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A common functional exon polymorphism in the microsomal triglyceride transfer protein gene is associated with type 2 diabetes, impaired glucose metabolism and insulin levels

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Abstract The microsomal triglyceride transfer protein (MTP) is required for the assembly and secretion of apolipoprotein B-containing lipoproteins. Emerging evidence has indicated that the functional MTP exon polymorphism I128T is associated with dyslipidemia and other traits of the insulin-resistance syndrome, and the T128 variant seems to confer a reduced stability of

MTP, resulting in reduced binding of LDL particles. The aim of the study was to elucidate the association of this MTP polymorphism with parameters of postprandial metabolism. A total of 716 male subjects from a postprandially characterized cohort (MICK) and a nested case-control study (EPIC) of 190 incident type 2 diabetes cases and 380 sex- or age-matched controls were genotyped for the I128T exon polymorphism. In comparison to homozygote subjects of the wild allele, carriers of the less common allele of the MTP T128 genotype showed significantly lower postprandial insulin levels ($P=0.017$), lower diastolic blood pressure ($P=0.049$) and had a lower prevalence of impaired glucose metabolism and diabetes type 2 ($P=0.03$) in the MICK. Consistent with this, we found a lower incidence of type 2 diabetes in male subjects of the nested case-control study in the T128 genotype ($P=0.007$). These results suggest that the rare allele of the MTP I128T polymorphism may be protective against impaired glucose tolerance, type 2 diabetes and other parameters of the metabolic syndrome.

Keywords Microsomal triglyceride transfer protein · Metabolic Intervention Cohort Kiel · Type 2 diabetes · Polymorphism · Postprandial metabolism · Insulin

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Introduction

Insulin resistance and type 2 diabetes in humans are associated with increased de novo lipogenesis, decreased fatty acid oxidation, increased VLDL production and hepatic steatosis. Several studies indicate that elevated plasma levels of lipoproteins in patients with diabetes are caused, at least in part, by an increased hepatic output of apoB-containing lipoproteins (Verges 1999; Taskinen 2002; Chan et al. 2004). Furthermore, intestinal TG-rich lipoprotein overproduction contributes to

the dyslipidemia associated with insulin resistance and diabetes (Haidari et al. 2002). The microsomal triglyceride transfer protein (MTP) is involved in the assembly of apoB-containing lipoproteins and enables the secretion of VLDLs by the liver and chylomicrons by the intestine (Wetterau et al. 1997; Bakillah and El Abbouyi 2003). It catalyzes the loading of lipids to the nascent apoB in the endoplasmic reticulum. This stabilizes the newly synthesized apoB (Gordon et al. 1996; Rustaeus et al. 1998) and facilitates further processing, leading to its secretion. Reduction of MTP activity in animals by inhibitors (Wetterau et al. 1998) or gene knockouts (Chang et al. 1999; Raabe et al. 1999; Leung et al. 2000) effectively lowers the fasting plasma lipoprotein level, whereas overexpression of hepatic MTP increases the plasma level of apoB-containing lipoproteins in mice (Tietge et al. 1999). In insulin resistance and type 2 diabetes, increased hepatic MTP mRNA levels have been associated with dyslipidemia (Taghibiglou et al. 2002). This may be due to impaired insulin action as insulin is repressing the MTP gene (Lin et al. 1995; Carpentier et al. 2002). A recent study demonstrated that improving insulin sensitivity is associated with the normalization of hepatic MTP expression and the reduction in VLDL secretion in insulin-resistant hamsters (Taghibiglou et al. 2000). On the other hand, increased fasting and postprandial triglycerides, increased dietary fat intake and fatty acids released from postprandial lipids are suggested to reduce insulin sensitivity of peripheral tissues (Schrezenmeir et al. 1993; Riccardi et al. 2004; Roden et al. 1996). Therefore variations in genes involved in chylomicron and VLDL production may contribute to the pathogenesis of the metabolic syndrome.

