Glycemic and insulnemic meal responses modulate postprandial hepatic and intestinal lipoprotein accumulation in obese, insulin-resistant subjects1–3

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ABSTRACT

Background: Exacerbated postprandial lipemia is a risk factor for cardiovascular disease and is linked to insulin status. Limited data on the effect of dietary carbohydrate on postprandial lipoprotein accumulation are available.

Objective: We tested the hypothesis that dietary carbohydrates with different glucose availability alter postprandial lipoprotein metabolism differently in obese, insulin-resistant subjects.

Design: After an overnight fast, 9 subjects with central obesity and insulin resistance but normal triacylglycerolemia randomly ingested 2 test meals with comparable amounts of fat (28–29 g) and digestible carbohydrate (91–94 g) but with different quantities of slowly available glucose (SAG) in cereal products (17 or 2 g SAG/100 g for biscuits and wheat flakes, respectively). Blood samples were collected before and for 6 h after meal intakes.

Results: The postmeal 0–2-h areas under the curve (AUCs) for glycemia and insulinemia were significantly lower (P < 0.05) after the biscuit meal than after the flakes meal. Plasma triacylglycerol concentrations increased significantly after the flakes meal but not after the biscuit meal (1.5-fold higher 0–6-h AUC for the flakes meal). Apolipoprotein B-100 concentrations in the triacylglycerol-rich lipoprotein fraction increased significantly 2 h after the flakes meal but not after the biscuit meal (3-fold higher 0–6-h AUC for the flakes meal). Apolipoprotein B-48 concentrations increased (P < 0.05) 4 h after the flakes meal but not after the biscuit meal (2.3-fold higher 0–6-h AUC for the flakes meal).


KEY WORDS Test meals, carbohydrate, slowly digestible carbohydrate, glycemic index, lipemia, triacylglycerols, triacylglycerol-rich lipoproteins, cholesterol, apolipoprotein B-100, apolipoprotein B-48, glucose, insulin, cardiovascular disease

INTRODUCTION

The healthy diet that is currently recommended in all industrialized countries to reduce the burden of cardiovascular disease is a low-fat, low-cholesterol, and high-carbohydrate diet. There is increasing interest in the effects of the amount and type of dietary carbohydrate on the metabolic profile and health-related issues, such as the metabolic syndrome and cardiovascular disease. Although the potential benefit of indigestible dietary fiber in such diets has generally been recognized, the effect of the kind of digestible carbohydrate is a matter of increasing concern (1–7). In fact, clinical studies indicate that highly digestible carbohydrate diets may lead to an elevation in fasting plasma triacylglycerol concentrations as a result of the accumulation of hepatic VLDL and chylomicron remnants due to altered lipoprotein secretion or clearance (3, 8, 9). Elevated fasting triacylglycerolemia and associated low HDL cholesterol are risk factors for cardiovascular disease (10). Moreover, epidemiologic studies have established a link between high dietary glycemic load and elevated cardiovascular risk (11). On the basis of the concept of the glycemic index (GI) (12), some clinical studies have shown that in comparison with high-GI diets, low-GI diets improve the metabolic profiles of healthy subjects (13, 14) and patients with type 2 diabetes, overweight subjects, and glucose-intolerant patients (15–19).

