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Comparison of the acute response to meals enriched with *cis*- or *trans*-fatty acids on glucose and lipids in overweight individuals with differing FABP2 genotypes

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Abstract

Trans-fatty acids have been implicated as a risk factor for cardiovascular disease and diabetes. In addition, a polymorphism at codon 54 (Ala54Thr) in the fatty acid–binding protein 2 (*FABP2*) gene has been suggested to modify an interaction between dietary fat and insulin sensitivity. We examined the postprandial metabolic profiles after meals enriched with C18:1*trans*- relative to a similar meal with C18:1*cis*-fatty acid in individuals who were either FABP2 Ala54 homozygotes or Thr54 carriers. Moderately overweight men and women ate 2 breakfast test meals, separated by 1 week, each providing 40% of their daily energy requirement and containing 50% of energy as fat. In one meal, 10% of energy was from C18:1*trans*, and in the other meal, the C18:1*trans* was replaced with C18:1*cis*. Metabolic parameters were assessed during an 8-hour period. Insulin and C-peptide levels increased more after the C18:1*trans* meal, and this was associated with a greater fall in free fatty acids. Postprandial glucose levels and oxidation of fatty acids and carbohydrate were not different between the 2 test meals. The Thr54 allele for FABP2 increased the rise in postprandial glucose but not triacylglycerols. Fractional triacylglycerol synthetic rates were higher after consumption of the C18:1*trans* meal relative to the C18:1*cis* meal only in Thr54 carriers. These data show that a single meal enriched with C18:1*trans*-fatty acids can significantly increase insulin resistance, and that in the presence of the FABP2 Thr54 allele, may contribute to increased partitioning of glucose to triacylglycerols and insulin resistance.

1. Introduction

A direct role for the amount and type of dietary fat in the development of insulin resistance and type 2 diabetes remains to be clearly established. A number of cross-sectional and prospective epidemiological studies have identified a positive association between the intake of total fat and the risk for development of either insulin resistance or type 2 diabetes, as shown by a recent review [1]. However, these associations are not consistently observed in large well-powered studies or are substantially attenuated after taking into consideration potential confounders such as body mass index (BMI), fiber intake, and magnesium intake [1]. Clinical studies have been equally equivocal with some studies demonstrating effects of fat intake on features of insulin sensitivity [2-4], whereas others show no effects [5,6].

Nonetheless, there are data suggesting a role for the type of dietary fat as opposed to total amount of fat in determining insulin sensitivity and development of type 2 diabetes. Pioneering animal studies conducted by Storlien and colleagues (reviewed in Reference [7]) showed that eating diets enriched with saturated or polyunsaturated fat induced severe insulin resistance, whereas diets enriched with monounsaturated fat were less detrimental, and omega-3 fatty acids from fish oils prevented the development of insulin resistance [8]. A similar pattern has been observed in some studies in humans [9-11].

The role of *trans*-fatty acids in the development of insulin resistance and type 2 diabetes has not been thoroughly

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explored. The Nurses' Health Study [12], the Health Professional's Follow-up Study [13], and the Iowa Women's Health Study [14] all reported increased risk for the development of type 2 diabetes with increased consumption of *trans* fat. However, in the latter 2 studies, this increased risk was no longer significant after multivariate adjustment. In clinical studies, the effects of *trans* fat on features of insulin sensitivity are conflicting [15,16].

Potential effects of individual fatty acids, including *trans*-fatty acids, may be partially determined by genetic variants in the intestinal fatty acid–binding protein 2 (*FABP2*), a candidate gene for diabetes [17]. A common alanine-to-threonine mutation at codon 54 in the *FABP2* gene has been associated with decreased insulin sensitivity on a high-fat diet [18]. The effect of the Thr54 FABP2 genotype is hypothesized to be due to increased affinity and transport of fatty acids across the intestine by the variant [19].

An observed greater transport of saturated (palmitic) versus unsaturated (oleic) fatty acids by FABP2 [19] raises the possibility that any effects of *trans*-fatty acids on insulin sensitivity may be more pronounced in individuals carrying the Thr54 FABP2 allele. In this article, we report the effects of eating a single meal enriched in either *cis* or *trans* C18:1 fatty acids on postprandial glucose and lipid metabolism in individuals with and without the Thr54 FABP2 allele.

