Interrelationships Between the Kinetics of VLDL Subspecies and HDL Catabolism in Abdominal Obesity: A Multicenter Tracer Kinetic Study

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Context: Low plasma high-density lipoprotein (HDL) cholesterol is a major abnormality in abdominal obesity. This relates due to accelerated HDL catabolism, but the underlying mechanism requires further elucidation. The relationships between HDL catabolism and other variables that may be modified in abdominal obesity, such as very low-density lipoprotein (VLDL) subspecies ($VLDL_1$, $VLDL_2$) kinetics, liver fat, or visceral adiposity, remain to be investigated.

Objectives: Our aim was to study the associations between HDL apolipoprotein (apo)-A-I fractional catabolic rate (FCR) and the kinetics of VLDL subspecies and estimates of liver and visceral and sc fat.

Design: We carried out a multicenter in vivo kinetic study using stable isotopes (deuterated leucine and glycerol) in 62 individuals with abdominal obesity.

Results: In a multivariate analysis, among the morphological and biological parameters that may predict apoA-I FCR, liver fat ($\beta = .400$, $P = .003$), and $VLDL_1$-apoB ($\beta = .307$, $P = .020$) were independently associated with apoA-I FCR. In a multivariate analysis, among the kinetic parameters, $VLDL_1$-triglycerides (TGs) indirect FCR ($\beta = -.357$, $P = .001$), $VLDL_1$-TG production rate ($\beta = 0.213$, $P = .048$), and apoA-II FCR ($\beta = .667$, $P < .0001$) were independently associated with apoA-I FCR. After adjustment for VLDL1-TG production rate, liver fat was no more correlated with apoA-I FCR. No association between apoA-I FCR and visceral fat was observed.

Conclusions: We show that $VLDL_1$ is an important independent determinant of apoA-I FCR and more precisely that apoA-I FCR is independently associated with both catabolism and the production of $VLDL_1$-TG. In addition, we show an association between liver fat and apoA-I FCR that is mostly mediated by $VLDL_1$-TG production. These data indicate that, in abdominal obesity, dysfunctional $VLDL_1$ metabolism is an important modulator of HDL apoA-I catabolism. (***J Clin Endocrinol Metab*** **99: 4281–4290, 2014)**

Abdominal obesity is part of the metabolic syndrome and is strongly associated with insulin resistance, dyslipidemia, and increased cardiovascular risk (1–4). Low high-density lipoprotein (HDL) cholesterol is a main feature of the dyslipidemia associated with abdominal obesity (5) that has been shown to be a main risk factor for cardiovascular disease in metabolic syndrome (3, 6). In vivo kinetic studies performed in abdominally obese in-

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Abbreviations: apo, apolipoprotein; AU, arbitrary unit; CETP, cholesteryl ester transfer protein; FCR, fractional catabolic rate; HDL, high-density lipoprotein; HDL-C, HDL cholesterol; HOMA-IR, homeostasis model assessment index of insulin resistance; LpA, lipoprotein A; PLTP, plasma phospholipd transfer protein; PR, production rate; TG, triglyceride; VLDL, very low-density lipoprotein.

dividuals have shown that low plasma concentration of HDL cholesterol is the consequence of increased HDL catabolism (7–9). However, among abdominally obese subjects, there is a large variability in apolipoprotein (apo)-A-I fractional catabolic rate (FCR) that requires investigation.

We have previously shown that HDL-apoA-I catabolism is positively correlated with very low-density lipoprotein (VLDL)-apoB production rate (8). However, some questions remained unanswered. Indeed, the link between apoA-I FCR and VLDL subspecies, whose evaluation is critical to the metabolic syndrome or type 2 diabetes, has not been studied. Lipoprotein kinetic studies have shown that VLDL are metabolically heterogeneous, with accumulating evidence demonstrating that both the production and catabolism of large triglyceride-rich $VLDL_1$ (Sf 60–400) and smaller cholesterol-rich $VLDL_2$ (Sf 20–60) are regulated independently of each other (10). The separate evaluation of $VLDL_1$ and $VLDL_2$ metabolism is important in the metabolic syndrome or type 2 diabetes, conditions in which the hepatic oversecretion of VLDLs is mainly due to increased secretion of the triglyceride-rich $VLDL_1$ particles (11, 12). Thus, it is important to analyze precisely the kinetic associations between HDL-apoA-I and both $VLDL_1$ and $VLDL_2$ lipoproteins.

$VLDL_1$ secretion has been shown to be positively correlated with liver fat and visceral fat (11). However, liver fat and visceral fat were not determined in previous kinetics studies of HDL-apoA-I, and it is not clear whether the association between HDL-apoA-I catabolism and the VLDL (or $VLDL_1$) secretion rate is a direct one or is indirectly mediated by the extent of ectopic fat in the liver and visceral/sc regions of the abdomen.

To extend our previous findings on the association between apoA-I and VLDL kinetics, we investigated in a relatively large multicenter tracer study the relationships of apoA-I catabolism with the kinetics of VLDL subspecies and hepatic, visceral, and sc fat compartments in abdominally obese individuals.

Research Design and Methods

Study cohort

Sixty-two subjects were recruited at three study centers according to the following inclusion criteria: men or postmenopausal women, 35–65 years of age, BMI greater than 25 kg/m^2 and less than 40 kg/m^2, abdominal obesity according to National Cholesterol Education Program/Adult Treatment Panel III (waist circumference >88 cm for women and >102 cm for men), and at least one lipid abnormality (plasma triglycerides >1.7 mmol/L and <4.5 mmol/L and/or HDL cholesterol <1.29 mmol/L for women and <1.03 mmol/L for men).