Recently, the impact of common MTP polymorphisms on lipid metabolism and obesity-related phenotype were investigated. The results of these studies are inconsistent. However a functional MTP promoter polymorphism -493G/T (rs1800591) seemed to be protective against traits of the metabolic syndrome (Austin et al. 1998; Sposito et al. 2004). This SNP -493G/T is in complete linkage disequilibrium with the exon polymorphism I128T (rs3816873) (Ledmyr et al. 2002).

Functional studies of I128T polymorphism indicate that the T128 variant confers a reduced local structural stability in the N-terminal domain, leading to reduced binding of MTP to LDL particles (Ledmyr et al. 2004). This impaired function could have functional significance on glucose and lipid metabolism.

We investigated the association between the MTP exon polymorphism and postprandial parameters in the Metabolic Intervention Cohort Kiel (MICK). In addition, the association of the polymorphism I128T with type 2 diabetes was examined in 190 incident diabetic patients and 380 age- and sex-matched controls, which are part of the European prospective investigation into cancer and nutrition cohort [(EPIC)-Potsdam cohort].

Material and methods

Metabolic Intervention Cohort Kiel

Seven hundred fifty-five male subjects aged 45–65 years were recruited from the registry office of the town of Kiel, Germany. The recruitment period lasted from January 2003 to March 2004. Exclusion criteria were as follows: known diabetes type 1 or 2, diseases with impairment of nutrient digestion or metabolism, use of lipid-lowering drugs or hormones, surgery on the intestine in the past 3 months, hypo- or hyperthyroidism, chronic renal disease, hepatitis, cholestasis, alcohol abuse or cancer. Body weight, height, waist and hip circumference were determined at recruitment by means of standardized procedures (Klipstein-Grobusch et al. 1997; Callaway et al. 1988). Blood pressure was measured with a mercury sphygmomanometer on the right arm, with the subject supine in a quiet room. A standardized oral glucose tolerance test (OGTT) was performed according to WHO guidelines (Alberti and Zimmet 1998). A total of 725 participants performed OGTT and oral metabolic tolerance test (OMTT), 16 subjects participated only in OGTT and not OMTT for various reasons (denied participation, intake of exclusion medication). Seven hundred forty-four subjects participated in OMTT. One hundred thirty-five men were diagnosed with impaired glucose metabolism (fasting glucose > 110 mg/dl or glucose > 140 mg/dl after 2 h), 49 had type 2 diabetes mellitus (fasting glucose > 126 mg/dl determined on two different occasions or glucose > 200 mg/dl after OGTT), 549 had normal glucose tolerance. Genotyping was performed successfully in 704 subjects. Serum and plasma were separated from whole blood by centrifugation and stored at –70°C for later determinations. Serum triglycerides and plasma glucose, serum cholesterol and HDL cholesterol were determined using enzymatic methods with a clinical analyzer KL20i (Kone, Finland). Plasma insulin was measured with a standard radioimmunoassay (Adultis, Germany). All analyses were performed in duplicate.

Oral metabolic tolerance test in MICK

At least 3 days after OGTT, participants visited the department after a 12-h overnight fast for an OMTT. An intravenous catheter equipped with disposable obturators was inserted into a forearm vein for blood sampling, and a fasting blood sample (0 h) was obtained. Following this, the subjects drank 500 ml of a standardized high-fat mixed meal containing 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 (milkfat, 51.6 kcal%; 65% saturated, 35% unsaturated fatty acids), 10 g of alcohol (6.9 kcal%), 600 mg cholesterol and 30,000 IU retinyl palmitate. The total energy content was 1,017 kcal

(4,255 kJ). The test meal was drunk within 15 min. Blood withdrawal was repeated at 30 minutes and hourly 1–9 h after starting ingestion of OMTT. Subjects were allowed to walk or sit, as they wished, but not to eat or exercise during the test. Drinking water was permitted ad libitum.