2. Subjects and methods

2.1. Subjects

Healthy, nonsmoking, overweight men and women were recruited from the greater Baton Rouge area by advertisement. Inclusion criteria were age between 21 and 65 years, BMI of less than 32 kg/m^2, no medication use (except birth control pills), fasting glucose of less than 7.0 mmol/L, triacylglycerols of less than 4.52 mmol/L, low-density lipoprotein cholesterol (LDL-C) of less than 4.92 mmol/L, and fasting insulin of more than 41.7 pmol/L. In addition, serum triacylglycerols and LDL-C had to be greater than the 10th percentile for age, race, and sex to exclude individuals with abnormal fat metabolism. Participants were additionally selected to provide roughly equal numbers of individuals with and without the Thr54 FABP2 allele. A total of 22 participants were selected, 12 with genotype Ala/Ala, 8 with genotype Thr/Ala, and 2 with genotype Thr/Thr at codon 54 in FABP2.

All subjects gave written informed consent before participation, and the consent form and protocol were approved by the Pennington Biomedical Research Center Institutional Review Board.

2.2. Diets

Participants were provided for 16 days with a basal 24% fat diet containing 7% of energy as saturated fat, 7% of energy as polyunsaturated fat, and 10% of energy as monounsaturated fat. On days 10 and 16, participants were given a high-fat test meal (egg, mushroom, and potato quiche), providing 40% of the individual's daily energy need, with 50% of energy from fat. The 2 test meals were provided in random order to each participant. The C18:1*cis* test meal (control) contained 15% of energy as saturated fat, 15% as polyunsaturated fat, and 20% as monounsaturated fat with C18:1*cis*. For the C18:1*trans* test meal, 10% of the C18:1*cis* was replaced with C18:1*trans*-fatty acids.

All diets and test meals were prepared by the Pennington Metabolic Kitchen. Subjects and data collection staff were masked to the type of test meal being provided.

2.3. Experimental procedures

The test meals were administered at 8:00 AM and were consumed within 20 minutes. Blood was sampled hourly for 8 hours and assayed for glucose, insulin, C-peptide, triacylglycerols, and free fatty acids. The time of presentation of the meal was taken as 0 hour. Indirect calorimetry for substrate oxidation was performed before the meal and after the meal test, during the first 30 minutes of each hour up to 8 hours.

2.4. Laboratory measures

Serum glucose, triacylglycerols, total cholesterol, high-density lipoprotein cholesterol (HDL-C), and free fatty acids were assayed by established enzymatic procedures (Beckman Synchron CX7 or CX5; Beckman Coulter, Brea, CA). Plasma insulin and C-peptide were measured on an Immulite autoanalyzer (DPC, Los Angeles, CA). Urinary nitrogen was analyzed using pyrochemiluminescence on an Antek 9000 (Antek, Houston, TX).

2.5. Metabolic rate and substrate oxidation

Sensormedic 2900Z metabolic carts (Sensormedics, Yorba Linda, CA) were used to measure resting metabolic rate and postprandial energy expenditure and substrate oxidation. Resting metabolic rate was measured in overnight-fasted subjects for 30 minutes after a 30-minute rest period. Fat and carbohydrate oxidation was calculated as described by Jequier et al [20]. Protein oxidation was calculated from urinary nitrogen excretion. The precision of these instruments has been shown to be ±5% in our hands.

2.6. Cholesterol and triacylglycerol fractional synthetic rates

Cholesterol and triacylglycerol synthesis were measured during a 24-hour period by measuring the incorporation of deuterium into lipids [21,22]. On the test day, subjects were provided a dose of 1.2 g D_2O/kg of body water before consumption of the test meal. Blood was drawn before the dose and again 24 hours after the dose. A urine sample was collected 24 hours after the dose for determination of plasma water enrichment.

