
<td>58 ± 7</td>
<td>59 ± 11</td>
<td>0.75</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>76.9 ± 13.9</td>
<td>86.2 ± 17.2</td>
<td>79.0 ± 9.9</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>28.2 ± 4.2</td>
<td>30.1 ± 4.9</td>
<td>29.6 ± 1.1</td>
<td>0.26</td>
</tr>
<tr>
<td>Percentage body fat (%)</td>
<td>38.0 ± 9.1</td>
<td>37.0 ± 7.8</td>
<td>44.8 ± 1.6</td>
<td>0.90</td>
</tr>
<tr>
<td>VO₂max (L/min)</td>
<td>1.90 ± 0.43</td>
<td>2.04 ± 0.49</td>
<td>1.81 ± 0.02</td>
<td>0.45</td>
</tr>
<tr>
<td>VO₂max (mL · kg⁻¹ · min⁻¹)</td>
<td>24.9 ± 4.7</td>
<td>24.0 ± 4.7</td>
<td>23.2 ± 3.2</td>
<td>0.55</td>
</tr>
</tbody>
</table>

1 FABP2, fatty acid–binding protein 2 gene; Ala54, alanine-encoding allele in codon 54 of the intestinal FABP2 gene; Thr54, threonine-encoding allele; OGTT, oral-glucose-tolerance test; PPLT, postprandial lipemia test; VO₂max, maximal oxygen uptake. Comparisons between genotype groups were performed by using unpaired t tests for quantitative factors and chi-square tests for categorical factors.

2 

3 Data missing on 4 subjects.

Body composition

Body fat mass, as a percentage of total body mass, was measured by using whole-body dual-energy X-ray absorptiometry (model DPX-L; Lunar Corporation, Madison WI) as described elsewhere (24).

Statistical analyses

FABP2 genotype distributions were evaluated for conformity with Hardy-Weinberg equilibrium with the use of a chi-square test. Descriptive statistics are presented separately for Ala54-homozygous, heterozygous, and Thr54-homozygous persons; however, because the sample sizes for Thr54-homozygous subjects were small (Table 1), data from those subjects were pooled with data from heterozygous subjects for comparisons of FABP2 genotype groups. Before statistical analyses, residuals were evaluated for variance homogeneity and distribution normality. Traits that were not normally distributed (ie, insulin sensitivity index, insulin, insulin AUC, and triacylglycerols), were log-transformed for analysis to achieve uniformity of variances and normal distributions for the residuals, and then they were back-transformed for presentation. Genotype differences in subject characteristics were assessed with unpaired t tests for quantitative factors and with chi-square tests for categorical factors. Genotype differences in the time-dependent changes in triacylglycerols and FAs during the PPLT were compared with the use of repeated-measures 3-factor (time and genotype with repeated measures on subject) analysis of covariance, which included age, percentage body fat, and fasting analyte concentration as covariates; Tukey’s test was used for post hoc comparisons. Genotype differences in other PPLT-related outcomes and in the OGTT-related outcomes were analyzed with the use of a one-factor (ie, genotype) statistical model that included age and percentage body fat as covariates. Data are presented as means ± SEs unless noted otherwise. All analyses were conducted with an α error rate of 0.05 and were performed with the use of SAS for WINDOWS software (version 9.1; SAS Institute Inc, Cary, NC).

RESULTS

Genotype distribution

The frequency of the Thr54 allele of the FABP2 gene was 0.28, which is similar to that reported by others (2). The FABP2 genotype distributions for the sampled population were not different (P ≤ 0.05) from Hardy-Weinberg–predicted distributions regardless of whether the larger (n = 122) or smaller (n = 36) sample with PPLT data was used for these estimates.

Subjects

Data about subject characteristics are presented in Table 1. In the 122 subjects who underwent OGTTs and in the 36 subjects who also underwent PPLTs, none of the subject characteristics were significantly different between genotype groups. The subjects were overweight or obese, on average, as indicated by the high means for body mass index (in kg/m²) and percentage body fat. Genotype was not associated with weight or body mass index in the 122 subjects who underwent OGTTs or in the 36 subjects who also underwent PPLTs. Cardiorespiratory fitness, as assessed by maximal oxygen uptake, was low in both groups according to published standards (25), which is reflective of the sedentary lifestyle of the recruited subjects. Four of the participants who were assessed for both glucose tolerance and postprandial lipemia were taking β-hydroxy-β-methylglutaryl coenzyme A reductase inhibitors; however, these medications have...
little or no effect on plasma triacylglycerol. Furthermore, the 4 subjects who were taking β-hydroxy-β-methylglutaryl coenzyme A reductase inhibitors were equally divided between the genotype groups. Exclusion of these subjects did not alter any of the findings (data not shown).

