Regional Fat Deposition as a Factor in FFA Metabolism

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Key Words

body fat distribution, obesity, body composition, isotope dilution techniques

Abstract

Humans have a large variability in body fat distribution, which has tremendous implications for metabolic health. Obese individuals with an upper-body-fat distribution have increased health complications such as dyslipidemia, hypertension, insulin resistance, and type 2 diabetes in comparison with lower-body-obese individuals. Additionally, females have more body fat, a greater proportion of fat in their lower body, and much less visceral fat than do lean males at the same body mass index. The reasons for these differences in body fat distribution have not been clearly identified but could be important. Herein we review what has been learned about regional differences in triglyceride storage capacity and lipolysis as they relate to the causes and consequences of regional fat accumulation. Both sex and site differences in regional fat storage have been described. In contrast, with the exception of variations between men and women in the contribution of visceral adipose tissue to hepatic FFA delivery, most studies have failed to show important sex differences in regional lipolysis in vivo.

Contents

INTRODUCTION

Importance of Regional Fat Distribution

DEXA: dual-energy X-ray absorptiometry

CT: computed tomography

The large variability in human body fat distribution has tremendous implications for metabolic health. Obese individuals with an upper-body-fat distribution have increased health complications such as dyslipidemia, hypertension, insulin resistance, and type 2 diabetes in comparison with lower-body-obese individuals (47). Additionally, females have more body fat, a greater proportion of fat in their lower body, and much less visceral fat than do lean males at the same body mass index. The reasons for these differences in body fat distribution have not been clearly identified but could be important. Regional differences in triglyceride storage capacity (71) and/or lipolysis (101) have been proposed as determining regional fat accumulation, and in vitro studies of regional adipocytes have suggested both mechanisms may be operative. Sex differences in regional storage capacity of meal triglycerides have been reported previously (77, 93, 99). Additionally, investigators attempting to find variations in regional lipolysis in vivo (36, 63) have been unable to document important sex differences in this regard.

POTENTIAL ROLE OF MEAL FAT UPTAKE AND REGIONAL BODY FAT DISTRIBUTION

Methodology

In order to quantitatively measure meal fat uptake, it is also necessary to accurately and reliably measure regional body fat distribution. Many methods of assessing total body fat are available today, each with their limitations. Skinfold thickness is the cheapest and most accessible measurement of body fat, but the accuracy and reproducibility is highly variable depending on the skill of the individual taking the measurements. Underwater weighing and bioelectrical impedance (34) analysis can also be used to determine total body fatness, but regional body fat distribution is not readily attainable. Dual-energy X-ray absorptiometry (DEXA), which has historically been used for measurement of bone mineral density, has become the most widely used and accepted means for determining total and regional fat-free and fat mass (102). Computer software can be used to analyze DEXA scans for upper- and lower-body fat/fat-free mass, but no distinction can be made between subcutaneous and visceral fat. For this, computed tomography (CT) scans can be used to obtain abdominal slices that can be examined, in combination with DEXA, to determine visceral fat content (39). Being able to accurately measure regional fatness allows further study of the uptake of fatty acids into fat and the release of fatty acid from fat in the context of the regional fat content.

Meal fatty acids labeled with stable (^{13}C and ^{2}H) and radioactive (^{14}C and ^{3}H) isotopes have been used in clinical research to monitor the fate of dietary fat (17, 42, 50, 77, 81, 93, 95, 103). In particular, carbon isotopes have a long history of use. When ^{13}C- or ^{14}C-labeled fatty acids are given in meals, the isotopically labeled carbon atoms from the oxidation of triglyceride fatty acids are converted to $^{13}CO_2$ or $^{14}CO_2$. The majority of the labeled CO_2 produced is excreted in the

