Medical Consecuences of Obesity

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Abstract: Adipose tissue lipolysis provides circulating FFAs to meet the body's lipid fuel demands. FFA release is well regulated in normal-weight individuals; however, in upper- body obesity, excess lipolysis is commonly seen. This ab- normality is considered a cause for at least some of the metabolic defects (dyslipidemia, insulinresistance) associated with upper-body obesity. ''Normal'' lipolysis is sex-specificand largely determined by the individual's resting metabolic rate. Women have greater FFA release rates than men without higher FFA concentrations or greater fatty acid oxidation, indicating that they have greater nonoxidative FFA disposal, although the processes and tissues involved in this phenom- enon are unknown. Therefore, women have the advantage of having greater FFA availability without exposing their tissues to higher and potentially harmful FFA concentrations. Upper- body fat is more lipolytically active than lower-body fat in both women and men. FFA released by the visceral fat depot contributes only a small percentage of systemic FFA delivery. Upper-body subcutaneous fat is the dominant contributor to circulating FFAs and the source of the excess FFA release in upper-body obesity.We believe that abnormalities in sub-cutaneous lipolysis could be more important than those in visceral lipolysis as a cause of peripheral insulin resistance. Understanding the regulation of FFA availability will help to discover new approaches to treat FFA-induced abnormal- ities in obesity.—Koutsari, C., and M. D. Jensen. Free fatty acid metabolism in human obesity. J. Lipid Res. 2006. 47: 1643–1650.

Obesity is a global public health concern (1–3). It is well established that obesity, particularly upper-body obesity, is a major contributor to chronic disease and disability, such as dyslipidemia, hypertension, type 2 diabetes, and car- diovascular disease (4). A major link between upper-body obesity and metabolic complications is excessive adipose tissue lipolysis. Under normal conditions, FFA release from adipose tissue is well regulated, allowing appropriate availability of FFAs to meet the energy requirements of the tissues. Increased adiposity can result in excess FFA release relative to tissue needs. The resultant higher FFA concen trations can induce muscle (5) and hepatic (6) insulin resistance, endothelial (7) and pancreatic b-cell (8) dys- function, and increased VLDL triglyceride production (9). Thus, although adipose tissue is an excellent site for stor- age of energy and can provide FFAs at times of lipid fuel demands, appropriate regulation of its function is nec- essary for optimal health in humans.

Although upper-body obesity has been associated with a number of metabolic abnormalities, lower-body adiposity has been associated with a more favorable metabolic pro- file (10–13). It is currently unknown whether the accu- mulation of subcutaneous fat in the lower-body region exerts a direct protective effect against the unfavorable consequences of obesity or merely serves as a marker for the "healthy" regulation of other fat stores. However, these

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observations illustrate the complexity of the links between obesity, body fat distribution, and metabolic health.

The determination of lipolysis rates in humans in vivo requires the use of radioactive or stable isotopic tracers (fatty acids or glycerol). An infusion of a labeled glycerol tracer is easy to do and has been used for the measurement of whole-body glycerol release. It has been argued that glycerol release is considered a quantitative measure of whole-body lipolysis (19–24), but recent evidence suggests that the assumptions used to consider systemic glycerol release as an accurate measure of basal adipose tissue lipolysis may not be valid (25, 26). For example, under postabsorptive conditions, *1*) hepatic glycerol uptake is much more efficient than hepatic FFA uptake, greatly affecting the splanchnic FFA-to-glycerol release ratio; *2*) the glycerol entering the circulation from hepatic VLDL triglyceride production can be significant, and the portion of lipoprotein lipase-derived glycerol that enters the plasma can be quite variable; and *3*) muscle and adipose tissues are capable of taking up glycerol from the cir- culation (5,6). All of these factors introduce significant concerns in using systemic glycerol turnover rate as a quantitative measure of adipose tissue lipolysis. Therefore, we prefer FFA tracers for this purpose, despite the greater difficulty encountered in preparing these tracers for re- search studies.

Radiolabeled (^{3}H and ^{14}C) fatty acids for the study of adipose tissue lipolysis offer many advantages. Although it is necessary to use albumin to allow FFA tracers to become soluble in aqueous solutions for intravenous infusion, the small mass of tracer (often in the microgram to few milligram range) requires little albumin and can be accomplished relatively quickly. The study of whole-body and especially regional FFA flux with radiotracers requires extremely accurate and precise measurement of FFA specific activity (SA) (dpm/nmol). Early studies of FFA kinetics used the approach of measuring FFA radioactivity and concentrations. FFAs were isolated from plasma with extraction (10), and separate aliquots were assayed for radioactivity (dpm/ml) and fatty acid content (nmol/ml). By dividing the former by the latter, FFA SA (dpm/nmol) was calculated. Although this is an easy method for mea- suring FFA SA, it has the disadvantage that low FFA concentrations ($\sim$50 mmol/l) are difficult to measure accurately with most assays. In addition, the FFA concen- tration and SA measurements are linked, making it impossible to draw legitimate conclusions about FFA clear- ance. FFA clearance is calculated using the FFA turnover/ disappearance (FFA tracer infusion rate 4 steady-state FFA SA) divided by the FFA concentation. This method for measuring FFA flux requires that FFA concentration be used in both the numerator (for the calculation of FFA SA) and the denominator, which compromises the validity of the FFA clearance values.

