Greater dietary fat oxidation in obese compared with lean men: an adaptive mechanism to prevent liver fat accumulation?

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Hodson L, McQuaid SE, Humphreys SM, Milne R, Fielding BA, Frayn KN, Karpe F. Greater dietary fat oxidation in obese compared with lean men: an adaptive mechanism to prevent liver fat accumulation? Am J Physiol Endocrinol Metab 299: E584–E592, 2010. First published July 13, 2010; doi:10.1152/ajpendo.00272.2010.—Liver fat represents a balance between input, secretion, and oxidation of fatty acids. As humans spend the majority of a 24-h period in a postprandial state, dietary fatty acids make an important contribution to liver fat metabolism. We compared hepatic fatty acid partitioning in healthy lean (n = 9) and abdominally obese (n = 10) males over 24 h. Volunteers received three mixed meals adjusted for basal metabolic rate. U-13C-labeled fatty acids were incorporated into the meals, and [2H2]palmitate was infused intravenously to distinguish between sources of fatty acids incorporated into VLDL-TG. Immunoaffinity chromatography was used to isolate VLDL-TG of hepatic origin. Liver and whole body fatty acid oxidation was assessed by isotopic enrichment of 3-hydroxybutyrate and breath CO2. We found a similar contribution of dietary fatty acid oxidation to VLDL and VLDL-TG in the two groups over 24 h. The contribution of fatty acids from splanchnic sources was higher (P < 0.05) in the abdominally obese group. Ketogenesis occurred to a significantly greater extent in abdominally obese compared with lean males, largely due to lessened downregulation of postprandial ketogenesis (P < 0.001). The appearance of 13C in breath CO2 was also greater (P < 0.001) in abdominally obese compared with lean men. Hepatic elongation and desaturation of palmitic acid were higher (P < 0.05) in abdominally obese than in lean males. Oxidation of dietary fatty acids and hepatic desaturation and elongation of palmitic acid occurred to a greater extent in abdominally obese men. These alterations may represent further pathways for redirection of fatty acids into export from the liver or oxidation to prevent liver fat accumulation. Very low-density lipoprotein; stable isotopes; postprandial metabolism; oxidation; abdominal obesity; desaturation

ABDOMINAL OBESITY IS ASSOCIATED WITH liver fat accumulation (31), which in turn is associated with overproduction of very low-density lipoprotein-triglyceride (VLDL-TG) (1, 15), a risk factor for cardiovascular disease (36). Characterization of the pathways of hepatic fatty acid esterification and oxidation may help to understand why liver fat accumulates.

During the postprandial period, fatty acids from dietary sources, the lipolysis of peripheral and visceral adipose tissue, hepatic de novo lipogenesis (DNL), and hepatic cytosolic TG (19) contribute to VLDL-TG production. High concentrations of plasma insulin, such as those seen in obesity, (21) affect the contribution of these sources of fatty acids to VLDL-TG (25). The effect of adiposity per se has not been studied, but it could be speculated that as a consequence of visceral fat accumulation there would be an increased flux of visceral fatty acids to the liver (35) that could provide a substantial source for VLDL-TG production and potentially liver fat deposition.

Transformations of fatty acids in the hepatic cytosolic TG pool might affect their subsequent fate. For example, palmitate and stearate may be desaturated by the enzyme stearoyl-CoA desaturase (SCD), the enzyme responsible for the synthesis of monounsaturated fatty acids (18). Recently, it has been demonstrated that measuring the ratios of SCD product and precursor fatty acids in VLDL-TG is reflective of hepatic SCD expression (38). Measuring SCD activity in vivo in humans is difficult, but we have recently demonstrated dietary-induced differences in hepatic SCD activity by using stable isotope methodology (10).

The ketone body 3-hydroxybutyrate (3-OHB) is a product of acetyl-CoA that is liberated from hepatic fatty acid β-oxidation, and blood levels of 3-OHB reflect hepatic ketogenesis (23). The major precursors for 3-OHB formation are nonesterified fatty acids (NEFAs) (23). It has been calculated that, over a concentration range of plasma NEFA between 200 and 400 μmol/l, 7–13% of fatty acids are converted to ketone bodies during fasting (7). In the postprandial state, precursors would include fatty acids arising from adipose tissue lipolysis and dietary spillover fatty acids. Whether fatty acids released from lipolysis of cytosolic TG are oxidized is less clear (3, 20). Few studies have investigated the influence of adiposity on 3-OHB production. Lower production (42) and fasting concentrations (45) of 3-OHB have been reported in obese compared with lean subjects. It is not known whether adiposity affects the postprandial suppression of 3-OHB production. It could be hypothesized that a lower partitioning of fatty acids toward 3-OHB production in obesity, resulting from hyperinsulinemia, may contribute to liver fat accumulation.