Given the observed general trends toward increased prevalences of obesity, the metabolic syndrome, and type 2 diabetes, the best, suitable diet for such patients is thus questioned (20, 21). In addition to other traits (22), altered postprandial lipoprotein metabolism is now an acknowledged feature of the metabolic syndrome (23–32) and type 2 diabetes (33, 34) and is involved in increased cardiovascular risk (35–39). A positive relation between fasting hyperinsulinemia and altered postprandial lipemia has been reported repeatedly (23–25, 27, 29, 31, 32, 34, 40), but...
the exact role of insulin in the regulation of postprandial lipemia still remains poorly understood, especially because insulin resistance and compensatory hyperinsulinemia coexist in these patients. Both imbalances could play an important role in stimulating or repressing the expression of numerous genes and related metabolic pathways (3, 9). We recently showed that postprandial hyperinsulinemia (modulated by using different test meals or euglycemic-hyperinsulinic clamp) is a determinant of the late postprandial accumulation of really derived apolipoprotein (apo) B-48-containing chylomicrons in healthy humans (41). This led us to suggest that postprandial hyperinsulinemia could be particularly involved in the alteration of postprandial intestinal triacylglycerol-rich lipoprotein (TRL) metabolism whereas insulin resistance could be mainly responsible for altered hepatic TRL metabolism (3, 8, 9). We therefore anticipated that subjects with insulin resistance and elevated postprandial hyperinsulinemia would have postprandial alterations in both hepatic and intestinal lipoproteins. Thus, we designed the present study to test the hypothesis that sources of dietary carbohydrates with different slowly digestible carbohydrate contents could induce different glycemic and insulimic responses that alter postprandial lipoprotein metabolism differently in insulin-resistant subjects.

SUBJECTS AND METHODS

Subjects

Nine nondiabetic, android-type obese subjects (8 women with a waist circumference > 88 cm and 1 man with a waist circumference > 102 cm) with a mean age of 35 y (range: 25–45 y) were recruited after medical examination to participate in the study. Before participating in the study, all subjects gave their written informed consent to a protocol approved by the local Medical Ethics Committee (Comité Consultatif pour la Protection des Personnes se prêtant à des Recherches Bio-médicales, Marseille 1). None of the subjects suffered from any digestive disease or were receiving any drug treatment that could influence carbohydrate or lipid metabolism. The subjects’ mean (±SEM) body mass index (in kg/m²) was 36.4 ± 1.8, and the subjects’ mean weight was 100 ± 3.7 kg. We aimed to select subjects with normal triacylglycerolemia to avoid too much imbalance in lipid metabolism. Mean fasting serum concentrations were as follows: glucose, 5.6 ± 0.2 mmol/L; insulin, 12.8 ± 1.5 mU/L, or 88.2 ± 10.3 pmol/L; triacylglycerols, 1.1 ± 0.7 mmol/L; total cholesterol, 5.5 ± 0.4 mmol/L. All the selected subjects with central obesity had insulin resistance according to their homeostasis model assessment scores (42), with a mean value of 3.04 ± 0.3. As pointed out in other studies (43, 44), a strong negative correlation has been found between the homeostasis model assessment score and insulin sensitivity as checked by using a hyperinsulinic clamp in healthy subjects or patients with type 2 diabetes. The subjects were instructed to avoid alcohol consumption and intense exercise for 36 h before being tested and to consume a moderate amount of carbohydrates the day before the study. The subjects were asked to have a light standard dinner before 2100 on the evening before the experiment. The usual basal diet of each subject was monitored through the use of a 3-d food record during the first week of the experiment, and calculations were made with the GENI software package (Micro 6, Nancy, France). The subjects consumed a typical Western diet, with moderate energy consumption (mean: 9731 kJ/d, or 2328 kcal/d). Alcohol intake was negligible.

Test meals

Two different test meals were designed, and they differed essentially in the source of carbohydrate. The 2 test meals had similar energy content (2821 and 2871 kJ); had similar amounts of fat (29 and 28 g; ≈38% of energy), carbohydrates (94 and 91 g; ≈55% energy), and protein (18 and 24 g); and were composed of commercially available foods provided by Danone Vitapole (Palaiseau, France) (Table 1). The carbohydrate sources compared were cereal foods: experimental plain wheat biscuits (biscuit meal) and usual ready-to-eat wheat flakes (flakes meal). The cereal products were processed differently, which led to different contents of slowly available glucose (SAG; 17 g SAG/100 g compared with 2 g SAG/100 g for the biscuit and the flakes meals, respectively; reference 45); however, the carbohydrate contents of the 2 meals were similar [72% (wt:wt) and 78% (wt:wt) for the biscuit and the flakes meals, respectively]. The SAG content has been negatively correlated with GI (45).