Table 1
Participant characteristics

	FABP2 genotype		
	Ala/Ala	Thr/*	Combined
n	12	10	22
Men/women	6/6	4/6	10/12
African Americans	3	1	4
Age (y)	42.8 ± 3.6	36.9 ± 3.1	40.1 ± 2.5
BMI (kg/m^2)	25.0 ± 0.8	26.5 ± 1.3	25.7 ± 0.7
Total cholesterol (mmol/L)	4.41 ± 0.16	4.31 ± 0.23	4.36 ± 0.13
Triacylglycerol (mmol/L)	0.99 ± 0.08	1.25 ± 0.12[a]	1.10 ± 0.07
LDL-C (mmol/L)	2.86 ± 0.14	2.66 ± 0.22	2.77 ± 0.13
HDL-C (mmol/L)	1.09 ± 0.05	1.07 ± 0.05	1.08 ± 0.04
Glucose (mmol/L)	5.1 ± 0.1	4.9 ± 0.1	5.0 ± 0.1
Free fatty acids (mmol/L)	0.40 ± 0.05	0.52 ± 0.05	0.46 ± 0.04
Insulin (pmol/L)	46.5 ± 7.0	65.4 ± 13.2	54.6 ± 7.0
C-peptide (nmol/L)	0.66 ± 0.07	0.70 ± 0.07	0.68 ± 0.07

[a] $P < .05$, significantly different than Ala/Ala individuals after adjustment for sex.

2.7. Calculation of postprandial insulin sensitivity

As an index of postprandial insulin sensitivity, we calculated the product of insulin and glucose concentrations at each time point. The product of insulin and glucose concentrations or its inverse is used as the primary component of numerous measures of insulin sensitivity [23]. Our decision to use this simple product rather than one of the established indexes (eg, HOMA-IR or QUICKI) is based on our desire not to have the values obtained in the postprandial state compared against values obtained with indexes designed to be calculated with fasting levels and/or levels obtained during a defined oral glucose tolerance test.

2.8. Genotyping

FABP2 genotypes were determined by restriction enzyme digestion after polymerase chain reaction amplification as described elsewhere [18].

2.9. Statistical analysis

Analysis of variance was used to compare the effects of test meal composition, FABP2 genotype, and their interactions. Sex and age were used as covariates in the analysis.