expired air, so that breath samples can be analyzed to measure meal fatty acid oxidation. Yet, some difficulties exist when one chooses to use carbon-labeled fatty acids. A controlled environment is needed for frequent collection of breath samples in order to determine the production rates of the labeled CO_2 per unit time and to calculate cumulative recovery over the study period. Additionally, with the use of carbon tracers, respiratory gas exchange measurements are needed because the CO_2 flux is needed to calculate production rates. This is time consuming and restrictive of daily activity (1). Finally, the potential exists for isotopic exchange of the carbon tracer at several steps along the tricarboxylic acid cycle (87, 88), resulting in an incomplete label ($^{14}CO_2$ or $^{13}CO_2$) excretion and, therefore, an underestimation of fatty acid oxidation. The label fixation also appears to differ depending upon whether the fatty acid is labeled on an even or an odd carbon; as a result, many studies use fatty acids labeled on the first carbon, e.g., [1-^{14}C]oleate. A solution to these problems has been to adjust fatty acid oxidation from CO_2 recovery using a correction factor, which requires an additional study day (84, 85, 87, 88). The advantage of this approach, however, is the ability to measure rates of meal fatty acid oxidation over time and to assess how interventions affect rates of oxidation.

Given some of the difficulties in using carbon tracers of meal fat, the use of deuterium- or tritium-labeled fatty acids provides a good alternative. The loss of deuterium/tritium label in the tricarboxylic acid cycle is minimal and therefore should not require a correction for exchange reactions (68, 77, 97). The use of hydrogen labeling eliminates the need for frequent sampling as well as the measurement of respiratory gas exchange. Hydrogen labels, when oxidized, appear as ^2H_2O or ^3H_2O and mix with the body water pool. Other than minimal losses as urine and insensible water (82, 83), the remaining tracer provides a cumulative record of fat oxidation that is easily collected by obtaining urine samples. The disadvantage of using hydrogen-labeled fatty acids is that measuring oxidation rates still requires frequent sampling of body water (blood, saliva, or urine). In general, however, carbon or hydrogen tracers may be used to measure meal fat oxidation and uptake, as long as the limitations of each method are acknowledged.

A meal triglyceride or fatty acid may take several potential pathways upon ingestion. One of these is oxidation, which is the easiest pathway to measure in human study participants. By using these methods (44, 77, 83, 93, 97) it is possible to trace the fate of the fat from a single meal toward oxidation and, therefore, how a variety of interventions or conditions may affect meal (exogenous) fat oxidation (4, 6, 7, 93, 95). Furthermore, exogenous fat oxidation may be combined with indirect calorimetry to assess the contribution of endogenous fats as well.

It is also possible to measure the appearance of the labeled triglycerides into the plasma chylomicron pool. Meal fatty acids first appear in chylomicrons (77, 99), but also in the free fatty acid (FFA) fraction (78) and then in VLDL-triglycerides (31, 32). Thus, the metabolic fate of ingested fat can be quite complex. In general, meal fat is largely cleared from the plasma compartment within 24 hours (40), presumably partitioned between oxidation and storage elsewhere in the body.

Tracer methodology can also be used to assess triglyceride storage by adipose tissue. Adipose tissue lipoprotein lipase (LPL) activity (20) and arteriovenous balance (14–16, 63) measurements are used as measures of the ability to take up and store triglyceride. Unfortunately, LPL activity measures only one component of the processes that regulate the storage of fatty acids in adipose tissue, and measuring the rate of uptake using arterial-venous balance techniques is usually done over more limited periods of time, which may miss some of the integrated uptake of dietary fat. An approach developed by Björntorp et al. (9) involved administering meals containing a radiolabeled fatty acid tracer and performing adipose tissue biopsies following meal

VLDL: very-low-density lipoproteins

LPL: lipoprotein lipase

absorption. This allowed investigators to have an integrated measure of meal fatty acid storage in adipose tissue. This technique has been applied by several groups (40, 54–56, 77, 93, 99) to directly measure the uptake of dietary fat by adipose tissue in humans in vivo under a variety of conditions. Uptake of dietary fatty acids into visceral fat depots can be assessed, but this requires combining the meal tracer study with planned surgical interventions (40, 55) and is therefore more difficult. Meal fat uptake into skeletal muscle can also be assessed through biopsies (5). Meal fat uptake into an organ such as liver, adipose tissue, or muscle can also be ascertained by measuring the arterio-venous differences across the regions of interest (15, 63). This, however, requires many assumptions and calculations, whereas biopsies provide a direct measure of meal fat uptake.

