Menopausal status and abdominal obesity are significant determinants of hepatic lipid metabolism in women

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Background

Android fat distribution (abdominal obesity) is associated with insulin resistance, hepatic steatosis and greater secretion of large very low density lipoprotein (VLDL) particles in men. Since abdominal obesity is becoming increasingly prevalent in women we aimed to investigate the relationship between android fat and hepatic lipid metabolism in pre- and post-menopausal women.

Methods and Results

We used a combination of stable isotope tracer techniques to investigate intrahepatic fatty acid synthesis and partitioning in 29 lean and 29 abdominally obese women (android fat/total fat 0.065 (0.02-0.08) and 0.095 (0.08-0.11) respectively). Thirty women were pre-menopausal aged 35-45 and they were matched for abdominal obesity with 28 post-menopausal women aged 55-65. As anticipated, abdominal obese women were more insulin resistant with enhanced hepatic secretion of large (404±30 v 268±26 mg/kg lean mass, P<0.001) but not small VLDL (160±11 v 142±13). However, post-menopausal status had a pronounced effect on the characteristics of small VLDL particles which were considerably triglyceride (TG)-enriched (production ratio of VLDL$_2$-TG:apolipoprotein B 30±5.3 v 19±1.6, P<0.05). In contrast to post-menopausal women, there was a tight control of hepatic fatty acid metabolism and TG production in pre-menopausal women, whereby oxidation (r_s=-0.49, P=0.006), *de novo* lipogenesis (r_s=0.55, P=0.003) and desaturation (r_s=0.48, P=0.012) were closely correlated with abdominal obesity-driven large VLDL-TG secretion rate.

Conclusions

In women, abdominal obesity is a major driver of hepatic large VLDL particle secretion whereas post-menopausal status was characterised by increased small VLDL particle size. These data provide a mechanistic basis for the hyperlipidemia observed in post-menopausal obesity.

Key words: apolipoproteins, cholesterol, lipids, lipoproteins, menopause, women

Introduction

The menopause is associated with increased cardiovascular disease (CVD) and once women develop acute coronary symptoms, they have worse short- and long-term outcomes than men [1]. Many different factors contribute, including marked hormonal changes [2], changes in metabolic profile associated with increased risk of the metabolic syndrome [3], and relative increase in intra-abdominal fat with age [4]. Accumulation of intra-abdominal fat is associated with increased waist circumference and liver fat [5], overproduction of very low-density lipoprotein (VLDL), and decreased catabolism of apolipoprotein (apo)B-containing particles in men [6]. The catabolism of apoB-containing particles is partly determined by plasma apoC-III concentrations, and higher plasma apoC-III has been associated with dyslipidemia in obese men [7]. Although abdominal obesity tends to be associated with obesity in men, data from the USA has been used to estimate that 40 % of women have an abdominal fat distribution pattern as defined by waist:hip ratio [8].

Normally, fasting plasma TG is determined by two distinct sub-classes of VLDL [9]; $VLDL_1$ is larger and more TG-rich than $VLDL_2$, the latter can either be secreted directly from the liver, or formed by the peripheral hydrolysis of $VLDL_1$. Hypertriglyceridemia is associated with atherogenic dyslipidemia including the production of small dense LDL, lower HDL cholesterol and accumulation of postprandial TG-rich lipoproteins [10]. In men with type 2 diabetes, the secretion of $VLDL_1$ is associated with liver fat, hypertriglyceridaemia and increased atherogenic risk [11].

Impaired hepatic fatty acid oxidation has been reported to be related to obesity and insulin resistance by some [12, 13] but not all [14]. Few detailed studies have investigated $VLDL_1$ and $VLDL_2$ kinetics in women and none have compared the kinetics of VLDL or apoC-III in pre- and post-menopausal women. We hypothesized

that $VLDL_1$-TG and –apoB secretion would be higher in abdominally-obese compared with abdominally lean women and aimed to investigate the effect of menopause status on this relationship by measuring hepatic *de novo* fatty acid synthesis (DNL), oxidation and desaturation in relation to $VLDL_1$ and $VLDL_2$ kinetics in pre- and post-menopausal women.

Materials and Methods

Subjects. We recruited sixty healthy White Caucasian women from local advertising and the Oxford Biobank as previously reported [15] equally into pre- and post-menopausal groups aged 35-45 and 55-65 respectively. The age groups ensured peri-menopausal women were not included and postmenopausal status was defined as absence of menses for at least 12 months and FSH > 30 IU/L. Since we also wished to investigate the effect of android fat (abdominal obesity), we used waist circumference, a marker of android fat, to facilitate recruitment of women into groups with low or high android fat. For simplicity we have referred to the group with low android fat as ‘lean’. A waist circumference of ≥ 80 cm was selected as the proxy measure of high android fat, with increased risk of CVD in Europid women defined by the International Diabetes Federation [16] and additionally, we recruited women into small waist (<80cm, n=30), or large waist (80 – 84 cm, n=5; 85 – 91 cm, n=5; and 92 – 110 cm, n=5) categories in both menopausal groups. This was to ensure a good range of android fat in our cohort, and ensure exact matching of abdominal obesity between menopausal groups. Other inclusion and exclusion criteria have been previously described in a study relating to energy intake in a sub-set of the participants [15] but briefly, women were excluded if they had any condition or treatment that would affect metabolic or hormonal status (including smoking, diabetes or hormone replacement therapy), or had BMI <18.5 or >34.9. Smokers or women exceeding alcohol consumption guidelines of 2-3 units per day were also excluded [17]. All participants gave informed, written consent and the study was approved by the Oxfordshire Clinical Research Ethics Committee. Participants attended the Clinical Research Unit prior to the metabolic day in order to be given deuterated water for consumption the evening before the study day, and to give a

blood sample for background isotopic enrichment measurements relating to the measurement of *de novo* lipogenesis (DNL, see below).

Measurement of liver, subcutaneous and visceral fat and body composition. Intra-hepatic fat was measured by magnetic resonance spectroscopy, visceral and subcutaneous fat were measured by magnetic resonance imaging after an overnight fast and within two weeks of the study day [18], whole body composition and fat distribution (eg android and gynoid fat) were measured using DEXA [15].