The fat was provided in the form of a biscuit, flakes, yogurt, soft cheese, or milk and as palm oil homogenized in dairy products (Table 1). Most fatty acids were saturated (saturated fatty acids: 53.1% and 56.2% in the biscuit and the flakes meals, respectively; monounsaturated fatty acids: 37.4% and 36.3% in the biscuit and the flakes meals, respectively; polyunsaturated fatty acids: 9.5% and 7.5% in the biscuit and the flakes meals, respectively).

Each subject ingested the 2 test meals in a random order in the outpatient metabolic ward (Department of Endocrinology, Diabetes, and Nutrition, La Timone University Hospital, Marseille, France); the 2 test meals were separated by a 1-wk interval. After the subjects had fasted overnight, an antecubital vein was catheterized with intravenous cannulae equipped with disposable obturators (Jelco-Critikon, Chatenay-Malabry, France). A baseline (0 h) fasting blood sample was collected. Then the subjects ingested the test meal within 20 min. The countdown was fixed at the middle of food intake. Blood samples were collected every

| Food composition and nutrient and energy contents of the 2 test meals* |
|----------------------------------|-----------------|
| **Foods (g)**                   | **Biscuit meal** (high SAG) | **Flakes meal** (low SAG) |
| Plain biscuit                   | 100              | —                          |
| Extruded wheat flakes           | —                | 95                         |
| Unsweetened yogurt (0% fat)     | 250              | —                          |
| Fresh cheese                    | —                | 120                        |
| Whole milk                      | 7                | 250                        |
| Sugar                           | 13               | 10                         |
| Palm oil                        | 17               | 25                         |
| Carbohydrates                   | 94               | 91                         |
| Starch                          | 51               | 53                         |
| Sugars                          | 43               | 39                         |
| SAG                             | 17               | 2                          |
| RAG                             | 50               | 66                         |
| Fat                             | 29               | 28                         |
| Protein                         | 17               | 25                         |
| Energy (kJ)                     | 2821             | 2871                       |

* SAG, slowly available glucose; RAG, rapidly available glucose.
half hour during the first 2 h and every hour until 6 h after the meal as described previously (25, 41, 46).

Analytic determinations

Plasma and serum were immediately separated from whole blood by centrifugation (910 \times g, 10 °C, 10 min). Plasma glucose, triacylglycerol, total cholesterol, HDL-cholesterol, and LDL-cholesterol concentrations were measured by using an enzymatic procedure with commercial kits (Boehringer Mannheim, Meylan, France) as described previously (41). Insulin concentrations were measured by using an immunoenzymatic method with commercial kits (Boehringer Mannheim). Nonesterified fatty acid concentrations were measured by using an enzymatic colorimetric procedure with kits purchased from Randox (Amtrim, United Kingdom).

The chylomicron fraction (Sf \geq 400) was isolated from 1.5 mL plasma layered under 1.5 mL NaCl (9.0 g/L) by ultracentrifugation (33 810 \times g, 15 °C, 6 min) with the use of a Beckman TLX100 ultracentrifuge (Palo Alto, CA) and a 100.3 rotor as previously reported (25). The TRL fraction (Sf \geq 20; chylomicron plus VLDL) was isolated from 1.5 mL plasma layered under 1.5 mL NaCl (9.0 g/L) by ultracentrifugation (540 960 \times g, 15 °C, 160 min). LDL and HDL particles were then isolated by sequential ultracentrifugation (41). Triacylglycerols and cholesterol were assayed in lipoprotein fractions by using an enzymatic procedure with commercial kits. Chylomicron sizes were measured at 20 °C on suspended, freshly prepared samples by using photon correlation spectroscopy with a particle-size analyzer (SEMAtech, Nice, France) as described previously (25).

Apo B-48 and apo B-100 were assayed by using enzyme-linked immunosorbent assay methods as described previously (41, 47). Briefly, assessment of apo B-48 was performed by using a competitive enzyme-linked immunosorbent assay with a specific apo B-48 antibody obtained in rabbits. A 96-well microtiter plate (Maxisorp; Nunc, Polylabo, France) was coated with a C-terminal apo B-48-specific heptapeptide. Plasma samples were incubated with Triton X-100 (Euromedex, Souffleweyersheim, France) to allow competition between immobilized antigen and plasma apo B-48. Apo B-48-containing chylomicrons were used as the standard. Peroxidase-labeled anti-rabbit immunoglobulins and their substrates allowed color development.

