Genes Nutr (2012) 7:437–445
DOI 10.1007/s12263-012-0280-z

RESEARCH PAPER

The effect of FABP2 promoter haplotype on response to a diet with medium-chain triacylglycerols

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Received: 17 August 2011 / Accepted: 3 January 2012 / Published online: 24 January 2012
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Abstract The fatty-acid-binding protein-2 (*FABP2*) gene has been proposed as a candidate gene for diabetes because the encoded protein is involved in fatty acid absorption and therefore may affect insulin sensitivity and glucose metabolism. The rare haplotype (B) of its promoter was shown to be associated with a lower risk for type 2 diabetes. The aim of this study was to investigate whether a polymorphism in the *FABP2* promoter does affect the metabolic response to either an medium-chain triacylglycerol (MCT) or an long-chain triacylglycerol (LCT) diet, which were suggested to differ in transport mechanisms, in affinity to *FABP2*, in activating transcription factors binding to the *FABP2* promoter and in their effects on insulin sensitivity. We studied 82 healthy male subjects varying in the *FABP2* promoter (42 homozygous for common haplotype (A), 40 homozygous for the rare haplotype (B)) in an interventional study with either an MCT or LCT diet over 2 weeks to examine gene–nutrient interaction. The saturation grade of MCT was adjusted to that of the LCT fat. We determined glucose, insulin, triacylglycerols (TGs), chylomicron triacylglycerols and cholesterol before and after a standardised mixed meal before and after the intervention. HDL cholesterol increased in all groups, which was most pronounced in subjects homozygous for the common promoter haplotype A who received MCT diet ($P = 0.001$), but not significant in homozygous rare haplotype B subjects who received MCT fat. Subjects homozygous for *FABP2* haplotype A showed a significant decrease in fasting and postprandial glucose ($P = 0.01$, 0.04, respectively) and a decrease in insulin resistance (HOMA-IR, $P = 0.04$) during LCT diet. After correction for multiple testing, those effects did not remain significant. Fasting and postprandial triacylglycerols, LDL cholesterol, chylomicron TGs and cholesterol were not affected by genotype or diet. MCT diet increased HDL cholesterol dependent on the FABP2 promoter haplotype. The effects of the promoter haplotype B could be mediated by PPARγ, which is upregulated by medium-chain fatty acids.

Keywords FABP2 · Promoter · Polymorphism · Mutation · SNP · MCT · Gene diet interaction · Postprandial metabolism

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Abbreviations

AUC	Area under the curve
BMI	Body mass index
BP	Blood pressure
FA	Free fatty acids
FABP2	Fatty-acid-binding protein-2
HDL	High-density lipoprotein
LCT	Long-chain triacylglycerols
LDL	Low-density lipoprotein
n.s.	Not significant
IGT	Impaired glucose tolerance
MCT	Medium-chain triacylglycerols
MCFA	Medium-chain fatty acid
MICK	Metabolic Intervention Cohort Kiel
OMTT	Oral metabolic tolerance test
OGTT	Oral glucose tolerance test
TG	Triacylglycerols
WHR	Waist-to-hip ratio

Introduction

The intestinal fatty-acid-binding protein-2 (FABP2) regulates the intracellular concentration of free fatty acids (FA) in intestinal cells. It contains a single ligand binding site that has high affinity for saturated and unsaturated fatty acids (Baier et al. 1995). FABP2 transports FA from the plasma membrane to the endoplasmic reticulum where the FA are esterified with glycerol-3-phosphate (G3P) to form triacylglycerols (TGs). The TGs are incorporated into chylomicrons that are transported via lymph into the circulation. The *FABP2* gene has been proposed as a candidate gene for type 2 diabetes because the encoded protein is involved in fatty acid absorption and therefore may affect insulin sensitivity and glucose metabolism (Randle et al. 1963; Baier et al. 1995).

Numerous studies have assessed the association of *FABP2* gene variants with insulin resistance and type 2 diabetes (Baier et al. 1995; Bach et al. 1996; Hegele et al. 1997; Agren et al. 1998; Marin et al. 2005). The association of a threonine coding *FABP2* variant with insulin resistance appears to be confined to individuals who are consuming a high-fat diet (Ball 1993; Binnert et al. 1998). Another study found that Thr54 homozygous had a greater decrease in cholesterol and apoB during a diet high in soluble fibre than Ala54 homozygous subjects (Nosaka et al. 2003; Tholstrup et al. 2004).

