Adipose Tissue Compartments and the Kinetics of Very–Low-Density Lipoprotein Apolipoprotein B-100 in Non-obese Men

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We examined the association between the kinetics of very–low-density lipoprotein (VLDL) apolipoprotein B-100 (apoB) and intraperitoneal, retroperitoneal, subcutaneous abdominal, and total adipose tissue masses (IPATM, RPATM, SAATM, TATM, respectively) in 14 healthy, non-obese men (body mass index [BMI] < 30 kg/m^2). Hepatic secretion of VLDL-apoB was measured using an intravenous infusion of 1-[^{13}C]-leucine. Isotopic enrichment of VLDL-apoB was measured using gas chromatography-mass-spectrometry and a multicompartmental model (Simulation, Analysis, and Modeling Software [SAAM II]) used to estimate the fractional catabolic rate (FCR) of VLDL-apoB. IPATM, RPATM, and SAATM (kg) were quantified between T11 and S1 using magnetic resonance imaging (MRI); TATM (kg) was determined using bioelectrical impedance. Insulin resistance was estimated by homeostasis model assessment (HOMA) score. In stepwise regression analysis, IPATM was the best predictor of the hepatic secretion of VLDL-apoB (r = .58, P < .05) and TATM the best predictor of the FCR of VLDL-apoB (r = -.56, P < .05). After adjusting for TATM, IPATM explained 59% of the variance in VLDL apoB secretion (P = .03). None of the fat compartments were significantly associated with VLDL-apoB kinetics after adjusting for HOMA score. The findings suggest that in non-obese men the quantity of both intraperitoneal and total fat are significant predictors for the kinetics of VLDL-apoB, which in turn, determines plasma triglyceride concentrations; these associations may, in part, be mediated by variations in insulin resistance, particularly among individual who are not ostensibly obese. Our preliminary results need confirmation in a larger study.

DIFFERENCES IN THE regional accumulation of fat may account for variation in risk of cardiovascular disease in non-obese individuals.[1,2] This may relate to heterogeneity in the metabolic properties and anatomical location of adipocytes[3] and the consequences of this on insulin resistance and dyslipidemia.[4] The precise contributory roles of subcutaneous, visceral, and total fat accumulation, however, remain unclear.[5-7]

The hepatic secretion rate of very–low-density lipoprotein (VLDL) apolipoprotein B-100 (apoB) is an important determinant of the flux of proatherogenic lipoproteins.[8] Hepatic oversecretion of apoB has been correlated with angiographic coronary artery disease,[9] and elevated plasma concentrations of apoB powerfully predict coronary disease in unselected populations.[10] The metabolism of VLDL-apoB in vivo is controlled by the hepatic availability of lipid substrates[11,12] and by level of insulin resistance via partly interrelated mechanism.[13,14] The contribution of different fat compartments to the kinetics of VLDL-apoB has not yet been investigated, particularly in individuals who are not obese. While clinical anthropometric measurements may be used to assess regional adiposity,[15] accurate quantitation of body fat compartments requires imaging techniques, such as magnetic resonance imaging (MRI).[16]

In the present study of non-obese men, we investigated the association between the VLDL-apoB metabolism, measured with stable isotope and mass spectrometry, and adipose tissue compartments, measured with MRI and bioelectrical impedance.

MATERIALS AND METHODS

Subjects

We studied 14 consecutive healthy men selected from the community with body mass index (BMI) less than 30 kg/m^2. We aimed to explore the associations between apoB kinetics and fat compartments in a small cohort of men who were not obese, as defined by their BMI. We excluded patients with diabetes, renal failure, proteinuria, hypothyroidism, or other conditions known to influence lipid metabolism, as well as those using lipid-regulating therapy. Subjects were consuming ad libitum, weight-maintenance diets and were not on medications. Volunteers gave written consent, and the study was approved by the local ethics committee.

Investigational Protocols

Weight, height and waist and hip circumference were measured using standard methods. BMI and waist:hip ratio were derived. Nutrient intake was assessed by 24-hour dietary record. All measurements in the metabolic ward were performed after a 14-hour fast in a temperature-controlled room. Body composition was estimated at rest in the supine position after emptying bladder using a Holtain Body Composition Analyser (Holtain, Dyfed, UK) from which total adipose tissue mass (TATM) and fat free mass (FFM) were derived; technical error less than 3%. MRI of 8 transaxial segment (field of view, 40 to 48 cm; 10 mm thickness) at intervertebral levels form T11 to the S1 was performed using a 1.0T Picker MR scanner (Picker International, Cleveland, OH), and a T1 weighted fast spin echo sequence with a high fat:water signal ratio.[17] Subcutaneous abdominal adipose tissue (SAAT), intraperitoneal adipose tissue (IPAT), and retroperitoneal adipose tissue (RPAT) areas were calculated by summing the relevant adipose tissue pixel units with purpose-designed software. Corresponding adipose tissue volumes were derived by the method of Ross et al,[18] from which SAAT mass (M), IPATM, and RPATM were calculated by

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multiplying the density of adipose tissue (0.9196 kg/L). The imaging protocol has a technical error of less than 10% and is highly correlated with measurements obtained from imaging of the abdominal region using contiguous transaxial slices (R^2 = 99%, n = 4).