Assessment of apo B-100 in TRL was performed by using a noncompetitive sandwich enzyme-linked immunosorbent assay. Briefly, a 96-well microtiter plate was coated with 2G8 monoclonal anti--apo B-100 antibody (Mona, Moscow), which does not cross-react with apo B-48 (48). TRL samples were added, and the apo B-100-containing VLDLs that reacted with the monoclonal antibody were quantified after the addition of first an anti--apo B-100 polyclonal antibody (Calbiochem, Meudon, France) and then of peroxidase-labeled immunoglobulins. The color was developed and measured as described above. Apo B-100–containing LDLs were used as the standard.

After the 6-h postprandial blood sampling, each subject was injected with 80 IU heparin/kg (Choay, Gentilly, France). A postheparin blood sample was drawn after 10 min for subsequent determination of lipoprotein lipase and hepatic lipase activities as reported previously (41).

Statistical analysis

In this randomized study, each subject ingested the 2 test meals and served as his or her own control. Results are given as means ± SEMs. Absolute postprandial changes are given as concentration values. The 0–2-h and 0–6-h areas under the curve (AUCs) were calculated from incremental postprandial variations (postprandial values minus baseline value) by using the trapezoidal method. The data could not be normalized, and thus we used nonparametric tests. The statistical significance (P < 0.05) of the meal effect was assessed by using the Wilcoxon test for nonparametric values. In each meal group, the time effect during the postprandial period was assessed by using repeated-measures analysis with the nonparametric Friedman test for global interaction; when the interaction was significant, detailed comparisons were performed by using the Wilcoxon test (SPSS 11.5 for WINDOWS; SPSS Inc, Chicago).

RESULTS

Ingestion of the 2 test meals significantly increased glycemia as shown in Figure 1A. Glycemia increased significantly (P < 0.05) 30 min after meal ingestion and was significantly higher after the flakes meal than after the biscuit meal (7.61 ± 0.57 compared with 6.36 ± 0.36 mmol/L). The incremental 0–2-h AUC for glycemia (Figure 1A, inset) was significantly higher after the flakes meal than after the biscuit meal (1.41 ± 0.58 compared with 0.77 ± 0.28 mmol·h/L).

Insulinemia increased significantly 30 min after ingestion of the 2 test meals, and significantly higher insulin concentrations were observed 1 and 1.5 h after the flakes meal than after the biscuit meal (Figure 1B). As shown in the inset of Figure 1B, the incremental insulin postprandial response was significantly higher after the flakes meal than after the biscuit meal from 1 h (1.41 ± 0.18 compared with 0.77 ± 0.13 compared with 0.99 ± 0.3 mmol/L). The incremental 0–6-h AUC for plasma triacylglycerols (1.10 ± 0.57 compared with 0.57 ± 0.28 mmol·L·h/L) and from 0 to 6 h (AUC: 737.5 ± 121.4 pmol·L·h/L) compared with 737.5 ± 124.1 pmol·L·h/L).

As shown in Figure 1C, triacylglycerolemia increased significantly 1 h after the flakes meal, and significantly higher peak concentrations were observed after the flakes meal than after the biscuit meal from 1 h (1.41 ± 0.18 compared with 1.03 ± 0.14 mmol/L) up to 4 h (1.25 ± 0.13 compared with 0.99 ± 0.3 mmol/L). The incremental 0–6-h AUC for plasma triacylglycerols was significantly higher after the flakes meal than after the biscuit meal (Figure 1C, inset). Incremental 0–6-h AUC values for TRL triacylglycerols (1.10 ± 0.39 and 1.28 ± 0.53 mmol·h/L for the biscuit and the flakes meals, respectively) and chylomicron triacylglycerols (0.56 ± 0.22 and 0.62 ± 0.24 mmol·h/L for the biscuit and the flakes meals, respectively) were not markedly different after the 2 test meals. Mean chylomicron sizes increased from 60 nm at baseline to 100–120 nm 2 h after meal intake but decreased after 6 h; there were no significant differences in chylomicron sizes between the 2 test meals (data not shown).