Exclusion criteria were HDL cholesterol below 0.6 mmol/L, total cholesterol above 6.5 mmol/L or genetic hyperlipidemia, apoE2/E2 or apoE4/E4 homozygosity, type 2 diabetes treated with oral agents and/or insulin, a history of cardiovascular disease, systolic blood pressure above 160 mm Hg or diastolic blood pressure above 95 mm Hg, a history of surgical procedures for weight loss, the presence of any clinically significant endocrine disease, severe hepatic impairment (aspartate aminotransferase or alanine aminotransferase greater than 3 times the upper limit of normal) or renal function (creatinine clearance <30 mL/min), or proteinuria (>30 mg/dL). Subjects were not allowed any lipid-lowering drugs, antiobesity drugs, nonselective β-blockers, or agents known to affect lipid metabolism. Individuals with histories of alcohol and/or drug abuse, current smoking, or smoking cessation within the past 3 months were also excluded.

Subjects were advised to follow a weight-maintenance diet for 6 weeks before the kinetic studies. Body weight was measured with participants wearing undergarments or very light clothing and no shoes. Subjects with greater than 3% variation in weight during this period were excluded from the study. Waist circumference was recorded at the midpoint between the lower rib margin and the iliac crest. Three consecutive readings were taken and the mean was recorded.

Study design

The protocol included three study visits comprising a fasting kinetic study, determination of intraabdominal fat depots, and a heparin test on separate dates. The ethics committee at each site approved the study design and each subject gave written informed consent before participation in the study (trial registered as number NCT00408148).

Kinetic protocol, isolation of lipoproteins, and biochemical analyses

The subjects were admitted at 7:30 AM and baseline blood samples for the kinetic study and biomarkers (apoA-I, apoA-II, apoB, apoCIII, apoE, lipoprotein A (LpA)-I, glucose, insulin, and LDL particle size) were taken. At 8:00 AM, a bolus injection of [1,1,2,3,3-$^2H_5$]glycerol (500 mg) and [5,5,5-$^2H_3$]leucine (7 mg/kg) was given and blood drawn as previously described (13). Isolation of $VLDL_1$ and $VLDL_2$ and measurements of isotopic enrichment of leucine in apoB and glycerol in triglycerides were performed as previously described (13). Total apoB and triglyceride content in $VLDL_1$ and $VLDL_2$ were determined at 0, 4, and 8 hours after tracer injection. Biochemical analyses were performed and LDL peak size was measured as previously described (14).

Isolation of apolipoproteins and glycerol: measurement of isotopic enrichment

$VLDL_1$ and $VLDL_2$ were isolated from plasma as previously reported (13). HDL-apoA-I and HDL-apoA-II were isolated from plasma by sequential ultracentrifugation, separated by SDS-PAGE, and blotted on to a polyvinylidene fluoride membrane. ApoB (isolated from $VLDL_1$ and $VLDL_2$) and ApoA-I and apoA-II (isolated from HDL) were hydrolyzed, derivatized, and subjected to gas chromatography mass spectrometer to measure tracer leucine enrichment, as previously reported (13, 15).

Triglycerides were isolated from $VLDL_1$ and $VLDL_2$ fractions and the tracer glycerol enrichment determined as previously reported (13).

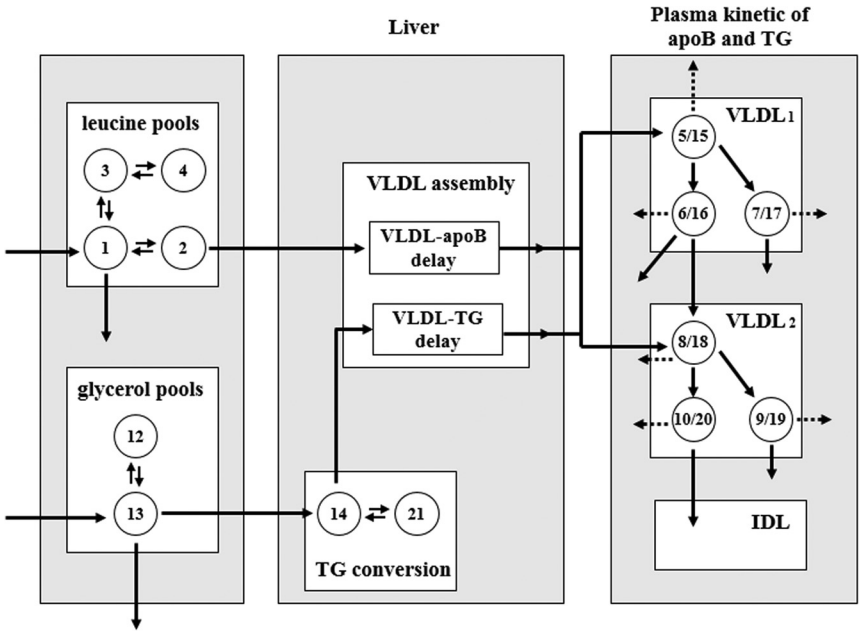

Figure 1. Model for kinetic analysis. The model includes separate modules for leucine and glycerol. The free leucine plasma kinetics is modeled by two pools (3 and 4) and a plasma compartment (1), which interchange materials with an intracellular compartment (2). Compartment 2 feeds the apolipoprotein B100 (apoB) synthetic machinery. For glycerol, the plasma compartment (13) is connected to a pooling compartment (12) and feeds TG synthesis, which consists of a fast pathway (14) and a slow pathway (21). The assembly of lipoprotein is modeled by separate delays for apoB and TG. The plasma kinetics of apoB and TG is modeled by a four-compartment hydrolysis chain, consisting of compartments 5, 6, 8, and 10 for apoB. Each apoB compartment, i, has an associated TG compartment, i+10, denoted as 15, 16, etc. Compartments 5/15 and 6/16 are associated with $VLDL_1$, together with a slowly decaying compartment 7/17. Compartments 8/18 and 10/20 together with the slowly decaying compartment 9/19 form the $VLDL_2$ module are shown. Solid arrows show the removal of whole particles and dashed arrows show the removal of TG.

