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A High Fat Diet and the Thr54 polymorphism of FABP2 Reduces Plasma Triglyceride-Rich Lipoproteins

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Abstract

The Thr54 allele of the fatty acid binding protein 2 (FABP2) DNA polymorphism is associated with increased triglyceride-rich lipoproteins (TRL). We hypothesized that the TRL response to diets of varied fat content is affected by the FABP2 A54T polymorphism, specifically that a high fat diet would reduce TRL and that the T54 allele would have an enhanced response. Sixteen healthy, post-menopausal women completed a cross-over dietary intervention that included three 8-week, isocaloric diet treatments. The treatments consisted of high fat (HF, 40% of energy as fat), low fat (LF, 20% of energy), and low fat + n-3 fatty acids (LF+n-3, 20% of energy plus 3% as n-3 fatty acids). Eight subjects were homozygous for the wild-type (A/A) of the FABP2 polymorphism while eight subjects had at least one Thr54 allele (7 = A/T, 1 = T/T). HF diet showed significantly reduced plasma triglycerides (TG), chylomicron TG, and very-low density lipoprotein TG from baseline in all participants. Although, carriers of the Thr54 allele of the FABP2 polymorphism had significantly reduced TLR, there is no evidence of an interaction which does not support our hypothesis. The Ala54 allele did not influence the dietary effects on the plasma lipids.

Keywords

Dietary fat; Omega-3 fatty acids; Fatty acid binding protein 2; Triglyceride rich lipoprotein; Single nucleotide polymorphisms; Women

1. Introduction

Higher concentrations of triglycerides (TG) and triglyceride-rich lipoproteins (TRL) such as chylomicrons, very low density lipoproteins (VLDL) and their respective remnants are known cardiovascular risk factors [1-3]. The current cardiovascular disease (CVD) primary prevention plan from the National Cholesterol Education Program (NCEP) is to reduce

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dietary total and saturated fat [4]. Studies have shown that individual response to the recommended NCEP low-fat diet varies significantly, although the group mean may show a beneficial plasma lipid response [5,6]. Schaefer et al. attributed the inter-individual differences to genetics, since other variables such as diet, body weight, compliance and lifestyle were well controlled [5].

Genetic variation in fatty acid binding protein 2 (FABP2) has been associated with alterations in lipid metabolism. FABP2 is expressed in the enterocytes of the intestine and aids in the absorption and transportation of long chain fatty acids. A single nucleotide polymorphism (SNP) occurs at codon 54 of the FABP2 gene resulting in an alanine (wild-type) to threonine (mutated-type) substitution (A54T) in the protein [7]. The T54 allele has a greater affinity for long chain fatty acids than the A54 allele and results in a greater flux of fatty acids across the enterocytes and into the plasma [8]. The FABP2 polymorphism has been associated with dyslipidemia [9] and an increase in plasma TRL [10]. Recently, Zhao et al. found that carriers of Thr54 allele have higher fasting plasma TG than non-carriers in a meta-analysis [11] of available.

In addition to the role of total fat intake in triglyceride response, the type of fat consumed affects TRL concentrations. Polyunsaturated fatty acids (PUFAs), especially omega-3 (n-3) fatty acids, are recommended to help lower plasma triglycerides [4,12]. The mechanism by which n-3 lower triglycerides is unclear, however research suggests that n-3 binds to nuclear receptors, such as peroxisome proliferator activator receptors (PPARs), and decreases hepatic triglyceride and VLDL synthesis and secretion [13].

In this study, we hypothesized that the TRL response to diets of varied fat content is affected by the FABP-2 A54T polymorphism, specifically that a high fat diet would reduce TRL and that the T54 allele would have an enhanced response. Our aims were to examine TRL response to three whole food diets with varying amounts and types of dietary fat (high fat, low fat and low fat supplemented with n-3 fatty acids), and to investigate the role of DNA polymorphisms in FABP2 in modifying the TRL response.

2. Methods and Materials

2.1 Study Design

Seventeen healthy, post-menopausal women were recruited from the Minneapolis-St. Paul, MN area and enrolled in a randomized, cross-over designed feeding trial at the University of Minnesota to evaluate the effects of the diets on sex hormone concentrations [14].

