Kinetic and Related Determinants of Plasma Triglyceride Concentration in Abdominal Obesity: a Multicenter Tracer Kinetic Study

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Running title: Predictors of $VLDL_1$-TG metabolism in obesity

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ABSTRACT

***Objectives*:** Patients with obesity and diabetes have increased risk for cardiovascular disease. A major cause is an atherogenic dyslipidemia related primarily to elevated plasma concentrations of triglyceride-rich lipoproteins. The aim of this study was to clarify determinants of plasma triglyceride concentration. We focused on factors that predict the kinetics of $VLDL_1$ triglycerides.

Approach and Results: A multicentre study employing dual stable isotopes (deuterated leucine and glycerol) and multicompartmental modelling was performed to elucidate the kinetics of TG and apoB in $VLDL_1$ in 46 subjects with abdominal obesity and additional cardiometabolic risk factors. Results showed that plasma triglyceride concentrations were dependent on both the secretion rate [r=0.44, P<0.01; r=0.45, P<0.01] and fractional catabolism [r=0.49, P<0.001; r=0.55, P<0.001] of $VLDL_1$-TG and apoB. Liver fat mass was independently and directly associated with secretion rates of $VLDL_1$-TG [r=0.56, P<0.001] and apoB [r=0.53, P<0.001]. Plasma apoC-III concentration was independently and inversely associated with the fractional catabolisms of $VLDL_1$-TG [r=0.48, P<0.001] and apoB [r=0.51, P<0.001].

Conclusions: Plasma TG concentrations in abdominal obesity are determined by the kinetics of $VLDL_1$ subspecies, catabolism being mainly dependent on apoC-III concentration and secretion on liver fat content. Reduction in liver fat and targeting apoC-III may be an effective approach for correcting TG metabolism atherogenic dyslipidaemia in obesity.

Nonstandard Abbreviations and Acronyms:

apo	apolipoprotein
FCR	fractional catabolic rate
FDCR	fractional direct catabolic rate
FTR	fractional transfer rate
LPL	lipoprotein lipase
SR	secretion rate
TG	triglycerides
TRLs	triglyceride-rich lipoproteins

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of morbidity and mortality, despite recent significant advances in management strategies to lessen CVD risk factors.[1] A major cause is an atherogenic dyslipidemia related primarily to elevated plasma concentrations of triglyceride-rich lipoproteins (TRLs).

Elevation of $VLDL_1$ triglycerides is the major determinant of plasma triglyceride concentration in normal subjects and insulin resistant individuals.[2] The plasma concentration of $VLDL_1$ is a function of hepatic secretion and the clearance of triglyceride-rich remnant particles from the circulation.[3, 4] We have earlier shown that liver fat and hyperglycemia are associated with increased secretion $VLDL_1$ particles from the liver, and that suppression of $VLDL_1$ secretion by insulin is impaired in subjects with increased hepatic fat content leading to oversecretion of $VLDL_1$ particles.[5, 6] However, the mechanism(s) for the disturbed removal of $VLDL_1$-triglycerides are less clarified.

The enzyme LPL has a critical role in hydrolyzing plasma triglycerides and in hepatic uptake of remnant particles.[7] Upon production by the underlying parenchymal cells, LPL is transported and attached to the capillary endothelium by the protein GPIHBP1.[8] The critical role of LPL for the hepatic removal of remnant particles originating from TRLs, and for the conversion of large $VLDL_1$ particles into smaller $VLDL_2$ particles and intermediate–density lipoprotein (IDL),[9] was recently illustrated in studies in subjects with LPL gene mutations.[10] Because LPL is rate limiting for plasma triglyceride clearance and tissue uptake of fatty acids, the activity of LPL is carefully controlled via multiple mechanisms at both the transcriptional and post–translational level.[7, 11] Whereas LPL is predominantly a triglyceride lipase, hepatic lipase is both a phospholipase and a triglyceride lipase that plays an important role in the conversion of VLDL to LDL.[12]

Insulin is a major regulator of LPL synthesis and activity.[11] Several apolipoproteins including the apoC family, apoA5, apoE and angiopoietin–like 4 (Angptl4) are also known to modulate LPL activity and action.[11, 13-18] In particular apoC-III has emerged as a clinically important predictor for hypertriglyceridemia, as it both inhibits LPL–catalyzed hydrolysis of TRLs[19, 20] and attenuates the uptake of TRL remnants by the liver.[21, 22] In addition, also the cholesterol transfer protein (CETP) has been shown to affect TRL composition and metabolism.[23, 24] Thus, the prevailing idea is that the concerted actions of lipolytic enzymes, apolipoproteins and transfer proteins determine TRL metabolism and thus plasma triglyceride concentrations. However, there is a clear lack of data on the interplay between these key players and $VLDL_1$-triglyceride kinetics.