Several studies found positive effects of MCT fat on body weight and weight control (Asakura et al. 2000); medium-chain fatty acids (MCFA) are preferentially oxidised rather than deposited in adipose tissue triacylglycerols (Tholstrup et al. 2004). They increase thermogenesis and seem to increase satiety via increasing plasma levels of hydroxybutyrate (Hill et al. 1989; Van Wymelbeke et al. 2001). Conflicting results have been reported about the effects of chronic administration of MCT on plasma glucose, insulin, triacylglycerols and cholesterol levels (Eckel et al. 1992; Asakura et al. 2000); (Tholstrup et al. 2004; Marten et al. 2006; Han et al. 2007; Oikari et al. 2008). The discrepancies could be due to different study design or different genetic background of the study subjects (Marten et al. 2006). Moreover, differences, such as the type of fatty acid or fibre consumed with the background diet, might interact with functional differences due to genetic variation and may have resulted in phenotypic differences. However, another general limitation of former studies is the difference in saturation grade between the test diets. The content of saturated fat was much higher in MCT rather than LCT (mostly polyunsaturated) fats used in those intervention studies (Eckel et al. 1992; Asakura et al. 2000; Van Wymelbeke et al. 2001). This difference could have masked the positive effect of MCT. Additionally, the administered fats did not take into account the different caloric density of MCT and LCT fat.

There are six known polymorphisms in the promoter of the *FABP2* gene, which are in perfect linkage disequilibrium (LD) and reside in two haplotypes (Geschonke et al. 2002; Damcott et al. 2003; Formanack and Baier 2004). We and others could show that the rare haplotype B in the *FABP2* promoter is associated with insulin resistance (Helwig et al. 2007), type 2 diabetes (Formanack and Baier 2004; Li et al. 2006) and hypercholesterolemia (Damcott et al. 2003). Reporter gene assays indicated a higher responsiveness to PPARγ/RXR of *FABP2* promoter B versus promoter A.

FABP preferentially binds long-chain fatty acids (Lowe et al. 1987; Richieri et al. 1994) but also medium-chain fatty acids (Huang et al. 2002), and its PPARγ induced promoter activity is dependent on genetic variation (Helwig et al. 2007). PPARγ is upregulated by medium-chain fatty acids (Yonezawa et al. 2004) and long-chain fatty acids itself and is therefore a target for gene–diet interaction studies. We hypothesised that subjects with a variation in *FABP2* promoter haplotype might have different responses to medium- and long-chain fatty acid diets.

Methods

Subjects

Subjects were recruited with regard to their *FABP2* promoter haplotype carrier-ship from a prospective intervention cohort, and the details of the recruitment were described recently (Rubin et al. 2010; Helwig et al. 2007).

Table 1 Baseline characteristics of the subjects (mean ± SD, *P* values obtained from one-way ANOVA)

n	A/LCT 21	B/LCT 20	A/MCT 21	B/MCT 20	*P*
Age	58.4 ± 5.3	60.4 ± 5.3	59.2 ± 4.5	59.0 ± 5.6	0.67
BMI	27.9 ± 3.2	27.2 ± 4.3	26.2 ± 3.3	26.6 ± 3.8	0.49
Waist	102.5 ± 10.0	100.5 ± 11.0	99.5 ± 11.8	98.9 ± 10.0	0.72
BP syst	120 ± 11.6	113 ± 14.8	120 ± 14.7	120 ± 17.2	0.22
BP diast	75 ± 7.0	70 ± 9.7	80 ± 7.2	70 ± 11.3	0.01

The study was approved by the Ethics committee of the University Clinic of Kiel. The study was performed according to the Declaration of Helsinki, and informed consent was obtained from all subjects. We selected 82 male, healthy unrelated subjects with regard to their FABP2 haplotype carrier-ship from the overall cohort consisting of 755 men. Inclusion criterion was male subjects with homozygosity for either of the *FABP2* promoter haplotypes A or B. Exclusion criteria were as follows: known type 2 diabetes, diseases with impairment of nutrient digestion or metabolism, an intake of lipid-lowering drugs or hormones, visceral surgery in the past 3 months, hypo- or hyperthyroidism, chronic renal disease, hepatitis, cholestasis, alcoholism or cancer. Baseline characteristics of the subjects are given in Table 1. An OGTT was performed in all subjects in order to diagnose type 2 diabetes and impaired glucose metabolism.