Dietary compliance

Quantitative nutritional analyses were performed on 7-d food records from 41 of the Ala54 homozygotes and 39 of the Thr54 carriers. No differences were observed between the Ala54 homozygotes and the Thr54 carriers in daily energy intake (1652 ± 66 and 1538 ± 69 kcal/d, respectively; \( P = 0.24 \)), percentage of energy from fat (27 ± 1% for both; \( P = 0.62 \)), daily fiber intake (17 ± 1 and 16 ± 1 g/d, respectively; \( P = 0.42 \)), or daily sugar intake (70 ± 4 and 66 ± 5 g/d, respectively; \( P = 0.49 \)).

Glucoregulatory function

Fewer Thr54 carriers than Ala54-homozygous subjects had clinically normal glucose tolerance (Table 2). Of the subjects with abnormal glucose tolerance, most were prediabetic according to recent clinical standards (13), and, although diabetic subjects were excluded during the screening process, results from 2 of the enrolled subjects in the Thr54 carrier group indicated provisional diabetes compared with none of the subjects in the Ala54 homozygous group (13). The insulin sensitivity index was significantly lower in Thr54 carriers than in Ala54-homozygous subjects. Although glucose AUCs and 120-min glucose concentrations did not differ significantly between the genotype groups, fasting glucose was higher in the Thr54 carriers than in the Ala54 homozygotes. Insulin AUC and fasting insulin were significantly higher in the Thr54 carrier group than in Ala54 homozygotes, which is consistent with insulin resistance. Thr54 carriers tended (\( P = 0.07 \)) to have higher 120-min insulin values than did the Ala54-homozygous persons, but the difference was not significant. These results were essentially unchanged when the 2 persons with provisional diabetes were excluded from the analysis. Furthermore, when the OGTT data from the smaller subset of subjects who underwent PPLTs were analyzed, the statistical results remained the same except that the \( P \) value for the percentage of subjects with normal glucose tolerance changed from 0.05 to 0.07 and the \( P \) value for insulin AUC changed from 0.03 to 0.15.

Postprandial lipemia and lipid oxidation rates

Fasting triacylglycerol concentrations were not different between genotype groups in the 36 subjects who underwent the PPLT (Table 3) or in the larger group of subjects who underwent both the OGTT and the PPLT (data not shown, \( P = 0.95 \)). In response to the high-fat meal, plasma triacylglycerol concentrations increased after the consumption of the high-fat meal (Figure 1) such that the final triacylglycerol concentrations were 2-fold fasting triacylglycerol concentrations (\( P < 0.0001 \)). The changes in triacylglycerol concentrations after the high-fat meal did not differ between Ala54 homozygotes and Thr54 carriers (\( P = 0.85 \) for time × genotype interaction). Furthermore, the postprandial triacylglycerol responses, as reflected in triacylglycerol AUC, did not differ significantly between the Ala54 homozygotes and Thr54 carriers regardless of whether the responses were reported as baseline-adjusted total AUC or AUC above baseline triacylglycerol concentrations (Table 3).

Fasting serum concentrations of FAs did not differ significantly between genotype groups (Table 3). In response to the high-fat meal, serum FA concentrations decreased significantly below baseline at the 60- and 90-min time points and rose significantly above baseline during the last 30–60 min of the 4-h test (Figure 1). The time-dependent FA responses to the high-fat meal did not differ between Ala54 homozygotes and Thr54 carriers (\( P = 0.26 \) for time × genotype interaction). Furthermore, the AUC for FAs did not differ significantly between genotype groups (Table 3).

Fasting lipid oxidation rates did not differ significantly between FABP2 genotype groups (Table 3). In contrast, the 120-min lipid oxidation rates tended (\( P = 0.08 \)) to be higher in the Thr54 carriers, and the 240-min lipid oxidation rates were significantly higher (\( \approx 60\% \)) in the Thr54 carriers than in the Ala54-homozygous persons (Table 3).