In this study, we performed lipoprotein kinetic studies in 46 middle–aged men and women with abdominal obesity and additional cardiometabolic risk factors to clarify determinants of plasma triglyceride concentration. Specifically we focused on factors associated with $VLDL_1$ triglyceride kinetics.

MATERIALS AND METHODS

Materials and Methods are available in the online-only Data Supplement

RESULTS

Characteristics of the abdominally obese population—The clinical and biochemical characteristics of 46 middle–aged men (*n*=37) and women (*n*=9) are shown in Table 1. The subjects were abdominally obese, with a mean BMI of 32.3±3.3, large waist circumference (108.5±8.5 cm) and high insulin resistance (mean HOMA–IR value of 3.2±2.0). In addition, the subjects exhibited the typical dyslipidemia of the metabolic syndrome with high plasma triglycerides and low HDL cholesterol. Table 2 presents the kinetic data for triglycerides and apoB100 in $VLDL_1$ particles and supplementary Table I summarizes the kinetic data for $VLDL_2$. The kinetics of $VLDL_1$–triglycerides and $VLDL_1$-apoB were highly correlated (supplementary Figures I and II) across a large range of kinetic parameters (Table 2).

The kinetic parameters describe secretion of lipoproteins and triglycerides from the liver ($VLDL_1$-

triglyceride and $VLDL_1$-apoB secretion rates; SR) and removal of TG from $VLDL_1$.The triglycerides are removed from $VLDL_1$ by three pathways: particles transferred from $VLDL_1$ to $VLDL_2$ due to lipolysis (characterized by the $VLDL_1$ fractional transfer rate; FTR), particles removed by direct catabolism (i.e., $VLDL_1$ particle uptake by cells), and TG removal by hydrolysis. The latter two are combined into the fractional direct catabolic rate (FDCR). Total catabolism of $VLDL_1$ is summarized as FCR.

$VLDL_1$–triglyceride kinetics are linked to apoC-III, but not to LPL or hepatic lipase—Table 2 shows the correlations between kinetic parameters of triglycerides and apoB in $VLDL_1$. The catabolism of $VLDL_1$–triglycerides, calculated as the fractional clearance rate (FCR), did not correlated with any of the conventional cardiometabolic risk-factors (supplementary Table II), but was strongly correlated with plasma apoC-III concentration. As expected, apoC-III concentration was tightly associated with plasma triglyceride concentration ($r=0.84$, $P<0.001$) (supplementary Table II).

In contrast, neither activity nor mass of post-heparin lipoprotein lipase which is regulated by apoC-III correlated with the plasma triglyceride concentration or $VLDL_1$-triglyceride kinetics (Figure 1 A-B). Furthermore, hepatic lipase activity did not correlate with $VLDL_1$–triglyceride catabolism (Table 3). However, LPL mass correlated with $VLDL_2$-TG and apoB FCR (supplementary Table III).

ApoC-II correlated with apoC-III (supplementary Table II), but did not correlate with $VLDL_1$-triglyceride kinetics (Table 3). ApoE correlated strongly with apoCII, apoCIII and plasma triglycerides (supplementary Table II). Surprisingly, apoA5 did not show a correlation with plasma triglyceride concentration or $VLDL_1$ particle kinetics (Table 3 and supplementary Table II). In a stepwise multivariable regression, which included variables with univariable correlation $P<0.10$, only apoC-III remained an independent predictor of $VLDL_1$-TG FCR and apoC-III and hepatic lipase were independent predictors of $VLDL_1$-apoB FCR (supplementary Table IV C-D). ApoC-III and apoE also correlated with the $VLDL_2$-TG FCR (supplementary Table III).

Indices of $VLDL_1$-TG catabolism are stronger predictors of plasma triglycerides than secretion rate—The concentration of triglycerides in plasma is the balance between secretion and removal of $VLDL_1$–triglycerides. Thus, the concentration of plasma triglycerides can be illustrated as the consequence of a "*Synthesis pathway"* and a *"Clearance pathway"* (Figure 2).

