Prandial Hypertriglyceridemia in Metabolic Syndrome Is Due to an Overproduction of Both Chylomicron and VLDL Triacylglycerol

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The aim was to determine whether fed VLDL and chylomicron (CM) triacylglycerol (TAG) production rates are elevated in metabolic syndrome (MetS). Eight men with MetS (BMI 29.7 ± 1.1) and eight lean age-matched healthy men (BMI 23.1 ± 0.4) were studied using a frequent feeding protocol. After 4 h of feeding, an intravenous bolus of 2H5-glycerol was administered to label VLDL1, VLDL2, and TAG. 13C-glycerol tripalmitin was administered orally as an independent measure of CM TAG metabolism. Hepatic and intestinal lipoproteins were separated by an immunoaffinity method. In MetS, fed TAG and the increment in TAG from fasting to feeding were higher (P = 0.03 and P = 0.04, respectively) than in lean men. Fed CM, VLDL1, and VLDL2 TAG pool sizes were higher (P = 0.006, P = 0.03, and P < 0.02, respectively), and CM, VLDL, and VLDL2 TAG production rates were higher (P < 0.002, P < 0.05, and P = 0.06, respectively) than in lean men. VLDL1, VLDL2, and CM TAG clearance rates were not different between groups. In conclusion, prandial hypertriglyceridemia in men with MetS was due to an increased production rate of both VLDL and CM TAG. Since both groups received identical meals, this suggests that in MetS the intestine is synthesizing more TAG de novo for export in CMs. Diabetes 62:4063–4069, 2013

An abnormally elevated blood triacylglycerol (TAG) level in the postprandial period is a feature of metabolic syndrome (MetS) and is predictive of an increased risk of cardiovascular disease (1–3). Hypertriglyceridemia is due to excess triglyceride-rich lipoproteins (TRLs): VLDLs synthesized by the liver, containing the higher–molecular weight form of apolipoprotein (apo)B100, and chylomicrons (CMs), which are synthesized in the intestine in response to an intake of dietary fat and contain the lower–molecular weight form of apoB, apoB48. Both VLDL and CMs share a common lipolytic pathway and are hydrolyzed by lipoprotein lipase, an enzyme predominantly found on the endothelial surfaces of the capillaries of adipose tissue and heart and skeletal muscle (4).

Postprandial hypertriglyceridemia in MetS may be due to the overproduction of intestinal or hepatic TRLs, impaired clearance, or a combination of both. Insulin resistance is associated with a postprandial increase in apoB48 particles (5), and some studies suggested that this is due to impaired catabolism of intestinally derived TRL and remnant lipoprotein TAG (6,7). However, the small intestine is capable of utilizing endogenous substrates for TAG synthesis. Duez et al. (8) have used a constant feeding protocol combined with an infusion of labeled leucine to measure apoB48 kinetics, a surrogate measure of intestinal TRL kinetics, in men with a range of insulin sensitivity. The study showed that insulin resistance was associated with increased intestinal apoB48 production rate. In addition, diet-induced insulin resistance in the Syrian golden hamster has been shown to be associated with a marked increase in intestinal lipoprotein production rate in both the fasting and the fed states (9), which could be reduced by treatment with rosiglitazone (10). Since insulin resistance is associated with elevated nonesterified fatty acid (NEFA) flux from adipose tissue, the mechanism that leads to apoB48 overproduction may be increased delivery of NEFAs to the enterocyte, since an acute elevation of NEFAs in hamsters has been shown to increase basal intestinal apoB48 production (11).

A number of studies have shown that VLDL apoB100 and VLDL TAG production rate is increased by insulin resistance (12,13) in the fasted state, but no studies have measured VLDL TAG production rate quantitatively, in the fed state, in MetS. We have recently demonstrated that intravenously administered 2H5-glycerol is incorporated into CM TAG and can be used to measure both CM and VLDL TAG kinetics in a frequent feeding study (14). In the current study, we have used this methodology to investigate whether the greater increase in postprandial TAG in MetS compared with lean healthy subjects is due to an increase in CM and/or VLDL TAG production rate or a decrease in clearance rate. We hypothesized that an increased synthesis of both CM and VLDL TAG in MetS would be the major cause of the increased postprandial TAG.