Ideally, FFA SA should be determined independent of FFA concentration. An analytical technique developed in our laboratory (3) allows the accurate determination of FFA SA using HPLC. By collecting the HPLC fraction and measuring the radioactivity (dpm) while simulta- neously measuring the absolute fatty acid content (nmol) in that fraction, the SA (dpm/nmol) can be determined independent of FFA concentration. Another major strength of this method is that the measurement of SA is independent of variations in recovery, because the re- coveries of tracer and tracee are linked. Furthermore, by adding an internal standard (we use [^{2}H$_{31}$]palmitate be- cause of its favorable chromatographic properties) and creating a six point standard curve, plasma concentra- tions of individual plasma fatty acids can be measured down to $\sim$5 mmol/l with accuracy and precision.

We have shown that this method can measure the inflow of a known infusion of exogenous FFAs during adipose tissue lipolytic inhibition with $\sim$90% accuracy (6). Thus, isotope dilution techniques can be used for quan- titatively accurate measurements of FFA inflow into the plasma space, providing that the appropriate analytical techniques, infusion-sampling mode, and equations are used (31–33).

FFA turnover using stable isotopic tracers

The major disadvantages of radiolabeled fatty acid tracers are the radiation exposure and the requirement for radioactivity-approved research facilities. The use of stable isotopic tracers, such as [1-^{13}C]palmitate, for the measurement of FFA turnover overcomes these issues. Indeed, [1-^{13}C]palmitate has been widely used for the determination of FFA kinetics (9). However, the use of 1-^{13}C-labeled fatty acids is not without disadvan- tages overcome the rapid FFA turnover, the high natural abundance of ^{13}C, and the relatively low preci- sion of most GC-MS equipment, a high tracer infusion rate (0.04 mmol/kg body mass/min) is necessary. This FFA infusion rate requires a large amount of albumin and is very time-consuming to prepare. For example, a 3 h FFA tracer infusion study may require as much as 25 g of albumin.

Another approach is to use gas chromatography/com- bustion/isotope ratio mass spectrometry (GC/C/IRMS) because of its superior sensitivity and lower detection limit by 1 order of magnitude. The use of a GC/C/IRMS system requires less 1-^{13}C-labeled fatty acid to be infused; how- ever, its sensitivity is somewhat compromised as a result of the high natural abundance of ^{13}C. This can be largely overcome by using [U-^{13}C]palmitate (or other uniformly labeled FFAs) as a tracer, which allows further reduc- tions in the tracer infusion rate without sacrificing sensi- tivity (11). Ultralow infusion rates (postabsorptive state,

0.05 nmol/kg body mass/min) of [U-^{13}C]palmitate in combination with GC/C/IRMS analysis provided palmi- tate flux values identical to those obtained with established radiotracer methods in a variety of conditions (4). De- spite the high cost of [U-^{13}C]palmitate, the reduced prep- aration time and required amounts of tracer and albumin make it a highly advantageous stable isotopic fatty acid tracer for FFA turnover studies in humans.

Assessment of body fat distribution

Measurement of regional fat content is important when examining the fat depots that best relate to the metabolic complications of obesity. Furthermore, accurate quantifi- cation of regional body fat is crucial when assessing the contributions of the different sources of circulating FFAs. Accurate and precise determination of body fat distribution depends on imaging techniques, namely MRI, computed tomography (CT), and dual-energy X-ray absorptiometry (DEXA). DEXA measures the mass of total-body and regional fat with low radiation exposure (12). However, DEXA cannot distinguish between subcutaneous and visceral fat. Multi-slice CT and MRI are the gold standards for differentiating between these two fat depots. We have found that a combination of single-slice CT at the L_2-L_3 or L_3-L_4 interspace (to determine the visceral-to-total ab- dominal adipose tissue ratio) and DEXA-measured total abdominal fat provides an estimate of visceral fat mass that correlates extremely well (r 5 0.98, P , 0.001) with multi- slice CT-measured visceral fat (3). This combined ap- proach provides complete body composition information and substantially reduces radiation exposure without com- promising the accuracy of visceral mass determination.