None of the subjects was diabetic according to WHO guidelines (Alberti and Zimmet 1998). Forty-two subjects were homozygous for the common haplotype A and 40 subjects homozygous for the rare haplotype B. Out of the selected 82 subjects, 32 subjects were carriers of the rare exon genotype 12Thr. Forty-seven subjects were homozygous for exon genotype Ala12.

Diet

The subjects from the two genetic groups were randomised to receive either MCT- or LCT-based test fats, resulting in four test groups (haplotype A/LCT fat ($n = 21$), haplotype A/MCT fat ($n = 21$), haplotype B/LCT fat ($n = 20$), haplotype B/MCT fat ($n = 20$)) (Fig. 1). The saturation grade of the MCT fat was adjusted to that of the LCT fat by mixing MCT oil with high-oliec sunflower oil, resulting in a content of MCFA of 40%. The composition of the test fats are shown in Table 2. The LCT group received 40 g of fat, the MCT group 44 g fat, to secure isocaloric amounts of fat. Subjects were advised to exchange their habitual daily fat with the test fat and to maintain their habitual food pattern. Compliance was considered sufficient if the serum cholesterol fatty acid content for medium-chain fatty acids (C8–C12) after MCT diet or long-chain fatty acids (C16–C22) after LCT diet increased by at least 5%. Participants were

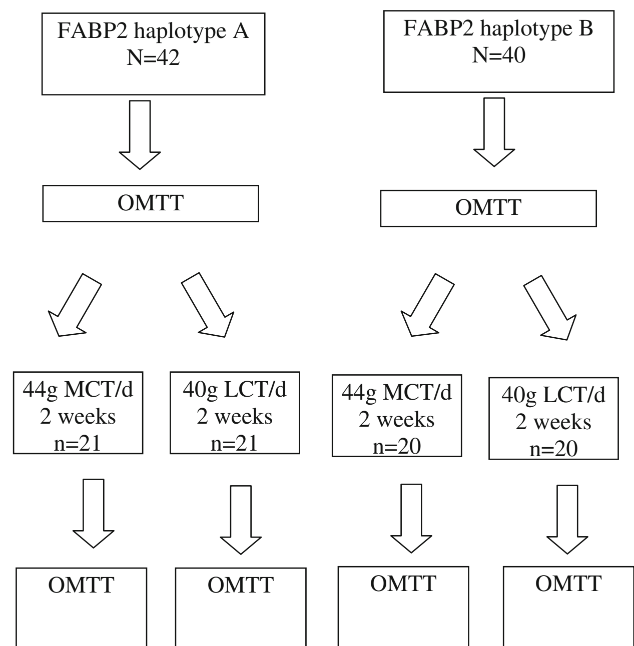

Fig. 1 Study design. *OMTT* oral metabolic tolerance test, *MCT* medium-chain triacylglycerols, *LCT* long-chain triacylglycerols

Table 2 Composition of the test fat

Fatty acid	Palm oil (LCT) (%)	Oil mixture (MCT) (%)
C6		0.1
C8		28.7
C10		12.5
C12	0.2	<0.1
C14	1.1	0.1
C16	44.5	2.4
C16:1	0.2	<0.1
C18	4.4	1.9
C18:1	38.7	40.8
C18:2	9.9	10.7
C18:3	0.3	< 0.1
C20	0.4	0.2
C20:1	0.1	0.1
C22	0.1	0.5
C24		0.2

instructed not to change their eating habits and physical activity routine, and not to use any dietary supplements of vitamins, minerals or special oil preparations. A 24-h food recall was performed on day 0 and day 14 as described in detail by (Johnson et al. 1996). Briefly, this recall consisted of a short list of all foods and drinks consumed, a detailed description and a review with the interviewer probing for information on time/occasion, forgotten foods and food details. Recalled portion sizes and household implements such as bowls were used to provide accurate estimates of consumption during a 24-h recall (Chambers et al. 2000).