Modeling

Apoprotein enrichment data were modeled using SAAM-II (The Epsilon Group) (16). The injected amount of $[^2H_3]$leucine and $[^2H_5]$glycerol, the leucine and glycerol pool sizes in $VLDL_1$ and $VLDL_2$, and the enrichment curves of plasma leucine and glycerol in $VLDL_1$ and $VLDL_2$ leucine and glycerol were used for a multicompartment model that allowed simultaneous modeling of apoB and triglycerides kinetics as previously described (13) and shown in Figure 1. ApoA-I modeling was performed using a multicompartment model as previously detailed (17). Briefly, the apoA-I model includes a four-compartment subsystem (compartments 1–4) that describes 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 apoA-I into plasma. Compartment 6 describes the kinetics of apoA-I in the plasma HDL fraction. ApoA-II modeling was performed using the apoA-I model. The FCR was equivalent to the loss from compartment 6, and the PR (mg/$kg^{-1} \cdot d^{-1}$) was calculated as the product of FCR and apoA-I (or apoA-II) pool sizes.

Determination of liver and sc and visceral fat

Liver fat was determined using proton magnetic resonance spectroscopy, and sc abdominal and visceral fat were measured by magnetic resonance imaging as previously described (11).

Analytical procedures

Fasting plasma glucose, triglycerides, HDL cholesterol, LDL cholesterol, and plasma liver enzymes were determined by standard procedures. Plasma apoA-I, apoA-II, apoB, apoE, and adiponectin were measured by an ELISA. Cholesteryl ester transfer protein (CETP) activity was determined as the capacity of a plasma sample to promote the transfer of radiolabeled cholesteryl esters ([^{3}H]cholesteryl ester) from [^{3}H]cholesteryl ester -HDL to apoB-containing lipoproteins (18). Plasma phospholipid transfer protein (PLTP) activity was determined as the capacity of a plasma sample to induce the transfer of radiolabeled [^{14}C]dipalmitoyl phosphatidylcholine from [^{14}C]dipalmitoyl phosphatidylcholine liposomes to an excess of isolated HDL (19). Plasma CETP and PLTP activity levels were related to the activity in a reference plasma analyzed in each run and are expressed in arbitrary units (AU).

Statistical analysis

Data are reported as mean ± SD. Statistical calculations were performed using the SPSS software package (SPSS Inc). For continuous variables, a Kolmogorov-Smirnov analysis was performed to test for normality. The Pearson correlation coefficients (r) were determined by linear regression analysis. Statistical significance of the correlation coefficients was determined by the method of Fisher and Yates. Multivariable analyses were performed by stepwise linear regression, including into the model all the variables that correlated in univariate analysis with $P \leq .10$ and potential confounding factors such as age, gender, and study center. For multivariable analyses, data that were not normally distributed were log transformed. A two-tailed probability level of $P = .05$ was accepted as statistically significant.

Results

Main characteristics of the abdominally obese population

The clinical and biochemical characteristics of the population are shown in Table 1. The subjects were abdominally obese, with a mean BMI of 32.3 ± 3.33 kg/m^2, large waist circumference (108 ± 8 cm), and high insulin resistance [mean homeostasis model assessment index of insulin resistance (HOMA-IR) value of 3.14 ± 1.88]. In addition, the subjects also exhibited the typical dyslipidemia of the metabolic syndrome with high plasma triglycerides and low HDL cholesterol (HDL-C) concentrations.

Table 1. Clinical and Biochemical Characteristics of the Abdominally Obese Individuals

	Mean ± SD
Age, y	51.5 ± 8.1
Gender, M/F	50/12
BMI, kg/m^2	32.3 ± 3.33
Waist, cm	108 ± 8
Hip, cm	110 ± 7
Total fat, %	29.7 ± 6.5
Liver fat, %	7.7 ± 6.6
Visceral fat, kg	2.50 ± 0.85
Subcutaneous fat, kg	27.02 ± 6.92
Total cholesterol, mmol/L	4.77 ± 0.72
TGs, mmol/L	1.98 ± 0.71
LDL cholesterol, mmol/L	2.90 ± 0.67
HDL cholesterol, mmol/L	0.97 ± 0.15
$VLDL_1$-TG, mg/dL	77 ± 34
$VLDL_1$-apoB, mg/dL	3.46 ± 1.76
ApoA-I, mg/dL	118 ± 14
ApoA-II, mg/dL	32 ± 5
Fasting glucose, mmol/L	5.63 ± 0.55
Plasma insulin, mU/L	12.21 ± 6.74
HOMA-IR	3.14 ± 1.88
CETP activity, AU	215 ± 32
PLTP activity, AU	4948 ± 1091

Abbreviations: BMI, body mass index; F, female; M, male.