### Table 2

Oral-glucose-tolerance test (OGTT) outcomes according to FABP2 genotype

<table>
<thead>
<tr>
<th>FABP2</th>
<th>Ala54Ala (n = 58)</th>
<th>Ala54Thr (n = 59)</th>
<th>Thr54Thr (n = 5)</th>
<th>P for Ala54Ala compared with Thr54 Carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal glucose tolerance (% of group)</td>
<td>67</td>
<td>53</td>
<td>20</td>
<td>0.05</td>
</tr>
<tr>
<td>ISI</td>
<td>3.9 (0.2, 0.2)</td>
<td>3.3 (0.2, 0.2)</td>
<td>3.0 (0.5, 0.6)</td>
<td>0.02</td>
</tr>
<tr>
<td>Glucose AUC (mmol/L · min)</td>
<td>911 ± 26</td>
<td>938 ± 26</td>
<td>957 ± 89</td>
<td>0.43</td>
</tr>
<tr>
<td>Fasting glucose (mg/dL)</td>
<td>5.0 ± 0.1</td>
<td>5.3 ± 0.1</td>
<td>5.6 ± 0.3</td>
<td>0.003</td>
</tr>
<tr>
<td>120-min glucose (mg/dL)</td>
<td>6.6 ± 0.2</td>
<td>6.9 ± 0.2</td>
<td>6.8 ± 0.8</td>
<td>0.43</td>
</tr>
<tr>
<td>Insulin AUC (×10³ pmol/L · min)</td>
<td>49.6 (2.7, 2.8)</td>
<td>57.3 (3.1, 3.3)</td>
<td>59.8 (10.5, 12.7)</td>
<td>0.03</td>
</tr>
<tr>
<td>Fasting insulin (pmol/L)</td>
<td>73.6 (3.3, 3.4)</td>
<td>83.3 (3.7, 3.9)</td>
<td>86.7 (12.6, 14.7)</td>
<td>0.05</td>
</tr>
<tr>
<td>120-min insulin (pmol/L)</td>
<td>337.3 (25.6, 27.7)</td>
<td>408.4 (30.7, 33.2)</td>
<td>462.7 (109.4, 143.4)</td>
<td>0.07</td>
</tr>
</tbody>
</table>

1. \( n = 122 \). FABP2, fatty acid–binding protein 2 gene; Ala54, alanine-encoding allele in codon 54 of the intestinal FABP2 gene; Thr54, threonine-encoding allele; ISI, insulin sensitivity index; AUC, area under the curve. Frequency data were analyzed by using a chi-square test, and quantitative data were analyzed by using a one-factor (ie, genotype) ANOVA, which included age and percentage body fat as covariates.
2. Defined as fasting glucose concentrations <5.6 mmol/L and 2-h glucose concentrations <7.8 mmol/L (13).
3. Determined according to the method of Matsuda and DeFronzo (18).
4. x ± SE, − SE in parentheses (all such values). These outcomes required log transformation before statistical analyses.
5. Least-squares x ± SE (all such values).