Postmenopausal status was confirmed by subjects being at least 1 year post menses which was also confirmed by FSH levels in women 55 years or less. Inclusion criteria included age 45-70 years, postmenopausal and not taking hormone replacement therapy, healthy, weight stable for the last six months, a BMI between 19 and 32 kg/m², and consumption of a “typical” American diet with no special dietary practices such as vegetarianism. Subjects were excluded if they used prescription medications or over-the-counter non-steroidal anti-inflammatory medications, smoked, or had a known chronic disease. One subject was not included in the final analysis due to a laboratory equipment error which resulted in unusable triglyceride data.

Complete details of the dietary treatments are described in the paper by Young [14]. Briefly, in a complete feeding study, the subjects were provided each of three isoenergetic, controlled diets: high fat (45% energy as fat, HF), low fat (20% of energy as fat, LF), low fat + n-3 fatty acids (23% energy as fat, LFn-3) in random order with a wash out of 6-12 weeks between treatments. The diets contained a ratio of 1:1:1 for saturated, monounsaturated, and polyunsaturated fatty acids, and the LFn-3 diet contained an additional 3% of energy from

n-3. The nutrient composition of the diets is shown in Table 1. Subject compliance with the diets was greater than 99% as assessed by compliance questionnaire (14).

All study visits were performed at the University of Minnesota General Clinical Research Center. Fasting blood samples were collected at baseline and 8 weeks of each diet period by the nursing staff, centrifuged at low speeds to obtain plasma, and stored at -80°C until triglyceride analysis. Blood was also obtained during a single clinic visit for DNA extraction.

This study was approved by University of Minnesota Committee for the Use of Human Subjects in Research and the U.S. Army Medical Research and Materiel Command's Human Subjects Research Review Board. Written informed consent was obtained from all study participants.

2.2 Biochemical Analyses

Chylomicrons, as well as chylomicron remnants (CR) and VLDL, were isolated by salt density gradient ultracentrifugation, as previously described by Tsai et al [15]. Collection of two sub-fractions, Svedberg units of flotation (S_f) >400 containing chylomicrons, and S_f 20-400 containing VLDL and CR, were obtained from baseline and 8-week plasma samples.

The triglyceride analysis is based on the work of McGowen et al. and Fossati et al [16,17] using Infinity Triglyceride Liquid Stable Reagent (Thermo Electron Corp. Waltham, MA). Samples were run in duplicate and with internal controls. Plasma triglyceride intra- and inter-assay CV's were 5.4% and 20.0%, respectively. Analysis of the FABP2 polymorphism was conducted using an amplification and restriction enzyme digestion technique initially described by Baier et al. [7].

2.3 Statistical Analysis

All statistical analyses were conducted using Proc Mixed in SAS statistical software version 9.2 (SAS Institute Inc. Cary, NC). Repeated-measures analysis of variance was conducted to determine the effect the three different diets and the DNA polymorphisms had on plasma triglycerides. The triglyceride endpoints had baseline values subtracted for analysis. The general linear model for repeated-measures procedures was used to test the main effects of genotype, and diet and gene X diet interactions. Due to the small sample size and few degrees of freedom, we could only analyze the interaction of FABP2 and diet. Pairwise comparisons between treatments were based on the least squares means from the mixed model. The treatment randomization groups are unbalanced and therefore treatment order was added to the model for statistical analysis. Differences were considered statistically significant at $P < 0.05$. All data in the text and tables are given as means $\pm$ standard error.

3. Results

The baseline characteristics of the study subjects separated into FABP2 Ala54/Thr54 genotype groups are presented in Table 2. The mean age of all the subjects was 56.3 ± 1.5 years. The mean BMI of the subjects was $27.7 \pm 1.0 \text{ kg/m}^2$. Fifteen subjects were Caucasian and one was African-American. No carryover effect of the diets was detected and the order in which the diets were given was not significant for any endpoints.