Although it is commonly said that FFA release is abnormal in obesity, this actually requires an understand- ing of what is "normal" FFA flux. Unfortunately, even after 40 years of active research, there is no complete consensus on the mode of expression of systemic FFA flux. Some investigators normalize FFA turnover rate to fat-free (or lean) body mass, whereas others normalize it to fat mass or total body mass. Finally, some prefer to present the absolute FFA flux values (mmol/min), not dividing by body mass or any body compartment. The different modes of data presentation appear to reflect the different points of view of the investigators. For example, FFA flux can be seen as the rate of FFA release from the adipose tissue or as the outflow rate of FFA from the systemic circulation to fatty acid-consuming tissues. Table 1 provides FFA flux values in different modes of expression in lean and obese individuals from studies conducted in different laborato- ries. Lean body mass and fat-free mass are used inter- changeably in this review for simplicity.

By dividing systemic FFA flux by fat mass, the focus becomes the release of FFA from

body fat stores. In this way, the rates of lipolysis of obese and lean individuals are compared on the basis of their different adiposity levels. In most (7) but not all (8) studies in which basal FFA turnover rate was expressed per unit of fat mass, FFA release rates (mmol/kg fat/min) were >50% less in obese than in lean individuals. This indicates that FFA availability is not in direct proportion to adipose triglyceride store. It has been argued that this downregulation of FFA release per unit of fat mass is attributable to the fasting hyperinsulinemia of obesity, which may be ad-vantageous by preventing massive increases in plasma FFA concentrations.

Another line of thinking is that the overall rate of lipolysis is governed by the requirements of the fat-free tissue mass rather than the fat stores or the total tissue mass (4). In other words, because FFA disposal occurs predominantly by fat-free tissues such as muscle and liver, it is preferable to correct FFA lipolysis rates for differ- ences in fat-free mass when comparing lean and obese volunteers. When such a correction is made, postabsorp tive FFA lipolysis (mmol/kg fat-free mass/min) is usu- ally greater in obese than in lean volunteers by z60%. Furthermore, we observed that FFA flux relative to lean body mass is higher in upper-body obese (UBO) than in lower-body obese (LBO) women and lean women, which indicates that there are major differ- ences in the regulation of adipose tissue lipolysis between these two obesity phenotypes (4,5). There are, how- ever, studies in which FFA lipolysis corrected for fat-free mass was not significantly different between UBO and lean women (10).

It is evident that depending on the mode of expression that is chosen, basal FFA lipolysis in obese individuals can be lower, higher, or not different compared with that in lean individuals. The obvious question is how FFA flux data should be presented. First, we have to examine whether the modes of presentation described above are legitimate or not. The answer is that the per-mass expressions for FFA flux (and probably for most physio- logical variables) can lead to erroneous conclusions. This means of data expression assumes that the two variables (the numerator and denominator) are associated in a ratio standard manner. That is, the rate of FFA release into the bloodstream is directly proportional to the tissue mass such that the line of the regression passes through the origin. Unfortunately, the regression line fitting the data (FFA flux versus mass) does not have a slope of 1 or an intercept of 0. We believe that the use of the per-mass standards for FFA flux can result in misleading conclu- sions if the persons being studied differ significantly in lean body mass or resting energy expenditure (REE). Fur- thermore, expressing systemic FFA release per total fat mass implies that lipolytic homogeneity exists between the different fat depots, which, as will be shown below, is not the case in humans in vivo.

To address the unsettled issue of normal lipolysis, we investigated the association between basal FFA flux, body composition, REE, and hormone concentrations in 50 men and women with a wide range of body fat content and distribution (13). We found that FFA release rates were not significantly correlated with fat-free mass for the group as a whole but were highly correlated with REE as mea- sured by indirect calorimetry. Multivariate regression analyses revealed that REE, sex, and plasma epinephrine predicted most of the interindividual variability in FFA release, whereas total fat mass and fat-free mass were not significant predictors. Indices of insulin resistance (fasting plasma insulin or plasma insulin area under the curve during oral glucose tolerance test) did not help predict FFA release after accounting for REE.