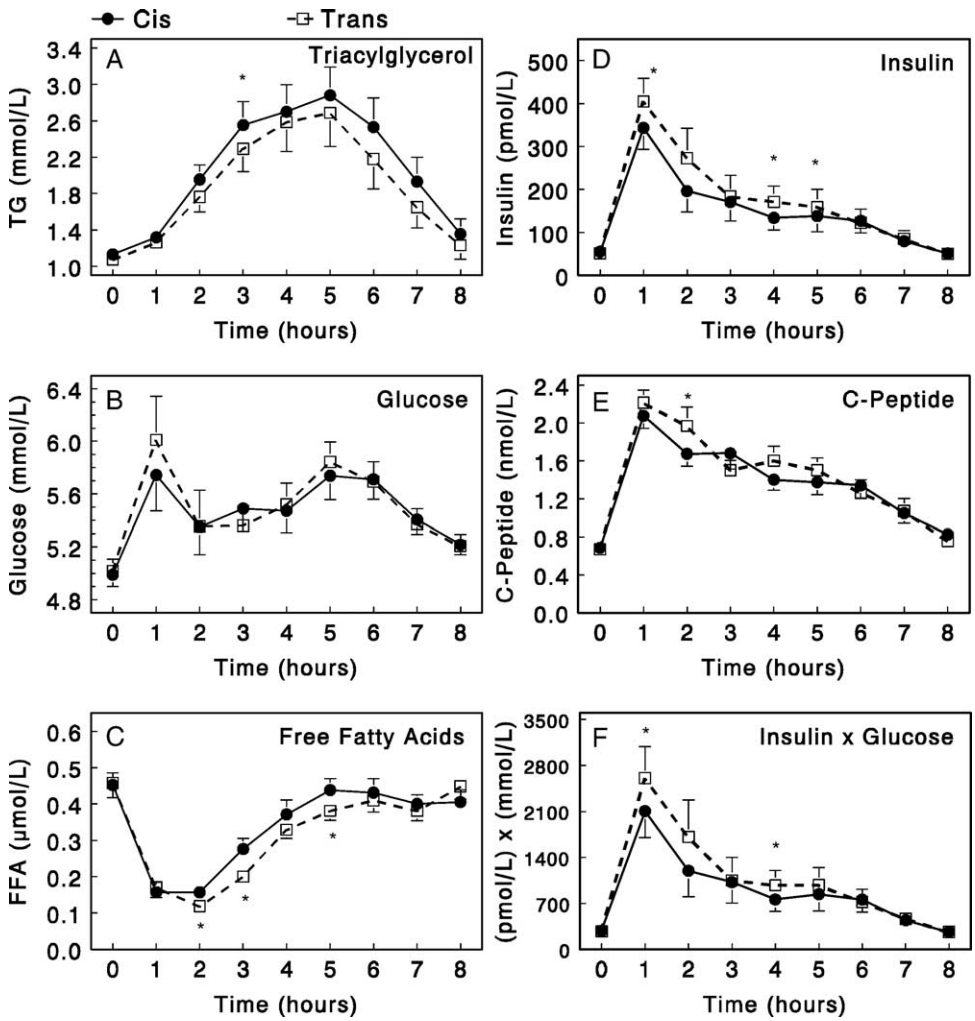

Fig. 1. Effect of test meals during 8 hours on postprandial triacylglycerol (A), glucose (B), free fatty acids (C), insulin (D), C-peptide (E), and the product of insulin and glucose concentrations (F). Data are plotted as mean ± SEM. Asterisks indicate significant differences between test meals at a given time point.

For genotype analysis, genotypes Thr/Thr and Thr/Ala were combined (Thr54 group) and compared against those with an Ala/Ala genotype (Ala54 group). A P value of less than .05 was considered significant. All data are presented as means ± SE.

3. Results

3.1. Participant characteristics

The study population was middle-aged (40.1 ± 2.5 years), 55% female, and 18% African American. The BMI averaged 25.7 ± 0.7 kg/m^2 and was slightly higher in the Thr54 group (Table 1). Mean total cholesterol, LDL-C, and triacylglycerol values averaged from fasting samples obtained before consumption of each test meal indicated that the participants were healthy without marked hyperlipidemias. Values for fasting glucose, free fatty acids, insulin, and C-peptide were within the reference range. Fasting lipids, glucose, free fatty acids, insulin, and C-peptide values were not different between test days. After covariate adjustment for differences due to sex, fasting triacylglycerol values were significantly (P = .02) greater in the Thr54 group than in the Ala54 group.

3.2. Postprandial response: effect of trans-fatty acids

The test meals were well tolerated by the participants and were consumed within the allotted 20-minute period. The test meals produced a marked postprandial triacylglycerolemia, which peaked between 4 and 5 hours and returned to preprandial levels by 8 hours (Fig. 1A). Replacement in the test meal of 10% of energy from C18:1*cis* with C18:1*trans* resulted in a slightly lower postprandial triacylglycerol response. However, part of this difference was because of a lower fasting (0 hour) triacylglycerol level. When expressed as an increment above fasting levels (Table 2), differences in the magnitude of the postprandial triacylglycerolemia between test meals were no longer significant (P = .10).

Postprandial glucose levels did not differ between the control and C18:1*trans* test meals (Fig. 1B, Table 2). However, postprandial free fatty acid levels declined to a greater extent and remained lower for a greater length of time after the C18:1*trans* test meals relative to the control meal (Fig. 1C), although the total area under the curve (AUC) during the 8 hours was not different (Table 2). Insulin levels increased to a greater extent at 1 hour and remained elevated up to 5 hours after consumption of the C18:1*trans* test meal versus the control test meal (Fig. 1D), leading to a greater 8-hour insulin AUC (Table 2). This was largely paralleled by changes in C-peptide, with greater postprandial levels observed after the C18:1*trans* test meals relative to the control test meal (Fig. 1E). The postprandial changes in the product of insulin and glucose concentrations, an index of relative insulin sensitivity, was greater after the consumption of the C18:1*trans* test meal versus the control test meal (Fig. 1F) as was the 8-hour AUC (Table 2).