Eight of our subjects were homozygous for the FABP2 wild-type, Ala54/Ala54 (A/A, 50% of our population), 7 subjects were heterozygotes, exhibiting Ala54/Thr54 (A/T, 44%), and 1531 subject was homozygous for the mutation, Thr54/Thr54 (T/T, 6%). Because there was a single 154Thr54/Thr54 subject and no repeated-measures of analysis of variance calculations could be performed on a single subject, it was included in the Ala54/Thr54

group for statistical analysis. These results are consistent with previous studies of Caucasians stating the prevalence of wild-type homozygotes to be 50%, heterozygotes to be 45%, and mutation homozygotes to be 5% [10,18]. There were no statistically significant differences in age, BMI, plasma TG, chylomicron TG, VLDL TG, between the FABP2 genotype groups at baseline.

Table 3 illustrates the change from baseline for TG concentrations in response to dietary treatments. Analysis of mean fasting plasma TGs in response to diet resulted in a statistically significant reduction from baseline with the HF diet ($P = 0.012$), but not with the LF or LFn-3 diets, although there were no observed differences between treatments. Plasma TGs were also significantly reduced from baseline in carriers of the Thr54 allele after completion of the HF diet ($P = 0.003$), but not after consuming the LF or LFn-3 diets, shown in Table 4 and illustrated in Figure 1A. The plasma triglyceride response was not statistically significantly different between the diets or the FABP2 genotype groups.

Fasting chylomicron subfraction TG was significantly reduced from baseline with both the HF ($P = 0.027$) and LF diets ($P = 0.023$), but not with the LFn-3 diet, shown in Table 3. Carriers of the Thr54 allele had significantly reduced chylomicron triglyceride after consuming the HF diet ($P = 0.008$) shown in Table 4 and Figure 1B. No difference was observed in chylomicron triglyceride between the diets or by genotype groups.

VLDL and CR subfraction triglyceride was significantly reduced from baseline after consuming the HF diet ($P = 0.010$) and the reduction was statistically significantly different from the LF diet ($P = 0.009$) and LFn-3 diet ($P = 0.006$), shown in Table 3. Carriers of the Thr54 allele exhibited significantly reduced VLDL and CR triglyceride ($P = 0.006$), shown in Table 4 and Figure 1C, compared to baseline in response to the HF diet, but not the LF or LFn-3 diets.

The main effects of diet, FABP2, and diet x FABP2 were non-significant covariates for any of the endpoints, with their p -values shown in Table 4.

4. Discussion

In this study we evaluated the effects of dietary fat and fatty acid intake and FABP2 genotype on TRL response. Our findings show that carriers of the Thr54 allele of the FABP2 polymorphism had significantly decreased plasma TG, chylomicron TG, and VLDL and CR TG after consumption of the HF diet. Homozygotes of the Ala54 allele, alone or in combination with the diets, did not show significant changes from baseline with any diet.

A meta-analysis of 60 controlled feeding studies confirmed that replacing carbohydrates with dietary fat will decrease fasting serum TG [19]. High fat, low CHO diets, with and without n-3 supplementation, have previously been shown to decrease fasting and postprandial triglycerides [20,21]. Our results suggest that an elevated n-3 intake with a low fat, high CHO diet does not play a large role in decreasing fasting triglycerides in postmenopausal women.

Volek et al. observed decreased fasting and postprandial TG in response to a HF, low CHO diet in 10 healthy normolipidemic, postmenopausal women, and suggested a mechanism for the decrease in fasting triglycerides [22]. They propose that a high fat, low CHO diet would induce an increase in lipoprotein lipase (LPL) activity, presumably to allow fatty acids to play a larger role in the energy supply to peripheral cells. The authors also state that a decrease in the rate of VLDL production contributes to a reduced postprandial lipemia because a larger VLDL-TG pool competes with dietary TG for removal during postprandial

periods. Therefore, a decrease in TG is expected in response to a high fat diet due to an increase in LPL activity, which would increase the rate of removal of TG from the plasma.