$VLDL_1$–triglyceride secretion was strongly correlated ($P<0.01$) with liver fat content, total fat mass and body fat, and glucose (see Table 2 for *r* and P values). In stepwise multivariable regression, only liver fat content ($P<0.01$) and total fat mass ($P<0.05$) were independent predictors of $VLDL_1$–triglyceride secretion (adjusted $r^2=0.34$) (supplementary Table IV A). For $VLDL_1$–apoB, only liver fat content ($P<0.001$) was an independent predictor of secretion (adjusted $r^2=0.25$) (supplementary Table IV B). Secretion rates explained 19-20% of the variation in plasma triglyceride concentrations in the study subjects (*i.e.,* the r^2-value of $VLDL_1$-TG SR in Table 3). Importantly, the kinetic parameters in the *"Clearance pathway"* were stronger predictors of plasma triglycerides than secretion. The FCR of $VLDL_1$–triglycerides explained 24% of the variation in plasma triglycerides (Table 3), whereas the FTR explained 37% (Table 3). The corresponding percentages for $VLDL_1$–apoB were 30% and 46% (Table 3). In addition, direct clearance (*i.e.,* removal of whole particles and removal of lipids by hydrolysis of $VLDL_1$–triglycerides) explained only 9% (Table 3).

In a multivariable regression model, $VLDL_1$-triglyceride kinetics explained 76% of the variation in the total plasma triglycerides (supplementary Table IV E). The corresponding number for $VLDL_1$–apoB was 63% (supplementary Table IV F). Thus, in subjects with abdominal obesity and dyslipidemia, the dynamics of $VLDL_1$ particles has a profound effect on the plasma triglyceride concentration. In contrast to $VLDL_1$ kinetics, $VLDL_2$ kinetics had little predictive power on plasma triglycerides (supplementary Table III).

DISCUSSION

We carried out a large kinetic study in subjects with abdominal obesity and additional cardiometabolic risk factors to clarify the predictors of the kinetics of $VLDL_1$-triglycerides. Our results show that kinetic parameters of $VLDL_1$-TG catabolism are stronger determinants of the plasma triglyceride concentration than indices for the increased secretion of $VLDL_1$ particles. The catabolism of $VLDL_1$–

triglycerides did not correlate with any of the conventional cardiometabolic risk factors, but showed a strong correlation with the plasma concentration of apoC-III and apoE. Their plasma concentrations were also strongly and directly associated with the plasma triglyceride concentration.

The prevailing notion regarding the function of apoC-III is that it is an antagonist to apoC-II and apoE, impairing intravascular lipolysis by LPL and liver clearance of apoB lipoproteins. This concept is supported by *in vitro* evidence showing that apoC-III noncompetitively inhibits LPL[25, 26] and by the markedly accelerated catabolism of TRLs in human subjects with a genetic deficiency of apoC-III[19]

Also, apoC-III strongly inhibits the in vitro binding of apoB lipoproteins to the hepatic LDL receptor.[22] Recently, loss–of–function mutations in apoC-III were shown to associate with reductions in the risk of ischemic vascular disease and ischemic heart disease in the general population.[27, 28] Thus, apoC-III emerges as an important drug target for reducing residual cardiovascular risk.[29] Indeed, inhibition of apoC-III by antisense oligonucleotides has recently been shown to reduce plasma levels of apoC-III and triglycerides in humans.[30] In addition, pharmacological intervention has been shown to influence the apoCIII levels in parallel with decreased plasma triglycerides.[31-33]

However, the molecular mechanisms for how apoC-III induces hypertriglyceridemia are complex and further research is required.[34] For example, in a Phase 2 study, three LPL deficient patients were treated with an inhibitor of APOC3 messenger RNA. After 13 weeks, plasma apoC-III levels were reduced by 71 to 90% and triglyceride levels by 56 to 86%.[35] These data support the role of apoC-III as a key regulator of LPL-independent pathways of triglyceride metabolism.[36, 37] Consistent with this result, kinetic studies indicate that VLDL with apoC-III show faster, not slower, lipolytic conversion rates to smaller lipoproteins than particles without it.[38]

Our results also showed that the plasma concentration of apoC-II correlated with the plasma concentration of apoC-III in line with our previous findings.[2] However, it did not correlate with turnover of $VLDL_1$-triglycerides. Interestingly, the lipoprotein concentrations of apoC-II and apoC-III are independently regulated in VLDL particles. This independence leads to varying ratios of the two apolipoproteins. This is important since the apoCII/apoCIII ratio may be a critical factor in the regulation of lipolysis of VLDL particles.[31, 39]