Update on Research Findings

When assessing regional disposal of meal fat, the measurement of tracer oxidation is imperative to gaining a more complete understanding of the processes that occur. Some of the earlier studies of meal fat uptake into adipose tissue did not measure meal fat oxidation (9, 55, 56) and thus provided an incomplete picture of meal fat trafficking. The oxidation of meal fats is influenced by a myriad of factors. For example, physical activity or inactivity can alter the portion of meal fat that is targeted to oxidation versus nonoxidative pathways, at least over the short term (**Figure 1**). Another consistent finding that must be taken into account when designing studies to address meal fat utilization is that the level of oxidation is specific to fatty acid type. In general, oxidation decreases with fatty acid chain length and degree of saturation (17, 43, 44, 53, 80, 98). **Figure 2** illustrates some of the variability in the percent of the individual fatty acid doses recovered from a single meal after 9–13 hours using ^{13}C tracers that were not corrected for sequestration (4, 43, 62, 95–98). Some of these differences may be attributable to variations in gastro-intestinal handling (41, 62), but there may also be differences in the handling of fatty acids on a cellular level (11). Additionally, the amount of fat given in a test meal may affect the partitioning of fat toward oxidation. Sonko et al. (89) reported an inverse relationship in the size of the fat load and postprandial oxidation when the meal fat

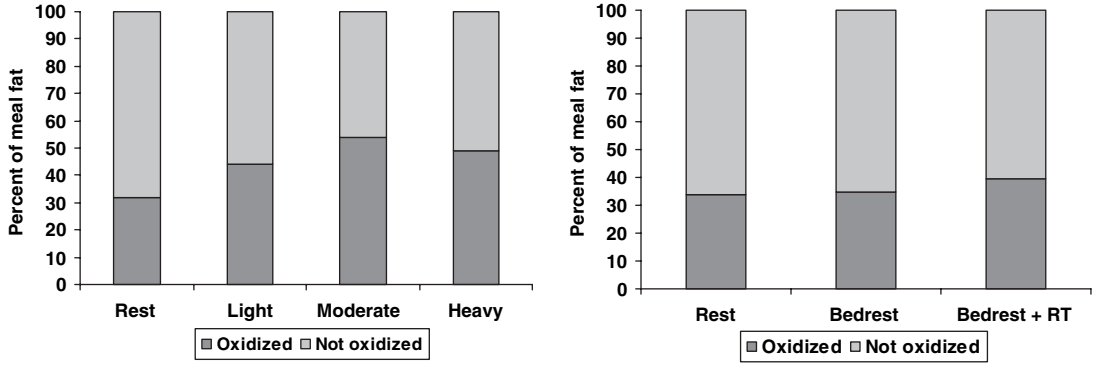

Figure 1

The partitioning of meal fat tracers between oxidation and temporary storage. The 11.5-hour cumulative oxidation of oleate given in a meal 30 minutes after the completion of isocaloric cycling exercise at light, moderate, or heavy intensity compared with rest is shown in the left panel (adapted from Reference 98). The right panel is a depiction of the seven-hour postdose meal oleate oxidation at ambulatory rest and after three months of head-down tilt bed rest, without and with added resistance training (RT) (adapted from Reference 4).

amount was greater than 50 grams (**Figure 3**). We have also recently reported that ingestion of a 70% of energy from fat, hypercaloric meal resulted in a decrease of ~13% in the fraction of the meal fat being oxidized over 24 hours compared with an isocaloric meal containing 30% of energy from fat (99).