Table 2. Kinetic Data for apoA-I, apoA-II, $VLDL_1$-TG, $VLDL_2$-TG, $VLDL_1$-apoB and $VLDL_2$-apoB Metabolism in the Abdominally Obese Individuals

	Mean ± SD [ranges]
ApoA-I FCR, pool · d^{-1}	0.29 ± 0.07 [0.14–0.44]
ApoA-I PR, mg · kg^{-1} · d^{-1}	15.16 ± 3.88 [8.11–23.53]
ApoA-II FCR, pool · d^{-1}	0.27 ± 0.08 [0.14–0.54]
ApoA-II PR, mg · kg^{-1} · d^{-1}	3.86 ± 1.37 [1.75–8.96]
$VLDL_1$-TG direct FCR, pool · d^{-1}	7.52 ± 5.50 [1.06–25.33]
$VLDL_1$-TG indirect FCR, pool · d^{-1}	2.72 ± 1.47 [0.69–7.94]
$VLDL_1$-TG total FCR, pool · d^{-1}	10.24 ± 5.84 [2.71–30.81]
$VLDL_1$-TG PR, mg · kg^{-1} · d^{-1}	292.92 ± 124.62 [121.96–625.75]
$VLDL_2$-TG FCR, pool · d^{-1}	14.02 ± 6.79 [5.41–34.63]
$VLDL_2$-TG PR, mg · kg^{-1} · d^{-1}	110.51 ± 53.30 [38.97–274.30]
$VLDL_1$-apoB direct FCR, pool · d^{-1}	2.90 ± 2.67 [0.00–9.56]
$VLDL_1$-apoB indirect FCR, pool · d^{-1}	4.63 ± 2.06 [1.14–10.07]
$VLDL_1$-apoB total FCR, pool · d^{-1}	7.53 ± 3.22 [2.48–18.51]
$VLDL_1$-apoB PR, mg · kg^{-1} · d^{-1}	8.22 ± 3.14 [3.60–16.45]
$VLDL_2$-apoB FCR, pool · d^{-1}	5.68 ± 1.96 [2.57–11.90]
$VLDL_2$-apoB PR, mg · kg^{-1} · d^{-1}	7.04 ± 2.76 [1.08–16.91]

Table 2 presents the kinetic data for apoA-I, apoA-II, $VLDL_1$-triglycerides (TGs), $VLDL_2$-TGs, $VLDL_1$-apoB, and $VLDL_2$-apoB of the abdominally obese population.

Correlations between main lipid, morphological, and kinetic parameters

The correlation coefficients between the main lipid, morphological, and kinetic parameters are shown in Table 3. apoA-I FCR was positively correlated with BMI, sc fat, liver fat, HOMA-IR, plasma TGs, $VLDL_1$-TGs and $VLDL_1$-apoB concentrations and negatively with HDL-C, HDL-C to apoA-I ratio, and HDL-C to apoA-II ratio. As far as kinetic parameters are concerned, apoA-I FCR was positively correlated with apoA-I production rate (PR), apoA-II FCR, apoA-II PR, $VLDL_1$-triglycerides PR, and $VLDL_1$-apoB PR. A borderline negative correlation was observed between apoA-I FCR and $VLDL_1$-TG indirect FCR ($r = -0.247$, $P = .054$).

Independent predictors for apoA-I catabolism

Because there was a strong correlation between apoA-I FCR and apoA-I PR ($r = 0.900$, $P < .0001$), we focused on independent factors regulating apoA-I FCR by multivariable analyses.

First, we analyzed the morphological and biological parameters that may predict apoA-I FCR. With this multivariable statistical model, liver fat and plasma TGs were found to be independent predictor variables for apoA-I FCR (Table 4, predictor variables, model 1). When plasma TGs were replaced into the model, by $VLDL_1$-TG concentration, both liver fat and $VLDL_1$-TG concentration were found to be independent predictor variables for apoA-I FCR (Table 4, predictor variables, model 2). When plasma TGs were replaced into the model, by $VLDL_1$-apoB concentration, both liver fat and $VLDL_1$-apoB concentration were found to be independent predictor variables for apoA-I FCR (Table 4, predictor variables, model 3). The introduction of both $VLDL_1$-TG and $VLDL_1$-apoB into the model gave identical results with those obtained with model 3.

Next, we analyzed the morphological and biological parameters that may be consequent variables of apoA-I FCR. With this multivariable statistical model, the HDL-C to apoA-I ratio and age were independently associated with apoA-I FCR (Table 4, consequential variables).

We finally analyzed the kinetic parameters that may be independently associated with apoA-I FCR. For this purpose, we performed a multivariable analysis using all kinetic parameters that were correlated in univariate analysis with apoA-I FCR with a value of $P < .10$, except apoA-I PR. apoA-I FCR was independently associated with apoA-II FCR ($P < .0001$), $VLDL_1$-TG indirect FCR ($P = .001$), and $VLDL_1$-TG PR ($P = .048$) (Table 5).

Together all three variables explained 64.7% of the variability in apoA-I FCR.

Liver fat, $VLDL_1$ production, and apoA-I catabolism

Because liver fat was associated with both apoA-I FCR and $VLDL_1$ production ($VLDL_1$-TG PR and $VLDL_1$-apoB PR) and apoA-I FCR was associated with $VLDL_1$ production ($VLDL_1$-TG PR and $VLDL_1$-apoB PR), we wanted to test whether the association between liver fat and apoA-I FCR was driven by $VLDL_1$ production. After adjustment for VLDL1-TG PR, liver fat was not significantly correlated with apoA-I FCR.

Discussion

In a large multicenter in vivo kinetic study in abdominally obese individuals, we show that kinetics of $VLDL_1$ is an important independent determinant for apoA-I FCR and more precisely that apoA-I FCR is independently associated with both catabolism and production of $VLDL_1$-TG. In addition, we show an association between liver fat and apoA-I FCR that is mostly mediated by the hepatic secretion of $VLDL_1$-TG.