Parks et al. found that fasting TG concentrations increased by 60% after consuming a low-fat, high carbohydrate diet and concluded that a low fat, high carbohydrate whole food diet reduced VLDL clearance [23]. They proposed that the reduced VLDL clearance could be the result of competition between VLDL and CR for TG hydrolysis. Mittendorfer et al. found that fasting VLDL was significantly higher after a high carbohydrate diet than after a high fat diet [24]. They proposed that an increased rate of VLDL secretion resulted in an elevated plasma TG. Thus, high and low fat diets play a role in fasting triglyceride metabolism.

The LFn-3 diet treatment did not produce any change in response variables. Previous studies produced mixed results, but gave reason to hypothesize that a significant intake of n-3 would influence TG concentrations. A study of postmenopausal women given 2.8g/day of DHA for 4 weeks showed a decrease in TG concentrations [25]. A systematic review of n-3 and CVD risk factors showed a significant reduction in TG in response to n-3 given upwards to 5.9 g/day in the reviewed study diets, and that the results were dose dependent [26]. The LFn-3 diet treatment we administered included 3% of the total energy as omega-3 fatty acids. A subject on our 2,000 kcal/day LFn-3 study diet would consume 6.7g/day of n-3 from whole food sources with less than half as long chain n-3 from marine sources. This amount is consistent with the study by Stark et al. that produced a reduction in TG. Potential reasons for our finding may be that many studies use hypertriglyceridemic subjects and that our participants high n-3 diet was low in total fat and high in CHO. . Balk et al. showed in their systemic literature review that higher baseline concentrations of TG were associated with greater reductions in TG in response to n-3 intake [25]. As our subjects were healthy and not on lipid lowering medication, their lower baseline TG masked the potential to identify change in TG response to a high n-3 diet.

We found that carriers of the Thr54 allele exhibited reductions from baseline in fasting plasma TG, chylomicron TG, and VLDL and CR TG in response to the HF diet. For each of these endpoints, the decrease from the interaction of the Thr54 allele and HF diet was not statistically different from the effect of the HF diet alone. Agren et al. previously showed that after a fat test meal, the Thr54 allele was associated with increases in postprandial chylomicron and VLDL TG [10]. Our findings are contrary to the majority of the literature on the Thr54 polymorphism of FABP2, but the majority of studies on FABP2 involve individuals with Type II diabetes. Since the HF diet significantly decreased the same endpoints in all of the subjects as it did in just the Thr54 carriers, we can assume that the HF diet was driving the changes in the endpoints by reducing total CHO intake.

Chamberlain et al. found that carriers of the Thr54 allele had increased TG if they consumed greater than 53.2 g/d of saturated fat [27]. Our HF diet consisted of 13.3% of total energy as SFA. In a typical 2000 kcal/d diet, that would equate to roughly 29.5 g/d SFA, well below their value of 53.2 g/d. Perhaps there is a SFA intake amount at which the Thr54 becomes more influential than the diet and produces an increase in TG; below that amount the diet is more influential than the Thr54 polymorphism in determining plasma TG concentration.

We found no significant change from baseline in our TG endpoints in Ala54 allele homozygotes after completing any of the three diets. Marin et al. found a similar lack of change in plasma free fatty acid concentration after consuming a high SFA diet, LF diet, and high MUFA diet in Ala54 homozygotes [28].

One limitation of our study is that we analyzed fasting samples. It is possible that increased VLDL secretion due to a high CHO diet may not be observed in fasting samples [29]. The

use of fasting samples decreased the range of concentration for chylomicrons. Chylomicrons are numerous postprandially due to the influx of dietary lipids, but concentrations are much lower after fasting. Thus, the dynamic range of chylomicrons is decreased in a fasting sample. We were unable to evaluate changes in chylomicron concentrations as we used fasting rather than postprandial plasma samples. The other limitations of our study include our small sample size, the inclusion criteria, which consisted of healthy women not on lipid-lowering medication. Such a small sample may not allow adequate power needed to detect differences in our end points. Also, the low number of subjects hindered our ability to draw a genotypically diverse group from which we could better analyze the DNA polymorphisms.