Metabolic study day. Participants arrived after an overnight fast and after consuming deuterated water ($^{2}H_2O$, in order to measure *de novo* lipogenesis, DNL) (3 g/kg body water) at 8 and 10 pm the evening before the study day and then continued to consume enriched water (2.5 g per 500mL water), in order to achieve and maintain a plasma water enrichment of 0.3 % [19]. A cannula was placed in an antecubital vein in order to take blood samples for the estimation of DNL in $VLDL_1$- and $VLDL_2$-palmitate, and background isotopic enrichments for the kinetic studies. Another cannula was placed in the contra lateral arm to administer intravenous boluses of [$^{2}H_3$]leucine (7 mg/kg) and [$^{2}H_5$]glycerol (500 mg), whilst an intravenous infusion of [U-^{13}C]palmitic acid, potassium salt complexed with albumin [20] at 0.03 µmol/kg/min, was started. Blood samples were taken for a further 8h and $VLDL_1$ and $VLDL_2$ isolated from plasma using density gradient ultracentrifugation [20]. Due to technical problems, one participant did not receive the palmitate infusion, one participant's infusion was stopped early and one participant did not complete the metabolic study day.

Biochemical analyses. Blood samples were drawn into heparinized syringes (Sarstedt, Leicester, UK) and plasma rapidly separated at 4°C. Plasma metabolites were analyzed enzymatically [20], insulin was measured by radioimmunoassay (Millipore (UK) Ltd, Watford, UK) and HOMA-IR was calculated as an index of insulin resistance [21]. A time averaged area-under-the-curve (AUC) for plasma 3-hydroxybutyrate (3OHB) and non-esterified fatty acids (NEFA) was calculated from hourly values taken during the study. Serum steroids (cortisol, dehydroepiandrosterone (DHEA) and androstenedione were measured by liquid chromatography/tandem mass spectrometry (LC/MS-MS) using a Waters Xevo mass spectrometer with Acquity uPLC system as described previously [22]. [$^2H_5$]glycerol in plasma, $VLDL_1$ and $VLDL_2$-TG (to trace TG) and [$^2H_3$]leucine in plasma, $VLDL_1$-and $VLDL_2$-apoB (to trace whole particles) were measured by GC-MS [23]. [U-^{13}C]palmitic acid was measured in plasma NEFA and $VLDL_1$ and $VLDL_2$-TG by GC-MS [20] and the proportion of FAs in VLDL-TG that were derived from non-systemic sources was calculated [20], assuming that 16:0 is representative of all FAs. Mathematical modelling of VLDL kinetics ($VLDL_1$-TG, $VLDL_2$-TG, $VLDL_1$-apoB, $VLDL_2$-apoB production and clearance) was calculated from [$^2H_5$]glycerol and [$^2H_3$]leucine enrichments in plasma and lipoprotein fractions [11]. See Figures S1 and S2 for examples of raw data used for modelling. VLDL-TG production rates were corrected for lean mass in order to consider delivery of TG to muscle as previously described [24] but not corrected when considering hepatic FA trafficking. Total plasma apoC-III and apoC-III in plasma devoid of apoB-containing particles were measured using a Hydragel LP CIII Electroimmunodiffusion kit (Sebia, France) with appropriate standards and quality controls according to the manufacturer’s instructions. By difference, we calculated apoC-III concentrations in apoB-containing particles (apoC-III LpB). ApoCIII kinetic modelling was carried out as previously described [25] and

assumes (consistent with previous studies, and earlier radiotracer studies), that apoCIII exchanges between VLDL and HDL particles, and therefore that measuring apoCIII kinetics in plasma is valid.

The ratio of [U-^{13}C]16:1n-7/[U-^{13}C]16:0 in $VLDL_1$ and $VLDL_2$-TG was determined as a short-term index of hepatic stearoyl-CoA desaturase (SCD) activity (the 'isotopic desaturation index') and also the SCD16 and SCD18 fatty acid ratios [26]. FA methyl esters prepared from $VLDL_1$ and $VLDL_2$-TG FAs [20] were analysed by GC [13] to quantify 16:0 and 16:1n-7, and by GC-IRMS to measure isotopic enrichment [26]. Hepatic DNL was measured on the study day, based on the incorporation of ^{2}H in plasma water (Finnigan GasBench-II (ThermoFisher Scientific, UK) and into $VLDL_1$- and $VLDL_2$-TG palmitate using GC-MS [27]. For simplicity, this is referred to as '%DNL' and represents synthesis of fatty acids from precursors such as sugars and amino acids [28].

FA rate of appearance (R_aNEFA) was calculated from the [U-^{13}C]16:0 infusion rate and enrichment in the plasma NEFA fraction and R_dNEFA was assumed to equal R_aNEFA [24].

Statistical analysis. Statistical analysis was performed using SPSS Statistics 19 (IBM, SPSS products, Chertsey, UK). Two-way ANOVA was used to determine the effect of abdominal obesity and menopausal status (fixed factors) on each dependent variable, and interaction between the fixed factors. A significant interaction term indicated that the relationship between the dependent variable and abdominal obesity was significantly different in pre- and post-menopausal women.

Associations between variables were carried out using Spearman’s rank correlation coefficient (univariate analysis).

In order to visualise relationships between metabolic variables, we plotted significant correlations between metabolic and anthropometric variables related to hepatic FA partitioning using ‘hive plots’ [29]. Each variable is represented by a node and the nodes are joined by blue (significant positive correlations) or red (significant negative correlations) lines. The nodes are placed on three duplicated radial axes which represent grouped variables (anthropometric and metabolic variables/$VLDL_1$ or $VLDL_2$). The axes are duplicated in order to allow for representation of correlations within the variable group e.g. there are lines joining the isotopic desaturation index and %DNL in $VLDL_1$ for pre- and post-menopausal women, representing significant positive correlations.

Power calculation. Using data from a study of the reproducibility of relevant kinetic parameters (VLDL TG and apoB100 secretion rates, VLDL-TG clearance rate, Ra NEFA [30], and DNL [19], separate power calculations were carried out and the numbers in pre- and post-menopausal groups to detect a 40% difference with power of 0.80 at α of 0.05 were 4, 8, 9, 10 and 15 respectively (in each group). A difference of 40 % was considered to be clinically significant and was within the range of differences previously reported in other studies[11].

Results

Sixty women were recruited: mean age was 41.0 years (range 35-45) for pre-menopausal and 58.1 years (55-64) for post-menopausal women. Mean age when divided according to abdominal obesity was 49.3 (35-64) and 49.3 (35-63) for lean and abdominally obese women respectively. Plasma FSH concentrations ranged from 3.0-21.3 and 46.5-125 IU/L in pre- and post-menopausal women respectively (confirming menopausal status). Fifty-eight women from whom DEXA scans were available are included in this study, divided according to menopause status and android fat measurement (corrected for total fat), for statistical analyses. Lean women had a mean android fat of 0.065 (SD 0.013) and abdominally obese women had a mean value of 0.094 (SD 0.008). Gynoid fat was significantly lower, and intra-abdominal fat was significantly higher in post-menopausal women, despite being matched for abdominal obesity (Table 1). Liver fat was generally low although six women, all abdominally-obese, had values of >5 %. BMI was not significantly different between menopausal groups and ranged from 21.5 to 33.0 kg/m^2 in abdominally-obese and 19.5 to 27.6kg/m^2 in abdominally lean women. Thus some abdominally lean women would be classified as overweight by BMI, and some abdominally-obese women would be classified as lean by BMI.

