Apolipoprotein B-100 Kinetics in Visceral Obesity: Associations With Plasma Apolipoprotein C-III Concentration

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Obesity is strongly associated with dyslipidemia, which may account for the associated increased risk of atherosclerosis and coronary disease. We aimed to test the hypothesis that kinetics of hepatic apolipoprotein B-100 (apoB) metabolism are disturbed in men with visceral obesity and to examine whether these kinetic defects are associated with elevated plasma concentration of apolipoprotein C-III (apoC-III). Very–low-density lipoprotein (VLDL), intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) apoB kinetics were measured in 48 viscerally obese men and 10 age-matched normolipidemic lean men using an intravenous bolus injection of d^3-leucine. ApoB isotopic enrichment was measured using gas chromatography-mass spectrometry (GCMS). Kinetic parameters were derived using a multicompartmental model (Simulation, Analysis, and Modeling Software II [SAAM-II]). Compared with controls, obese subjects had significantly elevated plasma concentrations of plasma triglycerides, cholesterol, LDL-cholesterol, VLDL-apoB, IDL-apoB, LDL-apoB, apoC-III, insulin, and lathosterol ($P < .01$). VLDL-apoB secretion rate was significantly higher ($P = .034$) in obese than control subjects; the fractional catabolic rates (FCRs) of IDL-apoB and LDL-apoB ($P < .01$) and percent conversion of VLDL-apoB to LDL-apoB ($P < .02$) were also significantly lower in obese subjects. However, the decreased VLDL-apoB FCR was not significantly different from the lean group. In the obese group, plasma concentration of apoC-III was significantly and positively associated with VLDL-apoB secretion rate and inversely with VLDL-apoB FCR and percent conversion of VLDL to LDL. In multiple regression analysis, plasma apoC-III concentration was independently and significantly correlated with the secretion rate of VLDL-apoB (regression coefficient [SE] 0.511 [0.03], $P = .001$) and with the percent conversion of VLDL-apoB to LDL-apoB (-0.408 [0.01], $P = .004$). Our findings suggest that plasma lipid and lipoprotein abnormalities in visceral obesity may be due to a combination of overproduction of VLDL-apoB particles and decreased catabolism of apoB containing particles. Elevated plasma apoC-III concentration is also a feature of dyslipidemia in obesity that contributes to the kinetic defects in apoB metabolism.

VISCERAL OBESITY is strongly associated with insulin resistance and dyslipidemia and increased risk of cardiovascular disease.[1] Although the precise mechanism whereby visceral obesity results in dyslipidemia has not been established, this disturbance may be related to dysregulation of all aspects of apolipoprotein B-100 (apoB) metabolism. ApoB is a constitutively expressed glycoprotein that is synthesized in the liver and required for the hepatic secretion of very–low-density lipoprotein (VLDL). It has been suggested that VLDL-apoB secretion rate is dependent on the availability of cholesterol esters and triglycerides in the liver.[2,3] We have previously reported that visceral obese men had an increased hepatic production of VLDL apoB.[4] However, an integrated study of apoB metabolism in VLDL, intermediate-density lipoprotein (IDL), and low-density lipoprotein (LDL) compartments has not been fully examined in visceral obesity.

ApoC-III is an 8.8-kd glycoprotein, synthesized by the liver and intestine. ApoC-III plays a central role in regulating the plasma metabolism of triglyceride-rich lipoproteins (TRLs), including VLDL, and their remnants. In normolipidemic subjects, the majority of apoC-III is bound to high-density lipoprotein (HDL), while in hypertriglyceridemic subjects, the majority is bound to TRLs.[5] ApoC-III acts as an inhibitor of lipoprotein lipase (LPL) and of TRLs remnant uptake by hepatic lipoprotein receptors.[6,7] Elevated apoC-III may cause an accumulation in plasma of TRLs that has been shown to be strongly associated with hypertriglyceridemia and progression of coronary artery disease.[8,9] In obese subjects, apoC-III concentration has been previously found elevated and correlated to abnormal postprandrial response of TRLs.[10] To our knowledge, there is little information concerning the relationship between plasma apoC-III and apoB kinetics in nondiabetic, obese subjects with insulin resistance.