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the results of that study indicated that insulin sensitivity is ability in physical activity levels. To the best of our knowledge, results because most previous studies did not control for vari-
possible that the exercise habits of the subjects affected previous
may be due to many factors including the genetic background,
hanced glucose tolerance. The discrepant results between studies
findings were summarized in a review article (2), 8 found no relation, and 1
association between the
carriers, those subjects had greater postprandial lipid oxidation
homozygotes. Furthermore, although the postprandial li-
was not exaggerated in Thr54 carriers, those subjects had greater postprandial lipid oxidation
rate did Ala54 homozygotes.
The association of the Thr54 carrier genotype with glucose
intolerance and lower insulin action in the current study is con-
sistent with some, but not all, previous findings. Of the 17 studies
whose findings were summarized in a review article (2), 8 found
associations between the Thr54 allele and lower glucose toler-
ance or lower insulin action, whereas 8 found no relation, and 1
study found an association between the Thr54 allele and en-
hanced glucose tolerance. The discrepant results between studies
may be due to many factors including the genetic background,
age, and body fatness of the study subjects. However, it is also
possible that the exercise habits of the subjects affected previous
results because most previous studies did not control for vari-
ability in physical activity levels. To the best of our knowledge,
only one study accounted for habitual physical activity levels,
and the results of that study indicated that insulin sensitivity is
≈26% lower in Thr54 carriers than in Ala54-homozygous
persons (26). It is also possible that habitual diet qualities such as
macronutrient composition are responsible for some of the dis-
crepant findings between studies. One previous study showed
that a short-term, high-saturated fat diet resulted in a stronger
association between FABP2 genotype and insulin action than did
consumption of either of 2 diets that were low in saturated fat,
including a diet that was similar to the standardized diet used in
the current study (27). Despite the fact that the subjects in the
current study consumed a low-fat diet for ≥2 wk before testing,
an association between the Thr54 carrier genotypes and glu-
coregulatory function persists after elimination of the potentially con-
foundering effects of diet and physical activity.
Contrary to our expectation that Thr54 carriers would have
greater postprandial lipemic responses to the high-fat meal than
would Ala54 homozygotes, the lipemic responses did not differ
significantly between genotype groups. Of 6 previous studies
that examined the role of FABP2 Ala54Thr genotype on post-
prandial triacylglycerol, 3 reported that subjects homozygous
for Thr54 had greater postprandial triacylglycerol AUCs than did
Ala54 homozygotes (7–9). In contrast, 2 studies that compared
Ala54 homozygotes with Thr54 homozygotes (10, 11) and 1
study that compared Thr54 carriers with Ala54 homozygotes
(12) did not find associations. Only 2 studies assessed the effects
of Ala54Thr genotype on postprandial FA responses; 1 of these
2 studies found no difference between FABP2 genotype groups
(9), and the other found that 7-h postprandial FAs were higher in
Thr54 homozygotes than in Ala54 homozygotes (10).
Several explanations are possible for the discrepant findings
among FABP2 genotype studies on postprandial lipemia. First,
the genotype effects may be evident only in Thr54-homozygous
persons. Although we had too few Thr54-homozygous subjects
to analyze separately, it should be noted that the postprandial
triacylglycerol and FA responses were substantially higher in
those subjects. Furthermore, all of the previous studies that found
FABP2 Ala54Thr genotype effects on postprandial lipemia com-
pared homozygous groups (7–9). Physical activity and diet may
also have contributed to the discrepant study findings, because no
prior studies accounted for the effects of habitual physical activity
levels and only one controlled for diet composition (10).
Although we experimentally controlled for these factors in
the current study, it cannot be determined whether these factors
affected the results because we studied only sedentary persons
consuming a low-fat diet. Another explanation for the discrep-
ancies between study findings is that the fat composition of the
test meals may have differed between studies. This explanation
seems unlikely, however, because equivocal results were pro-
duced from studies, including the current study, that used dairy

### TABLE 3
Postprandial lipemia according to FABP2 genotype group

<table>
<thead>
<tr>
<th>FABP2 genotype</th>
<th>Ala54Ala (n = 12)</th>
<th>Ala54Thr (n = 22)</th>
<th>Thr54Thr (n = 2)</th>
<th>P for Ala54Ala compared with Thr54 carriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting TG (mmol/L)</td>
<td>1.21 (0.17, 0.20)²</td>
<td>1.18 (0.13, 0.14)</td>
<td>2.08 (0.66, 0.97)</td>
<td>0.91</td>
</tr>
<tr>
<td>TG total AUC (mmol/L · min)</td>
<td>486 ± 22 ²</td>
<td>493 ± 16</td>
<td>597 ± 54</td>
<td>0.56</td>
</tr>
<tr>
<td>TG incremental AUC (mmol/L · min)</td>
<td>143 ± 22</td>
<td>151 ± 16</td>
<td>267 ± 36</td>
<td>0.54</td>
</tr>
<tr>
<td>Fasting FA (mmol/L)</td>
<td>0.437 ± 0.057</td>
<td>0.362 ± 0.042</td>
<td>0.220 ± 0.142</td>
<td>0.22</td>
</tr>
<tr>
<td>FA AUC (mmol/L · min)</td>
<td>87.2 ± 6.8</td>
<td>80.4 ± 4.9</td>
<td>109.0 ± 17.0</td>
<td>0.57</td>
</tr>
<tr>
<td>Fasting lipid oxidation (% of TEE)</td>
<td>30.2 ± 6.5</td>
<td>40.8 ± 4.8</td>
<td>41.1 ± 16.2</td>
<td>0.18</td>
</tr>
<tr>
<td>120-min lipid oxidation (% of TEE)</td>
<td>12.1 ± 6.6</td>
<td>25.6 ± 4.9</td>
<td>37.8 ± 16.5</td>
<td>0.08</td>
</tr>
<tr>
<td>240-min lipid oxidation (% of TEE)</td>
<td>29.7 ± 5.6</td>
<td>47.5 ± 4.3</td>
<td>46.4 ± 14.2</td>
<td>0.01</td>
</tr>
</tbody>
</table>