Hepatic fatty acid partitioning has been investigated in the fasting state (23) because it allows kinetic modeling, since fatty acid flux is in a steady state. Recently, various models of postprandial lipemia have been used to investigate the contributions of fatty acids to TRL-TG (2, 11, 44) and VLDL-TG (24, 25). Although these studies have been very informative, we know that repeated meals can markedly affect postprandial lipid handling (17, 40). Therefore there is a need to investigate hepatic fatty acid partitioning after multiple meals representative of normal daily life. The

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hepatic partitioning of fatty acids may also be influenced by adiposity. Since people with abdominal obesity are likely to have more liver and visceral fat (31), we hypothesize that the hyperinsulinemia resulting from abdominal obesity will increase the partitioning of fatty acids toward esterification with a greater contribution of fatty acids from splanchnic sources (25) to VLDL-TG, and this will be at the expense of oxidation, which will result in lower 3-OHB and $^{13}$CO$_2$ production. We aimed to study hepatic fatty acid partitioning in a group of healthy men in relation to adiposity over 24 h with three mixed meals.

**EXPERIMENTAL PROCEDURES**

**Subjects.** Nine lean and ten abdominally obese males, comparable for age (22–58 yr), were recruited from the Oxford Biobank (43) and from the wider Oxford community. All subjects attended a screening visit to ensure suitability for the study: all subjects were healthy, had an absence of any medication, were nonsmoking, and had moderate alcohol consumption. The inclusion criteria for the abdominally obese group were BMI between 27 and 35 kg/m$^2$, waist circumference >99 cm, fasting glucose <6.1 mmol/l, fasting plasma TG <3.0 mmol/l, and nonsmoking status. Fat mass was estimated by bioelectrical impedance. Some data from eight of the lean males have been reported previously (40). Prior to the study day, subjects were asked to avoid foodstuffs naturally enriched in $^{13}$C for 48 h and refrain from strenuous exercise and alcohol for 24 h before the study. The study was approved by the Oxfordshire Clinical Research Ethics Committee, and all subjects gave written informed consent. The study also involved measurements of tissue metabolism by selective venous catheterization. Data from those aspects will be published separately.

**Study day.** Subjects arrived at the clinical research unit after an overnight fast. After cannulation of the femoral artery, an intravenous infusion of $[^2H_2]$palmitic acid (16:0; isotope purity 97%, CK Gas Products) complexed with albumin (Blood Transfusion Service, John Radcliffe Hospital, Oxford, UK) was started (infusion rate 0.01 μmol kg$^{-1}$ min$^{-1}$) as previously described (40). A baseline (time 0) blood sample was taken, and subjects were fed the first of three isoenergetic mixed test meals that were each tagged with a unique $^{13}$C-labeled fatty acid to trace the fate of dietary fatty acids (40) (Fig. 1; for further detail see supplementary information in the online version of this paper). Samples were taken at 29 time points over the 24 h for the measurement of plasma TG concentrations, over 12 time points for the isotopic enrichment of plasma TG and NEFA (40) and at 0, 5, 10, 15, 18, and 24 h for the analysis of VLDL-TG.

Samples of breath were collected at 29 time points into EXETAINER$^{®}$ tubes (Labco, High Wycombe, Buckinghamshire, UK) for measurement of $^{13}$CO$_2$ enrichment.

To assess differences in the metabolic handling of the tracer fatty acids, we fed [U-$^{13}$C]linoleic acid, [U-$^{13}$C]oleic acid, and [U-$^{13}$C]palmitic acid simultaneously in a single test meal and compared the appearance of all three fatty acids in chylomicron-TG (26). Accordingly, the three fatty acids used in the sequential meals had a similar appearance in chylomicron-TG (26) and plasma TG (40) after feeding.