In the present study, we used a stable isotope technique to test the hypothesis that the hepatic secretion and catabolism of apoB in VLDL, IDL, and LDL compartments are disturbed in men with visceral obesity. We also wished to explore the relationship between the kinetics of apoB metabolism and plasma apoC-III levels in obesity.

SUBJECTS AND METHODS

Subjects

Forty-eight obese men (body mass index [BMI] greater than 29 kg/m^2, waist circumference greater than 100 cm, waist-to-hip ratio greater than 0.97) and 10 age- and sex-matched normolipidemic lean men (plasma triglycerides less than 1.2 mmol/L and total cholesterol less than 5.2 mmol/L) while consuming ad libitum, weight-maintaining diets were recruited for the study. None of the subjects had diabetes mellitus (excluded by oral glucose tolerance test), apolipoprotein E2/E2 genotype, macroproteinuria, creatinemia (>120 μmol/L), hypothyroidism, or abnormal liver enzymes; or consumed more than 30 g alcohol/day. None reported a history of cardiovascular disease or were taking

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medication or other agents known to affect lipid metabolism. The study was approved by the Ethics Committee of the Royal Perth Hospital, and informed consent was obtained before the study was started.

Clinical Protocols

All subjects were admitted to the metabolic ward in the morning after a 14-hour fast. They were studied in a semirecumbent position and allowed to drink only water. Venous blood was collected for measurements of biochemical analytes. Plasma volume was determined by multiplying body weight by 0.045. In obese subjects, the plasma volume was modified by multiplying a factor to take into consideration the decrease in relative plasma volume associated with an increase in body weight as described by Riches et al.[4] Arterial blood pressure was recorded after 3 minutes in the supine position using a Dinamap1846 SX/P monitor (Critikon Inc, Tampa, FL). Dietary intake was assessed for energy and major nutrients using at least two 24-hour dietary diaries and subsequently analyzed using DIET 4 Nutrient Calculation Software (Xyris Software, Queensland, Australia).

A single bolus of d^3-leucine (5 mg/kg of body weight) was administered intravenously within a 2-minute period into an antecubital vein via a 21-gauge butterfly needle. Blood samples were taken at baseline and after injection of the isotope at 5, 10, 20, 30, 40 minutes and 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, and 10 hours. Subjects were then given a snack and allowed to go home. Additional fasting blood samples were collected in the morning on the following 4 days of the same week (24, 48, 72, and 96 hours).

Isolation and Measurement of Isotopic Enrichment of VLDL, IDL, and LDL apoB

VLDL, IDL, and LDL were isolated from 3 mL plasma by sequential ultracentrifugation in a Centrikon T-1190 centrifuge (Kontron Instruments, Milan, Italy) at densities (d) of 1.006, 1.019, and 1.063 g/mL, respectively. The apoB-100 fraction was precipitated by addition of an equal volume of 100% isopropanol as described by Egusa et al.[11] The precipitate was then delipidated with isopropanol, dried, and hydrolyzed by the addtion of 2 mL of 6 mol/L hydrochloric acid. After the hydrolysis at 105°C for 24 hours, samples were dried and reconstituted with 1 mL 50% acetic acid. The free amino acids were separated and purified by cation-exchange chromatography using AG 50 W-X8 resin (BioRad, Richmond, CA). Samples were derivatized using acetonitrile and N-methyl-N-(tert-butyldimethylsilyl)-trifluoroacetamide and reconstituted in toluene for gas chromatography-mass spectrometric (GCMS) analysis (Hewlett Packard HP 5890 Series II Plus gas chromatograph coupled to an HP 5989B Mass Spectrometer, Hewlett Packard, Palo Alto, CA). Plasma amino acids were also separated by cation exchange chromatography, derivatized, and analyzed as described above for the determination of plasma leucine isotopic enrichment. Isotopic enrichment was determined by selected ion monitoring of derivatized samples at a mass to charge ratio (m/z) of 305 and 302 and using electron-impact ionisation. Tracer to tracee ratios were derived from isotopic ratios for each sample.