European investigation into cancer and nutrition

Study subjects were taken from the EPIC-Potsdam. This population-based, prospective study comprises a total of 27,548 people from the area of Potsdam, Germany. Baseline examination was conducted between 1994 and 1998 and included anthropometric and blood-pressure measurements, blood sampling, a self-administered food-frequency questionnaire and a personal interview on lifestyle habits and medical history. During the first follow-up, on average 2.3 years after recruitment, 192 incident cases of type 2 diabetes mellitus were identified and confirmed by the primary care physicians (Klipstein-Grobusch et al. 1997; Alberti and Zimmet 1998). Cases were matched with two control subjects each, by age and sex ($n=384$). Genotyping was performed successfully in 190 cases and 380 controls. Gender distribution of the nested case-control study was 59% male and 41% female subjects with a mean age of 55.5 years (35–65 years). All study participants had given informed consent, and the genotype assessment was approved by the local ethics committee. Information on drug use was obtained at baseline and comprised details of all medications taken during the previous 4 weeks. Total cholesterol and HDL cholesterol were measured with enzymatic colorimetric methods (Boehringer Mannheim, Mannheim, Germany; Boeing et al. 1999).

Genetic analyses

DNA was isolated from buffy coats (100 μ l) using E.Z.N.A. Blood DNA MiniKits (Peqlab Biotechnologie GmbH, Erlangen, Germany) according to the manufacturer's instructions. Genotyping of MTP cSNP I128T (rs3816873) with the TaqMan system was performed in the MICK. rSNP -493G/T (rs1800591) was genotyped as an internal genotyping control as this SNP is in almost complete linkage disequilibrium (Ledmyr et al. 2002). In the EPIC, only cSNP I128T was genotyped, because of failure of the -493G/T assay. Fluorescence was measured with ABI Prism 7900 HT sequence detection system (ABI, Foster City, CA, USA). Sequences of TaqMan assay primers and probes are available on request.

Statistical analyses

The study populations were tested as a whole and cases/controls, for the distribution of genotypes according to the Hardy-Weinberg equilibrium (χ^2 test). Differences in

allele frequency between controls and patients with diabetes and/or impaired glucose metabolism were compared using χ^2 test. In both study groups, some data on genotyping, biochemical, blood pressure and anthropometric measurements were missing, and those cases were therefore excluded from statistical analysis. Full analysis sets were available for a final EPIC study sample of 184 cases and 380 controls and for 680 subjects from MICK. Results were expressed as median values and interquartile ranges (IR). Continuous variables from homozygous TT and combined heterozygote and homozygote C allele carriers were compared using the Wilcoxon rank sum test. In a logistic regression analysis with impaired glucose metabolism as response variable, odds ratios (OR) and corresponding 95% confidence intervals (CI) were estimated with and without considering BMI categories (<25, 25–29.9, 30–34.9, 35–39.9, >40) in the model.

The 0–9 h area under the curve (AUC) was calculated by the trapezoidal method. Insulin sensitivity was estimated with the HOMA model: HOMA, insulin (mU/l) $\times$ glucose (mg/dl).

All statistical tests were two-sided with a 5% level of significance. Statistic analysis was conducted using the Statistics Package for the Social Sciences 11.5 (SPSS, Chicago, IL, USA).

Results

The I128T MTP exon polymorphism was investigated in 716 male subjects of the MICK and in 190 incident diabetic patients and 380 age- and sex-matched controls, which are part of the EPIC-Potsdam cohort. The frequencies of the MTP 128 variant (T) were 26% in MICK and 25% in EPIC (Table 1), which is similar to -493T in other populations. The genotype distributions in both study populations were in Hardy-Weinberg equilibrium. T128 carriers (IT and TT) were combined for statistical analysis due to low frequency (6%) of 128T homozygote subjects.