**Analyses.** Whole blood was collected into heparinized syringes (Startstedt, Leicester, UK). Plasma was rapidly separated as previously described (25) for the measurement of metabolite and insulin concentrations. Plasma NEFA and TG, lipoprotein-TG, and alanine aminotransferase (ALT) were determined enzymatically as previously described (8). Apolipoprotein B (apoB) and C-reactive protein (CRP; high-sensitivity assay) were analyzed by turbidimetric methods. γ-Glutamyl transferase (γ-GT) was analyzed using a routine biochemical service. Whole blood was added to perchloric acid (PCA) for analysis of 3-OHB as described previously (28).

Separations of Svedberg flotation rate (S$_{20-400}$) chylomicrons and VLDL-rich fraction (S$_{20-400}$) were made by sequential flotation using density gradient ultracentrifugation (29). The S$_{20-400}$ fraction was then further separated by immunoaffinity chromatography directed against apoB-100 and the bound (VLDL) and unbound (chylomicron remnant-rich fraction) fractions were collected (24). The chylomicron remnant TG concentration was calculated from isotopic enrichment values in the unbound fraction (see supplementary information).

**Fatty acid analysis.** Specific fatty acid composition and isotopic enrichment in NEFA and TG were measured as previously described.
(24). Known weights of internal standards were added prior to lipid extraction so that fatty acid concentrations could be determined. Fatty acid compositions (µmol/100 µmol total fatty acids) in these fractions were determined by gas chromatography (13), and the linoleate, oleate and palmitate concentrations were determined as previously described (26).

Analysis of $[^{2}H_{2}]$palmitate and $[^{13}C]^{2}$C enrichments in plasma lipids and $[^{13}C]^{2}$C in breath CO$_{2}$. $[^{2}H_{2}]$palmitate enrichments in the fatty acid methyl ester (FAME) derivatives of plasma NEFA and VLDL-TG were determined by gas chromatography–mass spectrometry (GC-MS) (8). The $[^{13}C]^{2}$C ratios in [U-$^{13}$C]linoleate, [U-$^{13}$C]oleate, and [U-$^{13}$C]palmitate were measured in the plasma NEFA, TG, chylomicron-TG, and VLDL-TG FAME derivatives using a Delta Plus XP GC-combustion-isotope ratio MS (GC-C-IRMS; Thermo Electron, Bremen, Germany) (9). The $[^{13}C]^{2}$C ratio in breath samples was also measured by GC-C-IRMS (9). Tracer-to-tracee ratios (TTRs) of a baseline measurement (before administration of the stable isotope tracer) were subtracted from each sample TTR to account for natural abundance. TTRs for $[^{2}H_{2}]$palmitate and for [U-$^{13}$C]linoleate, [U-$^{13}$C]oleate, and [U-$^{13}$C]palmitate were multiplied by the corresponding linoleate-, oleate-, and palmitate- NEFA or TG concentrations to give tracer concentrations. The rate of expiration of $[^{13}C]^{2}$C in breath was calculated by multiplying the estimated VCO$_{2}$ (12) by the enrichment of breath CO$_{2}$.

Analysis of $[^{13}C]^{3}$-OHB enrichment. To assess ketone body production arising from the oxidation of dietary fatty acids, we measured isotopic enrichment from U-$^{13}$C-labeled fatty acids appearing in 3-OHB in deproteinized blood using a modified method of Beylott et al. (6). TTRs for 3-OHB (M+2)/(M+0) were multiplied by the corresponding blood 3-OHB concentration determined enzymatically to give breath $[^{13}C]^{3}$-OHB concentrations (µmol/l).

Calculations and statistics. Calculations of the contribution of different sources of fatty acids to VLDL-TG were performed as previously reported [online APPENDIX (25)], but for this study we used meal TTR rather than chylomicron TTR. The contribution from splanchnic lipolysis (mainly visceral adipose tissue) together with hepatic sources (such as DNL and hepatic TG) will be referred to as splanchnic sources. The contribution of chylomicron-derived spillover fatty acids to VLDL-TG was not calculated during the overnight splanchnic sources. The contribution of chylomicron-derived spillover and chylomicron remnants to VLDL-TG at five time points (iAUC 915 µmol/l) and 3-OHB concentrations over 24 h than the lean males (AUC 1,588 ± 142 vs. 1,080 ± 70 µmol/l and 667 ± 84 vs. 425 ± 3 µmol/l, P = 0.007 and 0.022, respectively; Fig. 2, A and B). However, the magnitude of change in plasma TG over the 24 h was similar between the groups (iAUC 1,105 ± 240 vs. 1,552 ± 181 µmol/l), but abdominally obese males had higher Sf20–400 lipoprotein-TG responses than lean males (AUC 283 ± 19 vs. 309 ± 12, lean vs. abdominally obese men). By 24 h, plasma TG, glucose, and insulin concentrations were very similar to baseline values in both groups.