Quantification of apoB and Other Analytes

Plasma samples were combined to yield 5 pooled VLDL, IDL, and LDL samples/patient study (ie, 3 plasma aliquots pooled at regular time intervals during the isotope infusion day and 2 aliquots pooled from days 2/3 and days 4/5 postinfusion, respectively). A modified Lowry method was used to determine the apoB-100 concentration in each lipoprotein fraction.[12]

Plasma cholesterol and triglyceride concentrations were determined by standard enzymatic methods using a Hitachi 917 Biochemical Analyzer (Hitachi Ltd, Tokyo, Japan). HDL-cholesterol was measured by an enzymatic colorimetric method using a commercial kit (Boehringer Mannheim, Mannheim, Germany). LDL-cholesterol was calculated using the Friedewald equation. Non–HDL-cholesterol was derived as total cholesterol minus HDL-cholesterol. Apolipoproteins A-I and B were determined by immunonephelometry. ApoC-III was measured by immunoturbidimetric assay (Daichi, Toyko, Japan). Plasma nonesterified fatty acids (NEFAs) were measured by an enzymatic, colorimetric method using a commercial kit (Randox, Antrim, UK). Plasma insulin was measured by radioimmunoassay (DiaSorini s.r.l., Saluggia, Italy). Plasma glucose concentration was measured by an hexokinase method on a Hitachi 917 Biochemical Analyzer (Hitachi Ltd). Insulin resistance was estimated using the homeostasis model assessment (HOMA) formula: fasting insulin (mU/L) $\times$ fasting plasma glucose (mmol/L)/22.5 as described by Matthews et al.[13] Plasma lathosterol concentration was assayed by a modification of the method of Mori et al[14] using GCMS. Genomic DNA was extracted by the standard Triton X-100 procedure and the genotype for apoE determined as described by Hixson et al.[15] Plasma liver (alanine transferase, asparate transferase, alkaline phosphatase) and muscle (creatinine kinase) enzymes were analyzed on a Hitachi 917 Biochemical Analyzer (Hitachi Ltd).

Model of apoB Metabolism and Calculation of Kinetic Parameters

A multicompartmental model (Fig 1) was used to describe VLDL-, IDL-, and LDL-apoB leucine tracer/tracee ratios. In multicompartmental modeling, each compartment or pool represents a group of kinetically homogenous particles. In this study, the Simulation, Analysis, and Modeling Software II (SAAM II) program (SAAM Institute, Seattle, WA) was used to fit the model to the observed tracer data. Metabolic parameters were subsequently derived from the model parameters giving the best fit. Part of the model consists of a 4-compartment subsystem (compartments 1 through 4) that describe plasma leucine kinetics. This subsystem is connected to an intrahepatic delay compartment (compartment 5) that accounts for the time required for the synthesis and secretion of apoB into plasma. This model provides for the direct secretion of apoB into the VLDL, IDL, and LDL fractions. Compartments 6 through 10 are used to describe the kinetics of apoB in the VLDL fraction. Compartments 6 through 9 represent a delipidation cascade. It is assumed that the residence time of particles in each compartment of the cascade is the same. In addition, the fraction of each compartment in the cascade converted to the slowly turning over VLDL compartment (compartment 10) is the same. VLDL particles in compartment 9 can be converted to IDL or removed directly from plasma. Plasma IDL kinetics are described by 2 compartments, com-