ApoE, a major ligand for the LDL receptor, is considered to promote hepatic clearance of chylomicron and VLDL remnants.[40] However, apoE correlated strongly with apoCII, apoCIII and plasma triglycerides. An explanation for this might be that apoC-III has been proposed to override the positive effects of apoE on clearance of TLRs, when both are present.[41] ApoA5 is proposed to play an important role in regulating the plasma triglyceride levels, but it did not correlate with plasma triglycerides or kinetics of $VLDL_1$. This data do not support a role for plasma apoA5 in regulating $VLDL_1$ kinetics, and is in agreement with results by Chan et al.[42]

An unexpected finding in our study was that neither LPL activity nor mass correlated with $VLDL_1$–TG clearance. These results may indicate that either LPL is not regulating the rate of lipolysis, or that LPL activity measurements do not adequately reflect the *in vivo* rate of lipolysis. The measurements were performed after injection of heparin, a procedure that releases LPL from endothelium.[43, 44] However, the physiopathological relevance of this post-heparin lipolysis assay has been questioned because it has never been demonstrated that the bulk of endothelium–bound LPL is physiologically active.[45] It has been recently shown that a small part of LPL is associated to circulating lipoproteins in nonheparinized plasma, raising the possibility that the lipolysis mediated by this circulating LPL might reflect the overall LPL–dependent triglyceride hydrolysis in plasma.[45-49] It has further been proposed that LPL bound to VLDL particles is not only responsible for hydrolyzing apoB lipoproteins at the endothelium but also facilitating receptor-mediated uptake during circulation.[50]

The protocol for the analysis of the postheparin LPL activity was carefully standardized. This is critical since lipolysis and clearance of TRLs are enhanced early after heparin injection. Later, when heparin and lipase concentrations have decreased, both lipolysis and particle clearance are slower than in controls. Indeed, heparin treatment in humans leads to delayed clearance of chylomicron TGs and particles due to a temporary depletion of endothelial LPL with impaired lipolysis of TG-rich lipoproteins.[51]

We neither found any correlation between adiponectin and VLDL kinetics despite the fact that plasma adiponectin has been proposed to be an important regulator of basal VLDL-TG secretion and

catabolism.[52-54] The reason for this difference is unclear.

This study represents the largest kinetic study performed to date, but it has some limitations. Our results are based on correlational analyses, and need to be formally tested in intervention studies that specifically target apoB and apoC-III secretion. Furthermore, the study subjects are extensively phenotyped obese Caucasians. Thus, the results may not apply to other patient groups. In addition, it could be hypothesized that exclusion of hypertriglyceridemic individuals with plasma TG above 4.5 mmol/L may have affected the relationship between LPL mass or activity and VLDL kinetic parameters. We also combined women (n=9) and men (n=37) in the analyses, but the results were very similar when men only were analyzed (supplementary Table V). To improve the precision of the kinetic estimates, we used a combined model in which the triglyceride and apoB kinetics were estimated together. For comparison, we also modeled the triglyceride and apoB kinetics independently and the two approaches showed good agreement (supplementary figure II). This result is in line with data by Ramakrisnan et al showing that TG and apoB kinetics are identical along the VLDL delipidation.[55]

In conclusion, our results further show that the turnover of $VLDL_1$–triglycerides is linked to apoC-III, but not to post-heparin LPL activity of LPL mass, and that the $VLDL_1$-triglyceride clearance is a stronger determinant of the plasma triglyceride concentration than increased secretion of TRLs. These results recognize apoC-III as a key target for reducing residual cardiovascular risk, and question the clinical relevance of measuring post-heparin LPL activity except for identifying subjects with LPL deficiency and suspected functional mutations in LPL.

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SIGNIFICANCE

Despite tremendous success in lowering age-adjusted morbidity and mortality from atherosclerotic cardiovascular disease, the disease has not been eradicated, not even for patients on maximal medical therapy. In particular, subjects with obesity, type 2 diabetes and insulin resistance remain at a high risk for CVD. A major cause is an atherogenic dyslipidemia, which consists of elevated plasma concentrations of both fasting and postprandial triglyceride-rich lipoproteins (TRLs), small dense low-density lipoprotein (LDL) and low high-density lipoprotein (HDL) cholesterol. The different components of the dyslipidemia are metabolically linked and driven by increased plasma concentration of triglyceride-rich lipoproteins (TRLs). Thus, the underlying disturbances are hepatic overproduction of large triglyceride-rich $VLDL_1$ and delayed clearance of TRLs. The aim of this study, which represents the largest kinetic study performed until date, was to clarify determinants of plasma triglyceride concentration. We focused on factors that predict the kinetics of $VLDL_1$ triglycerides.