Abdominally obese males had higher plasma TG and Sf20–400 lipoprotein-TG concentrations over 24 h than the lean males (AUC 1,588 ± 142 vs. 1,080 ± 70 µmol/l and 667 ± 84 vs. 425 ± 3 µmol/l, P = 0.007 and 0.022, respectively; Fig. 2, A and B). However, the magnitude of change in plasma TG over the 24 h was similar between the groups (iAUC 1,105 ± 240 vs. 1,552 ± 181 µmol/l), but abdominally obese males had higher Sf20–400 lipoprotein-TG responses than lean males (AUC 915 ± 116 vs. 17 ± 177 µmol/l, P = 0.001, respectively; Fig. 2, A and B). Over the 24-h period, abdominally obese compared with lean men had a twofold higher concentration of chylomicron-derived remnant TG in plasma (AUC 55 ± 15 vs. 21 ± 5 µmol/l, P = 0.035, respectively).

Incorporation of labeled meal fatty acids into plasma lipids. Lean and abdominally obese males exhibited similar patterns of incorporation of [U-$^{13}$C]linoleate, [U-$^{13}$C]oleate, and [U-$^{13}$C]palmitate into plasma TG (Fig. 3, A and B), the plasma systemic NEFA pool (Fig. 3, C and D) and VLDL-TG (Fig. 3, E and F).

Incorporation of fatty acids into VLDL-TG. We determined the different fatty acid sources in VLDL-TG at five time points.

<table>
<thead>
<tr>
<th>Table 1. Subject characteristics</th>
<th>Lean Males</th>
<th>Abdominally Obese Males</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>Age, yr</td>
<td>37 ± 4</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>BMI, kg/m$^2$</td>
<td>22 ± 1</td>
<td>31 ± 4***</td>
</tr>
<tr>
<td>Waist circumference, cm</td>
<td>81 ± 1</td>
<td>108 ± 2***</td>
</tr>
<tr>
<td>Total body fat mass, %</td>
<td>15 ± 1</td>
<td>25 ± 1***</td>
</tr>
<tr>
<td>HOMA</td>
<td>2.1 ± 0.1</td>
<td>3.1 ± 0.5*</td>
</tr>
<tr>
<td>Fasting concentrations‡</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total cholesterol, mmol/l</td>
<td>4.0 ± 0.3</td>
<td>4.7 ± 0.3</td>
</tr>
<tr>
<td>HDL cholesterol, mmol/l</td>
<td>1.1 ± 0.1</td>
<td>1.0 ± 0.0</td>
</tr>
<tr>
<td>Triglyceride, mmol/l</td>
<td>0.9 ± 0.1</td>
<td>1.2 ± 0.1*</td>
</tr>
<tr>
<td>Nonesterified fatty acids, µmol/l</td>
<td>599 ± 51</td>
<td>568 ± 43</td>
</tr>
<tr>
<td>Glucose, µmol/l</td>
<td>5.2 ± 0.1</td>
<td>5.2 ± 0.1</td>
</tr>
<tr>
<td>Insulin, µmol/l</td>
<td>63 ± 3</td>
<td>93 ± 13*</td>
</tr>
<tr>
<td>Alanine aminotransferase, U/l</td>
<td>13 ± 2</td>
<td>24 ± 4*</td>
</tr>
<tr>
<td>γ-glutamyl transferase, U/l</td>
<td>19 ± 3</td>
<td>27 ± 4</td>
</tr>
<tr>
<td>C-reactive protein, mg/l</td>
<td>0.8 ± 0.5</td>
<td>1.7 ± 0.5*</td>
</tr>
<tr>
<td>Blood 3-hydroxybutyrate, µmol/l</td>
<td>128 ± 34</td>
<td>130 ± 19</td>
</tr>
<tr>
<td>Plasma apolipoprotein B, g/l</td>
<td>0.7 ± 0.0</td>
<td>0.9 ± 0.1*</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE. HOMA, homeostasis model assessment. ‡Measured in plasma unless otherwise stated. *P ≤ 0.05, ***P < 0.001 lean vs. abdominally obese males.
over the 24-h period. The contribution of endogenous systemic NEFA to VLDL-TG at 24 h was similar between abdominally obese (70 ± 8%) and lean (84 ± 5%) men (Table 2).