We propose that resting energy requirements are a major factor determining the rate at which adipose tissue releases FFA into the circulation in resting humans. This is supported by the observation that individuals in whom palmitate release rates were higher than their REE- predicted normal lipolysis had higher plasma palmitate concentrations and vice versa (12). The best approach to compare groups is to match them on the basis of REE, which usually can be accomplished by matching for fat- free mass. If this cannot be done, linear regression analysis using REE as a covariable can overcome the nonmatching issue. We

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suggest that comparing FFA release per unit of tissue mass be reserved for instances in which, for ex- ample, one is comparing lipolytic rates between different adipose depots in the same individual, rather than when comparing whole body rates between persons of differ- ing characteristics. Provided that cells that could be adversely affected by increased FFA concentrations are not the same cells res- ponsible for the increased FFA clearance in women, these tissues (muscle, pancreatic b cells, etc.) most likely cannot detect the greater FFA "flux" in women per se. Thus, to the extent that the cells/tissues responsible for the higher FFA clearance are not adversely affected, the fact that women have the same FFA concentration at higher flux rates gives them the advantage of having greater FFA availability with- out exposing "FFA-sensitive" tissues to higher and poten- tially harmful FFA concentrations. Because women do not seem to have adverse health consequences despite greater FFA flux, we suspect that the greater FFA clearance in women is not into tissues that can be harmed by high FFA exposure (e.g., muscle).

By combining measures of leg and splanchnic blood flow, FFA balance, body composition analysis, and the isotope dilution technique, we compared the lipolytic rates of upper-body and lower-body fat tissue in the postabsorptive state in lean men and women (5). We found that upper-body adipose tissue FFA release (mmol/ kg fat/min) was significantly greater than lower-body FFA release in both sexes. In women, average FFA release rates from the upper-body and lower-body adipose tissue were 41 and 18 mmol/kg fat/min, respectively. Corresponding values in men were 53 and 27 mmol/kg fat/min. Therefore, upper-body fat is lipolytically more active than lower-body fat in both men and women. FFA release from leg, splanchnic, and upper-body subcutaneous fat averaged 20, 14, and 65% of systemic FFA flux, respective- ly. Correlations between systemic FFA flux and regional FFA release were similar between sexes. These results provided strong evidence of regional adipose tissue heterogeneity but also suggested that regional differences in postabsorptive lipolytic rates are not a mechanism for differences in body fat distribution between men and women. A recent study that compared fat mobilization from gluteal and subcutaneous abdominal adipose tissue in lean men in vivo confirmed that lower-body fat (stored either in legs or buttock) is sluggish in terms of fatty acid release (14).

We also studied UBO, LBO, and lean women in an attempt to examine regional FFA release in groups with distinct body fat distribution and adiposity levels. We found that postabsorptive leg fat FFA release rate (mmol/ kg fat/min) was similar between UBO and LBO women and was efficiently downregulated in both groups com- pared with lean women. Upper-body FFA release was downregulated in LBO but not in UBO women. Net splanchnic FFA release was similar between obese and lean women. Collectively, these studies indicated that upper- body subcutaneous (nonsplanchnic) fat is the source of the excess FFA release in UBO women and the major contributor to systemic FFA release in both sexes in the resting postabsorptive state.

Visceral fat has been suggested to be causally related to insulin resistance (15, 16). Little information on the contribution of visceral lipolysis to FFA delivery to the liver and systemic FFA availability exists in humans. If the contribution of visceral fat is high in upper-body obesity, this may indicate an important role for visceral lipolysis in hepatic and systemic FFA metabolism. Thus, understand- ing of visceral adipose tissue metabolism can help determine the potential importance of visceral fat depots in FFA-induced insulin resistance.

Unfortunately, measurement of net or new FFA release by the splanchnic region (using splanchnic arteriovenous balance and isotope dilution techniques) does not measure visceral adipose tissue lipolysis, because the liver removes a substantial portion of both visceral and systemic FFAs that flow through the portal vein. The FFAs entering the splanchnic bed from the systemic circulation can be partially taken up by nonhepatic splanchnic tissues and then by the liver, whereas visceral fat-derived FFAs are only taken up by the liver. This creates an unknown in the mathematical attempts to understand visceral lipolysis when

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dealing with hepatic vein data. We tested whether it is possible to predict the fraction of FFAs delivered to the liver that originate from visceral lipolysis by modeling data obtained from arterial and hepatic vein sampling without collecting portal vein blood (57). To this end, we per- formed studies of intrasplanchnic FFA kinetics in dogs with hepatic vein, portal vein, and arterial catheters (16). We found that the values predicted by the mathematical model were highly correlated with the observed values of visceral adipose tissue contribution of FFAs to hepatic FFA delivery. The model was especially good when plasma FFA concentrations were normal or high but was less good when FFA concentrations were low. On average, the model slightly overestimated the relative contribution of visceral fat (15% predicted vs. 11% measured). Specifically, much has been learned about the contri- bution of FFAs to systemic health and metabolic dysfunc- tion during the past 10–20 years. Excess FFAs, created experimentally in lean, healthy adults, can recreate many of the metabolic abnormalities seen in visceral/upper- body obesity, a condition associated with excess FFAs.

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