Our novel findings from this study include a reduction from baseline in fasting plasma TG, chylomicron TG, and VLDL and CR TG in carriers of the Thr54 allele of the FABP2 polymorphism after completion of a 8-week controlled whole foods HF diet. The Ala54 allele did not significantly alter any TG concentrations after completion of the HF, LF or LFn-3 diets. Few studies have examined the interaction of diet and DNA polymorphisms with a cross-over design controlled-feeding study of similar length involving varying amounts and types of dietary fat.

In conclusion, our results indicate that consumption of a high fat diet was associated with significant reductions in plasma TG, chylomicron TG, and VLDL and CR TG. Carriers of the Thr54 allele of FABP2 in particular demonstrated significant reductions in these lipid parameters in response to HF although there is no evidence of an interaction between the diet and the polymorphism. Consumption of the HF, LF, or LFn-3 diet did not significantly change TG, chylomicron TG, or VLDL and CR TG in Ala54 homozygotes of the FABP2 polymorphism.

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Abbreviations

LRP	LDL-receptor related protein
CR	chylomicron remnant
FABP2	fatty acid binding protein 2
SNP	single nucleotide polymorphism
VLDL	very low density lipoprotein
TG	triglycerides
TRL	Triglyceride rich lipoprotein

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Figure 1.

Repeated measures analysis of variance with all values reported as mean change from baseline with standard error bar, $n = 8$ for each genotype group. Bar graph showing change from baseline of plasma triglyceride in each Fatty Acid Binding Protein 2 (FABP2) genotype group after consuming a High Fat, Low Fat, and Low Fat with high n-3 fatty acid diet. Error bars indicate standard error. A/A; Ala54 homozygous group for FABP2 polymorphism. A/T; Ala54/Thr54 heterozygotes and Thr54 homozygous group for FABP2 polymorphism. * indicates a significant change from baseline, $P < 0.05$.

Figure 2.

Repeated measures analysis of variance with all values reported as change from baseline mean with standard error bar, $n = 8$ for each genotype group. Bar graph showing change from baseline of chylomicron triglyceride in each Fatty Acid Binding Protein 2 (FABP2) genotype group after consuming a High Fat, Low Fat, and Low Fat with high n-3 fatty acid diet. A/A; Ala54 homozygous group for FABP2 polymorphism. Error bars indicate standard error. A/T; Ala54/Thr54 heterozygotes and Thr54 homozygous group for FABP2 polymorphism. * indicates a significant change from baseline, $P < 0.05$.

Figure 3.

Repeated measures analysis of variance with all values reported as mean change from baseline with standard error bar, $n = 8$ for each genotype group. Bar graph showing change from baseline of VLDL and chylomicron remnant triglyceride in each Fatty Acid Binding Protein 2 (FABP2) genotype group after consuming a High Fat, Low Fat, and Low Fat with high n-3 fatty acid diet. A/A; Ala54 homozygous group for FABP2 polymorphism. Error bars indicate standard error. A/T; Ala54/Thr54 heterozygotes and Thr54 homozygous group for FABP2 polymorphism. * indicates a significant change from baseline, $P < 0.05$.

Table 1

Nutrient Distribution of Diets (% of total energy)

	CHO	PRO	FAT	PUFA	MUFA	SFA
HF	45	15	40	13.3	13.3	13.3
LF	65	15	20	6.7	6.7	6.7
LFn-3	62	15	23	9.7	6.7	6.7

Dietary Fiber 10-12 g/1000kcal

Cholesterol 100 mg/1000kcal

All values are percent of total energy (calculated). CHO; carbohydrate, PRO; protein, PUFA; poly-unsaturated fatty acid, MUFA; mono-unsaturated fatty acid, SFA; saturated fatty acid, HF; high fat diet, LF; low fat diet, LFn-3; low fat + omega-3 diet.