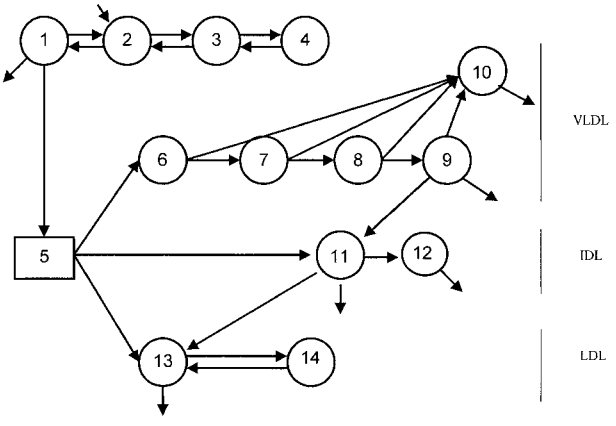

Fig 1. Multicompartmental model for apoB metabolism.

partments 11 and 12. Compartment 12 represents a slowly turning over pool of IDL particles. IDL in compartment 11 can be converted to LDL, compartment 13, or be removed directly from plasma. The LDL section of the model consists of 2 compartments. Compartment 13 describes plasma LDL, and compartment 14 is an extravascular LDL exchange compartment. It is assumed that all LDL is cleared via compartment 13. VLDL, IDL, and LDL apoB metabolic parameters, including secretion rate, fractional catabolic rate (FCR), and percent conversion of VLDL to IDL and LDL were derived following a fit of the compartment model to the apoB tracer/tracee ratio data.

Statistical Analysis

All analyses were performed using SPSS 10.1 (SPSS, Chicago, IL). Group characteristics were compared by *t* tests, after logarithmic transformation of skewed variables where appropriate. Associations were examined by simple and multivariate linear regression methods. Statistical significance was defined at the 5% level using a 2-tailed test.

RESULTS

Table 1 shows the clinical and biochemical characteristics of obese and lean men. Age and blood pressures were not significantly different between the groups. As anticipated, the obese group had a significantly higher body weight, BMI, waist circumference, and waist-to-hip ratio ($P < .001$) compared with the lean group. Although plasma glucose and NEFAs were not significantly different between the groups, the obese subjects had significantly elevated fasting insulin concentrations and were considered insulin resistant on the basis of the HOMA score ($P < .001$). The obese group had significantly higher plasma cholesterol, triglycerides, non–HDL-cholesterol, LDL-cholesterol, apoB-100, and apoC-III ($P < .01$), but lower HDL-cholesterol ($P < .05$) compared with the lean group. Total body cholesterol synthesis, as reflected by plasma lathosterol concentration, was also significantly higher in the obese than control subjects ($P = .003$). Thirty-one of the obese men were E3/E3 homozygotes, 2 were E2/E3 heterozygotes, 13 were E3/E4 heterozygotes, and 2 were E4/E4 homozygotes. Five of the lean men were E3/E3 homozygotes, 2 were E2/E3 heterozygotes, 1 was an E3/E4 heterozygote, and 1 was an E4/E4 homozygote. One subject in the lean group did not consent to give blood for DNA analysis. There were no statistically significant differences in the frequency distribution of E alleles between the groups. Average daily energy intake was significantly higher in the obese than control subjects (9,904 ± 197 kJ *v* 7,316 ± 682 kJ, $P = .004$). The proportion of energy intake from carbohydrates, protein, fat, and alcohol did not differ between the 2 groups.