RESEARCH DESIGN AND METHODS

Participants. This study was approved by the East Kent National Health Service Research Ethics Committee and the University of Surrey Ethics Committee. Written informed consent was provided by all participants prior to inclusion in the study. Eight men with MetS and eight age-matched lean healthy men were studied. MetS was defined as central obesity (increased waist circumference ≥94 cm) plus any two of the following four factors: triglycerides ≥1.7 mmol/L, HDL cholesterol <1.03 mmol/L, systolic blood pressure (BP) ≥130 mmHg or diastolic BP ≥85 mmHg, or fasting plasma glucose ≥5.6 mmol/L. With the exception of one subject, all subjects could be defined as having MetS without using the BP criteria. This subject had raised waist circumference and raised blood glucose, and plasma triglyceride at screening was 1.65 mmol/L. All men had an apoE3E3 genotype. The exclusion criteria were a diagnosis of diabetes, hepatic and renal disorders, fasting plasma triglyceride >5 mmol/L, cholesterol >7 mmol/L, and use of statins, fibrates, or metformin.

Experimental design. All subjects underwent an 11 h feeding study after an overnight fast. Waist circumference was measured around the umbilicus. Body composition was measured using Tanita BC-418 Scales (Tokyo, Japan).
indwelling cannula was inserted into an antecubital vein for blood sampling. Baseline samples were taken to measure the fasting lipid profile, glucose, and insulin. All subjects were fed six high-fat (83.3%; 23% saturated, 33% mono- unsaturated, 24% polyunsaturated fatty acids), low-carbohydrate (12.2%), and low-protein (4.5%) liquid meals, 497 kcal per meal, at 2-hourly intervals (at −240, −120, 0, 120, 240, and 360 min). The aim of the feeding protocol was to increase fasting plasma TAG levels twofold and to maintain this for the duration of the study. This feeding protocol was successful at achieving steady state TAG levels. The first 4 h (−240 to 0 min) were to enable a TAG steady state to be achieved prior to administration of the tracers. The meal, composed of 125 mL milk shake (Tesco, U.K.), 20 mL double cream, 15 mL olive oil, and 5 mL water, was prepared immediately prior to consumption and was consumed within 1 min by the subject. Tripalmitate (13C3-glyceryl; 10 mg per kilogram body weight) was prepared immediately prior to consumption and was consumed within 1 min.

**Isotopic enrichment determination.** The 13C/12C isotope ratio determination of oral glycerol tracer was performed as previously described (14). A single pool model was used to describe CM TAG kinetics and a two-pool model to describe VLDL1 TAG compartment in the intestine. The VLDL TAG model included a compartment for VLDL1 TAG in the intestine. The VLDL TAG model included a compartment for VLDL1 TAG and a compartment for VLDL2 TAG with an input into both compartments from the glycerol precursor pool, a loss from each compartment, and a transfer from the VLDL1 TAG compartment to the VLDL2 TAG compartment. In a steady state, the fractional secretion rate is equal to the fractional catabolic rate (FCR), a measure of clearance. The production rate was calculated from the product of the fractional secretion rate and the TAG pool size. TAG pool size was calculated from the TAG concentration of the bound and unbound fraction multiplied by plasma volume. Plasma volume was calculated as described by Pearson et al. (16). Fasting insulin sensitivity was assessed by homeostasis model assessment of insulin resistance (HOMA-IR) (17).

**RESULTS**

**Body composition, insulin sensitivity, and fasting lipid profile.** Body weight, BMI, waist circumference, and fat mass were higher in the men with MetS than in the healthy, lean men (all P < 0.001). Fat-free mass was not different between groups. Glucose and insulin concentrations and HOMA-IR were higher in MetS (P = 0.01, 0.05, and 0.03, respectively). Fasting plasma TAG was higher and HDL cholesterol was lower (P = 0.04 and P < 0.04, respectively), but plasma cholesterol and NEFAs were not significantly different in MetS (Table 1).

**Prandial concentrations.** Plasma TAG, NEFA, glucose, and insulin during frequent feeding are shown in Fig. 1. Plasma TAG, SF >60 TAG, and SF 20–60 TAG were not significantly different between 0 and 420 min in either group. During feeding, mean plasma TAG, plasma glucose, and serum insulin were significantly higher in the men with MetS compared with the lean men (P = 0.03, 0.01, 0.05, respectively). The increment in plasma TAG from fasting to feeding was calculated as the difference between the mean TAG during frequent feeding and fasting plasma TAG. Comparison of measurements in the two groups was by unpaired two-tailed t test. A P value lower than 0.05 was considered to be significant.