Laboratory measurements

Blood was collected in the fasting state, 0.5 h postprandially (pp) and hourly until 9 h after ingestion of a standardised lipid load (oMTT) (Helwig et al. 2007; Rubin et al. 2008). The oMTT with a liquid volume of 500 ml contained the following ingredients: 30 g of protein (11.9 kcal%), 75 g of carbohydrate (29.6 kcal%; 93% sucrose, 7% lactose), 58 g of fat (51.6 kcal%; 65% saturated, 35% unsaturated fatty acids), 10 g of alcohol (6.9 kcal%), 600 mg cholesterol and 30,000 IU retinylpalmitate. The total energy content was 1,017 kcal (4,255 kJ). The fatty acid pattern (% w/w) of fat was as follows: caprone, 2%; capryl, 1.2%; caprine, 2.7%; laurine, 3%; myristine, 10.9%; palmitine, 28.4%; stearine, 13.1%; palmitoleine 2.4%; oleic, 27.1%; linolic, 2.4%; linolenic, 1.6%; acid and other fatty acids, 5.2%. Accordingly, the medium-chain fatty acids content was 8.9%. Serum and plasma was separated from whole blood by centrifugation (6°C, 10 min, $3000\times g$). Plasma and serum were stored at –20°C until analysis. Glucose and insulin were measured before and 30 min and every hour after meal ingestion; triacylglycerols and free fatty acids (NEFA) were assessed hourly during 9 h postprandially. Serum and chylomicron triacylglycerols, plasma glucose, fasting total cholesterol and chylomicron cholesterol, HDL cholesterol, LDL cholesterol and liver enzymes were determined by standard enzymatic methods using Konelab 20i auto analyzer (Kone, Finland). Plasma insulin was measured by radioimmunoassay (Adaltis, Germany). All samples were measured in duplicate.

Chylomicrons (Sf > 400) were isolated according to Mills and Weech (1989), clearing factor k was 407. Briefly, plasma (4 ml) was layered beneath 4 ml sodium chloride (density 1.006 g/ml), placed in a TFT 70.13 rotor (Kontron) and centrifuged at $46.095\times g$ (25.000 rpm) and kept at 15°C for 47 min. Chylomicrons in the top 2 ml were collected (Mills and Weech 1989).

Genotyping

Genomic DNA was isolated from 10 ml of frozen blood samples using the Gigakit DNA extraction kit (Invitec, Berlin, Germany). The following TaqMan® probes and primers were used: for the promoter site (rs2282688):

PCR forward primer: GGCAATGCTAAACACAATGC AAAA;
PCR reverse primer: TCACAACAGCAATTATCTTG TAAAGTAAGACT;
Taqman probe allele 1: AATCTTATTAACTTTAACTT TTC;
Taqman probe allele 2: TCTTATTAACTTTAGCTT TTC;

for the exon site (rs1799883):

PCR forward primer: AAGGAAGCTTGCAGCTCAT GAC;
PCR reverse primer: CACCAAGTTCAAAAACAACT TCAATG,
Taqman probe allele 1: ATCAAGCACTTTTC;
Taqman probe allele 2: TCAAGCGCTTTTC.

All primers and probes were constructed by Applied Biosystems (Foster City, CA, USA). TaqMan® analysis was performed as described elsewhere (Hampe et al. 1999). In brief, genomic DNA was arrayed and dried on 96-well plates. TaqMan® PCR was performed using Genesis pipetting robots (Tecan, Männedorf, Switzerland), ABI 9700 PCR machines (Applied Biosystems) and ABI 7700 and ABI 7900 fluorimeters (Applied Biosystems).

Both polymorphisms, *FABP2* A54T and promoter A/B, showed intermediate levels of linkage disequilibrium ($D' = 0.85$, $r^2 = 0.31$). The genotypic concordance between both SNPs equalled 0.60.

Power analysis

Power analysis is provided for the variable with the maximum standard deviation (iNEFA). With a type I error of 0.05 and 80% power, the minimum of subjects per group was $n = 17$.

Statistical analyses

SPSS (SPSS for Windows, version 14.0.0, LEAD Technologies Inc.) was used for statistical analysis. Values in the text are expressed as mean ± SEM, and differences were considered significant at $P < 0.05$. The 0–5 h and 0–9 h area under the curve (AUC), respectively, was calculated by the trapezoidal method.

Insulin sensitivity was estimated using the HOMA model: HOMA-R (insulin resistance): insulin (mU/l) × glucose (mmol/l)/22.5. In case of postprandial NEFA, the increase in NEFA (5–9 h) reflecting release from postprandially affluent triacylglycerols was calculated. Deviations from a normal distribution of parameters were tested

by Kolmogoroff–Smirnoff test. Comparison of baseline parameters in the four intervention groups was performed using one-way analysis of variance (ANOVA). Comparisons of parameters on day 0 and day 14 in the groups were performed using a *t* test for normally distributed parameters and a Wilcoxon test for non-normally distributed parameters. Bonferroni–Holm correction was applied to correct for multiple testing.