Anthropometric and metabolic variables in MTP 128I homozygotes and 128T carriers of the MICK and EPIC cohorts are shown in Table 1. In MICK, the carriers of different genotypes did not differ in BMI, WHR, waist circumference, fasting plasma total cholesterol concentrations and HDL concentrations (Table 2). Subjects carrying the T128 allele had lower levels of diastolic blood pressure compared with carriers of the I128 allele. In EPIC (Table 3), males homozygous

Table 1 Genotype and rare allele frequencies in MICK and EPIC according to MTP I128T polymorphism (rs3816873)

Cohort	II	IT	TT	T allele
MICK	0.54	0.40	0.06	0.26
EPIC	0.57	0.37	0.06	0.25

Table 2 Median values (1st–3rd quartiles) of anthropometric and metabolic variables according to MTP polymorphism I128T (rs3816873) in the MICK

	II	IT + TT	<i>P</i> ^a
Subjects (<i>n</i>)	397	324	
Age (years)	61 (57–63)	60 (56–63)	0.3
BMI (kg/m ²)	26.7 (24.7)	26.7 (24.6–29.8)	0.5
Waist (cm)	98.0 (93.0–107.0)	98.0 (92.3–107.0)	0.5
WHR	0.99 (0.95–1.03)	0.99 (94.9–1.0)	0.4
Syst BP (mmHg)	130.0 (120.0–140.0)	130.0 (120.0–140.0)	0.6
Diast BP (mmHg)	80.0 (70.0–90.0)	80.0 (70.0–85.0)	0.049*
Total cholesterol (mg/dl)	225.8 (201.9–251.6)	225.8 (199.0–251.9)	0.7
HDL cholesterol (mg/dl)	51.3 (42.9–61.4)	52.7 (43.2–61.4)	0.7
LDL cholesterol (mg/dl)	142.8 (122.5–164.1)	145.0 (122.3–166.6)	0.9
Fasting TG (mg × h/dl)	115.9 (87.3–165.2)	124.4 (85.6–170.5)	0.6
Pp TG (mg/dl)	1,543.4 (1,113.3–2,056.0)	1,538.6 (1,097.7–2,090.5)	0.9
Fasting glucose (mg/dl)	101.8 (95.1–110.8)	100.5 (94.9–108.4)	0.3
Pp glucose (mg × h/dl)			
OMTT	507.8 (471.9–546.0)	498.6 (466.6–551.4)	0.5
OGTT	447.0 (402.4–493.2)	440.0 (394.3–492.0)	0.3
Fasting insulin (mU/l)	12.0 (8.8–17.1)	11.7 (8.8–15.9)	0.3
Pp insulin (mU × h/l)			
OMTT	113.9 (161.2–240.0)	156.7 (107.1–237.3)	0.3
OGTT	148.0 (97.4–215.9)	130.8 (91.9–186.7)	0.017*
HOMA-R	3.20 (0.5–23.2)	3.09 (0.73–14.8)	0.7

^aWilcoxon rank sum test

Asterisks indicate statistical significance

Table 3 Median values (1st–3rd quartiles) of anthropometric and metabolic variables according to MTP polymorphism I128T (rs3816873) in the EPIC