Lipoprotein kinetic studies have shown that VLDLs are metabolically heterogeneous, with accumulating evidence demonstrating that both the production and catabolism of large $VLDL_1$ and smaller $VLDL_2$ are regulated independently (10). The separate evaluation of $VLDL_1$ and $VLDL_2$ metabolism is critical in the metabolic syndrome or type 2 diabetes in which variations in plasma TG concentrations are mainly related to differences in VLDL1, and hepatic overproduction of VLDLs is mainly due to increased hepatic secretion of $VLDL_1$ particles (11, 12). To enhance our understanding of the pathways leading to $VLDL_1$ and $VLDL_2$ and of the metabolic fate of these particles, we used a multicompartmental mathematical model that allows the kinetics of TGs and apoB100 in $VLDL_1$ and $VLDL_2$ to be simultaneously assessed after a bolus injection of glycerol and leucine. Using this model, we have gained further insight into the relationship between the metabolism of TG-rich lipoproteins and the catabolism of HDL and to show that $VLDL_1$ kinetics modulate HDL-apoA-I turnover.

We show that apoA-I FCR is independently associated with both catabolism and production of $VLDL_1$-TG, indicating that kinetics of $VLDL_1$ is an important independent determinant for apoA-I FCR. Our data indicate that $VLDL_1$-TG indirect FCR, representing the catabolism of $VLDL_1$ particles mediated by lipoprotein lipase, is an important factor that is negatively associated with HDL apoA-I FCR. Consistent with these data, increase in VLDL (or $VLDL_1$) FCR induced by n-3 polyunsaturated fatty acid supplementation or by rosuvastatin have been shown to be significantly associated with reduction of HDL-apoA-I catabolism (15, 20–22). Moreover, our data indicate that $VLDL_1$ PR is also an independent regulator of HDL-apoA-I catabolism. This is in line with data from a kinetic study performed in abdominally obese men that showed that the reduction of VLDL production by weight loss was accompanied by a significant decrease in HDL-apoA-I catabolism (23). Hence, our data strongly suggest that the hypercatabolism of HDL-apoA-I observed in abdominal obesity may be the consequence of dysregulated metabolism of $VLDL_1$ particles including both increased $VLDL_1$ production and reduced $VLDL_1$ catabolism. Increased production and reduced catabolism of $VLDL_1$ particles result in an expanded pool of $VLDL_1$, which are large triglyceride-rich lipoproteins. This may promote CETP-mediated triglyceride enrichment of HDL particles and, as a consequence, enhance HDL catabolism (24).

We also newly demonstrate that liver fat, assessed by proton magnetic resonance spectroscopy, is a positive and independent predictor of HDL apoA-I catabolism among morphological and biological variables. However, visceral fat was not found to be associated with HDL apoA-I FCR. Increased $VLDL_1$-apoB or $VLDL_1$-TG production rate has been shown to be positively correlated with liver fat (11). In our study, we showed that the correlation between liver fat and HDL apoA-I FCR was not significant after adjustment for VLDL1-TG PR. This suggests that the association between liver fat and apoA-I FCR is mostly mediated by the hepatic production of VLDL1-TG.

When analyzing the consequent variables associated with HDL apoA-I FCR, we found that HDL-C to apoA-I ratio was negatively associated with apoA-I catabolism. Thus, overcatabolism of HDL in abdominal obesity is associated with smaller size HDL particles with reduced cholesterol content. This is in line with the negative correlation between HDL particle size and apoA-I FCR previously reported (9). It is also consistent with increased triglyceride transfer from VLDL to HDL mediated by CETP that results in the formation of smaller triglyceride-rich HDL particles that are rapidly catabolized by hepatic lipase in insulin resistance.

In addition, we newly demonstrate an independent association between apoA-I and apoA-II catabolism. In several low HDL cholesterol states, apoA-I FCR and apoA-II FCR are modified to the same extent. For example, a parallel increase in apoA-I FCR and apoA-II FCR has been reported in patients with primary HDL deficiency (25) as well as in individuals with the metabolic syndrome (12). In addition, the link between apoA-I and apoA-II catabolism

Table 3. Pearson Correlation Coefficients in the 62 Abdominally Obese Individuals