Results

Anthropometric data

At baseline, the subjects of the four study groups did not differ in age, BMI, waist circumference or systolic blood pressure. The diastolic blood pressure was significantly different in the four groups (Table 1). As expected, BMI and waist were not significantly altered within 2 weeks intervention period. All subjects completed the study and reported having consumed the test fats. According to the 24-h recall, fat intake did not differ before and during the study within the groups (data not shown).

Cholesterol, triacylglycerol and free fatty acids

Table 3 shows the mean fasting concentrations of plasma cholesterol, triacylglycerols, glucose, insulin, HOMA and NEFA before and after the dietary intervention in the groups. At baseline, the four groups A/LCT (haplotype A/LCT diet), B/LCT (haplotype B/LCT diet), A/MCT (haplotype A/MCT diet) and B/MCT (haplotype B/MCT diet) did not significantly differ in total cholesterol, LDL cholesterol, HDL cholesterol, triacylglycerols and NEFA. In all subjects, HDL cholesterol increased after 2 weeks on the intervention diet, which was significant for all groups except the B/MCT group. After correction for multiple testing, only the A/MCT group showed a significant increase in HDL cholesterol ($P = 0.001$). Total cholesterol, LDL cholesterol, fasting and postprandial triacylglycerols and NEFA did not change significantly during the intervention in either group (Table 3).

Glucose, insulin and HOMA-IR

Fasting and postprandial glucose decreased in *FABP2* haplotype A carriers during intervention. This effect was significant only in subjects receiving the LCT diet ($P = 0.01$, $P = 0.04$, respectively). Accordingly insulin resistance, expressed as HOMA-IR, decreased significantly in this group, but not in the other groups ($P = 0.04$). The haplotype A subjects had a higher decrease in postprandial glucose concentrations after LCT diet (Table 3). However, accounting for multiple testing resulted in loss of significance for differences in glucose and HOMA-IR.

Discussion

Our study focused on the functional impact of *FABP2* promoter polymorphisms on the response to a diet, to analyse whether oral intake of MCT or LCT fat altered the effects on glucose and lipid metabolism caused by the reported functional differences attributable to these SNPs.

There are six known polymorphisms in the promoter of the *FABP2* gene, which are in perfect linkage disequilibrium (LD) and reside in two haplotypes (Geschonke et al. 2002; Damcott et al. 2003; Formanack and Baier 2004). Recent studies showed that the *FABP2* promoter haplotype has some impact on postprandial lipemia, depending on the Thr54Ala exon polymorphism allele (Helwig et al. 2007). It was shown that variation in the *FABP2* promoter affects gene expression, which could have implications for prior association studies (Formanack and Baier 2004).

We postulated that a MCT diet might have a positive impact on metabolic parameters and that this effect could be modulated by the *FABP2* genotype. We expected a lower impact of genotype on the response to an MCT than to an LCT diet because FABP2 binds preferentially long-chain fatty acids (Richieri et al. 1994, 2000). This is supported by higher postprandial lipemia after olive or sunflower oil rather than butter (Higashi et al. 1997; Mekki et al. 2002). A diet–gene interaction for the *FABP2* Thr54Ala polymorphism was shown for intervention with olive oil and butter, resulting in increased chylomicron cholesterol in T54 carriers only after olive oil (Dworatzek et al. 2004). This effect might have been induced by differences in the chain length or different in the saturation grade of the test fats, because both were changed between groups in this study.

In the presented study, fasting and postprandial glucose, insulin, HOMA and triacylglycerols did not change in either haplotype group during intervention (Table 3). In both haplotype groups, postprandial HDL increased during the intervention but only homozygous haplotype A carriers showed a significant increase after MCT diet, which was not seen after LCT diet. Up until now, an influence of *FABP2* promoter variability on the postprandial triglyceride metabolism has only been described in combination with the *FABP2* exon 2 polymorphism (A54T) (Helwig et al. 2007). The combination of the homozygosity of *FABP2* promoter BB and the homozygosity of exon polymorphism (T54T) was associated with increased postprandial triacylglycerol levels. Therefore, we additionally evaluated the data of the subgroup with the genotypes *FABP2* AA