After ingestion of the 2 meals, different postprandial patterns were observed for TRL apo B-100 and chylomycin apo B-48. Apo B-100 concentrations in the TRL fraction increased significantly after the flakes meal but not after the biscuit meal and peaked 2 h after meal ingestion (Figure 1D). At this time point, the mean TRL apo B-100 concentration after the flakes meal was significantly higher than that after the biscuit meal. For longer periods of time (3–6 h), apo B-100 concentrations did not differ significantly from baseline, and no further significant differences between the meals were found. The incremental 0–3-h (data not shown) and 0–6-h (Figure 1D, inset) AUCs for TRL apo B-100
FIGURE 1. Mean (±SEM) postprandial changes in metabolic variables during 6 h after ingestion of a biscuit meal (■ in main panels and in insets) or a flakes meal (▲ in main panels; □ in insets) (n = 9). A: Plasma glucose concentrations and 0–2-h and 0–6-h incremental areas under the curve (AUCs) (inset); B: plasma insulin concentrations and 0–2-h and 0–6-h incremental AUCs (inset); C: plasma triacylglycerol concentrations and 0–6-h incremental AUCs (inset); D: triacylglycerol-rich lipoprotein (TRL) apolipoprotein (apo) B-100 concentrations and 0–6-h incremental AUCs (inset); E: plasma apo B-48 concentrations and 0–6-h incremental AUCs (inset); F: plasma nonesterified fatty acid (NEFA) concentrations and 0–6-h incremental AUCs (inset).

* Significant difference between the biscuit meal and the flakes meal, \( P < 0.05 \) (Wilcoxon test for nonparametric values). There was a significant \( P < 0.05 \) meal × time effect for glucose, insulin, triacylglycerol, TRL apo B-100, and plasma apo B-48. There was a significant time effect for plasma NEFAs, \( P < 0.05 \) (repeated-measures analysis with the Friedman test for global interaction and the Wilcoxon test for detailed comparisons).
were 6.31- and 3.05-fold higher \( (P < 0.05) \), respectively, after the flakes meal than after the biscuit meal. Postprandial changes in plasma apo B-48 concentrations are shown in Figure 1E. Apo B-48 concentrations did not change noticeably after the biscuit meal but increased markedly after the flakes meal, and significantly higher peak values were observed 4 h after the flakes meal than after the biscuit meal. The incremental 0–6-h (Figure 1E, inset) and 3–6-h (data not shown) AUCs for apo B-48 were 2.3- and 3.4-fold higher \( (P < 0.05) \), respectively, after the flakes meal than after the biscuit meal.

After ingestion of the 2 test meals, plasma total cholesterol concentrations did not show a significantly different negative trend \((0–6-h AUC: -3.79 \pm 0.39 \text{ and } -4.46 \pm 0.97 \text{ mmol} \cdot \text{h/L after the biscuit and the flakes meals, respectively})\). Similarly, LDL-cholesterol \((0–6-h AUC: -2.97 \pm 0.31 \text{ and } -3.34 \pm 0.75 \text{ mmol} \cdot \text{h/L after the biscuit and the flakes meals, respectively})\) and HDL-cholesterol \((0–6-h AUC: -1.16 \pm 0.12 \text{ and } -1.25 \pm 0.21 \text{ mmol} \cdot \text{h/L after the biscuit and the flakes meals, respectively})\) concentrations did not differ significantly between the 2 test meals.

Plasma nonesterified fatty acid concentrations (Figure 1F) decreased significantly 1–4 h after the intake of each test meal but progressively returned to the baseline value after 5 h. No significant differences between the responses to the 2 meals were observed.