**TABLE 1** Subject characteristics (mean ± SEM)

|             | Lean | MetS | P value |
|-------------|------|------|---------|
| Age (years) | 59 ± 2 | 57 ± 2 | NS      |
| Body weight (kg) | 72.2 ± 1.7 | 91.8 ± 3.3 | P < 0.0001 |
| BMI         | 23.1 ± 0.4 | 29.7 ± 1.1 | P < 0.0001 |
| Waist (cm)  | 86.8 ± 1.9 | 105.3 ± 3.3 | P = 0.0003 |
| Fat mass (kg) | 12.7 ± 1.1 | 25.1 ± 2.0 | P = 0.0001 |
| Fat-free mass (kg) | 59.5 ± 1.6 | 65.9 ± 3.3 | NS      |
| Serum insulin (pmol/L) | 66.1 ± 7.5 | 118.3 ± 27.4 | P = 0.05 |
| Plasma glucose (mmol/L) | 5.0 ± 0.3 | 5.8 ± 0.1 | P = 0.01 |
| HOMA-IR     | 1.2 ± 0.1 | 2.2 ± 0.5 | P = 0.03 |
| Plasma triglyceride (mmol/L) | 1.1 ± 0.1 | 2.2 ± 0.5 | P = 0.04 |
| Plasma cholesterol (mmol/L) | 5.1 ± 0.4 | 5.1 ± 0.6 | NS      |
| Plasma HDL cholesterol (mmol/L) | 1.6 ± 0.2 | 1.2 ± 0.1 | P < 0.04 |
| Plasma NEFA (mmol/L) | 0.43 ± 0.06 | 0.53 ± 0.05 | NS      |
| Systolic BP (mmHg) | 123.8 ± 3.8 | 124.4 ± 4.9* | NS      |
| Diastolic BP (mmHg) | 81.5 ± 2.8 | 78.8 ± 2.6* | NS      |

*Two subjects were on antihypertensive medication.
(2.94 ± 0.87 mmol/L) than in the lean men (0.88 ± 0.19 mmol/L; P = 0.04). Plasma NEFA concentration did not differ between the two groups during feeding.

**CM enrichment profile with the oral 13C-glycerol tracer.** The enrichment of the 13C-glycerol tracer in the CM and VLDL1 TAG is shown in Fig. 2. The area under the curve for CM TAG enrichment was not different in the two groups. 13C-glycerol enrichment in VLDL1 TAG was <8% of CM enrichment 150 min after tracer administration in the lean men, demonstrating that the immunoaffinity method was efficiently separating the CM and VLDL fractions. There was a small rise in enrichment of VLDL1 TAG with 13C-glycerol during the remainder of the study. In the men with MetS, 13C-glycerol tracer enrichment in VLDL1
TAG, measured as area under the curve, was higher than in the lean men \((P = 0.05)\).

**VLDL and CM kinetics (measured with an intravenous \(^{2}H_5\)-glycerol tracer).** Plasma glycerol enrichment was not different in the two groups (data not shown). The enrichment of CM TAG, VLDL1, and VLDL2 TAG with the intravenous tracer, \(^{2}H_5\)-glycerol, in the lean men and the men with MetS is shown in Figs. 3 and 4A and B, respectively. In the men with MetS, CM, VLDL1, and VLDL2 TAG production rates were higher \((P < 0.002, P < 0.05, P = 0.057, \text{ respectively})\) (Fig. 5), and CM, VLDL1, and VLDL2 TAG pool sizes were higher \((P = 0.006, P = 0.03, P < 0.02, \text{ respectively})\) than in the lean men. There was no significant difference between the two groups in VLDL1, VLDL2, and CM TAG FCR, a measure of clearance.

**DISCUSSION**

In men with MetS, the increment in plasma TAG in response to frequent feeding was considerably higher than in age-matched healthy subjects despite both groups receiving identical meals. The higher-fed TAG level in MetS was due to a higher production rate of VLDL1, VLDL2, and CM TAG rather than reduced clearance. Previous studies have shown that prandial VLDL and CM particle production rate, measured by tracer labeling of apoB100 and apoB48, respectively, is increased in insulin-resistant subjects (8,18). However, these studies did not measure the kinetics of the TAG substrate within the particle. In the current study, we show for the first time that prandial VLDL and CM TAG production rate is increased using in vivo tracer labeling of TAG in MetS.