	Men		<i>P</i> ^a	Women		<i>P</i> ^a
	II	IT + TT		II	IT + TT	
Subjects (<i>n</i>)	197	135		126	108	
Age (years)	56.0 (52.0–60.0)	56.0 (52.0–60.0)	0.9	57.0 (51.0–60.0)	57.0 (50.0–62.0)	0.6
BMI (kg/m ²)	28.1 (25.8–30.4)	27.05 (25.0–29.8)	0.03*	27.75 (24.1–30.7)	26.97 (23.7–31.1)	0.5
Waist (cm)	99.5 (91.0–107.5)	96.0 (90.0–103.0)	0.01*	85.5 (76.0–96.0)	85.5 (77.8–93.0)	0.9
WHR	0.971 (0.928–1.017)	0.957 (0.907–0.995)	0.04*	0.828 (0.770–0.867)	0.826 (0.773–0.873)	0.6
Syst BP (mmHg)	135.0 (125.5–150.5)	134.5 (125.5–146.5)	0.6	131.0 (117.0–145.0)	132.5 (122.5–141.0)	1.0
Diast BP (mmHg)	89.0 (81.5–94.0)	87.5 (81.5–94.0)	1.0	83.5 (76.0–91.0)	85.0 (77.5–90.0)	0.7
Total cholesterol (mmol/l)	4.63 (4.16–5.37)	4.76 (4.20–5.40)	0.3	4.98 (4.37–5.58)	4.94 (4.29–5.66)	0.7
HDL-cholesterol (mmol/l)	0.88 (0.78–1.03)	0.93 (0.79–1.02)	0.2	1.09 (0.94–1.31)	1.10 (0.94–1.31)	0.8

^aWilcoxon rank sum test

Asterisks indicate statistical significance

and heterozygous for the rare T128 allele showed a significantly lower BMI, waist circumference and WHR compared with males homozygous for the G allele. Such an association was not found in females.

In the MICK, known diabetes was an exclusion criterion, but the prevalence of unknown diabetes and impaired glucose metabolism was high (25.2%). Subjects with the rare allele had a significantly lower prevalence of such an impairment of glucose metabolism (OR: 0.69, 95% CI: 0.49–0.97, *P*=0.03) than those with the common allele (Table 4). The OR estimates did not change

considerably after adjustment for BMI. The association between the MTP I128T polymorphism and glucose metabolism was confirmed in the EPIC cohort (Table 5). Male subjects with the rare allele had a significantly lower incidence of type 2 diabetes than males with the common allele (OR: 0.52, 95% CI: 0.32–0.84, *P*=0.007). However, male carriers of the rare variant in the EPIC tended to have lower BMI; nevertheless, after adjustment for this confounder, the lower risk in T carriers remained significant (OR: 0.56, 95% CI: 0.33–0.95, *P*=0.032; Table 5).

Table 4 Association of MTP I128T polymorphism (rs3816873) with impaired glucose metabolism in the MICK

Genotype	Controls	Cases	OR (95% CI)	<i>P</i>	OR ^a (95% CI)	<i>P</i>
II	269	111	1.00	0.03*	1.00	0.016*
IT + TT	254	71	0.69 (0.49–0.97)		0.65 (0.46–0.92)	

^aAdjusted for BMI

Asterisks indicate statistical significance

Table 5 Association of MTP I128T polymorphism (rs3816873) with type 2 diabetes in the EPIC

Gender	Genotype	Controls	Cases	OR (95% CI)	<i>P</i>	OR ^a (95% CI)	<i>P</i>
All	II	209	119	1.00	0.41	1.00	0.41
	IT + TT	174	72	0.80 (0.51–1.04)		0.85 (0.57–1.26)	
Women	II	86	41	1.00	0.68	1.00	0.43
	IT + TT	71	38	1.12 (0.65–1.93)		1.27 (0.70–2.33)	
Men	II	123	78	1.00	0.007*	1.00	0.032*
	IT + TT	103	34	0.52 (0.32–0.84)		0.56 (0.33–0.95)	

^aAdjusted for BMI

Asterisks indicate statistical significance

Since postprandial parameters are important for the development of insulin-resistance syndrome, we performed both an OGTT and an OMTT in the MICK (Fig. 1a, b). Postprandial insulin levels in response to the OGTT varied also among MTP genotypes, with consistently lower levels in T carriers (Fig. 1b; Table 2). The carriers of different genotypes did not differ in fasting or postprandial insulin after OMTT (Fig. 1a). The fasting concentrations of plasma glucose and insulin as well as triglycerides were not significantly different between MTP genotype groups (Fig. 1a; Table 2).