Lipoprotein lipase and hepatic lipase activities were determined in postheparin plasma 6 h after meal intake. No significant differences in enzyme activities after the biscuit and the flakes meals were observed (mean lipoprotein lipase activity: 0.99 \pm 0.15 and 0.93 \pm 0.23 \text{ mmol} \cdot \text{h}^{-1} \cdot \text{L}^{-1}, \text{respectively}; mean hepatic lipase activity: 0.57 \pm 0.09 and 0.66 \pm 0.07 \text{ mmol} \cdot \text{h}^{-1} \cdot \text{L}^{-1}, \text{respectively}).

**DISCUSSION**

In the present study, we tested the hypothesis that subjects with central obesity and some degree of insulin resistance have postprandial alterations in both hepatic and intestinal lipoproteins that are influenced by the glycemic and insulimemic responses to a meal. We found that in comparison with ingestion of a mixed meal rich in rapidly available glucose, ingestion of a meal rich in SAG lowered both the postprandial increase in insulinemia and the accumulation of circulating triacylglycerols and apo B-100– or apo B-48–containing TRL in those subjects.

The carbohydrate-rich foods provided by the 2 test meals contained markedly different amounts of SAG (17% in the flakes meal compared with 2% in the biscuit meal). As expected, the 2 mixed meals tested elicited markedly different glycemic responses, with a 1.8-fold higher increase in the plasma glucose 0–2-h AUC after the flakes meal than after the biscuit meal. In addition, the observed 0–2-h insulin postprandial response was 1.6-fold higher \( (P < 0.05) \) after the flakes meal than after the biscuit meal, which is in agreement with previous data showing that meals containing slowly digestible carbohydrates induce lower glycemic and insulimemic responses (45, 49).

The 2 different levels of postprandial hyperinsulinemia elicited by the 2 meals were accompanied by 2 different patterns for plasma lipids and lipoproteins. After the high-SAG biscuit meal, plasma triacylglycerols, TRL triacylglycerols, TRL apo B-100, and plasma apo B-48 showed low-to-moderate postprandial increases, as a likely response of normolipidemic subjects to the moderate amount (29 g) of fat provided by the test meal (47). In contrast, after the flakes meal, which was rich in rapidly available glucose and provided the same amount of fat, we observed exaggerated accumulations of plasma triacylglycerols, TRL apo B-100, and chylomicron apo B-48. Similar figures for plasma triacylglycerols and apo B-48 but not for apo B-100 were observed previously in healthy subjects after meals with different amounts or types of carbohydrate (41, 50). Other data obtained after the addition of glucose to fatty test meals have not been reproduced in healthy subjects (51). Moreover, in moderately overweight, nondiabetic men, ingestion of breakfasts with either high- or low-GI foods (detailed composition unknown) did not lead to differences in postprandial changes in triacylglycerol concentrations (17).

TRL particles that accumulate in the circulation after fatty meals are known to be of both hepatic and intestinal origin due to superimposition of the 2 secretory pathways (25, 32, 52). It is thus interesting to observe that the flakes meal, which elicited higher glycemic and insulimemic responses than did the biscuit meal, exacerbates the accumulation of apo B-100–containing TRL and plasma chylomicron apo B-48 postprandially. This indicates that the increase in triacylglycerol concentrations observed in plasma or lipoprotein fractions is, at least partly, a reflection of an increased number of lipoprotein particles present in the circulation postprandially. Another interesting finding was that the postprandial accumulation of apo B-100– and apo B-48–containing TRLs showed different time courses. A biphasic postprandial accumulation of TRL triacylglycerols was observed previously after high-carbohydrate meals but not after low-carbohydrate meals in healthy subjects (50). The observed early accumulation (2-h peak) of TRL apo B-100 (a marker of hepatically derived VLDL) in the plasma after the high-GI flakes meal may have resulted from the generated acute hyperinsulinism superimposed on a preexisting insulin-resistant state. Indeed, insulin resistance has been shown to weaken the repressive effect of insulin on hepatic VLDL secretion (8, 29, 30, 53), whereas postprandial hyperinsulinism does not generate any marked accumulation of apo B-100–containing TRL postprandially in healthy subjects (41). Another possibility is that a worsened repression of chylomicron concentrations by insulin, as observed in healthy subjects (41), leads to an early relative increase in chylomicron number that is preferentially cleared and therefore generates a more marked accumulation of VLDL at that time.