FIGURE LEGENDS

Figure 1. ***Correlations between postprandial lipoprotein lipase (LPL) activity and mass vs. $VLDL_1$-TG FCR.*** Correlations for between $VLDL_1$-TG FCR and postprandial measurements of (A) LPL activity (r=0.08, NS) or (B) mass (r=0.05, NS). *n*=46 in all correlations.

Figure 2. ***Key parameters linked to $VLDL_1$-TG secretion and catabolism ~~turnover~~.*** In a stepwise multivariable regression analysis, only liver fat content (P<0.01) and total fat mass (P<0.05) remained independent predictors of $VLDL_1$–triglyceride secretion rate. The plasma concentration of apoC-III was very tightly linked with plasma TG and the fractional catabolism of $VLDL_1$-TG. Indices of catabolism were stronger predictors of plasma triglycerides than parameters of secretion. In a multivariable regression model, $VLDL_1$-TG kinetics explained 76% of the variation in the total plasma triglycerides (supplementary Table IV E). The commonly observed associations between liver fat and fat mass *vs* plasma TG (dotted lines) are likely secondary and mediated via $VLDL_1$ SR. Likewise, the direct effect of apoC-III on plasma TG (dotted line), is likely explained by effect(s) of apoC-III beyond LPL-independent pathways of triglyceride metabolism.[36, 37]

Table 1. Characteristics of subjects studied

	Mean ± SD
Age (Years)	51 ± 8
Gender (F/M)	9/37
Weight (kg)	101.1 ± 14.1
BMI (kg/m^2)	32.3 ± 3.3
Waist (cm)	108.5 ± 8.5
Fat mass (kg)	30.5 ± 7.1
Liver fat (%)	5.8 (0.6–33.3)
Subcutaneous fat (cm^3)	4476 ± 1485
Visceral fat (cm^3)	2526 ± 920
Glucose (mmol/L)	5.5 (4.3–7.7)
Insulin (mU/L)	12.6 ± 7.1
HOMA–IR	3.2 ± 2.0
Plasma triglycerides (mmol/L)	1.8 (0.9–4.5)
HDL cholesterol (mmol/L)	0.99 ± 0.16
LDL cholesterol (mmol/L)	2.93 ± 0.67
LDL peak size (nm)	25.6 ± 1.0
ApoC-III (mg/dl)	9.0 ± 2.6
ApoC-II (mg/dl)	0.61 ± 0.19
ApoA5 (ng/ml)	274 ± 66
ApoAI (mg/dL)	119 ± 13
LPL activity (mU/ml)	133 (55–331)
HL activity (mU/ml)	305 ± 118
LPL mass (ng/ml)	282 (195–717)
PLTP activity (AU)	78.6 ± 18.3
CETP activity (AU)	72.5 ± 10.5
Adiponectin (µg/ml)	2.4 (0.9-10)
Resistin (ng/ml)	7.2 (4.9-18.6)
Leptin (ng/ml)	11.4 (2.5-69.5)
RBP4 (mg/L)	47 ± 11.7

Subject characteristics are given as mean ± SD for normally distributed variables and as median (min–max) for non–normally distributed variables. Abbreviations: BMI, body mass index; F, female; M, male

Table 2. Kinetic parameters of the subjects studied

Triglycerides	$VLDL_1$ FCR (pools/day)	9.4 (2.7–30.8)
	$VLDL_1$ FDCR (pools/day)	6.1 (1.1–25.3)
	$VLDL_1$ FTR (pools/day)	2.5 (0.7–7.9)
	$VLDL_1$ SR (mg/kg/day)	272 (122–626)
	$VLDL_1$ pool (mg/dl)	75 ± 35 (19-161)
Apo B100	$VLDL_1$ FCR (pools/day)	6.7 (2.5–18.5)
	$VLDL_1$ FDCR (pools/day)	2.4 (0.0–9.0)
	$VLDL_1$ FTR (pools/day)	4.4 (1.1–10.1)
	$VLDL_1$ SR (mg/kg/day)	8.2 ± 3.0 (3.6-16.4)
	$VLDL_1$ pool (mg/dl)	2.8 (0.78-7.1)