Table 1. Clinical and Biochemical Characteristics of Subjects at Baseline

	Lean (n = 10)	Obese (n = 48)	*P* Value
Age (yr)	53.1 ± 9.0	53.5 ± 9.0	.909
Body weight (kg)	78 ± 12.0	104 ± 15	.001
BMI (kg/m^2)	24.8 ± 2.9	33.6 ± 4.1	.001
Waist (cm)	91.0 ± 9.0	113 ± 9	.001
Waist-to-hip ratio	0.92 ± 0.06	1.01 ± 0.05	.001
Systolic blood pressure (mm Hg)	122 ± 12	133 ± 15	.066
Diastolic blood pressure (mm Hg)	71.9 ± 8.3	78.5 ± 10.1	.060
Fasting NEFAs (mmol/L)	0.28 ± 0.10	0.29 ± 0.13	.743
Fasting glucose (mmol/L)	5.35 ± 0.25	5.46 ± 0.72	.425
Fasting insulin (mU/L)	23.9 ± 4.2	33.8 ± 11.4	.001
Insulin resistance (HOMA score)	5.70 ± 1.20	8.36 ± 3.68	.001
Total cholesterol (mmol/L)	4.33 ± 0.34	5.95 ± 0.75	.001
Total triglyceride (mmol/L)	0.77 ± 0.25	1.90 ± 0.77	.001
HDL-C (mmol/L)	1.28 ± 0.30	1.04 ± 0.21	.034
Non–HDL-C (mmol/L)	3.05 ± 0.42	4.91 ± 0.67	.001
LDL-C (mmol/L)	2.70 ± 0.33	3.89 ± 0.68	.001
ApoB-100 (mg/dL)	78 ± 11	128 ± 19	.001
ApoC-III (mg/L)	118 ± 24	162 ± 34	.001
Lathosterol (μmol/L)	6.66 ± 1.10	11.1 ± 0.6	.003

NOTE. Values are means ± SEM.

Table 2. Plasma VLDL, IDL, and LDL ApoB-100 Concentration and Kinetic Parameters in the Two Groups

	Lean (n = 10)	Obese (n = 48)	*P* Value
ApoB-100 (mg/L)			
VLDL	52.4 ± 5.7	95.7 ± 5.5	.001
IDL	28.2 ± 4.1	40.1 ± 10.2	.002
LDL	390 ± 18	572 ± 17	.001
Secretion rate (mg/kg/d)			
VLDL	9.66 ± 1.17	14.7 ± 1.0	.034
IDL	7.39 ± 1.14	6.50 ± 0.44	.418
LDL	7.40 ± 1.28	5.66 ± 0.32	.215
Fractional catabolic rate (pools/d)			
VLDL	4.28 ± 0.55	4.08 ± 0.19	.690
IDL	6.07 ± 0.71	4.27 ± 0.23	.004
LDL	0.43 ± 0.07	0.27 ± 0.02	.001
Conversion (%)			
VLDL to LDL	50 ± 8	28 ± 3	.002
VLDL to IDL	58 ± 8	38 ± 3	.006
IDL to LDL	72 ± 10	78 ± 27	.511

NOTE. Values are means ± SEM.

Table 2 shows the plasma VLDL-, IDL-, and LDL-apoB concentrations and corresponding kinetic parameters in the subjects studied. Compared with control subjects, there was a significant increase in plasma concentrations of apoB in VLDL, IDL, and LDL ($P < .01$). The obese subjects had significantly higher hepatic secretion rates of VLDL-apoB compared with control subjects ($P = .034$). The IDL-apoB FCR, LDL-apoB FCR, and the percent conversion of VLDL to IDL and LDL-apoB were significantly lower in obese subjects ($P < .05$), but a significant difference was not found in the FCR for VLDL-apoB. In stepwise regression including a dummy variable referring to lean or obese group and a continuous variable for dietary energy intake, the former variable was the significant predictor of VLDL-apoB secretion ($P < .05$). Moreover, in a pooled analysis of both groups, dietary energy was not significantly correlated with any of the FCRs of apoB.

Table 3 shows the relationships between plasma apoC-III concentrations and apoB kinetic parameters in the obese subjects. In univariate regression analysis, there were statistically significant associations of plasma apoC-III concentration with VLDL-apoB ($r = +.735$, $P = .001$), IDL-apoB ($r = +.346$, $P = .016$), the secretion rate of VLDL-apoB ($r = +.470$, $P = .001$), the FCR of VLDL-apoB ($r = -.303$,

Table 3. Associations Between Plasma ApoC-III and ApoB Metabolic Parameters in the Obese Subjects