In fact, the insulin resistance–hyperinsulinism state is usually associated with fasting hypertriglyceridemia and hyper-VLDLemia in patients (23–25, 27–32, 34, 40), and both of these phenomena are stimulated by chronic high-carbohydrate feeding (3, 33, 54). Because fasting triglyceridemia is a known determinant of postprandial triglyceridemia, one can anticipate that much more marked and prolonged postprandial accumulation of apo B-100–containing TRL would occur in frankly hypertriglyceridemic, insulin-resistant subjects (25). This remains to be tested.

In addition, accumulation of a greater number of intestinal apo B-48–containing chylomicrons was observed after the flakes meal than after the biscuit meal, and a major late peak occurred at 4 h with the flakes meal. Such a late chylomicron apo B-48 peak has been observed in healthy subjects after high-GI meals only or after a euglycemic-hyperinsulinemic clamp (41) and in patients with type 2 diabetes (34). Alterations in intestinally derived lipoprotein secretion or clearance may explain these observations. Regarding secretion, some recent evidence indicates...
that dietary glucose may stimulate intestinal resecretion and the occurrence in plasma of triacylglycerols or cholesterol in triacylglycerol-rich particles (55, 56). Apparently contrarily, we suggested from previous data in healthy subjects (41) that hyperinsulinemia could delay the secretion of intestinal TRL, as already stated for the liver (57). Some limited experimental data support such an insulin-mediated inhibition of or delay in intestinal lipid secretion (58; A Harbis and D Lairon, unpublished observations, 2000). Thus, through a direct effect of glucose or an effect of induced hyperinsulinemia, meals rich in rapidly available glucose may noticeably alter intestinal secretion of chylomicrons, which may lead to an amplified and late accumulation of these particles and their remnants in the circulation after a meal; this possibility would account for the observations made in the present study. Nevertheless, the possible combined effect of insulin resistance and hyperinsulinism in this process is not known, and further studies are needed to firmly establish such mechanisms.

Regarding intestinal chylomicron clearance, one can suggest that the 2.3-fold higher apo B-48 AUC after the flakes meal than after the biscuit meal in the insulin-resistant subjects could have resulted from exacerbated competition for clearance between apo B-100—containing TRL particles (VLDL) and apo B-48—containing chylomicrons in the postprandial period, in which intestinal secretion dramatically increases after the digestion and absorption of meal fat. Finally, insulin is known to stimulate lipoprotein lipase activity in adipose tissue, an effect blunted in glucose-intolerant, obese subjects (59). This would explain the fact that the 2 meals did not induce noticeable differences in postheparin plasma activities. Men and women with central obesity and insulin resistance are known to have elevated concentrations of both apo B-100—and apo B-48—containing TRLs in the fasting state (25, 29, 32, 34, 41, 53) that mirror well the elevated postprandial concentrations observed in the present study and some others studies (25, 29, 32, 34). Indeed, the present data obtained in normolipemic subjects with central obesity and some degree of insulin resistance suggest that superimposition of dietarily induced, acute, important postprandial hyperinsulinemia onto a preexisting insulin-resistant state generates an exacerbated accumulation of postprandial TRLs originating from the liver and intestine. This would favor the residual accumulation of both liver and intestinal TRL particles in the fasting state, which would account for the fasting hypertriacylglycerolemia that is involved in the metabolic syndrome (22) and associated with increased cardiovascular risk (10). In contrast, low-fat meals rich in slowly available carbohydrates did not elicit such a detrimental postprandial pattern in these subjects in the present study.

DL conceived and designed the study, obtained financial support, discussed the data, and wrote the manuscript. M-CB and DR recruited the subjects. DR discussed the study design, managed the metabolic ward, and corrected the manuscript. AH and SP performed the daily work and part of the biochemical analyses. MS, A-ML, CD, and HP performed analyses and/or supervised biochemical analyses. AH, SV-B, and MC performed the data analysis. SV and VL provided advice and food-composition data and manufactured foods for the study.

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