	Age, y	BMI, kg/m^2	Visceral Fat	Subcutaneous Fat	Liver Fat	HOMA-IR	TGs
Age, y							
BMI, kg/m^2	0.126						
Visceral fat	0.035	0.461[a]					
Subcutaneous fat	0.021	0.813[b]	0.310[c]				
Liver fat	−0.053	0.567[b]	0.390[d]	0.481[b]			
HOMA-IR	0.173	0.490[b]	0.509[b]	0.469[a]	0.539[b]		
TGs	−0.040	0.385[d]	0.345[d]	0.246	0.353[d]	0.357[d]	
HDL-C	−0.042	−0.164	−0.148	−0.012	−0.50	−0.187	−0.312[c]
HDL-C/apoA-I	−0.122	−0.453[a]	−0.340[d]	−0.330[d]	−0.413[a]	−0.414[a]	−0.595[b]
HDL-C/apoA-II	−0.143	−0.298[c]	−0.309[c]	−0.283[c]	−0.199	−0.385[d]	−0.637[b]
$VLDL_1$-TG	−0.064	0.420[a]	0.461[a]	0.188	0.335[d]	0.403[d]	0.826[b]
VLDL1-apoB	0.016	0.411[a]	0.300[c]	0.259[c]	0.355[d]	0.300[c]	0.574[b]
apoA-I pool	−0.340[d]	0.486[b]	0.338[c]	0.474[a]	0.284[c]	0.117	0.266[c]
apoA-I FCR	−0.125	0.410[a]	0.129	0.334[d]	0.427[a]	0.271[c]	0.422[a]
apoA-I PR	−0.154	0.396[d]	0.031	0.367[d]	0.415[a]	0.235	0.434[a]
apoA-II pool	−0.355[d]	0.435[a]	0.412[a]	0.471[a]	0.284[c]	0.248	0.380[d]
apoA-II FCR	−0.158	0.310[c]	0.156	0.266[c]	0.307[c]	0.129	0.191
apoA-II PR	0.267[c]	0.336[d]	0.171	0.343[d]	0.329[d]	0.140	0.297[c]
$VLDL_1$-TG PR	0.049	0.440[a]	0.348[d]	0.509[b]	0.664[b]	0.377[d]	0.333[d]
$VLDL_2$-TG PR	−0.259[c]	0.280[c]	0.442[a]	0.230	0.179	0.156	0.142
$VLDL_1$-TG direct FCR	0.145	−0.048	−0.213	0.190	0.250	−0.097	−0.271[c]
$VLDL_1$-TG indirect FCR	−0.153	−0.086	0.031	0.018	−0.143	−0.147	−0.537[b]
$VLDL_1$-TG total FCR	0.097	−0.067	−0.193	0.183	0.200	−0.128	−0.390[d]
$VLDL_2$-TG FCR	−0.316[c]	0.060	0.119	0.054	0.134	0.051	−0.239
$VLDL_1$-apoB PR	−0.105	0.400[d]	0.323[c]	0.431[a]	0.574[b]	0.322[d]	0.430[d]
$VLDL_2$-apoB PR	−0.166	0.271[c]	0.335[d]	0.192	0.348[d]	0.165	0.255[c]
$VLDL_1$-apoB direct FCR	0.112	−0.005	−0.232	0.197	0.122	−0.053	−0.080
$VLDL_1$-apoB indirect FCR	0.021	−0.204	−0.122	−0.093	−0.163	−0.275[c]	−0.573[b]
$VLDL_1$-apoB total FCR	0.106	−0.135	−0.272[c]	0.102	−0.003	−0.219	−0.434[a]
$VLDL_2$-apoB FCR	−0.089	0.027	0.257[c]	−0.064	0.195	0.116	−0.112
CETP activity	0.336[#]	−0.028	−0.091	0.009	−0.081	0.177	−0.033
PLTP activity	−0.007	−0.018	−0.121	−0.027	−0.177	−0.120	0.145

	apoA-II FCR	apoA-II PR	$VLDL_1$-TG PR	$VLDL_2$-TG PR	$VLDL_1$-TG Direct FCR	$VLDL_1$-TG Indirect FCR	$VLDL_1$-TG Total FCR
Age, y							
BMI, kg/m^2							
Visceral fat							
Subcutaneous fat							
Liver fat							
HOMA-IR							
TG							
HDL-C							
HDL-C/apoA-I							
HDL-C/apoA-II							
$VLDL_1$-TG							
VLDL1-apoB							
apoA-I pool							
apoA-I FCR							
apoA-I PR							
apoA-II pool							
apoA-II FCR							
apoA-II PR	0.915[b]						
$VLDL_1$-TG PR	0.361[d]	0.331[d]					
$VLDL_2$-TG PR	0.267[c]	0.283[c]	0.229				
$VLDL_1$-TG direct FCR	0.077	−0.009	0.545[b]	−0.272			
$VLDL_1$-TG indirect FCR	0.209	0.156	−0.181	0.491[b]	0.107		
$VLDL_1$-TG total FCR	0.125	0.031	0.468[a]	−0.132	0.968[b]	0.353[d]	
$VLDL_2$-TG FCR	0.383[d]	0.355[d]	0.054	0.648[b]	−0.126	0.618[b]	0.037
$VLDL_1$-apoB PR	0.244	0.255[c]	0.758[b]	0.216	0.286[c]	−0.286[c]	0.197
$VLDL_2$-apoB PR	0.083	0.036	0.282[c]	0.497[b]	−0.099	0.003	−0.103
$VLDL_1$-apoB direct FCR	0.077	0.083	0.481[b]	−0.135	0.763[b]	0.020	0.723[b]
$VLDL_1$-apoB indirect FCR	−0.010	−0.122	−0.275[c]	0.045	0.310[c]	0.690[b]	0.465[a]
$VLDL_1$-apoB total FCR	0.058	−0.010	0.189	−0.094	0.772[b]	0.452[a]	0.840[b]
$VLDL_2$-apoB FCR	0.259[c]	0.149	−0.080	0.273[c]	−0.138	0.292	−0.056
CETP activity	−0.143	−0.197	0.083	−0.057	0.247	0.039	0.242
PLTP activity	−0.004	0.065	−0.095	−0.180	−0.181	−0.375[d]	−0.265[c]

VLDL1-apoB data were derived from 58 subjects and $VLDL_1$ TG kinetic data from 46 subjects.

[a] $P \leq .001$.

[b] $P \leq .0001$.

[c] $P < .05$.

[d] $P \leq .01$.