The oral tripalmitin tracer was labeled on the glyceryl moiety, and previous studies suggest that approximately 75% of this would be absorbed as monoacylglycerol (MAG) and resynthesized into TAG, with the remaining 25% being completely hydrolyzed to glycerol and NEFA (19). The amount of oral tracer administered was determined by body weight and so was 27% higher in the men with MetS. However, the enrichment (tracer-to-tracee ratio) of CM TAG with this tracer was similar in the two groups, demonstrating that there was greater dilution of this tracer with unlabeled TAG in the CM of men with MetS. This suggests that more intestinal TAGs were being exported in CM, which was derived from a nonoral route in these subjects. A greater production rate of CM TAG in MetS was confirmed from the kinetic measurements made using the \(^{2}H_5\) intravenous tracer. There are several possible sources of this nonoral TAG: 1) TAG synthesized from NEFA and glycerol imported from the circulation, 2) TAG synthesized from NEFA generated within the enterocyte from glucose (de novo lipogenesis [DNL]), or 3) the release of TAG or exchange of labeled MAG from the meal with unlabeled MAG from pre-existing storage pools as shown in Fig. 6.

Previous studies have shown that an acute increase in NEFA levels in healthy subjects increases apoB48 production rate (20). Interestingly, in the current study, neither fasting nor prandial NEFA concentrations were different in the two groups, suggesting this was not the driver for a higher synthesis rate of CM TAG in MetS. While the contribution of DNL to hepatic TAG synthesis is well-known (21), it is only recently that this pathway has been demonstrated to be important in enterocytes, and in an insulin-resistant hamster model, enterocyte DNL was shown to be increased (9,22). In the liver, DNL is an insulin- and glucose-dependent process under the control of specific transcription factors: sterol regulatory element binding protein 1c, which is activated by insulin, and

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**FIG. 3.** \(^{2}H_5\)-glycerol enrichment in CM in healthy subjects (○) and subjects with MetS (●) (mean ± SEM).

**FIG. 4.** \(^{2}H_5\)-glycerol enrichment in VLDL1 (◆) and VLDL2 (■) TAG in healthy subjects (A) and subjects with MetS (B) (mean ± SEM).
carbohydrate response element binding protein, which is activated by glucose (23). Carbohydrate response element binding protein is also expressed in the small intestine, and the elevated glucose in MetS may be responsible for an increase in DNL and CM TAG production rate.

Both indirect and direct evidence exist supporting the presence of cytoplasmic TAG storage pools in enterocytes, so an elevated number or size of these pools in MetS may also be a contributing factor to the increased CM TAG export. Storage pools of TAG have been demonstrated in

![Intestinal Lumen Diagram]

**FIG. 5.** TAG production rate (A), TAG FCR (B), and TAG pool size (C) for VLDL1, VLDL2, and CM in healthy subjects (gray columns) and subjects with MetS (black columns) (mean ± SEM). V1, VLDL1; V2, VLDL2. *P < 0.05, **P < 0.01, †P = 0.05.

![CM TAG Synthesis Diagram]

**FIG. 6.** Schematic of CM TAG synthesis in enterocytes, showing labeling of TAG with oral $^{13}$C-glycerol and intravenous $^2$H$_5$-glycerol. A: TAG synthesis from dietary NEFA and MAG. B: TAG synthesis from endogenous (circulating) NEFA and glycerol. C: TAG synthesis from glycerol and NEFA generated from glucose. D: TAG incorporation into CM from TAG stores.
mice enterocytes, and the TAG content was found to directly correlate with the amount of TAG consumed (24). In humans, sequential meal tests have shown that CMs secreted after a second meal carry TAG ingested in the first meal (25). Since mammalian enterocytes turn over every 3 to 4 days, these can only be very short-term stores (26). Higher food intake in the subjects with MetS could lead to larger TAG stores. To determine whether this source of TAG makes a major contribution to the elevated CM production rate, dietary intake would need to be fixed at the same level in the two groups of subjects for 3 days prior to the kinetic study.