	ApoC-III		
	R^2	Regression Coefficient (SE)	*P* Value
ApoB-100 concentration (mg/L)			
VLDL	54	.735 (.090)	.001
IDL	12	.346 (.466)	.016
LDL	6	.246 (.041)	.092
Secretion rate (mg/kg/d)			
VLDL	22	.470 (.644)	.001
IDL	0	−.009 (1.675)	.951
LDL	1	−.076 (2.277)	.606
Fractional catabolic rate (pools/d)			
VLDL	9	−.303 (3.605)	.036
IDL	7	−.266 (3.080)	.068
LDL	4	−.207 (47.09)	.157
Conversion(%)			
VLDL to LDL	14	−.380 (.071)	.008
VLDL to IDL	13	−.361 (.241)	.012
IDL to LDL	1	−.077 (.186)	.604

P = .036), and the percent conversion of VLDL to IDL-apoB (r = -.361, P = .012) and VLDL to LDL-apoB (r = -.380, P = .008). Figure 2 shows the correlations of plasma apoC-III concentrations with the secretion rate of VLDL-apoB, the FCR of VLDL-apoB, and the conversion of VLDL-apoB to LDL-apoB in the obese subjects. ApoC-III was also significantly associated with triglycerides (r = +.734, P = .001) and non–HDL-cholesterol (r = +.429, P = .002). There was a significant positive association between VLDL-apoB secretion rate and plasma triglycerides (r = +.351, P = .015), IDL-apoB (r = +.306, P = .035), and LDL-apoB (r = +.380, P = .008) levels. The LDL-apoB FCR was inversely associated with plasma total cholesterol (r = -.346, P = .016) and non–HDL-cholesterol (r = -.398, P = .005). In multiple regression analysis including age, body weight, energy intake, HOMA score, plasma lathosterol, and NEFAs, plasma apoC-III level was independently and significantly correlated to the secretion rate and percent conversion of VLDL to LDL-apoB (Table 4).

DISCUSSION

Our major findings were that compared with lean controls, men with visceral obesity had higher hepatic secretion of VLDL-apoB and lower catabolism of apoB, as reflected by lower FCRs of both IDL and LDL-apoB and decreased conversion of VLDL to IDL and LDL-apoB. We also demonstrated for the first time that plasma concentrations of apoC-III were positively associated with VLDL-apoB secretion rate and inversely associated with VLDL-apoB FCR and percent conversion of VLDL to LDL-apoB.

Previous studies using radioisotopes have examined the metabolism of apoB in obesity, but none focused on visceral obesity. Egusa et al[16] found that the hepatic secretion of VLDL-apoB was significantly increased in 9 obese Pima Indians compared with lean controls. Kesaniemi et al[17]