Meal fat that is not oxidized is largely stored in adipose tissue. When ingested, meal fat is processed into chylomicrons in the gut and delivered to the circulation. Muscle and adipose tissue LPL has been postulated to be the major regulator of uptake of meal triglycerides (22). LPL activity in human adipose tissue is modulated by physiological conditions such as feeding and fasting, with decreases in LPL activity taking place following weight loss (35, 91) and increases in adipose tissue LPL activity occurring during the postprandial period (23, 99, 104). Until recently, there was little evidence that regional differences in adipose tissue LPL activity are actually linked to the storage of dietary fat. We found that excess energy intake, achieved by a high-fat meal, results in preferential storage of dietary fat in lower-body subcutaneous (LBSQ) fat in lean women compared with lean men and that this is linked to greater postprandial LPL activation in leg fat (99). What we found most impressive is the great interindividual variability in fed state regional LPL activity (99). The source of this huge (10-fold in women) interindividual variability is unknown but likely plays a major role in determining interindividual differences in meal fat storage and potentially body fat distribution.

Meal-derived triglycerides that do not enter tissues due to incomplete chylomicron hydrolysis (chylomicron remnants) can be taken up by the liver, where they can be incorporated into VLDL particles. Heath et al. (32) provided direct evidence with a tracer study that up to 20% of meal fatty acids provided at breakfast have entered the VLDL triglyceride (VLDL-TG) pool after six hours. More recently, the same group showed that tracers of breakfast meal fat begin appearing in VLDL-TG one hour after the meal and increase to 40% of tracer incorporation at nine hours (31). Moreover, a lunch meal fat tracer given on the same day also rapidly appears in the VLDL-TG fraction. Whether this truly represents chylomicron remnant metabolism or the hepatic uptake of meal fatty acids that have entered the FFA pool during chylomicron hydrolysis (78) is unknown.

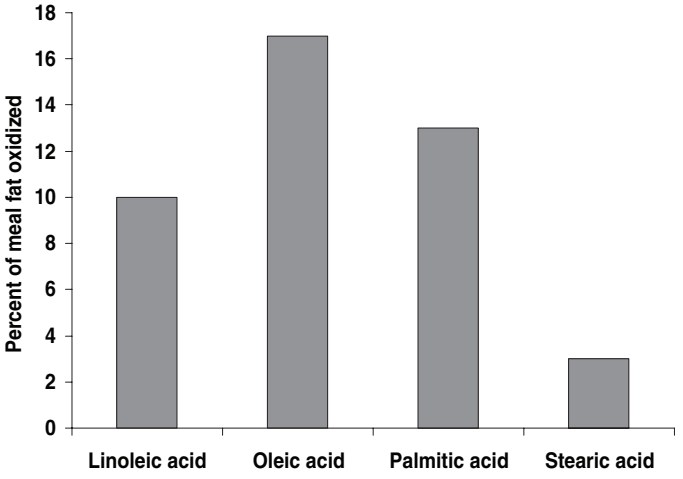

Figure 2

The mean percent oxidation of separate meal fatty acid tracers given in a single test meal. All cumulative recoveries were calculated between 9 and 13 hours postdose. A ^{13}C tracer at the C1 position was used for all tracers, and a correction factor for sequestration was not applied (4, 43, 62, 95–98).

Meal fat uptake into adipose tissue can be directly assessed through needle biopsies. Björntorp et al. (9) reported that in three men undergoing gallbladder surgery, the uptake of ^{14}C-palmitate from a meal increased in relation to fat cell size. Subsequently, Mårin et al. (56) recruited premenopausal women with a wide range of adiposity to determine meal fat uptake into the abdominal and thigh subcutaneous fat after either an overnight fast or a prior high-carbohydrate breakfast. The experimental meal provided ~73% of energy from fat using heavy cream, and meal fat uptake into adipose tissue was assessed with U-^{14}C-oleate 4 hours, 24 hours, 1 week, and 1 month after the test meal. At four hours after the test meal, uptake was greater in the abdomen than the thigh and greater in the previously fed versus fasted volunteers.