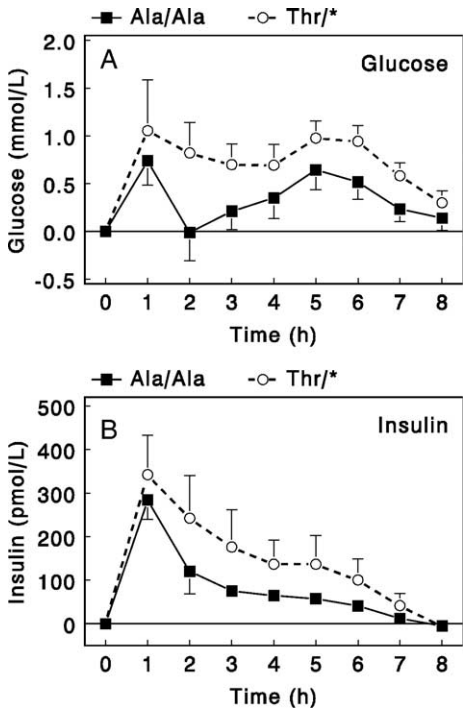

Fig. 2. Effect of FABP2 genotype on change from 0 hour on postprandial glucose (top panel) and insulin (bottom panel). Data are plotted as mean ± SEM.

Table 2
Effect of FABP2 genotype on postprandial response to test meals

	Ala/Ala		Thr/*		Significance
	C18:1*cis*	C18:1*trans*	C18:1*cis*	C18:1*trans*	
Triacylglycerol AUC (mmol/L × 8 h)	7.35 ± 1.46	6.72 ± 1.89	8.98 ± 2.28	7.36 ± 2.02	NS
Free fatty acids AUC (mmol/L × 8 h)	−0.95 ± 0.29	−0.94 ± 0.38	−0.97 ± 0.27	−1.55 ± 0.42	NS
Glucose AUC (mmol/L × 8 h)	2.90 ± 0.60	2.61 ± 1.23	5.70 ± 1.11	6.15 ± 1.25	FABP2
Insulin (pmol/L × 8 h)	597 ± 90	715 ± 146	1007 ± 396	1340 ± 444	Meal
C-peptide (nmol/L × 8 h)	10.7 ± 0.9	11.2 ± 1.1	12.1 ± 1.6	12.6 ± 1.7	NS
Insulin × glucose [(pmol/L × 8 h) × (mmol/L× 8 h)]	3629 ± 594	4498 ± 1132	7096 ± 3221	9364 ± 4105	Meal
Fat oxidation (kJ/8 h/kg LBM)	16.0 ± 1.2	16.9 ± 1.5	18.1 ± 1.5	18.0 ± 1.0	NS
Carbohydrate oxidation (kJ/8 h/kg LBM)	32.1 ± 2.3	32.5 ± 2.8	33.9 ± 2.9	33.3 ± 1.6	NS
Cholesterol FSR (pools per day)	0.090 ± 0.008	0.085 ± 0.009	0.096 ± 0.009	0.101 ± 0.010	NS
Triacylglycerol FSR (pools per day)	0.086 ± 0.007	0.076 ± 0.006	0.086 ± 0.005	0.103 ± 0.009	FABP2 × meal

LBM indicates lean body mass; FSR, fractional synthetic rate.

This was largely driven by differences in postprandial insulin levels.

The substitution of C18:1*trans* for C18:1*cis* had no effect on oxidation of either carbohydrate or fat (Table 2). Fractional synthetic rates for cholesterol and triacylglycerol measured during the 24 hours after consumption of the test meals did not differ between C18:1*trans* and C18:1*cis* control meals.

3.3. Postprandial response: effect of FABP2 genotype

Postprandial changes in triacylglycerols and free fatty acids did not differ as a function of FABP2 genotype. Individuals in the Thr54 group had greater postprandial increments in glucose when the response to both test meals were averaged (Fig. 2A, Table 2). Although the postprandial insulin response was greater in those individuals in the Thr54 group, this difference was not statistically significant. No trends in postprandial C-peptide levels across genotype were observed. Of interest, a significant genotype by meal interaction was observed for triacylglycerol fractional synthetic rate. In individuals in the Ala54 group, fractional synthetic rates for triacylglycerol were not affected by the fatty acid composition of the test meal. In contrast, individuals in the Thr54 group had a higher triacylglycerol fractional synthetic rate after consumption of the C18:1*trans* test meal versus the control meal.