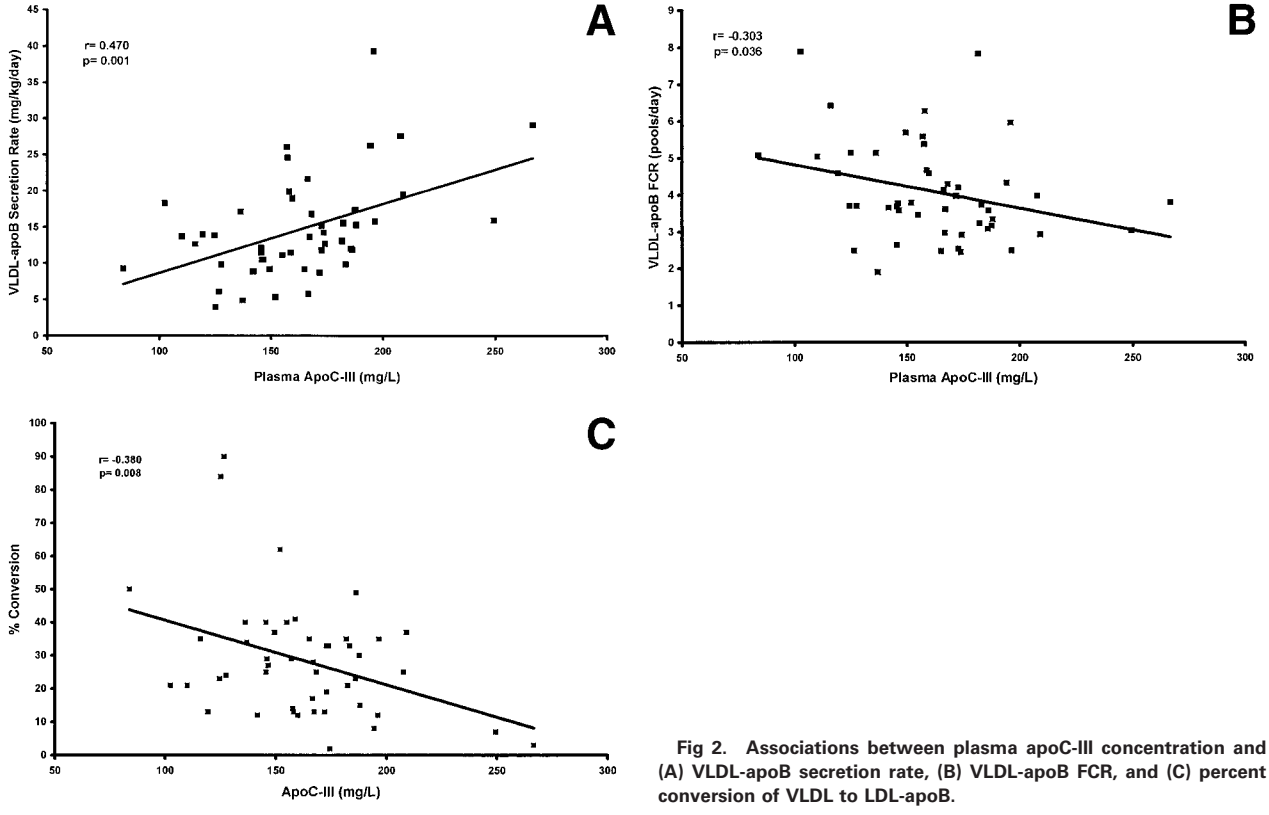

Fig 2. Associations between plasma apoC-III concentration and (A) VLDL-apoB secretion rate, (B) VLDL-apoB FCR, and (C) percent conversion of VLDL to LDL-apoB.

Table 4. Multiple Linear Regression Showing Association Between (A) Hepatic Secretion of VLDL ApoB-100 and (B) Percent Conversion of VLDL to LDL ApoB and Plasma ApoC-III Concentration in the Obese Subjects With Adjustments Made for Subject Age, Body Weight, Energy Intake, HOMA Score, and Plasma Concentrations of Lathosterol and NEFAs

Predictor Variable	Regression Coefficient (SE)	*P* Value
A		
ApoC-III (mg/L)	.511 (.026)	.001
Age (yr)	−.317 (.111)	.026
Body weight (kg)	−.089 (.069)	.529
Energy intake (kJ)	−.078 (.001)	.589
HOMA score	−.079 (.279)	.559
Lathosterol, (μmol/L)	−.217 (.226)	.121
NEFAs (mmol/L)	−.092 (7.327)	.503
B		
ApoC-III (mg/L)	−.408 (.001)	.004
Age (yr)	.160 (.006)	.265
Body weight (kg)	.198 (.003)	.179
Energy intake (kJ)	.145 (.001)	.334
HOMA score	−.215 (.014)	.128
Lathosterol (μmol/L)	−.274 (.011)	.060
NEFAs (mmol/L)	.085 (.365)	.553

NOTE. A, Adjusted R^2 = 28%, P = .005. B, Adjusted R^2 = 34%, P = 0.015.

reported that 4 obese subjects had an increased rate in the synthesis of VLDL-apoB. However, in these studies, the FCRs of apoB were not consistent, owing to small sample size and differences in population characterisctics and methods of data analysis. Using a stable isotope technique, we have previously reported that the disturbance of VLDL-apoB metabolism in visceral obesity was mainly due to an increase in hepatic secretion rather than a decrease in catabolism of apoB.[4] However, we did not examine IDL or LDL apoB metabolism in that study. Our present data extend previous studies by using a larger sample size, a nonradioactive label, and multicompartmental modelling of the kinetics of apoB. We also examine the association between plasma concentration of apoC-III and kinetics of apoB.