VLDL-apoB kinetic was measured following a primed (1 mg/kg), constant (1 mg/kg/h) intravenous infusion (10 hours) of 1-[^{13}C]-leucine (99.5% enrichment) (Tracer Technologies, Somerville, MA), as previously described in detail.[13,17,19] VLDL-apoB was isolated by preparative ultracentrifugation, precipitated by isopropanol, and quantified by the Lowry method.[20] We have shown that this technique is well correlated with an immunoturbidimetric method.[20] After hydrolysis and derivatization, isotopic enrichment E(t) of apoB with ^{13}C-leucine was estimated using electronic-impact ionization by gas chromatography mass spectrometry (GCMS) analysis (Hewlett Packard 5890, Palo Alto, CA). Tracer:tracee mass units (Z[t]) were used to derive the fractional catabolic rate (FCR) of VLDL-apoB from a 3-compartment model that has been described in detail elsewhere.[17] The pool size of VLDL-apoB was calculated from plasma volume (body weight × 0.045) multiplied by apoB concentration. The absolute hepatic secretion rate (ASR) of VLDL-apoB was estimated as pool size × FCR, expressed as mg/kg FFM/d.

Laboratory Measurements

Fasting cholesterol, triglyceride, and high-density-lipoprotein (HDL)–cholesterol were determined by standard enzymatic methods, with low-density lipoprotein (LDL)–cholesterol derived by the Friedewald equation. Plasma glucose and nonesterified fatty acids (NEFAs) were also measured by enzymatic colorimetric methods and insulin by immunoenzymometry. These methods have been described elsewhere.[17] Insulin resistance was calculated using the homeostasis model assessment (HOMA) score that uses the formula: fasting plasma insulin (mU/L) × glucose (mmol/L)/22.5.[21]

Statistical Analyses

Associations were examined by Pearson correlation coefficients (r), partial correlations adjusting for TATM or HOMA score, and stepwise regression analysis. Statistical significance was defined at the 5% level.

RESULTS

Table 1 shows the anthropometric characteristics of the 14 non-obese men. On average, the proportion of total adipose tissue as IPATM, RPATM, and SAATM was 11.1%, 1.4%, and 10.9%, respectively. Internal abdominal ATM (ie, IPATM + RPATM) and external abdominal ATM (ie, TATM–internal abdominal ATM) comprised 12.5% and 87.5%, respectively, of total fat mass.

Table 2 shows the biochemical characteristics of the subjects. As anticipated, they were not dyslipidemic, diabetic, or insulin resistant, and the VLDL-apoB kinetic data were consistent with other reference populations. Nutrient intake (mean ± SD) consisted of: total energy, 8,883 ± 1,801 kJ; carbohydrate, 41% ± 7%; fat, 31% ± 6%; protein, 22% ± 5%; and alcohol, 6% ± 5%.

Table 1. Anthropometric and Adipose Tissue Mass Characteristics of 14 Non-obese Men

Characteristics	Mean ± SD	Range
Age (yr)	48.8 ± 8.8	33.0–61.0
Weight (kg)	83.5 ± 11.0	66.6–98.6
BMI (kg/m^2)	26.0 ± 2.24	22.1–29.7
FFM (kg)	59.0 ± 8.70	40.1–72.2
Intraperitoneal ATM (kg)	2.59 ± 1.43	0.96–5.20
Retroperitoneal ATM (kg)	0.33 ± 0.22	0.08–0.71
Subcutaneous AATM (kg)	2.54 ± 1.01	1.39–4.85
Total ATM (kg)	23.3 ± 8.32	13.1–35.8

Table 2. Biochemical Characteristics and VLDL-apoB Kinetic Data

Characteristics	Mean ± SD	Range
Cholesterol (mmol/L)	5.29 ± 0.61	4.1–6.7
Triglyceride (mmol/L)	1.45 ± 1.11	0.50–3.80
HDL-cholesterol (mmol/L)	1.21 ± 0.33	0.80–1.80
LDL-cholesterol (mmol/L)	3.39 ± 0.45	2.70–4.10
Glucose (mmol/L)	5.04 ± 0.56	4.10–6.00
Insulin (mU/L)	6.26 ± 3.28	2.60–12.0
Insulin sensitivity (HOMA score)	1.41 ± 0.76	0.55–2.69
NEFAs (mmol/L)	0.90 ± 0.29	0.49–1.30
VLDL-apoB (mg/L)	44.1 ± 35.9	10.2–133.0
VLDL-apoB secretion (mg/d)	1173 ± 763	319–3,280
VLDL-apoB secretion (mg/kg FFM/d)	19.6 ± 12.4	6.48–55.0
VLDL-apoB FCR (pools/d)	10.9 ± 7.55	1.36–30.9