4. Discussion

Previous studies suggest that long-term consumption of different dietary fatty acids has varying effects on insulin action. In the present study, we observed that insulin levels were increased after a single meal in which 10% of energy from *trans*-fatty acids (C18:1*trans*) replaced an equivalent amount of C18:1*cis*-fatty acids in a common background meal. C-peptide concentrations were also significantly increased after the C18:1*trans* acid meal, suggesting that the observed increase in insulin was due primarily to an increase in insulin secretion. Although the glucose concentrations were not significantly different between test meals, the increased product of insulin and glucose concentrations is consistent with an acute increase in insulin resistance. The fall in free fatty acids after the *trans*-fatty acid test meal would be expected with the higher insulin concentrations when insulin acts on the more insulin-sensitive fat cell. The rise in plasma triacylglycerols was not different between the 2 test meals.

The stimulation of insulin secretion by fatty acids is well established [24]. Several studies have suggested that fatty acids differentially affect insulin secretion. Opara et al [25] demonstrated that medium-chain fatty acids stimulate basal insulin release compared with long-chain fatty acids, whereas saturated fatty acids inhibited insulin release in isolated pancreatic islet cells. However, other studies using either isolated pancreatic islets or perfused pancreas have shown that in the presence of elevated glucose levels, the ability of fatty acids to stimulate insulin secretion increases with fatty acid chain length and degree of saturation [26,27]. With respect to *trans*-fatty acids, in the perfused rat pancreas, insulin stimulation was slightly less with elaidic acid relative to oleic acid [27]. Contrary to this observation, a later study demonstrated that *trans*-fatty acids potentiated insulin secretion by isolated or perifused mouse islet cells relative to *cis* isomers of the same chain length [28]. Our data are consistent with the latter observation.

Our data are also consistent with those of Christiansen et al [15], who reported that both *trans* and saturated fatty acids increased postprandial insulin response relative to polyunsaturated fatty acids in obese patients with type 2 diabetes. However, in that study, participants had previously been fed with diets high in *trans*, saturated, and polyunsaturated fatty acids before their respective oral fat challenges. Thus, it was not possible to determine if the effects of the fatty acids were the result of short- or long-term feeding. Our results suggest that a single meal, high in *trans*-fatty acids, can have acute effects on the resulting postprandial insulin response.

The results of the present study do not show any difference in fat or carbohydrate oxidation between *trans*- and *cis*-fatty acid–enriched meals. We have previously reported a 4-week study in which fat oxidation was significantly higher during the high *trans*-fatty acid diet compared with a high–oleic acid diet [29]. Furthermore, DeLany et al [30] have previously reported immediate differences in the rate of oxidation of *cis*- and *trans*-fatty acids in lean men fed with ^{13}C-labeled fatty acids, such that C18:1*trans* was more highly oxidized than C18:1*cis* during a 9-hour period. Two things might explain these differences. First, the study reported here lasted only 8 hours as compared with the earlier 4-week study. Although the isotopically labeled *trans*-fatty acid was oxidized more rapidly, when mixed with the entire fatty acid pool and measured by metabolic cart as in the present study, the contribution of this single fatty acid may be too small to detect.

We did not observe any significant effects of *cis*- versus *trans*-fatty acids on postprandial lipemia. Our data are thus consistent with those of Tholstrup et al [31] who similarly found no differences between oleic acid and elaidic or linoleic acid on HDL-C, LDL-C, or total triacylglycerols after a meal, although saturated fatty acids did produce different lipemic responses.

As reviewed by Weiss et al [17], numerous studies have addressed the potential association of the Thr54 FABP2 variant with insulin resistance. It has been hypothesized that the 2-fold greater affinity for fatty acids with the Thr54 allele would increase the rate of fatty acid absorption leading to greater postprandial plasma fatty acid levels [32]. The resulting elevated postprandial fatty acid levels are suggested to induce insulin resistance in the muscles via the glucose–fatty acid cycle [17].

In support of this hypothesis, Baier et al [18] reported that in Pima Indians, the presence of the Thr54 allele was associated with lower insulin-stimulated glucose uptake, greater postprandial insulin responses to both an oral glucose load and a mixed meal, and greater fasting fat oxidation rates. A greater fasting rate, but not postprandial fat oxidation rate, has also been reported in Korean men [33]. Additional studies, using various methods to assess insulin sensitivity, have similarly demonstrated lower insulin sensitivity in individuals with at least one copy of the Thr54 allele [34-36]. In one study, this decrease in insulin sensitivity was only evident while participants were consuming a high-fat meal [37].