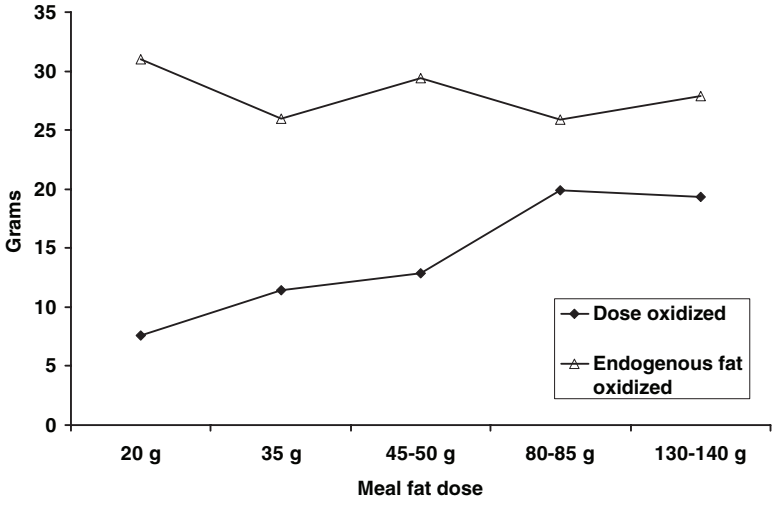

Figure 3

Evidence of meal fat oxidation with increasing meal fat content. Data adapted from Reference 89.

The specific activity in both adipose depots continued to increase until one month, suggesting a redistribution of meal fat from temporary storage in other tissues. The same group later reported that in men given a high-fat test meal, meal fat uptake into omental fat was greater than into subcutaneous abdominal fat. Although this may suggest that meal fat uptake into visceral fat is the cause of greater visceral adiposity in males compared with females (54), direct comparisons with females are largely lacking. We recently found that women also have greater omental than abdominal subcutaneous meal uptake of fatty acids (40).

Studies from our lab have looked at meal fat uptake and how it relates to regional differences in body fat distribution between males and females. Romanski et al. (77) found that meal fatty acid uptake was greater in abdominal subcutaneous fat than in thigh adipose tissue in both men and women, implying that differential meal fat storage does not entirely explain the sex differences in body fat distribution. The main sex difference was a greater percentage of dietary fat stored in subcutaneous adipose tissue in females compared with males. We have subsequently confirmed this pattern of meal fatty acid uptake (93), but also noted substantial intraindividual variability in femoral adipose tissue meal fat uptake in women that could not be explained by menstrual cycle effects.

Based upon studies using a high-fat meal (55, 56), we hypothesized that sex differences in regional fat uptake after a meal would become more apparent in conditions of energy imbalance (99) (**Figure 4**). We've recently reported that, when compared with a normal fat meal, a high fat meal results in more efficient uptake of meal triglyceride in leg adipose tissue in females than in males, whereas the uptake efficiency in abdominal fat does not differ between sexes. This suggests that when meal fat consumption results in net fat storage, females preferentially increase uptake in leg adipose tissue.

FFA KINETICS AND BODY FAT DISTRIBUTION

The relationship between obesity (as measured by body mass index) and components of the metabolic syndrome is even stronger if an upper-body fat distribution phenotype (as measured by waist circumference, waist-to-hip circumference ratio) (13, 18, 19, 25, 27, 28, 30, 67, 72, 92) is taken into account. Intra-abdominal fat (primarily omental and mesenteric—collectively referred to as visceral fat) is usually associated more strongly with these metabolic abnormalities (12, 45,