Table 3 shows the Pearson correlation coefficients between the adipose tissue compartments and biochemical and VLDL-apoB kinetic variables. The mass of all adipose tissue compartment was significantly and positively correlated with plasma triglyceride and VLDL-apoB concentration and insulin resistance measured by HOMA score. With the exception of SAATM, which was negatively correlated with HDL-cholesterol, none of the adipose tissue compartments was correlated with plasma cholesterol, HDL-cholesterol, LDL-cholesterol, or NEFA concentrations. The ASR of VLDL-apoB was only significantly correlated with IPATM. Neither RPATM, SAATM, or TATM was significantly correlated with VLDL-apoB ASR. The FCR of VLDL-apoB was only significantly correlated (negatively) with TATM. In stepwise regression, including all adipose tissue compartments, HOMA score, plasma NEFA, and age, IPATM was selected as the best predictor of the ASR of VLDL-apoB (r = .58, $P < .05$) and TATM the best predictor of the FCR of VLDL-apoB (r = -.56, $P < .05$). Internal abdominal ATM was also a better predictor of VLDL-apoB ASR (r = .572, $P < .05$) and conversely external ATM the best predictor of VLDL-apoB FCR (r = -.574, $P < .05$). Nutrient intake was not significantly correlated with any of the variables shown in Table 3. The results shown in Table 3 were also obtained after adjusting for age or dietary intake alone.

Table 4 shows the partial correlation coefficients between the adipose tissue compartments and VLDL-apoB kinetic variables. After adjusting for TATM, the ASR of VLDL-apoB was only significantly correlated with IPATM, a positive association with RPATM, just failing to reach statistical significance (P = .053). After adjusting for HOMA score, none of the adipose tissue compartments was correlated with VLDL-apoB kinetic data, the association of IPATM with VLDL-apoB ASR and TATM with VLDL-apoB FCR just failing to reach statistical significance (P = .08).

DISCUSSION

This correlational analysis suggests that in an unselected group of non-obese men intraperitoneal adipose tissue accumu-

Table 3. Associations (Pearson correlation coefficient) Between Adipose Tissue Compartments and Biochemical and VLDL-apoB Kinetic Variables of the Subjects

	Intraperitoneal ATM	Retroperitoneal ATM	Subcutaneous AATM	Total ATM
Cholesterol	.361	.249	.095	.210
Triglyceride	.770*	.781*	.700†	.564‡
HDL-cholesterol	−.271	−.367	−.539‡	−.301
LDL-cholesterol	−.186	−.287	−.265	−.108
HOMA score	.750†	.762†	.582‡	.626‡
NEFAs	−.197	−.182	.032	−.468
VLDL-apoB	.700†	.691†	.538‡	.609‡
ASR of VLDL-apoB	.579‡	.520	.234	.235
FCR of VLDL-apoB	−.313	−.300	−.421	−.563‡

*$P < .001$.
†$P < .01$.
‡$P < .05$.

lation is the fat compartment that best predicts the hepatic secretion of VLDL-apoB, and total adipose tissue mass best predicts the fractional catabolism of VLDL-apoB. These associations were, in part, related to differences in insulin sensitivity, as measured by HOMA score, and, in turn, accounted for variation in plasma triglyceride concentration.

While clinical measures of central fat accumulation have been closely correlated with dyslipidemia and insulin resistance,[1] the specific contributions of regional adiposity to these metabolic abnormalities require the use of imaging methods,[15] such as MRI or computerized axial tomography. Previous studies examining the metabolic association of adipose tissue compartments, measured using imaging techniques, have focused on insulin resistance. Abate et al[6,16] found that in both diabetic and nondiabetic men total body fat mass and subcutaneous abdominal fat mass were the best predictors of insulin resistance, measured by the hyperinsulinemic, euglycemic clamp technique. By contrast, other reports suggest that visceral fat is the best predictor of insulin resistance in obese women.[22] Furthermore, in non-obese women, total body fat mass was found to be the primary determinant of insulin resistance.[7] Our study of non-obese men are consistent with previous observations using insulin clamps[7,16] and extend these by focusing on the kinetics on VLDL-apoB. Other studies have also shown that insulin resistance and lipid substrate supply to the liver are both determinants of hepatic VLDL-apoB secretion.[11,13,14,23,24] We have previously reported that hepatic VLDL-apoB secretion is directly and strongly correlated with visceral adipose tissue mass before and after weight reduction in obese subjects,[17,25] consistent with the present observation. We have also previously shown that the waist:hip ratio independently predicts VLDL-apoB secretion in men with a wide range of adiposity.[19]