Our results partially confirm these previous findings. Individuals with at least one copy of the Thr54 allele had a 2-fold greater postprandial glucose response than those who were homozygous for the Ala54 allele. Although not significant ($P = .15$), those with the Thr54 allele had a 70% greater postprandial insulin response. These data are consistent with impaired insulin-mediated glucose uptake due perhaps to fatty acid–induced insulin resistance in the muscle as has been previously suggested [17].

If the Thr54 allele promotes increased rates of fatty acid absorption, then this could be readily reflected in alterations in postprandial triacylglycerolemia. In one study [38], subjects homozygous for the Thr54 allele were found to have a greater postprandial triacylglycerolemia after being given an oral fat load (heavy cream supplemented with fish oil). Furthermore, in those homozygous for the Thr54 allele, but not the Ala54 allele, postprandial triacylglycerolemia was correlated with insulin response, suggesting an association between triacylglycerolemia and insulin action in those with the Thr54 allele. The same authors later showed through fatty acid analyses that this increase was largely confined to increases in 14- to 18-carbon fatty acids in chylomicron and very-low-density lipoprotein triacylglycerols, with little apparent selectivity with respect to chain length or degree of unsaturation [39].

A direct test of an interaction between FABP2 genotype and the fatty acid composition of the oral fat load failed to demonstrate any significant interactions [40]. In this instance, the individuals possessing at least one Thr54 allele did not differ from those homozygous for the Ala54 allele with respect to postprandial triacylglycerolemia when given test meals containing safflower oil, olive oil, or butter. However, those with a Thr54 allele did experience a smaller postprandial insulin response. This, however, is in a direction opposite of that predicted from previous studies.

Based on the reported differences in the affinity of FABP2 for fatty acids [18], we had hypothesized that there would be an interaction between the FABP2 genotype and the fatty acid composition of the test meal. However, we found no significant interactions for any measured parameter with the exception of fractional triacylglycerol synthesis rates. Individuals with the Thr54 allele had a 20% higher fractional triacylglycerol synthesis rate after consumption of the C18:1*trans* test meal than the (C18:1*cis*) control meal. It is conceivable that the increased insulin levels due to the consumption of the high *trans*-fatty acid meal, coupled with the increased postprandial glucose levels in those with the Thr54 allele, favored increased lipogenesis.

The amount of *trans*-fatty acids consumed at this single meal was high relative to estimated average US intakes of 2% of energy [41]. Nonetheless, our findings may have implications with respect to the ongoing epidemic of obesity. In the Health Professional's Follow-up Study [42], a 2% increment in energy intake from *trans* fat was associated with a 0.77-cm gain in waist circumference during a 9-year period. This increment was only modestly attenuated after adjustment for changes in BMI, suggesting a specific role for *trans* fat on the development of abdominal obesity. Our findings suggest a potential mechanism wherein elevated postprandial insulin levels after consumption of meals high in *trans*-fatty acids might increase the activity of lipoprotein lipase levels in visceral adipose depots, thereby promoting increased abdominal fat deposition [42]. Abdominal fat accumulation may be further exacerbated in individuals bearing the Thr54 FABP2 allele where the consumption of a high *trans*-fatty acid meal additionally increases de novo lipogenesis. Given the rates of obesity in the United States and its impact on health, these conjectures may deserve additional attention in the form of well-controlled metabolic dietary studies.

In summary, the present study showed that the replacement of 10% of energy from C18:1*cis*-fatty acids with C18:1*trans*-fatty acids resulted in a greater rise in insulin, C-peptide, and in the product of insulin and glucose concentrations, suggesting increased insulin secretion and possibly insulin resistance. The greater fall in plasma free fatty acids with the C18:1*trans* test meal is consistent with the higher level of insulin. Fat and carbohydrate oxidation was unaffected by the test meals. In addition, individuals with at least one copy of the Thr54 allele for the FAPB2 had a greater postprandial glucose excursion than those who were homozygous for the Ala54 allele. Finally, individuals bearing the Thr54 FABP2 allele had a greater postprandial lipogenesis after consumption of a meal in which C18:1*cis*-fatty acids were replaced with C18:1*trans*-fatty acids.

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