Kinetic parameters are given as mean ± SD (min-max) for normally distributed variables and as median (min–max) for non–normally distributed variables. Triglyceride pool (mg/dl) pool can be converted to concentration (mmol/L) by multiplying with 0.0113 and apoB100 pool (mg/dl) can be converted to concentration (g/L) by multiplying with 0.01. FCR, fractional catabolic rate; FDCR, fractional direct catabolic rate, FTR, fractional transfer rate; SR, secretion rate.

Table 3. Correlations with kinetic parameters

	$VLDL_1$-Triglycerides				$VLDL_1$-apoB			
	FCR	FDCR	FTR	SR	FCR	FDCR	FTR	SR
Weight	–0.06	–0.12	0.06	0.25	–0.14	–0.01	–0.15	0.30*
BMI	–0.07	–0.06	–0.13	**0.43†**	–0.16	–0.04	–0.20	0.37*
Waist	–0.21	–0.13	–0.21	**0.40†**	–0.22	0.04	–0.31*	0.35*
Body fat	0.24	0.28	–0.08	**0.43†**	0.20	0.21	–0.13	0.26
Fat mass	0.18	0.17	–0.03	**0.51‡**	0.10	0.18	–0.18	**0.39†**
Lean mass	–0.17	–0.25	0.12	–0.02	–0.21	–0.11	–0.03	0.10
Liver fat	–0.01	–0.02	–0.19	**0.56‡**	–0.04	0.04	–0.28	**0.53‡**
Visceral fat	–0.16	–0.21	0.02	0.33*	–0.11	–0.01	–0.16	**0.40†**
Subcut fat	–0.25	–0.15	–0.37	0.18	–0.19	–0.07	–0.24	0.37
Glucose	0.15	0.09	–0.04	**0.40†**	0.11	0.21	–0.14	0.18
Insulin	–0.16	–0.14	–0.23	0.33*	–0.20	0.07	–0.37*	0.26
HOMA–IR	–0.10	–0.09	–0.21	0.37*	–0.14	0.10	–0.34*	0.27
P– triglycerides	**–0.49‡**	–0.30*	**–0.61‡**	**0.44†**	**–0.55‡**	–0.14	**–0.68‡**	**0.45†**
HDL cholesterol	–0.02	–0.11	0.03	–0.16	0.07	0.11	–0.03	–0.15
LDL cholesterol	0.25	0.17	0.17	0.00	0.25	0.04	0.16	0.03
ApoC-III	**–0.48‡**	–0.31*	**–0.57‡**	0.22	**–0.51‡**	–0.16	**–0.63‡**	0.33*
ApoC-II	–0.27	–0.16	–0.27	0.22	–0.27	–0.10	–0.24	0.26
ApoA5	–0.02	–0.04	0.06	0.09	0.04	–0.03	–0.09	–0.07
ApoE	–0.32*	–0.20	**–0.40†**	0.17	–0.37*	–0.22	–0.27	0.20
LPL activity	0.09	0.13	–0.14	0.03	0.18	0.15	0.01	0.14
HL activity	–0.26	–0.19	–0.17	0.15	–0.30	–0.07	–0.18	0.20
LPL mass	0.06	0.10	–0.07	0.01	0.15	0.18	0.03	0.05
Resistin	0.01	0.04	-0.01	-0.01	–0.05	–0.13	–0.02	–0.03
Adiponectin	–0.17	–0.12	–0.26	–0.03	–0.10	–0.11	–0.07	0.11
RBP4	–0.15	–0.12	0.01	0.02	–0.16	0.05	–0.27	0.12
PLTP	–0.26	–0.06	–0.36*	–0.05	–0.17	0.05	–0.29	0.15
CETP	0.17	0.14	–0.02	0.08	0.13	0.08	0.13	–0.05

Pearson correlations (r–values) between kinetic parameters and metabolic, lipid and lipase characteristics. Non-normally distributed variables were log transformed before analysis. FCR, fractional catabolic rate; FDCR, fractional direct catabolic rate, FTR, fractional transfer rate; SR, secretion rate. *, $P<0.05$; †, $P<0.01$; ‡, $P<0.001$. Correction for multiple testing was not performed due to the exploratory nature of the study.