Intraperitoneal adipocytes are more lipolytically active than subcutaneous adipocytes[26,27] and so, theoretically, could contribute more to the overall flux of fatty acids and glycerol to the systemic circulation. Direct release of lipid substrates from peritoneal adipocytes into the portal vein may have a direct effect on the liver, increasing in VLDL-apoB secretion and hepatic insulin resistance.[4,13,14,28] This may explain our findings that intraperitoneal fat predicted VLDL-apoB secretion in our subjects independent of total fat mass. There was also a suggestion that this effect was also independent of insulin resistance, but the small sample size did not allow us to fully elucidate this. Despite the potential metabolic importance of peritoneal fat accumulation, some in vitro studies suggest that basal lipolytic rate is greater, and insulin-mediating inhibition of lipolysis is less in subcutaneous abdominal adipocytes than in visceral adipocytes.[29-31] This supports the findings of Abate et al[6,16] in relation to insulin resistance, but apoB kinetics were not examined in their study. Because the quantity of total subcutaneous adipose tissue was greater than visceral adipose tissue mass in our subjects, the former would have made a greater contribution to both the overall circulating flux of NEFAs and, in turn, to peripheral insulin resistance.[3] Peripheral insulin resistance may decrease the clearance of VLDL-apoB by decreasing the expression and activity of endothelial-bound

Table 4. Partial Correlations Adjusted for TATM (A) and HOMA Score (B) Between Adipose Tissue Compartments and VLDL-apoB Kinetic Variables

	(A)			(B)			
	Intraperitoneal ATM	Retroperitoneal ATM	Subcutaneous ATM	Intraperitoneal ATM	Retroperitoneal ATM	Subcutaneous AATM	Total ATM
VLDL-apoB	.491*	.437	.226	.318	.284	.192	−.526†
ASR of VLDL-apoB	.588‡	.548§	.108	.445	.347	−.001	−.034
FCR of VLDL-apoB	.114	.256	−.076	−.112	−.087	−.301	−.488*

*$P = .08$.
†$P = .07$.
‡$P < .05$.
§$P = .053$.

lipoprotein lipase.[32,33] Our findings with both external and internal abdominal fat are consistent with the hypotheses that visceral adipocytes chiefly regulate hepatic VLDL-apoB secretion and subcutaneous adipocytes VLDL-apoB catabolism.

The method for measuring total adipose tissue mass in the present study was based on bioelectrical impedance, and this may be less accurate than imaging and densitometric techniques. However, we standardized our method by studying men only, in the resting phase, in a temperature-controlled room, and after bladder emptying.[15] With such a standardized protocol, bioelectrical impedance has been closely correlated with hydrodensitometry.[34] More detailed information could have been obtained by studying a large number of subjects and using insulin clamp and fatty acid turnover methods. We did not study VLDL subfractions, but would expect that the adipose tissue mass associations reported would be strongest with $VLDL_1$ than with $VLDL_2$-apoB.[23] The unaccounted variances in VLDL-apoB kinetics in our study might have been explained by other factors, such as genetic mutations in apoB, microsomal triglyceride-transfer protein, or lipoprotein lipase,[35] as well as by variations in the hepatic delivery of lipid substrates (triglyceride, cholesterol, fatty acids) via both the exogenous and endogenous pathway of lipoprotein transport.[11,12] These factors, as well as the contributory role of variations in habitual dietary intake, including alcohol, and exercise patterns merit further examination.[19]

This kinetic study, although small in size, affords a plausible explanation as to why central or visceral fat accumulation may increase the risk of cardiovascular disease in non-obese men.[1,2] However, our preliminary observation evidently needs to be confirmed with a larger sample size. The potential importance of our findings relates to the fact that hepatic oversecretion of apoB has been associated with coronary disease.[8,9] Plasma apoB concentrations have also been shown to be a significant predictor of cardiovascular risk in patients with or without insulin resistance.[8,10] Visceral fat accumulation may, however, also increase cardiovascular risk by non–lipid-related mechanisms.[1,4] We showed that the global distribution of adipose tissue is also potentially important in regulating catabolism of VLDL-apoB and contributing to dyslipidemia in men who are not ostensibly obese. Whether the relative importance of visceral, subcutaneous, and total adipose tissue mass in determining the kinetics of VLDL-apoB extend to the turnover of LDL or HDL lipoproteins in non-obese subjects requires investigation. Further studies should also explore these associations in women and in obese and diabetic subjects.

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