Disturbances in lipoprotein metabolism in visceral obesity may be due to insulin resistance and an elevated apoC-III level.[1,10] Insulin resistance has 3 potential effects on apoB metabolism. First, it increases NEFAs delivery to the liver for triglyceride synthesis by enhanced lipolysis in the abdominal fat, and consequently, the secretion of VLDL-apoB.[18,19] Second, it downregulates LDL receptor expression and activity,[20] thereby delaying the removal of apoB-containing lipoproteins from plasma. Third, it suppresses LPL activity,[21] which in turn, decreases the clearance of VLDL-apoB. These effects would collectively cause an accumulation of apoB in plasma. The role of apoC-III in modulating TRL metabolism has been well documented.[22] Increased apoC-III inhibits the lipolysis of VLDL-triglyceride by LPL,[6] and the hepatic uptake of TRL remnants by LDL receptors.[7] The precise reason for enhanced synthesis of apoC-III in obesity remains unclear, but may relate to the effect of insulin resistance in decreasing the transcription of peroxisome proliferator-activated receptor.[23]

The increased hepatic secretion of VLDL-apoB in our obese subjects might have been a consequence of resistance to inhibitory effects of insulin and, in part, mediated by elevated cholesterol synthesis, as reflected by the increased plasma lathosterol concentrations. Our regression analyses suggested that the increased VLDL-apoB secretion in our obese subjects was not related to variations in dietary energy intake or other nutrients, consistent with our previous data.[4] Studies performed in the immediate postprandial state may prove otherwise.[24] The lower FCRs of IDL-apoB and LDL-apoB might be due to the inhibitory effects of insulin resistance and elevated apoC-III on LDL receptor expression. These kinetic defects could account for the dyslipoproteinemia seen in our obese subjects. Since the percent conversion of VLDL to LDL-apoB was lower, other compensatory mechanisms, such as increased VLDL receptor activity, might have enhanced direct removal of VLDL particles by the liver and other extrahepatic tissues.[25] This possibility requires further investigation.

An important finding was that that plasma apoC-III concentration was elevated and significantly associated with VLDL secretion rate, VLDL FCR, VLDL- to IDL-, and LDL-apoB conversion, as well as with plasma triglyceride levels. ApoC-III may hence play an important role in determining the apoB metabolism. One cannot, however, infer a causal mechanism from the significant correlation found between plasma apoC-III levels and VLDL secretion rate. This association may indeed reflect the independent effect of insulin resistance in increasing hepatic output of both apoC-III and apoB.[18,23] The unexplained variance in the correlational analyses between apoC-III concentration and kinetic parameters of apoB may also be attributed to other factors, such as genetic mutations regulating delivery of lipid substrates to the liver and the intrahepatic processing of apoB.[26]

Our study does have limitations. It might have been preferable to estimate insulin resistance using an insulin clamp to provide a more reliable association between insulin resistance and apoB kinetics.[27] We did not measure plasma apoC-III in the VLDL and other TRLs. However, we anticipate that the majority of plasma circulating apoC-III is bound in TRL fraction in our obese subjects and, therefore, this limitation would not confound our results.[28,29] The kinetic bases for the elevated plasma apoC-III in obesity, including the relationship with NEFA flux, also require further investigation. Other studies should also determine the relative importance of different adipose tissue compartments in regulating apoB and apoC-III kinetics.

In conclusion, the present data demonstrate that plasma lipid and lipoprotein abnormalities in visceral obesity are due to a combination of overproduction of VLDL-apoB particles and catabolic defects in apoB-containing lipoprotein particles. Elevated apoC-III may be a causally or casually related to these kinetic defects. These abnormalities may also account for increased risk of atherosclerosis and coronary heart disease in visceral obesity.

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