Table 3 Blood lipids, glucose and insulin before and after diet with isocaloric MCT or LCT fats in 82 subjects (mean ± SD)

	Day 0	Day 14	Difference (%)	*P*
Total cholesterol (mg/dl)*				
A/LCT	208.6 ± 32.8	215.9 ± 36.1	+7.3 ± 21.9	0.12
B/LCT	220.9 ± 33.3	217.6 ± 31.3	−3.3 ± 18.5	0.21
A/MCT	212.4 ± 40.2	205.3 ± 37.7	−7.1 ± 17.4	0.79
B/MCT	213.8 ± 32.4	216.2 ± 29.7	+0.51 ± 14.0	0.78
HDL cholesterol (mg/dl)				
A/LCT	53.9 ± 16.5	57.3 ± 19.9	+3.4 ± 6.4	0.025
B/LCT	52.3 ± 9.2	55.2 ± 10.4	+2.8 ± 4.4	0.009
A/MCT	55.3 ± 16.9	61.0 ± 17.1	+5.6 ± 6.6	0.001[§]
B/MCT	57.3 ± 18.3	59.8 ± 19.8	+2.4 ± 7.1	0.16
LDL cholesterol (mg/dl)*				
A/LCT	137.0 ± 31.4	139.7 ± 30.8	+2.6 ± 18.1	0.33
B/LCT	146.0 ± 28.3	142.5 ± 28.5	−3.6 ± 17.4	0.31
A/MCT	138.6 ± 35.3	131.0 ± 34.3	−7.7 ± 15.9	0.61
B/MCT	142.5 ± 33.7	141.6 ± 30.0	−1.1 ± 15.4	0.62
Fasting triacylglycerols (mg/dl)				
A/LCT	131.9 ± 75.5	123.9 ± 70.1	−8.0 ± 52.4	0.49
B/LCT	139.7 ± 72.8	123.1 ± 56.8	−16.6 ± 63.9	0.26
A/MCT	117.0 ± 63.3	102.6 ± 47.1	−14.4 ± 43.2	0.14
B/MCT	107.5 ± 39.2	109.7 ± 60.9	+2.2 ± 36.2	0.79
Pp triacylglycerols (AUC)[b] (mg/dl*h)				
A/LCT	1,559.2 ± 799.6	1,503.5 ± 922.2	−55.7 ± 420.2	0.55
B/LCT	1,691.0 ± 783.9	1,512.3 ± 471.8	−178.7 ± 610.3	0.21
A/MCT	1,333.8 ± 598.4	1,221.0 ± 396.4	−112.9 ± 426.1	0.24
B/MCT	1,404.6 ± 490.7	1,355.5 ± 536.5	−49.0 ± 360.1	0.55
Fasting glucose (mg/dl)*				
A/LCT	103.8 ± 8.6	97.1 ± 11.9	−6.7 ± 11.5	0.01
B/LCT	100.4 ± 12.0	101.5 ± 8.2	+1.0 ± 8.8	0.30
A/MCT	101.7 ± 10.0	103.6 ± 12.6	+1.9 ± 5.3	0.92
B/MCT	100.8 ± 9.7	101.3 ± 6.9	+0.5 ± 7.4	0.30
Pp[a] glucose (AUC)[b] (mg/dl*h)				
A/LCT	524.3 ± 78.9	490.3 ± 38.9	−34.0 ± 75.8	0.04
B/LCT	497.5 ± 58.6	496.5 ± 54.7	−1.0 ± 55.9	0.88
A/MCT	501.6 ± 60.2	488.7 ± 62.6	−13.0 ± 32.4	0.27
B/MCT	516.2 ± 71.9	511.5 ± 51.4	−4.7 ± 38.4	0.78
Fasting insulin (mU/l)				
A/LCT	16.3 ± 8.1	13.4 ± 5.5	−2.9 ± 7.6	0.10
B/LCT	16.3 ± 8.8	15.6 ± 6.9	−0.70 ± 9.6	0.75
A/MCT	13.4 ± 4.6	13.9 ± 8.5	+0.7 ± 5.1	0.67
B/MCT	17.7 ± 12.2	16.3 ± 12.0	−1.6 ± 4.9	0.16
Pp[a] insulin (AUC)[b] (mU/l*h)				
A/LCT	171.7 ± 81.4	176.2 ± 75.5	−4.5 ± 54.0	0.70
B/LCT	198.4 ± 80.7	223.4 ± 112.0	−25.0 ± 73.2	0.14
A/MCT	185.8 ± 111.3	194.8 ± 170.9	−14.0 ± 94.8	0.55
B/MCT	215.9 ± 177.9	222.5 ± 222.1	−10.8 ± 63.9	0.46
Fasting HOMA-IR[c]				
A/LCT	4.1 ± 2.1	3.1 ± 1.2	−1.0 ± 2.1	0.04
B/LCT	4.1 ± 2.5	3.9 ± 1.9	−0.2 ± 2.7	0.78