Within 5 h of breakfast, dietary fatty acids (spillover fatty acids and chylomicron remnant TG) were incorporated into and represented 25% of VLDL-TG in lean and abdominally obese males, respectively. There was also a main effect of group when expressed as concentration of chylomicron remnant fatty acids in VLDL-TG. In this case, the differences were most marked during the latter part of the day (post-dinner and evening) when they were lower in the abdominally obese group (data not shown). Over time, abdominally obese males had a lower contribution of dietary fatty acids (P < 0.05) to VLDL-TG when expressed as a proportion; however, when expressed in absolute terms, the contribution was similar between the two groups (Table 2).

Splanchnic sources provided more fatty acids to VLDL-TG in abdominally obese than in lean males (P < 0.05) when expressed either in concentration terms or as a proportion (Table 2).

**DISCUSSION**

Humans spend most of each 24 h in a fed state, during which fatty acids from dietary sources play a major metabolic role (40). Our methodology allowed us to measure postprandial hepatic fatty acid partitioning by using a physiological three-meal protocol. We observed differences between lean and abdominally obese males over a 24-h period that would not have been as evident using a single-meal model. We demonstrate here that abdominally obese men have upregulation of pathways of fatty acid metabolism, namely desaturation by SCD and elongation and that these may be important for fatty acid esterification and export in VLDL-TG or oxidation. We also found evidence for increased oxidation along with increased utilization of dietary fatty acids for ketogenesis in the liver of the abdominally obese men. The upregulation of these pathways may underlie the relatively subtle differences, given the large difference in waist circumference, noted in the systemic concentrations of TG. In line with our previous work we found a greater contribution of fatty acids from splanchnic sources to VLDL-TG (25).

Hepatic fat accumulation represents a disturbed balance between fatty acid supply, including DNL, VLDL-TG secretion, and fatty acid oxidation. Our data shed new light on the regulation of oxidative disposal of fatty acids. Although abdominally obese and lean males had similar fasting concentra-
tions of blood 3-OHB, differences emerged over the postprandial periods, with abdominally obese males having significantly higher blood 3-OHB concentrations in contrast to our original hypothesis. A few studies have reported postprandial 3-OHB concentrations (14, 22, 25, 39), but none of these compared healthy lean and abdominally obese men. By measuring the incorporation of $^{13}$C from meal-derived fatty acids into blood 3-OHB, we found that, within 5 h of consuming a meal, a proportion of dietary-derived fatty acids entering the liver undergo β-oxidation and the acetyl-CoA liberated enters a pool that is used for ketogenesis. This occurred to a greater extent in abdominally obese than in lean males, and it would be reasonable to speculate that the higher concentration of 3-OHB and $^{13}$C-3-OHB noted in the abdominally obese group represents an upregulation of ketone body production to prevent hepatic fat accumulation. An alternative way of looking at these data is that abdominally obese males have hepatic insulin resistance leading to a lack of suppression in ketone body production in the postprandial period.

Additionally, abdominally obese males had greater breath $^{13}$CO$_2$, representing whole body oxidation of dietary fat, over the duration of the study. A plausible explanation for the higher
breath $^{13}$CO$_2$ in abdominally obese males is that dietary fatty acids are not rapidly taken up and stored in adipose tissue (27) but are taken up ectopically (32) in other tissues such as muscle and liver, leading to greater oxidation. The whole body oxidation is based on $^{13}$C derived from dietary fat only, and this could be an issue of partitioning. However, the organs that oxidize fatty acids are largely presented with NEFA, and the proportion of $^{13}$C in the NEFA fraction was actually lower in the abdominally obese group. This strongly suggests a mechanism beyond plasma concentrations, i.e., intracellular regulation.