¹ n = 36. FABP2, fatty acid–binding protein 2 gene; Ala54, alanine-encoding allele in codon 54 of the intestinal FABP2 gene; Thr54, threonine-encoding allele; AUC, area under the curve; TG, triacylglycerol; FA, fatty acid; TEE, total energy expenditure. Genotype differences were analyzed by using a one-factor (ie, genotype) ANOVA. All outcomes were adjusted for age and percentage body fat; TG total AUC and FA AUC were also adjusted for fasting TG and FA, respectively.
² Least-squares 𝒙 ± SE (all such values). These outcomes required log transformation before statistical analyses.
³ Least-squares 𝒙 ± SE in parentheses (all such values).
compared with covariates; Tukey’s test was used for post hoc comparisons. Included age, percentage body fat, and baseline values of the outcome as analyses were performed with the use of repeated-measures ANCOVA that included age, percentage body fat, and baseline values of the outcome as covariates; Tukey’s test was used for post hoc comparisons.

Results from the current study suggest that carriers of the FABP2 Thr54 allele have lower glucose tolerance, lower insulin action, and enhanced postprandial lipid oxidation rates than do Ala54 homozygotes, but that they do not differ from Ala54 homozygotes with respect to postprandial lipemia. We propose the following physiologic explanation for these results. Because of increased lipid transport across enterocytes (5) and the intestinal wall (6), Thr54 carriers may absorb dietary fat more rapidly, more completely, or both than do Ala54 homozygotes. To prevent an excessive rise in postprandial lipids that would occur with greater fat absorption, Thr54 carriers might have greater oxidative lipid disposal, which would be analogous to that occurring in persons following high-fat diets (29). According to the glucose-FA cycle, the increased lipid oxidation would impair glucose utilization and, consequently, impair glucose disposal and induce insulin resistance by inhibiting glycolysis through increases in the intracellular ratio of acetyl-coenzyme A to coenzyme A, increases in cytosolic citrate concentrations, and the inhibition of pyruvate dehydrogenase, phosphofructokinase, and hexokinase (30). It is also possible that more rapid or more complete absorption of dietary fat in Thr54 carriers could lead to nonoxidative lipid disposal in some tissues, which could further impair insulin action through intramuscular triacylglycerol accumulation (31), adipocyte hypertrophy (32), and overexpression of hepatic glucose-6-phosphatase (33). Although an early manifestation of insulin resistance in Thr54 carriers would be hyperinsulinemia, further deterioration in insulin action, development of insulin secretory insufficiency, or both would later result in glucose intolerance and the development of type 2 diabetes (34).

Conclusions

Results from the current study suggest that, in sedentary middle-aged to older nondiabetic persons following a low-fat diet, FABP2 Thr54 carriers have lower glucose tolerance and lower insulin action than do their Ala54-homozygous counterparts. Although it does not appear that FABP2 Ala54Thr genotype is associated with the lipemic response to a high-fat meal, Thr54 carriers have higher postprandial lipid oxidation rates than do Ala54-homozygous persons. These findings suggest that the association between the FABP2 Thr54 carrier genotype and insulin action are not mediated by postprandial lipemia, but the possibility that augmented lipid absorption causes insulin resistance in Thr54 carriers cannot be ruled out because adaptations such as increased lipid oxidation rates, as seen in the current study, may normalize postprandial lipemia but not prevent the adverse consequences of increased lipid oxidation.

The study design was developed by JMH, EPW, OK, and IAG; data collection was performed or supervised by all authors; data analyses and interpretation were performed by EPW and JMH; and the writing of the manuscript was performed by EPW, JMH, ARS, and JB. None of the authors had a personal or financial conflict of interest.
REFERENCES