Discussion

In the present study we investigated the relation of the common MTP I128T polymorphism to pivotal traits of the metabolic syndrome. Essentially, we found lower postprandial insulin levels, a decreased prevalence of IGT and a decreased incidence of type 2 diabetes in subjects carrying the less common allele. The -493G/T MTP polymorphism has been investigated in several other association studies. As described by Karpe et al., the exon and the promoter polymorphisms are in complete linkage disequilibrium (LD). In MICK, we also found complete LD (data not shown). Based on this, results of association studies should be independent of the SNP used for genotyping.

At present, the impact of the promoter polymorphism, on the one hand, and the exon I/T polymorphism, on the other hand, remains to be elucidated. In comparison to the I128T polymorphism, the functional implication of the promoter polymorphism is not in accordance with a number of association studies, since the protective allele (T) shows higher promoter activity (Karpe et al. 1998) than the risk allele. In contrast, the shorter half life and reduced LDL binding of the MTP T128 protein found by Ledmyr (2004) support most of the association studies, which report a risk-lowering effect of the minor allele. From the amino acid exchange I128T, a change of protein function may be expected because isoleucine as a hydrophobic amino acid is exchanged for threonine, which is hydrophilic and because the amino acid position 128 lies in the conserved lipoprotein N-terminal domain, which is binding the lipoprotein. The hydrophobicity of position 128 is conserved among different

species, which argues for its functional significance. Indeed, it has been shown by Ledmyr et al. (2004) that the T128 variant is more susceptible to proteolysis and that the T128–LDL complex is less stable than the I128–LDL complex. These results indicate that the I128T polymorphism confers a reduced local structural stability in the N-terminal domain, leading to reduced binding of MTP to LDL particles.

The MTP polymorphism has previously been reported to be associated with obesity. According to that, a genome-wide scan for abdominal fat identified a region on the long arm of chromosome 4, which is close to the MTP gene locus (Perusse et al. 2001). Subjects homozygous for the less common -493T allele showed lower BMI than carriers of the G allele (Ledmyr et al. 2002). In the EPIC, we found the same association in males (Table 3). A similar association was found in waist circumference as a more specific parameter of the metabolic syndrome. Accordingly, higher diastolic blood pressure, another component of the metabolic syndrome, was associated with the I128 allele in the MICK (Table 2).

For some authors, lower cholesterol and LDL levels were found in carriers of the rare MTP -493T allele (Karpe et al. 1998; Ledmyr et al. 2002, 2004). Some studies reported higher triglyceride levels in carriers of the rare allele (Juo et al. 2000; Chen et al. 2003). These associations could not be confirmed in other studies (Talmud et al. 2000; Couture et al. 2000; Lundahl et al. 2000). We also found no associations between the MTP I128T polymorphism and parameters of lipid metabolism. Neither postprandial triglycerides nor fasting triglycerides, LDL or HDL were different between MTP genotype groups. A lack of association with postprandial triglycerides was also shown by Lundahl et al. (2002), but carriers of the rare allele showed higher levels of apo-B48 in the small triglyceride lipoprotein fraction. A possible explanation for conflicting results is that study populations differed in age, ethnicity and disease status. For example, higher triglyceride levels were found in black males carrying the less common allele of the MTP promoter polymorphism (Juo et al. 2003).