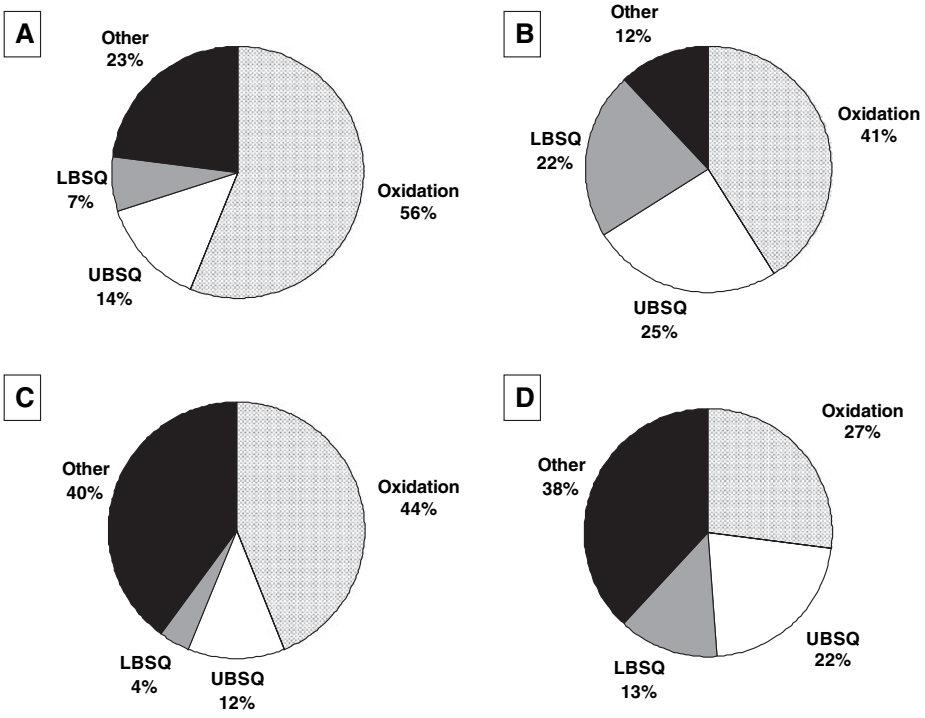

Figure 4

Fate, after 24 hours, of a ^{14}C-triolein meal fat tracer in men given a normal-fat meal (*A*) or a high-fat meal (*C*) and women given a normal-fat meal (*B*) or a high-fat meal (*D*). Meal fat disposal as oxidation or storage into lower-body subcutaneous (LBSQ) and upper-body subcutaneous (UBSQ) was measured. Tracer that was unaccounted for at 24 hours is depicted as "other." Data from Reference 99.

66, 75, 86) than is subcutaneous or total body fat, with some notable exceptions (26). The documented adverse effects of excess FFA on metabolic function and the finding that in vitro omental adipocyte lipolysis is increased compared with subcutaneous lipolysis prompted the hypothesis that excess visceral adipose tissue FFA release is the source of higher FFA concentrations in upper-body/visceral obesity.

Early studies of the relationship between adipocyte characteristics and obesity indicated that large fat cells are characteristic of upper-body obesity and the complications of obesity (10, 49, 51). Large fat cells are reported to have greater rates of basal lipolysis in vitro (49, 74), perhaps especially when they are from visceral depots (33) and men (70). Other studies have shown that visceral fat cells have the same lipolytic activity as abdominal subcutaneous adipocytes when adjusted for size (73) and are less active if visceral fat cells are smaller (70, 73). Despite the sometimes contradictory findings of in vitro studies, it was widely believed that large visceral fat depots flooded the liver and the systemic circulation with FFA (8, 48).

The effect of abnormally high FFA concentrations on glucose metabolism has been thoroughly documented. Elevation of FFA concentrations can induce peripheral (skeletal muscle) and hepatic insulin resistance (24, 46), increased VLDL triglyceride production (52), altered vascular reactivity (90), and dysfunctional pancreatic beta cell function (105). Lowering FFA concentrations in type 2 diabetes can improve insulin action with respect to glucose metabolism (79). The metabolic effects of high FFA concentrations at the level of the muscle appear to involve early steps in the insulin-signaling pathway (21, 76).