Post-menopausal women had significantly higher concentrations of plasma total, LDL, non-HDL cholesterol, apoCIII-LpB, plasma apoB and systolic BP than pre-menopausal women (Table 2). Women with abdominal obesity were more insulin resistant with a more adverse lipid profile (higher non-HDL cholesterol, plasma TG, $VLDL_1$- and $VLDL_2$-TG concentrations). One post-menopausal woman had impaired fasting glucose.

The rate of disappearance of FAs (R_dNEFA), expressed per kg lean mass was significantly higher in post- compared to pre-menopausal women (Table 3).

Release of FAs into plasma (R_aNEFA) per unit weight of adipose tissue was lower in women with abdominal obesity, but $VLDL_1$-TG and $VLDL_1$-apoB production were significantly higher. The ratio of $VLDL_2$-TG direct production: $VLDL_2$-apoB production was significantly higher in post- compared to pre-menopausal women, indicating production of larger particles.

There were no significant positive correlations between age and liver fat, $VLDL_1$-TG and $VLDL_2$-TG direct production, $VLDL_1$ and $VLDL_2$ direct apoB production, or $VLDL_1$ and $VLDL_2$-TG:apoB production ratios within menopausal groups.

Plasma apoC-III concentrations positively correlated with apoC-III production rate (r_s=0.59, P=9.0 x 10^{-7}) but not clearance rate, indicating plasma apoC-III concentrations were determined by production rate. Plasma, HDL- and apoC-III associated with lipoprotein B-containing particle (apoC-III LpB) concentrations were not affected by abdominal obesity, but plasma apoC-III LpB concentrations were higher in post-menopausal women.

Overall, mean %DNL was less than 10% in $VLDL_1$- and $VLDL_2$-palmitate (data not shown) and when corrected for flux from the liver, was not significantly different between menopausal groups, but was higher with abdominal obesity. Menopause status affected the relationship between abdominal obesity and 3OHB:NEFA, and abdominal obesity per se had a strong influence on factors related to FA partitioning (Table 4). Of note, the systemic FA contribution to $VLDL_1$-TG production was significantly higher in abdominally-obese women, in line with higher $VLDL_1$-TG secretion.

To explore FA partitioning in relation to metabolic and anthropometric measurements, we tabulated univariate correlations between relevant variables in pre- and post-menopausal women (selected data in Tables 5-8 and complete

analysis in Tables S1-S4). The data are illustrated in hive plots (Figure 1) which clearly show that the patterns of correlations are quite different in pre- and post-menopausal women. In particular, the density of correlations in the top left of the figure for pre-menopausal women (Figure 1A, anthropometric and metabolic variables with $VLDL_2$ metabolism) is markedly less for post-menopausal women (Figure 1B). Correlations relating to %DNL and VLDL production are shown in Figure 2A and B and between %DNL and plasma 3OHB in Figure 2C and D. The most marked univariate correlations relating to hepatic FA partitioning were between the isotopic desaturation index in $VLDL_1$ and $VLDL_2$-TG and plasma 3OHB AUC (Figure 2E and F). VLDL-ApoB and -TG production were highly correlated for $VLDL_1$ and less so for $VLDL_2$ (Figure 3). Serum cortisol concentrations were negatively correlated with WHR in pre- (r_s=-0.38, P=0.04) but not post-menopausal women. There was a significant correlation between abdominal fat and liver fat (r_s=0.50, P<0.001, n=60). The importance of menopausal status in this relationship is shown in the hive plots and Tables 5-8 which showed, remarkably, that a significant correlation between liver fat and abdominal obesity was observed only in pre-menopausal women.

We also took the opportunity to examine metabolic variables according to liver fat content because of the importance of liver fat with respect to the metabolic complications of obesity [32]. The median value in the cohort of 60 women was 0.85%. Of the 50 % of women with lower liver fat, seventeen were pre-menopausal and thirteen were post-menopausal. In general, significant effects reflected those found by considering women according to abdominal obesity (see Tables S5-S7). However, the effect of liver fat on LDL, HDL and non-HDL cholesterol as well as VLDL-TG production was less than for abdominal obesity.

Discussion

Using a combination of stable isotope tracer techniques, we investigated kinetic parameters of apoB, apoC-III and TG metabolism in pre- and post-menopausal women. We report for the first time that menopausal status is a determinant of hepatic TG flux through enhancement of adipose tissue NEFA flux, altered intra-hepatic FA partitioning and secretion of larger $VLDL_2$. VLDL-TG secretion is normally dependent on VLDL-apoB100 secretion [33] but we found that $VLDL_2$-TG secretion after the menopause was dissociated from $VLDL_2$-apoB production. Systemic FAs were the major source of $VLDL_2$-TG in all women, but both systemic and non-systemic FAs contributed to greater $VLDL_2$-TG secretion in post-menopausal women. We also report for the first time that $VLDL_1$-TG secretion is higher in abdominally-obese women. Our main findings are summarised in Figure S3.

$VLDL_1$ and $VLDL_2$ metabolism have not previously been measured in relation to menopausal and abdominal obesity status in women. We measured two aspects of VLDL secretion; VLDL-apoB secretion rate, which measures whole particle secretion, and VLDL-TG secretion, which tracks the lipid component. Using these two parameters we were also able to estimate the relative sizes of $VLDL_1$ and $VLDL_2$ at the point of hepatic secretion. $VLDL_1$ and $VLDL_2$ secretion rates were correlated but in agreement with previous findings, their metabolism was independent [34] as shown in hive plots.

$VLDL_1$-TG and $VLDL_1$-apoB production rates were significantly higher in the abdominally-obese compared to abdominally lean women. Higher $VLDL_1$-TG secretion was attributable to both systemic and non-systemic FA. There are no previous comparable studies but in lean and obese pre-menopausal women there were no differences in total VLDL-apoB or VLDL-TG secretion [35, 36]. Another study in pre-menopausal women found higher total VLDL-TG production in upper-body obese

compared with lean women [37], although production was not corrected for any measure of body mass.

$VLDL_2$-TG direct production was higher in post- compared to pre-menopausal women, due to production of TG-enriched $VLDL_2$. This has not been reported previously and the relevance is as yet, not clear, but small rather than large VLDL is implicated in atherosclerosis progression [38]. $VLDL_2$-TG production was higher in post-menopausal women than men matched for plasma TG concentrations [24] and as discussed by the authors, $VLDL_2$ is more efficiently converted to LDL than $VLDL_1$. Moderate hypercholesterolemia arises principally from overproduction of $VLDL_2$ particles in men [39]; our study was not designed to measure LDL kinetics but higher plasma and LDL cholesterol concentrations after the menopause were not accompanied by an increase in $VLDL_2$-apoB production.