Our data are in accord with the model proposed by Vedala et al. (44), whereby fatty acids enter hepatic pathways for immediate or delayed secretion. In a postprandial state, the appearance of $[^2H_2]$palmitate in VLDL-TG is very rapid (25). However, our data imply that fatty acids reaching the liver as chylomicron remnants enter the delayed secretory pathway. There appeared to be a longer delay in the appearance of chylomicron remnant fatty acids in VLDL-TG in the abdominally obese than in the lean males, and this could be due to abdominally obese males having a larger pool of cytosolic TG. The contribution of splanchnic fatty acids (i.e., from the hepatic cytosolic TG pool, visceral fat lipolysis, and DNL) to VLDL-TG was consistently higher in abdominally obese than in the lean males. These data suggest a profound difference between the groups, with the lean males able to “switch off” the contribution of splanchnic sources overnight, something abdominally obese males failed to do.

In summary, we investigated the regulation of hepatic pathways of fatty acid partitioning and compared handling of endogenous and exogenous fatty acids in healthy men who

### Table 2. Contribution of different fatty acid sources to VLDL-TG in lean and abdominally obese males

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Endogenous Systemic NEFA</th>
<th>Total Dietary Fatty Acids*</th>
<th>Splanchnic Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Lean</td>
<td>Abdominally Obese</td>
<td>Lean</td>
</tr>
<tr>
<td>Post-breakfast</td>
<td>35 ± 4</td>
<td>30 ± 3</td>
<td>25 ± 4</td>
</tr>
<tr>
<td>Post-lunch</td>
<td>30 ± 2</td>
<td>25 ± 3</td>
<td>39 ± 7</td>
</tr>
<tr>
<td>Post-dinner</td>
<td>23 ± 5</td>
<td>30 ± 4</td>
<td>53 ± 6</td>
</tr>
<tr>
<td>Evening</td>
<td>62 ± 4</td>
<td>51 ± 8</td>
<td>38 ± 3</td>
</tr>
<tr>
<td>Overnight</td>
<td>84 ± 5</td>
<td>70 ± 8</td>
<td>17 ± 2</td>
</tr>
</tbody>
</table>

Concentration, $\mu$mol/l

<table>
<thead>
<tr>
<th>Time Period</th>
<th>Lean</th>
<th>Abdominally Obese</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-breakfast</td>
<td>101 ± 17</td>
<td>124 ± 23</td>
</tr>
<tr>
<td>Post-lunch</td>
<td>83 ± 16</td>
<td>97 ± 16</td>
</tr>
<tr>
<td>Post-dinner</td>
<td>61 ± 9</td>
<td>109 ± 25</td>
</tr>
<tr>
<td>Evening</td>
<td>161 ± 22</td>
<td>188 ± 42</td>
</tr>
<tr>
<td>Overnight</td>
<td>200 ± 23</td>
<td>270 ± 50</td>
</tr>
</tbody>
</table>

Data are presented as means ± SE. *Based on appearance of $[^{13}C]$fatty acids i.e., dietary fatty acids fed over the 24-h study period. †$P < 0.05$ lean vs. abdominally obese males by repeated-measures ANOVA (main effect of group over whole experimental period).
differed in their adiposity. Our abdominally obese group had over twice the amount of body fat as the lean group and a waist circumference that was on average 33% higher. The metabolic processes in the liver were different between the two groups. Increases in the proportion of fatty acids being esterified or oxidized may be an important adaption to prevent the development of fatty liver and of dyslipidemia.

**ACKNOWLEDGMENTS**

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**Fig. 4.** Plasma NEFA [1-1H]6:0/16:0 tracer-to-tracee ratio (TTR; A, $P = \text{NS}$), VLDL-TG isotopic SCD index (B, $P = 0.008$), and isotopic elongation index (C, $P = 0.039$) in lean (●) and abdominally obese (○) males ($n = 9$ and 10, respectively). For explanation of indexes, see text. Data are presented as means ± SE.

**Fig. 5.** Plasma 3-OHB concentrations (A, $P = 0.007$) and enrichment of plasma 3-OHB (B, $P = 0.035$) and breath CO$_2$ (C, $P < 0.001$) with $^{13}$C from dietary fatty acids in lean (●) and abdominally obese (○) males ($n = 9$ and 10, respectively). Data are presented as means ± SE.
REFERENCES

No conflicts of interest are reported by the authors.

DISCLOSURES

Fellow; Fredrik Karpe was a Wellcome Trust Senior Clinical Research Fellow; Diabetologia 29: 90 –96, 1986.


Overproduction of large VLDL particles is driven by in-


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