Table 2

Baseline anthropometric characteristics and plasma lipid, glucose, and insulin concentrations according to FABP2 group

	FABP2 Groups			P-value
	Total (n = 16)	Ala54/Ala54 (n = 8)	Ala54/Thr54, Thr54/Thr54 (n = 8)	
Age (years)	56.3 ± 1.5	55.4 ± 1.4	57.3 ± 2.7	0.50
BMI (kg/m ²)	27.7 ± 1.0	27.7 ± 1.6	27.7 ± 1.3	0.98
Plasma TG (mg/dl)	93.5 ± 16.5	102.9 ± 29.1	84.1 ± 17.3	0.64
Chylomicron TG (mg/dl)	12.0 ± 4.3	13.2 ± 7.6	10.8 ± 4.5	0.81
VLDL and CR TG (mg/dl)	40.6 ± 10.2	47.4 ± 17.3	33.7 ± 11.7	0.58
Fasting Plasma Glucose (mg/dl)	107.7 ± 4.2	115.8 ± 6.1	99.6 ± 4.5	0.10

All values are mean ± standard error of subjects at screening. FABP2, fatty acid-binding protein 2; Ala54, alanine-encoding allele in codon 54 of the FABP2 gene; Thr54, threonine-encoding allele. The Thr54/Thr54 group had an n=1, thus this subject was included in the Ala54/Thr54 group for statistical analysis. BMI, body mass index; TG, triglyceride; VLDL, very low-density lipoprotein; CR, chylomicron remnant. There were no significant differences between the genotype groups by *t*-test, *P* < 0.05.

Table 3

Change from baseline of triglycerides and lipoprotein TG in response to the study diets

Diet	Plasma TG (mg/dl)	Chylomicron TG (mg/dl)	VLDL and CR TG (mg/dl)
HF	-35.3 ± 13.1 *	-8.4 ± 3.6 *	-20.1 ± 7.5 ^a
LF	-11.5 ± 12.9	-8.5 ± 3.5 *	-2.8 ± 7.4 ^b
LFn-3	-4.1 ± 13.1	-5.1 ± 3.6	-1.3 ± 7.5 ^b

All values as mean ± SE. TG, triglyceride; VLDL, very low-density lipoprotein; CR, chylomicron remnant. HF, high fat diet; LF, low fat diet; LFn3, low fat + omega-3 diet; Effects of the study diets on change in TG concentration were analyzed by repeated-measures analysis of variance. Means in a column with different superscript letters indicate they are significantly different ($P < 0.05$)

* indicates a significant change from baseline value, $P < 0.05$.

Table 4

Change from baseline in total triglycerides and triglyceride fractions values by FABP2 genotype after 8 weeks of respective study diets.

Genotype and Diet	Plasma TG (mg/dl)	Chylomicron TG (mg/dl)	VLDL and CR TG (mg/dl)
Ala54/Ala54 (n = 8)			
HF Diet	-20.6 ± 17.8	-4.9 ± 4.9	-16.8 ± 10.2
LF Diet	-14.3 ± 17.8	-9.6 ± 4.9	-3.3 ± 10.2
LFn-3 Diet	-3.3 ± 18.5	-6.6 ± 5.1	-0.36 ± 10.5
Ala54/Thr54, Thr54/Thr54 (n = 8)			
HF Diet	-50.1 ± 15.4 *	-11.9 ± 4.2 *	-25.1 ± 8.5 *
LF Diet	-8.7 ± 15.8	-7.4 ± 4.3	-2.2 ± 8.7
LFn-3 Diet	-4.9 ± 15.3	-3.7 ± 4.2	-2.2 ± 8.5
<i>P</i>			
Diet	0.068	0.592	0.009
FABP2	0.572	0.882	0.745
Diet X FABP2	0.380	0.333	0.759

All values as mean ± SE. Effects of the study diets on change in TG levels were analyzed by repeated-measures analysis of variance. Values below *P* are the p-value for the main effects of the covariates. FABP2, fatty acid-binding protein 2 gene; Ala54, alanine-encoding allele in codon 54 of the FABP2 gene; Thr54, threonine-encoding allele. The Thr54/Thr54 group had an n=1, thus the subject was included in the Ala54/Thr54 group for statistical analysis. TG, triglyceride; VLDL, very low-density lipoprotein; CR, chylomicron remnant. HF, high fat diet; LF, low fat diet; LFn-3, low fat + omega-3 diet

* indicates a significant change from baseline value, *P* < 0.05.