Data from persons with CHD revealed either no associations with MTP -493 genotype (Couture et al. 2000) or showed inconsistent results with lower cholesterol and increased CHD risk for T-allele carriers (Stan et al. 2005). If the risk for CHD were to increase, one

Fig. 1 Postprandial parameters according to MTP I128T polymorphism (rs3816873) in the MICK after **a** an oral metabolic tolerance test (OMTT) or **b** glucose tolerance test (OGTT). Mean ($\pm$ SEM) insulin and triglyceride values for concentration and area under the curve (AUC) in subject homozygotes for the MTP I128 polymorphism (II) in comparison to T128 after an **a** OMTT or **b** OGTT. Asterisk indicates significant difference from II genotype, $P < 0.05$. AUC units are insulin: mU $\times$ h/l; triglyceride: mg $\times$ h/dl; glucose: mg $\times$ h/dl

could argue that the favorable effects of the rare allele in our study depend on a survival effect of T carriers. A study of Nebel et al. (2005) argued against that, showing that the MTP -493T allele is not associated with longevity in the German population. However, the impact of the MTP promoter polymorphism on lipid metabolism may vary depending on environment, lifestyle and

diet. In an interventional study, the effects of low-fat diet depended on MTP -493 polymorphism (Vincent et al. 2002). Homozygous carriers of the rare allele showed a threefold greater reduction in LDL cholesterol in comparison to carriers of the common allele. Therefore, MTP gene-diet interaction might also explain the differences seen in different populations.

In the MICK, insulin sensitivity seemed to be higher in T128 carriers based on lower postprandial insulin levels and similar postprandial glucose levels after OGTT (Fig. 1b; Table 2). Moreover, in our study cohorts the T allele was associated with lower risk of impaired glucose tolerance and type 2 diabetes (Tables 4, 5). There are only few reports on the influence of the MTP gene on glucose metabolism or insulin levels. St-Pierre et al. (2002) performed a study on 105 carriers of the T allele in the -493 MTP promoter region versus 121 GG subjects. Carriers of the T allele showed significantly lower fasting levels of insulin. Another study in French-Canadian youth confirmed a tendency to lower insulin levels (Stan et al. 2005). One study revealed a tendency to higher insulin levels, but the subjects with the rare allele had a significantly higher BMI and waist circumference, for which the insulin levels were not adjusted (Ledmyr et al. 2002).

The basis for the association between MTP polymorphism and insulin sensitivity remains uncertain. The release of chylomicrons or VLDL seems to be similar in both genotypes based on the similar fasting triglyceride levels (Table 2) and similar postprandial increase in triglycerides after a fat-containing meal (Fig. 1). Therefore effects on fat absorption are unlikely to be the reason for differences in insulin sensitivity between the genotypes. Since a promoter-reporter construct containing the rare allele -493T shows higher activity than constructs with the common allele, increased MTP expression in subjects carrying the rare allele might be expected (Karpe et al. 1998). As Karpe et al. suggested, lipidation of immature VLDL particles will be more efficient if MTP activity is increased. This results in an increased proportion of larger VLDL species that are not direct precursors of LDL, thus accounting for the lower LDL cholesterol which was found in carriers of the T allele.

In the postprandial state, homozygote carriers of the T allele showed a markedly elevated accumulation of small and relatively lipid-poor apoB-containing lipoproteins (Lundahl et al. 2002). These may compete with larger triglyceride-rich lipoproteins for LPL and remnant receptors and thus reduce the unfavorable effects of postprandially fluid lipids on insulin sensitivity. Accordingly the postprandial triglyceride curve after OMTT was slightly shifted to the right in T128 carriers (Fig. 1a), which may indicate a slight delay in triglyceride clearance.

Interestingly, subjects with the rare allele have a lower incidence of liver steatosis (Bernard et al. 2000), and non-alcoholic steatohepatitis is less common in subjects with the T allele (Namikawa et al. 2004). Although we did not measure liver steatosis, it could be assumed that subjects with the rare allele have a lower incidence of insulin resistance and type 2 diabetes due to less accumulation of triglycerides in the liver. It remains to be elucidated how low the level of triglyceride accumulation in T carriers is.

In summary, we have shown that the T128 variant in the MTP gene is associated with lower postprandial

insulin and a reduced risk of impaired glucose tolerance and type 2 diabetes mellitus. The shorter half life and reduced LDL binding of the MTP T128 protein may explain our findings.

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