Menopausal status did not affect $VLDL_1$ or $VLDL_2$ clearance, in contrast to the work of Mittendorfer [40]. VLDL kinetics are sensitive to intra-abdominal and liver fat content [32], and discrepancies between published studies may be due to liver fat content, and/or kinetic parameters not corrected for adiposity or lean mass. Although estrogen per se may affect VLDL kinetics [41], other factors such as the changes in body composition accompany estrogen deficiency. We found increased concentrations of plasma total and LDL cholesterol, and apoB which are typical features of dyslipidaemia in post-menopausal women [42]. Additionally, we found significantly higher apoC-III LpB, in post-menopausal women. Since apoC-III plays a pivotal role in the development of hypertriglyceridemia [7], apoC-III may play a role in the development of dyslipidemia in older, post-menopausal women.

Higher R_dNEFA in post-menopausal women is consistent with the finding that exogenous estrogen reduced NEFA flux in post-menopausal women [43]. This suggests that higher NEFA flux in post-menopausal women is a result of estrogen

depletion. R_aNEFA, when corrected for fat mass was significantly lower with increasing abdominal obesity, in agreement with the concept of downregulated adipose tissue FA trafficking in obesity with reduced expression of lipolytic genes such as hormone sensitive lipase and adipose triglyceride lipase [44]. The relationship between obesity, insulin resistance and lipolysis is not clear in the literature and has been elegantly reviewed [45]. At a whole body level, lipolysis was similar in lean and abdominally obese groups but the contribution of systemic FA to increased $VLDL_1$-TG was significantly higher in abdominally-obese women, as was the contribution of non-systemic FA, with a tendancy for increased *de novo* hepatic FA secretion indicating an upregulation of secretion of FA from all sources. Higher secretion of *de novo* palmitate has previously been found in obese hypertriglyceridaemic men compared with lean normo-lipidaemic men and women [46]. Our findings of inverse correlations between plasma 3OHB and %DNL in $VLDL_1$-TG are in agreement with studies in healthy men and women [47]. Moreover, we found strong inverse correlations between the isotopic desaturation index in $VLDL_1$- and $VLDL_2$-TG and plasma 3OHB in the whole cohort. These two variables are not obviously related but provide the first evidence of a clear divergence of FA partitioning in humans *in vivo* such that hepatic desaturation of FAs was low when FA oxidation was high (and vice versa).

Serum cortisol concentrations were negatively correlated with WHR in pre- but not post-menopausal women. Cortisol status has previously been inversely related to WHR in women, although menopause status was not defined; this has been explained by a higher local clearance rate of cortisol in visceral fat, which has more glucocorticoid receptors than subcutaneous fat [48]. However, we found no correlation between serum cortisol concentrations and intra-abdominal fat area. In

agreement with previous studies of ageing [49] serum cortisol concentrations were higher in post-menopausal women.

Strengths of our study include the unique combination of kinetic and anthropometric measurements in large groups of well-matched women but a limitation is the cross-sectional design. Therefore we cannot ascribe causality to any of the correlations found. Post-menopausal women were older and therefore any effects of ‘menopausal status’ do not reflect a difference in hormone concentrations, but rather the natural course of events (menopause plus ageing with accompanying changes in body fat distribution). Indeed, post-menopausal women had equal abdominal obesity but higher intra-abdominal fat and less gynoid fat, demonstrating a change in body fat distribution [4]. Given the importance of estrogen in determining body fat distribution and direct effects on lipid metabolism, it may have been insightful to measure serum estrogen concentrations although it is clear that many factors beyond sex hormones contribute to lipid and lipoprotein metabolism [50]. The study design meant that we were able to look at correlations within each menopausal group. We also analysed our data according to liver fat and we found that overall, the results were similar to when we divided according to abdominal obesity. This is in contrast to findings in individuals with a large range of liver fat [32] where liver fat was found to be more discriminatory. However, we found that abdominal obesity in women was more related to impaired VLDL-TG secretion than liver fat. This suggests that other intra-hepatic factors are contributing to VLDL-TG secretion.

We did not include a comparator group of men but other groups have compared lipoprotein metabolism in men and women. One study found that VLDL-TG secretion rate was not significantly different in men and women [50] whereas another found that $VLDL_2$-TG but not $VLDL_1$-TG secretion rate was higher in women than men. We have previously reported no difference in the postprandial contribution

of dietary and non-systemic FA to VLDL-TG between insulin-sensitive men and women [13]. However, lipoprotein metabolism is dependent on a many factors and accumulation of excess body fat seems to affect lipid kinetics differently in men and women as recently discussed [50]. Total body fat and body fat distribution are obvious differences between men and women, and this study has highlighted the importance of body fat distribution in women.

Conclusions

$VLDL_1$ and $VLDL_2$ metabolism is complex in women and hive plots illustrate that the patterns of associations with metabolic variables are different between menopausal groups. A lack of significant correlation between hepatic $VLDL_2$-TG and $VLDL_2$-apoB production is intriguing and requires further study. Abdominal obesity was characterized by increased CVD risk factors such as $VLDL_1$-TG and –apoB production, liver fat and non-HDL cholesterol. Interestingly, this was observed despite a considerable overlap in BMI between abdominally lean and abdominally-obese groups. Our study is the first to report that $VLDL_1$-TG secretion is significantly higher in abdominally-obese women and accounts for increased plasma $VLDL_1$-TG and plasma TG concentrations. This is important because there is increasing evidence that there is a causal relationship between TG-mediated pathways and coronary heart disease [51]. Weight gain in post-menopausal women is likely to impact on both $VLDL_1$-TG and $VLDL_2$-TG secretory pathways with consequent implications for CVD risk.