Table 3. Continued

	HDL-C	HDL-C/apoA-I	HDL-C/apoA-II	$VLDL_1$-TG	$VLDL_1$-apoB	apoA-I Pool	apoA-I FCR	apoA-I PR	apoA-II Pool
Age, y									
BMI, kg/m^2									
Visceral fat									
Subcutaneous fat									
Liver fat									
HOMA-IR									
TGs									
HDL-C									
HDL-C/apoA-I	0.646[b]								
HDL-C/apoA-II	0.560[b]	0.622[b]							
$VLDL_1$-TG	−0.213	−0.483[b]	−0.575[b]						
VLDL1-apoB	−0.105	−0.326[d]	−0.344[d]	0.706[b]					
apoA-I pool	0.328[d]	−0.056	−0.100	0.287[c]	0.299[c]				
apoA-I FCR	−0.340[d]	−0.512[b]	−0.385[d]	0.443[a]	0.455[a]	−0.223			
apoA-I PR	−0.029	−0.380[d]	−0.281[c]	0.414[a]	0.481[b]	0.206	0.900		
apoA-II pool	0.247	−0.087	−0.460[a]	0.433[a]	0.326[d]	0.824[b]	0.177	0.279[c]	
apoA-II FCR	−0.150	−0.292[c]	0.230	0.136	0.244	−0.121	0.672[b]	0.612[b]	0.303[c]
apoA-II PR	−0.226	−0.226	−0.352[d]	0.230	0.290[c]	0.123	0.606[b]	0.652[b]	0.580[b]
$VLDL_1$-TG PR	−0.205	−0.480[b]	−0.305[c]	0.307[c]	0.287[c]	0.127	0.512[b]	0.404[d]	0.248
$VLDL_2$-TG PR	−0.065	−0.268[c]	−0.291[c]	0.336[d]	0.064	0.325[d]	0.083	0.008	0.397[d]
$VLDL_1$-TG direct FCR	−0.098	−0.020	0.121	−0.458[a]	−0.253[c]	−0.247	0.054	−0.019	−0.219
$VLDL_1$-TG indirect FCR	0.083	0.195	0.181	−0.518[b]	−0.480[b]	0.047	−0.247	−0.281[c]	0.015
$VLDL_1$-TG total FCR	−0.071	0.030	0.159	−0.562[b]	−0.359[d]	−0.221	−0.012	−0.089	−0.202
$VLDL_2$-TG FCR	0.058	−0.051	−0.021	−0.085	−0.108	0.293[c]	0.053	0.017	0.275[c]
$VLDL_1$-apoB PR	−0.184	−0.401[d]	−0.302[c]	0.437[a]	0.367[d]	0.081	0.422[a]	0.347[d]	0.191
$VLDL_2$-apoB PR	−0.242	−0.307[c]	−0.193	0.360[d]	0.307[c]	0.068	0.190	0.088	0.038
$VLDL_1$-apoB direct FCR	0.066	−0.093	0.079	−0.277[c]	−0.288[c]	−0.104	0.075	0.094	−0.073
$VLDL_1$-apoB indirect FCR	0.002	0.247	0.330[d]	−0.640[b]	−0.521[b]	−0.211	−0.224	−0.292[c]	−0.306[c]
$VLDL_1$-apoB total FCR	0.056	0.081	0.277[c]	−0.613[b]	−0.547[b]	−0.222	−0.082	−0.109	−0.256[c]
$VLDL_2$-apoB FCR	−0.161	−0.129	0.027	−0.067	−0.056	−0.036	0.059	−0.073	−0.117
CETP activity	−0.177	−0.215	−0.106	−0.140	−0.072	−0.205	−0.076	−0.124	−0.149
PLTP activity	−0.057	−0.055	−0.216	0.130	0.180	0.048	−0.001	0.085	0.026

	$VLDL_2$-TG FCR	$VLDL_1$-apoB PR	$VLDL_2$-apoB PR	$VLDL_1$-apoB Direct FCR	$VLDL_1$-apoB Indirect FCR	$VLDL_1$-apoB Total FCR	$VLDL_2$-apoB FCR	CETP Activity	PLTP Activity
Age, y									
BMI, kg/m^2									
Visceral fat									
Subcutaneous fat									
Liver fat									
HOMA-IR									
TG									
HDL-C									
HDL-C/apoA-I									
HDL-C/apoA-II									
$VLDL_1$-TG									
VLDL1-apoB									
apoA-I pool									
apoA-I FCR									
apoA-I PR									
apoA-II pool									
apoA-II FCR									
apoA-II PR									
$VLDL_1$-TG PR									
$VLDL_2$-TG PR									
$VLDL_1$-TG direct FCR									
$VLDL_1$-TG indirect FCR									
$VLDL_1$-TG total FCR									
$VLDL_2$-TG FCR									
$VLDL_1$-apoB PR	−0.120								
$VLDL_2$-apoB PR	0.021	0.546[b]							
$VLDL_1$-apoB direct FCR	−0.113	0.383[d]	−0.346[d]						
$VLDL_1$-apoB indirect FCR	0.204	−0.223	0.197	−0.095					
$VLDL_1$-apoB total FCR	0.044	0.176	−0.162	0.771[b]	0.561[b]				
$VLDL_2$-apoB FCR	0.625[b]	−0.065	0.323[c]	−0.373[d]	0.322[d]	−0.104			
CETP activity	−0.14	−0.090	−0.107	0.085	0.102	0.136	−0.019		
PLTP activity	−264[c]	0.024	−0.082	0.030	−0.308[c]	−0.172	−0.160	−0.23	

Table 4. Mutivariable Analysis With apoA-I FCR as Dependent Variable (With Morphological and Biological Parameters)