Table 3 continued

	Day 0	Day 14	Difference (%)	*P*
A/MCT	3.3 ± 1.3	3.6 ± 2.8	+0.3 ± 1.7	0.47
B/MCT	4.5 ± 3.5	4.1 ± 3.1	−0.5 ± 1.3	0.14
Pp[a] HOMA-IR[c] (insulin × glucose AUC)				
A/LCT	90,077 ± 45,605	87,308 ± 40,635	−2,769 ± 29,909	0.68
B/LCT	99,176 ± 41,830	114,110 ± 67,814	14,934 ± 48,332	0.13
A/MCT	96,141 ± 68,489	102,083 ± 99,232	6,445 ± 49,604	0.61
B/MCT	117,769 ± 108,715	123,912 ± 136,435	5,048 ± 40,537	0.58
INEFA[d] (mmol/l)				
A/LCT	−0.5 ± 0.4	−0.4 ± 0.5	0.1 ± 0.7	0.49
B/LCT	−0.5 ± 0.5	−0.4 ± 0.3	0.2 ± 0.5	0.16
A/MCT	−0.7 ± 0.7	−0.7 ± 0.7	0.04 ± 0.6	0.87
B/MCT	−0.4 ± 0.3	−0.4 ± 0.4	−0.06 ± 0.6	0.67

Parameters tested for differences between days 0 and 14 by paired *t* test (normally distributed parameters) or Wilcoxon test (non-normally distributed parameters, marked with asterisk), respectively

[§] Significant after Bonferroni–Holm correction for multiple testing

[a] *Pp* postprandial

[b] *AUC* area under the curve

[c] *HOMA-IR* homeostasis model assessment of insulin resistance

[d] *INEFA* increase in non-esterified fatty acids (NEFA 5–9 h)

+A54A and *FABP2* BB + T54T. In the total sample as well as in these subsets, we did not find differences in the effect of MCT/LCT diet on the metabolic parameters except HDL cholesterol.

There are different possible explanations for our findings. Compared to other MCT intervention studies, we administered a higher daily amount of MCT (44 g) compared to the LCT diet (40 g). This was to compensate for the lower energy density of MCT fat and was not accounted for in former studies (Eckel et al. 1992; Asakura et al. 2000; Van Wymelbeke et al. 2001). The significant positive effect of MCT fat on HDL cholesterol only in haplotype A subjects can be explained by a higher basal *FABP2* promoter activity of these subjects (Helwig et al. 2007), which is probably associated with a higher binding capacity and oxidation of fatty acids.

In former reporter gene assays, the common *FABP2* A haplotype showed a higher basal promoter activity but a lower responsiveness to PPARγ/RXR of FABP2 compared to the rare B haplotype (Helwig et al. 2007). Therefore, the amount of polyunsaturated fatty acids in the diet could contribute to an upregulation of FABP2 expression in haplotype B subjects and diminish the difference in haplotypes A and B subjects. Furthermore, we cannot exclude emerging positive effects of MCT after a longer dietary period.

In conclusion, with the exception of HDL cholesterol, the insulin and lipid metabolism of *FABP2* promoter haplotype A and B subjects did not respond differently to administration of MCT diet even though the saturation grade was equal to that of the LCT diet.

Acknowledgments None of the authors had any financial or personal conflicts of interest. This work was financially supported by the BMBF Project "Fat and metabolism—gene variation, gene regulation and gene function" MN (0312823A/B). DR, UH, JS, MP and SD were responsible for the study design; DR, UH and DM were responsible for data collection; DR, SF, MN and AR were responsible for data analysis; and DR, MN, UF, FD, SS and JS were responsible for writing the manuscript. We thank A. Thoss, M. Hartelt, M. Gerull and S. Kaschner for excellent technical assistance.

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