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Conflict of Interest Disclosures

None

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Figure legends

Figure 1. Significant correlations between variables relating to VLDL-TG metabolism represented as hive plots for pre-menopausal (Figure 1A) and post-menopausal (Figure 1B) women. Each variable is represented by a node and the nodes are joined by blue (significant positive correlations) or red (significant negative correlations) lines. The thickness of the line represents the strength of the correlation. The nodes are placed on three duplicated radial axes which represent grouped variables (anthropometric and metabolic variables/$VLDL_1$ or $VLDL_2$). Individual nodes are coded as indicated and specific correlation coefficients are given in Supplemental Material. Node codes: **A**, liver fat (%); **B**, total body fat (kg); **C**, android fat/total fat; **D**, gynoid fat/total fat; **E**, visceral fat (cm^2); **F**, subcut fat (cm^2); **G**, NEFA (µmol/l); **H**, 3OHB (AUC); **I**, HOMA-IR; **K**, VLDL-TG SCD isotopic index; **M**, VLDL-TG SCD18 index; **O**, VLDL-TG 18:2n-6 (%); **Q**, VLDL-TG production per day; **S**, VLDL-TG SCD16; **U**, VLDL-TG DNL (%); **W**, VLDL-TG production/apoB production. Abbreviations: subcut, subcutaneous; NEFA, plasma non-esterified fatty acids; 3OHB, plasma 3-hydroxybutyrate; HOMA-IR, homeostatic model assessment of insulin resistance; VLDL, very low-density lipoprotein; TG, triglyceride; SCD, stearoyl-CoA desaturase; SCD18, 18:1 n-9 / 18:0 ratio in VLDL-TG; SCD16, 16:1 n-7/16:0 ratio in VLDL-TG; DNL, hepatic *de novo* lipogenesis; apoB, apolipoprotein B.

Figure 2. Correlations between $VLDL_1$-TG production (mg/day) and the proportion (%) of DNL fatty acids $VLDL_1$-TG (Figure 2A), $VLDL_2$-TG direct production (mg/day) and the proportion (%) of DNL fatty acids $VLDL_2$-TG (Figure 2B), the proportion (%) of DNL fatty acids $VLDL_1$-TG and the AUC for plasma 3-hydroxybutyrate (µmol/L) (Figure 2C), the proportion (%) of DNL fatty acids $VLDL_2$-TG and the AUC for plasma

3-hydroxybutyrate (μmol/L) (Figure 2D), and the association between plasma 3-hydroxybutyrate concentrations (μmol/L) and the isotopic desaturation index ([$U^{13}C16{:}1n\text{-}7$ / $U^{13}C16{:}0$]*1000) in $VLDL_1$-TG (Figure 2E) and $VLDL_2$-TG (Figure 2F) in pre-(●) and post- (○) menopausal women.

Figure 3. Correlations between $VLDL_1$-apoB production (mg/day) and $VLDL_1$-TG production (mg/day) (Figure 3A), $VLDL_2$-apoB production (mg/day) and $VLDL_2$-TG direct production (mg/day) (Figure 3B) in pre-(●) and post- (○) menopausal women.

Table 1. Body composition in women according to menopausal status and abdominal obesity

	Pre-menopausal (n=30)	Post-menopausal (n=30)†	Lean (n=29)	Abdominally obese (n=29)	P_{meno}	$P_{Abd\ obesity}$
Waist (cm)	83.5 (1.8)	82.1 (1.4)	77.1 (0.86)	88.6 (1.5)	NS	<0.001
BMI (kg/m^2)	24.9 (0.6)	24.8 (0.4)	23.2 (0.36)	26.6 (0.54)	NS	<0.001
WHR	0.85 (0.01)	0.84 (0.01)	0.82 (0.009)	0.87 (0.01)	NS	0.001
Gynoid fat	5.3 (0.25)	5.0 (0.14)	4.6 (0.17)	5.6 (0.20)	NS	<0.001
Gynoid fat ¥	0.24 (0.07)	0.21 (0.05)	0.25 (0.006)	0.20 (0.004)	<0.01	<0.001
Android:gynoid ratio	0.35 (0.02)	0.39 (0.02)	0.27 (0.015)	0.47 (0.015)	<0.05	<0.001
Intra-ab fat (cm^2)	40.7 (4.1)	53.3 (5.5)	26.5 (2.0)	67 (4.6)	<0.05	<0.001
Subcut fat (cm^2)	225.0 (17.0)	241.0 (14.0)	181 (11)	282 (14)	NS	<0.001
Fat mass (kg)	23.2 (1.3)	23.4 (0.9)	19.0 (0.72)	27.6 (0.88)	NS	<0.001
Lean mass (kg)	42.4 (0.9)	39.4 (0.8)	39.5 (0.89)	42.4 (0.87)	<0.05	<0.001
Fat:lean mass	0.54 (0.03)	0.60 (0.02)	0.49 (0.21)	0.65 (0.015) *	<0.05	<0.001
Liver fat (%)	0.78 (0.25–11.5)	0.97 (0.44–6.8)	0.61 (0.25-2.1)	1.3 (0.32-11.5)	NS	<0.001

Data presented as mean (sem) or median (range); † n=30 for post-menopausal women apart from data derived from DEXA measurements which were n=28 (gynoid fat, android: gynoid ratio, fat mass, lean mass and fat:lean mass). ¥ corrected for total fat mass in order to investigate differences in body fat distribution. Abbreviations: BMI, body mass index; WHR, waist to hip ratio; Intra-ab fat, intra-abdominal fat; Subcut fat, subcutaneous fat; Statistical significance based on 2-way ANOVA: P_{meno} Statistical significance for an effect of menopausal status; $P_{Abd\ obesity}$ Statistical significance for an effect of abdominal obesity; *P<0.05 for interaction between abdominal obesity and menopausal status.

Table 2. Biochemical and metabolic variables in women according to menopausal status and abdominal obesity

	Pre-menopausal (n=30)	Post-menopausal (n=30) †	Lean (n=29)	Abdominally obese (n=29)	P_{meno}	$P_{Abd\ obesity}$
Total chol (mmol/l)	4.9 (0.1)	5.9 (0.2)	5.3 (0.2)	5.5 (0.2)	<0.001	NS
LDL chol (mmol/l)	2.9 (0.1)	3.8 (0.2)	3.1 (0.1)	3.5 (0.2)	<0.001	<0.05
HDL chol (mmol/l)	1.6 (0.1)	1.7 (0.1)	1.8 (0.07)	1.4 (0.06)	NS	<0.001
Non-HDL chol (mmol/l)	3.3 (0.1)	4.2 (0.2)	3.5 (0.15)	4.0 (0.18)	<0.001	<0.01
TG (mmol/l)	0.9 (0.1)	0.9 (0.1)	0.72 (0.05)	1.09 (0.15)	NS	<0.01
$VLDL_1$-TG (μmol/l)	142 (33–2083)	226 (82–1090)	181 (26)	369 (72)	NS	0.001
$VLDL_2$-TG (μmol/l)	142 (39–1061)	189 (78–488)	154 (17)	247 (34)	NS	<0.01
Plasma apoC-III (mg/l)	28.7 (1.9)	33.8 (1.5)	31 (1.7)	31 (2.0)	0.06	NS
apoCIII-LpB (mg/l)	11.9 (0.9)	15.5 (1.0)	13 (0.9)	14 (1.1)	<0.01	NS
ApoC-III Lp nonB (mg/l)	16.8 (1.4)	18.4 (1.0)	18 (1.2)	17 (1.2)	NS	NS
Plasma apoB (g/l)	0.73 (0.51-1.27)	0.89 (0.51–1.37)	0.78 (0.51–1.23)	0.88 (0.51–1.27)	0.001	<0.05
$VLDL_1$-apoB (g/l)	0.006 (0.001–0.05)	0.007 (0.004–0.03)	0.005 (0.001–0.03)	0.008 (0.004–0.05)	NS	<0.05
$VLDL_2$-apoB (g/l)	0.018 (0.004–0.13)	0.023 (0.01–0.06)	0.018 (0.004–0.04)	0.023 (0.01–0.13)	NS	<0.05
Insulin (mU/l)	11.5 (0.9)	10.5 (0.4)	9.2 (0.44)	12.8 (0.79)	NS	<0.001
Glucose (mmol/l)	5.0 (0.1)	5.1 (0.1)	4.9 (0.08)	5.2 (0.07)	NS	<0.05
HOMA-IR	3.1 (0.3)	2.8 (0.1)	2.4 (0.14)	3.5 (0.24)	NS	<0.01
NEFA (μmol, AUC)	591 (33)	626 (25)	633 (32)	579 (27)	NS	NS
Plasma 3OHB (μmol, AUC)	156 (13.5)	130 (13.5)	160 (14)	126 (13)	NS	<0.05
Systolic BP (mmHg)	114 (2.2)	126 (2.5)	119 (2.8)	121 (2.5)	0.001	NS
Diastolic BP (mmHg)	75 (1.4)	75 (2.3)	75 (1.7)	76 (1.8)	NS	NS