If elevation of FFA concentrations can impair insulin action and have other untoward metabolic effects, an understanding of the factors that regulate FFA concentrations is vital. Suppression of lipolysis, whether by insulin (38) or by pharmacological agents (59), results in reduced FFA concentrations, whereas stimulation of lipolysis (epinephrine, growth hormone) increases FFA concentrations. An

FFAs: free fatty acids

exception is what occurs during the onset of exercise, when FFA concentrations fall because the uptake of FFA from the circulation increases to a greater extent than the increase in adipose tissue lipolysis (100). Another exception to the general rule that concentrations reflect lipolysis is the discrepancy between FFA concentrations and flux between women and men; women have 40% greater rates of lipolysis than men at the same plasma FFA concentrations (64) even when adjusted for resting energy expenditure (the best correlate of FFA flux). If one takes into account sex-specific biologic relationships, plasma FFA concentrations are largely determined by the integrated rate of adipose tissue lipolysis (except with exercise). FFA concentrations in turn can affect the ability of insulin to modulate glucose production and uptake. The in vitro differences in regional adipocyte lipolysis suggest, but do not prove, that regional variations in FFA release in vivo could have a major influence on plasma FFA concentrations, with visceral fat playing a disproportionate role.

To the extent that abnormally high FFAs create the metabolic abnormalities associated with obesity, understanding the regional differences in adipose tissue lipolysis in vivo should help resolve the issue as to whether visceral fat is the source of excess FFA in upper-body obesity. A series of studies conducted in our laboratory have documented heterogeneity of adipose tissue lipolysis in vivo, assessed the contribution of upper body subcutaneous, leg, and visceral fat to systemic FFA availability, and evaluated the contribution of visceral adipose tissue lipolysis to hepatic FFA delivery. We used isotope dilution techniques to measure systemic and regional FFA uptake/release in volunteers with hepatic vein, femoral vein, and femoral artery catheters in place. Body composition was measured using the combination of DEXA and CT imaging of the abdomen to quantify regional fat mass (39), and plasma flow was determined using indocyanine green. Systemic FFA (as reflected by arterial FFA concentrations) will affect muscle, pancreatic beta cells, and vascular function, whereas portal FFA concentrations will affect hepatic glucose (69) and VLDL triglyceride (52, 94) production. One can imagine that while portal FFA concentrations may be largely driven by visceral adipose tissue lipolysis (2, 37), systemic FFA concentrations may be less affected by visceral fat because the liver takes up a significant proportion (~50%) of the FFA delivered to it. Sorting out these issues is quite difficult because it is not feasible to measure portal FFA concentrations in humans, except under unique circumstances (94). We did find, however, that it is possible to estimate the proportion of hepatic FFA delivery that originates from visceral adipose tissue lipolysis (37).

We have found that lipolytic activity is greater in upper-body subcutaneous than in leg adipose tissue (per kg of fat) in lean and obese women (36, 60) and in lean and obese men (36, 65). Leg fat contributes ~15%–20% of basal, systemic FFA release in nonobese adults and an average was 28% of FFA release in obese men and women. Leg adipose tissue is exquisitely sensitive to insulin (58) and meal (29, 36) suppression. Upper-body subcutaneous fat accounts for the majority (~70%) of systemic FFA under basal (36, 57, 65) and insulin-suppressed conditions (3, 29, 36, 58). In fact, the greater postprandial FFA concentrations in upper-body obesity compared with lower-body obesity are completely accounted for by excess FFA release from upper-body subcutaneous, not visceral fat (29).