It has been clearly demonstrated that fasting VLDL TAG production rate is increased in insulin resistance (13). To the authors’ knowledge, only one previous study has measured VLDL TAG production rate after feeding in insulin-resistant subjects. In that study, a constant infusion of ex vivo-labeled VLDL TAG was used and VLDL TAG secretion rate was shown to be higher in men with type 2 diabetes than in healthy men (27). Although HOMA-IR was not reported in the latter study, patients with type 2 diabetes would be expected to be more insulin resistant than the subjects with MetS in the current study. The higher VLDL TAG production rate after feeding in MetS in the current study may be due to an increase in imported NEFA, DNL, or TAG storage pools as discussed for the enterocyte. In addition, the liver will take up recycled TAG from TRL, including CM. The enrichment of VLDL1 TAG with 13C-glycerol was very low initially but gradually increased with time, indicating recycling of CM remnants to the liver as demonstrated previously (28). That this was higher in MetS is also supported by the study of Hodson et al. (28), which showed 3.5-fold higher recycling of CM remnants in insulin-resistant subjects compared with insulin-sensitive subjects. In nonalcoholic fatty liver disease, the hepatic manifestation of MetS, 15% of hepatic TAG was from the diet, i.e., recycled CM TAG, while DNL was shown to account for 26% (29). However, insulin resistance measured by HOMA-IR was considerably higher than in the subjects with MetS in the current study. Hepatic DNL has been shown to be increased in subjects with insulin resistance (30,31) and has been directly linked to glucose and insulin levels (23). Fasting VLDL TAG production rate has also been shown to be correlated with hyperglycemia (32).

Insulin has been shown to suppress both apoB48 and apoB100 production rate during feeding in healthy subjects (33,34), and this inhibitory effect is blunted in type 2 diabetes (35). Fasting VLDL1 TAG production rate has also been shown to be inhibited by insulin, with a reduced effect in insulin resistance (36). The increased CM and VLDL TAG production rate in the presence of elevated prandial insulin levels in the men with MetS also suggests an impaired effect of insulin. Impaired insulin signaling has been demonstrated in enterocytes and hepatocytes from an insulin-resistant animal model (22).

While some previous studies have suggested that CM clearance is impaired in insulin resistance (7,37) and thus responsible for the elevated postprandial TAG, CM TAG clearance rate was not different in the two groups in the current study. This may be due to the different study design or less insulin resistance. In these previous studies (7,37), either a large oral fat load or an intravenous CM-like emulsion was administered. TRL apoB48 FCR has been shown to be similar in healthy subjects and subjects with insulin resistance studied with a continuous feeding protocol (8). The mean half-life for CM TAG (SF >60) in the current study can be calculated from the FCR to be 72 min in the healthy subjects and 86 min in MetS. This is considerably longer than the half-life for CM TAG (SF >400) previously reported to be 5–6 min in healthy subjects (38). In the density SF >400, CM are approximately 340 nm in diameter. In the SF >60 density, CM will include particles of this size but also particles as small as 40 nm, and this can explain the longer half-life. It has been reported that larger particles are cleared faster than smaller ones (39). The FCR for CM apoB48 in the density range SF >20 has been reported to be 5.0 pools/day (a half-life of 200 min), which is lower than in the current study but a similar order of magnitude (40).

The FCR for VLDL1 TAG in the two groups was in the range of previously reported measurements in fasting studies (32,41). VLDL TAG clearance was not impaired in the fed state in MetS in the current study. This supports the findings of a single-meal study in healthy men and men with type 2 diabetes that showed that although the basal fasting FCR was lower in men with type 2 diabetes, the postprandial FCR was not different in the two groups (27).

A limitation of this study was that the percentage of fat in the meal was considerably higher than would be expected in a physiological meal. Further studies need to be undertaken to confirm the findings of the study using a more physiological meal-feeding protocol.

In conclusion, prandial hypertriglyceridemia in men with MetS was due to an increased production rate of both VLDL and CM TAG. Since both groups received identical meals, this suggests that in MetS, the intestine is synthesizing more TAG de novo.

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F.S.-M., Y.M., and S.L. performed the clinical studies and performed the laboratory work. R.H. developed the model and advised on the modeling. F.S.-M. and A.M.U. analyzed all the data and wrote the manuscript. A.M.U. supervised the laboratory work and was the lead writer. All authors reviewed the manuscript. A.M.U. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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