Data presented as mean (sem) or median (range); † n=30 for post-menopausal women apart from AUC measurements for NEFA and 3OHB which are n=29

Abbreviations: Chol, cholesterol; LDL, low density-lipoprotein; HDL, high density-lipoprotein; VLDL, very low-density lipoprotein; ApoB, apolipoprotein; apoC-III LpB, apoC-III associated with lipoprotein B containing particles; BP, blood pressure; HOMA-IR, estimate of insulin resistance; Statistical significance based on 2-way ANOVA: P_{meno} Statistical significance for an effect of menopausal status; $P_{Abd\ obesity}$ Statistical significance for an effect of abdominal obesity; no significant interaction between abdominal obesity and menopausal status was found.

Table 3. Kinetic estimates relating to NEFA, VLDL and apoC-III metabolism in women according to menopausal status and abdominal obesity

	Pre-menopausal	Post-menopausal	Lean	Abdominally obese	P_{meno}	$P_{Abd\ obesity}$
R_aNEFA (μmol.min^{-1} per kg fat mass)	9.1 (0.8) n=30	10.0 (0.6) n=26	11 (0.8) n=28	8.2 (0.6) n=28	NS	0.01
R_dNEFA (μmol.min^{-1} per kg lean mass)	4.6 (0.3) n=30	5.8 (0.3) n=26	5.1 (0.4) n=28	5.3 (0.3) n=28	<0.05	NS
R_aNEFA (μmol.min^{-1})	193 (12) n=30	220 (12) n=28	197 (13) n=28	219 (11) n=28	0.05	NS
$VLDL_1$-TG Prod (mg/kg lean mass)	332 (35) n=26	350 (27) n=26	268 (26) n=24	404 (30) n=28	NS	0.001
$VLDL_2$-TG dirProd (mg/kg lean mass)	129 (12) n= 26	174 (12) n=26	142 (13) n=24	160 (11) n=28	<0.01	0.07
$VLDL_2$-TG indirProd (mg/ kg lean mass)	100 (21) n=25	110 (14) n=26	88 (17) n=24	120 (18) n=27	NS	NS
$VLDL_1$-TG FCR (pools/day)	29 (3.2) n=26	26 (2.5) n=27	31 (2.9) n=24	25 (2.8) n=28	NS	NS
$VLDL_2$-TG FCR (pools/day)	22 (2.3) n=26	26 (2.7) n=27	26 (2.6) n=24	22 (2.4) n=28	NS	NS
$VLDL_1$-TG FTR (pools/day)	6.8 (1.0) n=25	7.5 (1.0) n=27	7.9 (1.2) n=24	6.6 (0.8) n=27	NS	NS
$VLDL_1$-TG FDC (pools/day)	22 (3.2) n=26	18 (2.3) n=27	23 (3.0) n=24	18 (2.7) n=28	NS	NS
$VLDL_1$-apoB FDC (pools/day)	9.2 (1.7) n=28	7.5 (1.5) n=28	8.5 (1.5) n=26	8.5 (1.7) n=29	NS	NS
$VLDL_1$-apoB FTR (pools/day)	8.6 (1.0) n=27	8.2 (0.8) n=28	8.5 (1.0) n=26	8.1 (0.8) n=28	NS	NS
$VLDL_1$-apoB FCR (pools/day)	18 (1.9) n=28	16 (1.5) n=28	17 (1.6) n=26	16 (1.8) n=29	NS	NS
$VLDL_2$-apoB FCR (pools/day)	8.6 (0.8) n=28	7.7 (0.8) n=28	8.7 (0.8) n=26	7.8 (0.8) n=29	NS	NS
$VLDL_1$-apoB Prod (mg per day)	344 (38) n=28	316 (27) n=28	253 (26) n=26	397 (34)* n=29	NS	0.001
$VLDL_2$-apoB dirProd (mg per day)	304 (21) n= 28	278 (20) n=28	269 (19) n=26	311 (22)* n=29	NS	NS
$VLDL_2$-apoB indirProd (mg per day)	194 (34) n=28	163 (19) n=28	130 (18) n=25	215 (31) n=28	NS	<0.05
$VLDL_1$-TG Prod:$VLDL_1$ apoB Prod‡	42 (2.8) n=26	49 (5.9) n=27	45 (4.2) n=24	47 (5.2) n=28	NS	NS
$VLDL_2$-TG dirProd:$VLDL_2$ apoB Prod‡	19 (1.6) n=26	30 (5.3) n=27	21 (2.1) n=24	28 (5.1) n=28	<0.05	NS
ApoC-III FCR (pools/day)	1.1 (0.1) n=30	1.1 (0.1) n=30	1.1 (0.1) n=29	1.0 (0.09) n=29	NS	NS
ApoC-III PR (mg per kg/day)	1.5 (0.2) n=30	1.7 (0.1) n=30	1.6 (0.2) n=29	1.4 (0.1) n=29	NS	NS

Data presented as mean (sem)

Abbreviations: R_a, rate of appearance; R_d, rate of disappearance; TG, triacylglycerol; ApoB, Apolipoprotein B100; lean, lean tissue; Prod, production; dirprod, direct production; indirprod, indirect production FCR, fractional clearance rate; FTR, fractional transfer rate; FDC, fractional direct clearance; ‡mg/day; Statistical significance based on 2-way ANOVA: P_{meno} Statistical significance for an effect of menopausal status; $P_{Abd\ obesity}$ Statistical significance for an effect of abdominal obesity; *P<0.05 for interaction between abdominal obesity and menopausal status.