Although the net release of new FFA into the systemic circulation from the splanchnic bed accounts for only ~15% of systemic FFA, this does not fully reflect visceral adipose tissue lipolysis. As noted, the liver takes up a considerable fraction of FFA in the portal vein. Because some of the FFAs entering the splanchnic bed via the arterial supply are taken up by nonhepatic tissues before reaching the portal vein, FFA concentrations in the portal vein are not substantially greater than those typically seen in the arterial circulation (94). That said, the appearance of new FFA in the

hepatic vein is a direct measure of the contribution of visceral adipose tissue lipolysis to systemic FFA availability and thus of plasma FFA concentrations. Only 6%–17% of systemic FFAs come from the splanchnic bed under overnight postabsorptive conditions (65), although this can exceed 40% under hyperinsulinemic conditions (58). The latter observation suggests that visceral fat is more resistant to the antilipolytic effects of insulin than is subcutaneous fat, which is consistent with results from dog studies (61).

The issue of whether visceral obesity increases hepatic FFA delivery in humans appeared to be unanswerable without access to the portal vein. Through the use of mathematical modeling (that was able to be validated using animal models), we were able to test whether the proportion of hepatic FFA delivery that originates from visceral lipolysis could be predicted using data collected from hepatic vein catheterization (37). We compared the measured proportion of hepatic FFA delivery from visceral adipose lipolysis as measured by a portal vein catheter to that predicted using a modeling approach (37). The good agreement between measured and predicted values allowed us to apply this model to data collected in lean and obese men and women (65). From these experiments, we found that the percent of hepatic FFA delivery that comes from visceral adipose tissue lipolysis increases with the amount of visceral fat. In most nonobese adults, only 5%–10% of hepatic FFA delivery is predicted to come from visceral lipolysis, whereas this increases to an average of 20%–25% in visceral obesity (maximum values near 50% in some individuals). Of note, the contribution of visceral lipolysis to hepatic FFA delivery increased to a greater extent in women than in men as a function of visceral fat (65).

Although increasing visceral fat is associated with a greater potential delivery of FFA to the liver, systemic FFA still accounts for an average of >75% of hepatic FFA delivery even in persons with visceral obesity. In summary, visceral fat probably plays a role in the hepatic manifestations of visceral obesity, but to the extent that systemic FFA concentrations affect muscle, pancreatic beta cells, and vascular function, it is the abnormal function of upper-body nonsplanchnic fat that should draw our attention.

FUTURE DIRECTIONS

The factors that determine body fat distribution are still not known. How do environmental, hormonal, and genetic factors combine to promote greater fat gain in some depots relative to other depots in humans? What is the contribution of VLDL-triglyceride uptake by different depots to body fat distribution? Are there pathways of fatty acid accumulation in fat cells, such as de novo lipogenesis or direct FFA reuptake, that help to determine regional fatty acid balance? Finally, accumulation of fat up to a certain degree can be accomplished solely by adipocyte hypertrophy, but eventually new fat cells must be recruited. Some investigators believe that preadipocytes from various depots are differentially capable of proliferation and differentiation. How might these differences help determine body fat distribution? New methods and new experimental approaches are required to address these issues. If scientists successfully develop an understanding of the factors that regulate fat distribution, however, new opportunities may be created for novel therapies that create "healthy" fat distributions, if we cannot find the cure for obesity first.

SUMMARY POINTS

1. Adipose tissue uptake of meal-derived fatty acids is associated with postprandial lipoprotein lipase activity.

2. Upper-body subcutaneous fat is the major source of systemic free fatty acid (FFA).
3. Visceral fat contributes substantially to hepatic FFA delivery in those with excess visceral fat.
4. Physical activity increases the oxidation of dietary fatty acids.
5. Regional differences in meal fatty acid uptake into adipose tissue do not seem to account for sex-based differences in body fat distribution under energy balance conditions.
6. Regional differences in adipose tissue FFA release do not seem to account for sex-based differences in body fat distribution under fasted, fed, or exercise conditions.

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Errata

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