Variables	β	t	*P* Value	r^2	r^2 Change
Predictor variables					
Model 1					
Liver fat	***0.404***	***3.42***	***.001***	***0.265***	
TGs	***0.361***	***3.07***	***.004***	***0.383***	***0.118***
BMI	0.201	1.49	.142		
Age,	−0.146	−1.31	.196		
Subcutaneous fat	0.157	1.23	.223		
Visceral fat	−0.130	−1.02	.311		
HOMA-IR	−0.072	−0.54	.591		
Gender	−0.023	−0.20	.840		
Model 2					
Liver fat	***0.414***	***3.29***	***.002***	***0.265***	
$VLDL_1$-TG	***0.295***	***2.35***	***.023***	***0.342***	***0.077***
BMI	0.217	1.50	.140		
Subcutaneous fat	0.182	1.38	.175		
Visceral fat	−0.165	−1.20	.235		
Age	−0.134	−1.13	.262		
HOMA-IR	−0.098	−0.68	.499		
Gender	0.009	0.07	.941		
Model 3					
Liver fat	***0.400***	***3.14***	***.003***	***0.265***	
$VLDL_1$-apoB	***0.307***	***2.42***	***.020***	***0.346***	***0.081***
BMI	0.218	1.51	.136		
Age	−0.163	−1.39	.171		
Subcutaneous fat	0.161	1.21	.232		
Visceral fat	−0.087	−0.66	.509		
HOMA-IR	−0.049	−0.35	.726		
Gender	−0.034	−0.28	.778		
Consequential variables (age and gender in the model)					
HDL-C/apoA-I	***−0.593***	***−5.49***	***<.0001***	***0.305***	
Age	***−0.248***	***−2.29***	***.026***	***0.365***	***0.060***
Gender	0.120	1.04	.301		
HDL-C/apoA-II	0.035	0.24	.810		
HDL-C	0.004	0.03	.975		
apoA-I pool	−0.002	−0.02	.984		

Abbreviations: β, standardized coefficient; BMI, body mass index. Significant parameter values are shown in bold and italic.

For predictor variables, model 1, total $r^2 = 0.383$. For predictor variables, model 2, total $r^2 = 0.342$. For predictor variables, model 3, total $r^2 = 0.346$. For consequential variables, total $r^2 = 0.365$. Age and gender in the model.

is also suggested by a study showing that apoA-I facilitates hepatic lipase-mediated hydrolysis in apoA-II containing HDL particles (26). Collectively, our data indicate a robust, direct relationship between the catabolism of apoA-I and apoA-II, consistent with the tight structural nexus of these apoproteins in biogenesis and the disposal of HDL particles.

In the present study, we observe a very strong association between apoAI FCR and apoAI PR that has previ-

Table 5. Mutivariable Analysis With apoA-I FCR as Dependent Variable (With VLDL Subspecies and apoA-II Kinetic Parameters)

Variables	β	t	*P* Value	r^2	r^2 Change
ApoA-II FCR	***0.667***	***6.32***	***<.0001***	***0.448***	
$VLDL_1$-TG indirect FCR	***−0.357***	***−3.58***	***.001***	***0.610***	***0.162***
$VLDL_1$-TG PR	***0.213***	***2.04***	***.048***	***0.647***	***0.037***
Study center	−0.193	−1.66	.104		
ApoA-II PR	−0.366	−1.41	.166		
Age	−0.115	−1.16	.252		
BMI	0.121	1.09	.280		
$VLDL_1$-apoB indirect FCR	0.155	1.09	.280		
Gender	0.059	0.58	.560		
$VLDL_1$-apoB PR	0.060	0.42	.676		

Abbreviations: β: standardized coefficient; BMI, body mass index. Total $r^2 = 0.647$ (age, gender, and center in the model). Significant parameter values are shown in bold and italic.

ously been reported (8). Although a direct mathematical link exists between PR and FCR because PR is calculated with FCR as a variable, we cannot exclude balancing feedback mechanisms between apoAI FCR and apoAI PR. However, this hypothesis needs further investigation.

We consider that the strong association between $VLDL_1$ kinetics and HDL-apoA-I catabolism has important implications. For instance, in conditions of abdominal obesity, the reduction of hepatic secretion of $VLDL_1$, and/or an increase in the catabolism of $VLDL_1$ by weight loss and physical exercise will regulate the catabolism of HDL, resulting in a long-term increase in HDL cholesterol. In addition, an increase in HDL-apoA-I catabolism can result in dysfunctional, proatherogenic HDL particles, with an impaired capacity to effect cellular cholesterol efflux and a reduced antioxidative and anti-inflammatory properties (27). Hence, lifestyle interventions, such as weight regulation and aerobic exercise, may correct HDL overcatabolism and dysfunctionality by decreasing the hepatic secretion of the $VLDL_1$ subspecies.

Our investigation has the limitations of a cross-sectional design. We studied more men than women and might have missed gender differences in the relationship between the kinetics of VLDL subspecies and HDL apoA-I. We did not study the kinetics of HDL subspecies or the turnover of LpA-I and LpA-I:A-II particles. This requires further investigation but would expect that an expanded $VLDL_1$ pool size would result in accelerate catabolism in all HDL particles, with a preferential reduction in smaller size particles (12).

In conclusion, we demonstrated that $VLDL_1$ is an important independent determinant for apoA-I FCR and more precisely that apoA-I FCR is independently associated with both catabolism and production of $VLDL_1$-TG. In addition, we show an association between liver fat and apoA-I FCR that is mostly mediated by $VLDL_1$-TG production. These data indicate that, in abdominal obesity, dysfunctional $VLDL_1$ metabolism is an important modulator of HDL apoA-I catabolism.

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