Table 4 Variables relating to fatty acid metabolism in women according to menopausal status and abdominal obesity

	Pre-menopausal	Post-menopausal	Lean	Abdominally obese	P_{meno}	$P_{Abd\ obesity}$
Non-systemic FA - $VLDL_1$-TG (%)	15.5 (3.2) n=27	14.2 (2.6) n=23	9.5 (1.9) n=24	20 (3.4) n=26	NS	<0.05
Non-systemic FA - $VLDL_2$-TG (%)	17.2 (3.4) n=27	18.6 (2.6) n=23	11 (2.1) n=24	24 (3.3) n=26	NS	<0.01
Non-systemic FA contribution to $VLDL_1$-TG production (mg/day)	2943 (803) n=24	1678 (367) n=21	1180 (349) n=20	3290 (747) n=25	NS	<0.001
Non-systemic FA contribution to $VLDL_2$-TG direct production (mg/day)	1028 (197) n=24	1192 (181) n=21	668 (146) n=20	1453 (185)* n=25	<0.05	<0.001
Systemic FA contribution to $VLDL_1$-TG production (mg/day)	11814 (1307) n=24	11449 (956) n=21	9613 (946) n=20	13269 (1183) n=25	NS	<0.05
Systemic FA contribution to $VLDL_2$-TG direct production (mg/day)	4563 (511) n=24	5594 (389) n=21	4709 (441) n=20	5312 (486) n=25	0.06	NS
$VLDL_1$-TG isotopic desaturation index[a]	9.2 (3.0-29.2) n=30	10.5 (3.6-68.2) n=28	8.2 (3-29) n=28	10.6 (36-68) n=29	NS	0.06
$VLDL_2$-TG isotopic desaturation index[a]	9.0 (3.2-28.5) n=30	10.2 (4.9-60.7) n=28	8.5 (3.5-28) n=28	10.6 (4.9-61) n=29	NS	<0.05
$VLDL_1$-16:0 TG synthesised *de novo* (mg/day)[a]	118 (4.9-1444) n=26	283 (27.2-2564) n=26	114 (4.9-1444) n=23	309 (12-2564) n=28	NS	0.06
$VLDL_2$-16:0 TG synthesised *de novo* (mg/day)[a]	62 (0.42-351) n=26	102 (7.4-583) n=26	61 (42-351) n=23	117 (7.4-583) n=28	NS	<0.05
3OHB/NEFA	0.24 (0.012) n=30	0.22 (0.02) n=29	0.25 (0.02) n=29	0.21 (0.02) n=29**	NS	NS

Data presented as mean (SEM) or median (range). Statistical significance based on 2-way ANOVA: P_{meno} Statistical significance for an effect of menopausal status; $P_{Abd\ obesity}$ Statistical significance for an effect of abdominal obesity; *P<0.05, **P<0.01 for a statistically significant

interaction between abdominal obesity and menopausal status. Abbreviations: FA, fatty acid; VLDL, very low-density lipoprotein, TG, triglyceride; 3OHB, 3-hydroxybutyrate; NEFA, non-esterified fatty acids

Table 5. Correlation coefficients (r_s) for pre-menopausal women between selected variables relating to $VLDL_1$ metabolism, liver fat and intra-abdominal fat

	Total body fat (kg)	Android/ tot fat (kg)	Gynoid/ tot fat (kg)	Visceral fat (cm²)	Subcut fat (cm²)	HOMA-IR	Plasma NEFA* (µmol/L)	Plasma 3OHB* (µmol/L)	$VLDL_1$-TG prod/d	$VLDL_1$-TG SCD iso index	$VLDL_1$-TG SCD16	$VLDL_1$-TG SCD18	$VLDL_1$-TG DNL (%)	$VLDL_1$-TG 18:2n-6 (%)	$VLDL_1$-TG prod/apo B prod
Liver fat (%)	0.57 P=0.001	0.63 P<0.001	-0.39 P=0.034	0.71 P<0.001	0.47 P=0.009	0.63 P<0.001	-0.07 P=0.702	-0.42 P=0.022	0.40 P=0.045	0.41 P=0.025	-0.05 P=0.803	-0.33 P=0.078	0.47 P=0.009	-0.19 P=0.323	-0.29 P=0.150
Total body fat (kg)		0.68 P<0.001	-0.63 P<0.001	0.80 P<0.001	0.90 P<0.001	0.36 P=0.052	-0.00 P=0.982	-0.33 P=0.077	0.61 P=0.001	0.39 P=0.039	0.17 P=0.370	-0.13 P=0.480	0.49 P=0.006	-0.35 P=0.055	-0.07 P=0.739
Android/ tot fat (kg)			-0.74 P<0.001	0.78 P<0.001	0.63 P<0.001	0.53 P=0.003	-0.10 P=0.596	-0.37 P=0.046	0.53 P=0.005	0.35 P=0.057	0.09 P=0.629	-0.20 P=0.300	0.32 P=0.085	-0.07 P=0.699	-0.07 P=0.719

*AUC

Abbreviations: tot, total; Subcut, subcutaneous; HOMA_IR, homeostatic model assessment of insulin resistance; NEFA, non-esterified fatty acids; 3OHB, 3-hydroxybutyrate; VLDL, very low-density lipoprotein; TG, triglyceride, SCD, Stearoyl-CoA desaturase 1; prod, production; d, day; iso, isotopic; SCD16, ratio of 16:1n-7 / 16:0; SCD18, ratio 18:1n-9/18:0; DNL, *de novo* lipogenesis; AUC, area under the curve. See Supplemental Material for full statistical analysis.

Table 6. Correlation coefficients (r_s) for pre-menopausal women between selected variables relating to $VLDL_2$ metabolism, liver fat and intra-abdominal fat.

	Total body fat (kg)	Android/ tot fat (kg)	Gynoid/ tot fat (kg)	Visceral fat (cm^2)	Subcut fat (cm^2)	HOMA-IR	Plasma NEFA* (μmol/L)	Plasma 3OHB* (μmol/L)	$VLDL_2$-TG prod/d	$VLDL_2$-TG SCD iso index	$VLDL_2$-TG SCD16	$VLDL_2$-TG SCD18	$VLDL_2$-TG DNL (%)	$VLDL_2$-TG 18:2n-6 (%)	$VLDL_2$-TG prod/apo B prod
Liver fat (%)	0.57 P=0.001	0.63 P<0.001	-0.39 P=0.034	0.71 P<0.001	0.47 P=0.009	0.63 P<0.001	-0.07 P=0.702	-0.42 P=0.022	0.21 P=0.306	0.38 P=0.040	0.01 P=0.952	-0.37 P=0.042	0.42 P=0.021	-0.19 P=0.323	-0.29 P=0.150
Total body fat (kg)		0.68 P<0.001	-0.63 P<0.001	0.80 P<0.001	0.90 P<0.001	0.36 P=0.052	-0.00 P=0.982	-0.33 P=0.077	0.51 P=0.007	0.41 P=0.023	0.21 P=0.257	-0.24 P=0.202	0.41 P=0.023	-0.25 P=0.177	0.23 P=0.255
Android/ tot fat (kg)			-0.74 P<0.001	0.78 P<0.001	0.63 P<0.001	0.53 P=0.003	-0.10 P=0.596	-0.37 P=0.046	0.29 P=0.145	0.36 P=0.052	0.12 P=0.516	-0.31 P=0.092	0.22 P=0.240	-0.05 P=0.791	0.11 P=0.580

*AUC

Abbreviations: tot, total; Subcut, subcutaneous; HOMA_IR, homeostatic model assessment of insulin resistance; NEFA, non-esterified fatty acids; 3OHB, 3-hydroxybutyrate; VLDL, very low-density lipoprotein; TG, triglyceride, SCD, Stearoyl-CoA desaturase 1; prod, production; d, day; iso, isotopic; SCD16, ratio of 16:1n-7 / 16:0; SCD18, ratio 18:1n-9/18:0; DNL, *de novo* lipogenesis; AUC, area under the curve. See Supplementary Material for full statistical analysis.

Table 7. Correlation coefficients (r_s) for post-menopausal women between selected variables relating to VLDL$_1$ metabolism, liver fat and intra-abdominal fat

	Total body fat (kg)	Android/ tot fat (kg)	Gynoid/ tot fat (kg)	Visceral fat (cm^2)	Subcut fat (cm^2)	HOMA-IR	Plasma NEFA* (µmol/L)	Plasma 3OHB* (µmol/L)	VLDL$_1$-TG prod/d	VLDL$_1$-TG SCD iso index	VLDL$_1$-TG SCD16	VLDL$_1$-TG SCD18	VLDL$_1$-TG DNL (%)	VLDL$_1$-TG 18:2n-6 (%)	VLDL$_1$-TG prod/apo B prod
Liver fat (%)	0.28 P=0.150	0.26 P=0.184	-0.42 P=0.028	0.61 P<0.001	0.26 P=0.192	0.23 P=0.232	0.00 P=0.994	0.09 P=0.647	0.05 P=0.797	-0.11 P=0.595	-0.42 P=0.023	-0.26 P=0.173	0.04 P=0.838	0.11 P=0.578	0.26 P=0.200
Total body fat (kg)		0.78 P<0.001	-0.57 P=0.002	0.73 P<0.001	0.86 P<0.001	0.29 P=0.133	-0.09 P=0.648	0.19 P=0.326	0.34 P=0.093	-0.01 P=0.949	-0.13 P=0.512	0.22 P=0.279	0.01 P=0.967	0.32 P=0.106	0.35 P=0.077
Android/ tot fat (kg)			-0.76 P<0.001	0.72 P<0.001	0.69 P<0.001	0.35 P=0.064	-0.35 P=0.072	-0.14 P=0.475	0.57 P=0.003	0.23 P=0.246	-0.21 P=0.287	-0.05 P=0.788	0.19 P=0.342	0.29 P=0.143	0.25 P=0.225

*AUC

Abbreviations: tot, total; Subcut, subcutaneous; HOMA_IR, homeostatic model assessment of insulin resistance; NEFA, non-esterified fatty acids; 3OHB, 3-hydroxybutyrate; VLDL, very low-density lipoprotein; TG, triglyceride, SCD, Stearoyl-CoA desaturase 1; prod, production; d, day; iso, isotopic; SCD16, ratio of 16:1n-7 / 16:0; SCD18, ratio 18:1n-9/18:0; DNL, *de novo* lipogenesis;AUC, area under the curve. See Supplementary Material for full statistical analysis.

Table 8. Correlation coefficients (r_s) for post-menopausal women between selected variables relating to $VLDL_1$ metabolism, liver fat and intra-abdominal fat

	Total body fat (kg)	Android/ tot fat (kg)	Gynoid/ tot fat (kg)	Visceral fat (cm^2)	Subcut fat (cm^2)	HOMA-IR	Plasma NEFA* (µmol/L)	Plasma 3OHB* (µmol/L)	$VLDL_2$-TG prod/d	$VLDL_2$-TG SCD iso index	$VLDL_2$-TG SCD16	$VLDL_2$-TG SCD18	$VLDL_2$-TG DNL (%)	$VLDL_2$-TG 18:2n-6 (%)	$VLDL_2$-TG prod/apo B prod
Liver fat (%)	0.28 P=0.150	0.26 P=184	-0.42 P=0.028	0.61 P<0.001	0.26 P=0.192	0.23 P=0.232	0.00 P=0.994	0.09 P=0.647	-0.15 P=0.470	-0.05 P=0.797	-0.46 P=0.013	-0.44 P=0.016	0.11 P=0.564	0.15 P=0.450	0.11 P=0.594
Total body fat (kg)		0.78 P<0.001	-0.57 P=0.002	0.73 P<0.001	0.86 P<0.001	0.29 P=0.133	-0.09 P=0.648	0.19 P=0.326	0.18 P=0.380	-0.03 P=0.875	-0.12 P=0.554	-0.04 P=0.842	0.13 P=0.518	0.27 P=0.171	0.30 P=0.133
Android/ tot fat (kg)			-0.76 P<0.001	0.72 P<0.001	0.69 P<0.001	0.35 P=0.064	-0.35 P=0.072	-0.14 P=0.475	0.20 P=0.341	0.20 P=0.329	-0.23 P=0.244	-0.13 P=0.506	0.16 P=0.423	0.22 P=0.275	0.31 P=0.123

*AUC

Abbreviations: tot, total; Subcut, subcutaneous; HOMA_IR, homeostatic model assessment of insulin resistance; NEFA, non-esterified fatty acids; 3OHB, 3-hydroxybutyrate; VLDL, very low-density lipoprotein; TG, triglyceride, SCD, Stearoyl-CoA desaturase 1; prod, production; d, day; iso, isotopic; SCD16, ratio of 16:1n-7 / 16:0; SCD18, ratio 18:1n-9/18:0; DNL, *de novo* lipogenesis; AUC, area under the curve. See Supplementary Material for full statistical analysis.