Adipose tissue and fatty acid metabolism in humans

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BACKGROUND

Obesity is associated strongly with adverse health consequences in humans, including hypertension, dyslipidaemia and type 2 diabetes mellitus. An even stronger association has been noted between metabolic abnormalities and regional adiposity. Obese individuals with visceral or upper-body obesity are more likely to suffer from these health problems. Many of the metabolic abnormalities observed in the obese can be reproduced in the non-obese by artificially increasing plasma free fatty acid (FFA) concentrations. Plasma FFA normally originate from adipose tissue lipolysis and are the major circulating lipid fuel. Increasing FFA concentrations artificially can induce insulin resistance at the level of the muscle[1] and the liver[2], result in abnormal vascular reactivity[3], and create abnormal very low-density lipoprotein (VLDL) triglyceride production[4]. In addition, recent evidence indicates that elevated levels of FFA may play a role in pancreatic islet β-cell damage that could predispose to type 2 diabetes mellitus[5]. This is of special interest because elevated postabsorptive and postprandial plasma FFA concentrations are found in upper-body/viscerally obese humans. These higher concentrations are due to increased rates of adipose tissue lipolysis, as documented by isotope dilution techniques[6]. Thus, the fuel export function of adipose tissue is clearly abnormal in upper-body obesity; this dysfunction has been of interest to our laboratory for several years. In order to place the fuel export function of adipose tissue into perspective, however, we will first review body fat content and body fat distribution in non-obese adults and compare them with those observed in obese adults.

BODY FAT IN HUMANS

Figure 1 shows the average amounts of body fat found in lean (body mass index [BMI] 18–25) men and women and obese (BMI 30–37) men and women that we identified in a number of studies[6–13]. On average, lean women have almost twice as much body fat as lean men (29±4% versus 18±3%, mean±SD). Obese men have on average 30±5% body fat, similar to that observed in lean women, whereas obese women have 50±5% body fat. Thus, there are major differences in the amount of body fat between lean and obese men and women. There are also striking differences in the location of body fat storage between lean and obese men and women, and in different obesity phenotypes. The major, readily identifiable body fat depots are the upper-body subcutaneous fat, the intra-abdominal (visceral) fat—consisting primarily of the omental and mesenteric depots—and the lower-body (gluteofemoral) body fat. As can be seen in Figure 2, upper-body subcutaneous fat is the major body fat depot in lean and obese men and women. In a series of studies performed in our laboratory, we have found that in both lean men and women, an average of 53% of total body

Figure 1 **Mean±SD (standard deviation) of percentage body fat in lean men and women and obese men and women** (these data represent the average of several studies from the author's laboratory)

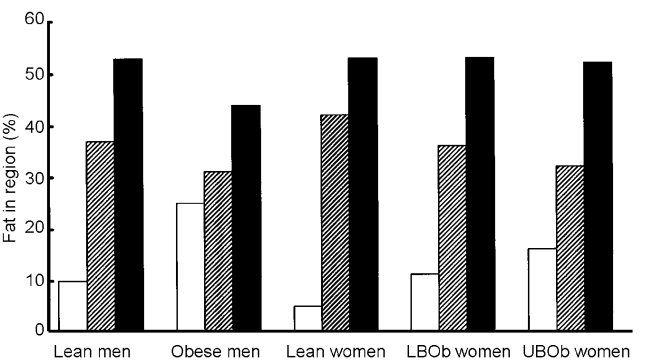

Figure 2 **Average percentage of adipose tissue mass stored in the visceral compartment, lower-body compartment, and upper-body subcutaneous compartment from different groups** (these results represent the mean values from several studies from the author's laboratory). LBOb=lower-body obese; UBOb=upper-body obese; □ visceral fat; ▨ lower body fat; ■ upper body subcutaneous fat

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fat is in the upper-body subcutaneous depot. This is quite similar to the portion of upper-body subcutaneous fat observed in both lower-body obese women and upper-body obese women (53±3% and 52±3%, respectively). In contrast, obese men have an average of 44% of body fat in the upper-body subcutaneous depot, with more visceral fat. In fact, the major difference between the different obesity phenotypes is the proportion of body fat stored in the intra-abdominal depot. Lean men store an average of 10% of their body fat in visceral adipose tissue, whereas in women the proportion is only 5%. Obese men have the highest proportion of body fat in the visceral depot (25%). There are significant differences between the relative proportions of body fat stored in the visceral compartment in lower-body obese (waist-to-hip ratio <0.8) versus upper-body obese women (waist-to-hip ratio >0.85). On average, lower-body obese women store only 11% of their body fat in the visceral fat compartment, whereas in upper-body obese women this averages 16%. Lower-body fat constitutes the remainder of body fat in each group.

APPROACHES TO STUDYING REGIONAL ADIPOSE TISSUE METABOLISM IN HUMANS

Variations in the functions of fat cells from different body fat depots have been assessed by both *in vitro* and *in vivo* measures. For example, *in vitro* studies have shown greater rates of lipolysis in adipocytes obtained from visceral fat compared with upper-body subcutaneous fat, which is in turn greater than lipolysis rates in gluteofemoral fat[14]. In contrast, lipoprotein lipase (LPL) activity, which is thought to be a major regulator of fat storage, is greater in gluteofemoral fat than in upper-body subcutaneous fat[15]. Some of the findings from *in vitro* studies have been confirmed *in vivo*, whereas others have not. There have also been reports of regional differences in the production of leptin and cytokines by adipose tissue.

Because of the potential role of FFA in mediating the adverse health consequences of obesity, and because of the strong association of body fat distribution with both fat distribution and abnormal FFA release, we investigated whether regional variations in FFA release are present *in vivo*. It is difficult to study these issues in humans, however. To accomplish this, it was necessary to employ a combination of techniques that provided measures of regional fat mass, regional FFA uptake and release, as well as regional blood flow. This allowed us to relate regional lipolysis to regional fat mass, and to assess the relative contribution of different fat depots to systemic FFA availability in humans. Dual energy X-ray absorptiometry (DEXA) was used as a primary body composition measurement tool because it not only allows the measurement of total body fat with excellent accuracy but can also provide measures of regional fat mass. Unfortunately, DEXA cannot distinguish intra-abdominal from subcutaneous abdominal fat; thus computed tomography (CT) imaging was needed to help assess visceral fat mass[16]. Isotope dilution techniques, using radiolabelled FFA tracers, can provide data on both systemic and regional FFA kinetics if combined with regional blood sampling. In our studies, this was provided by catheterization of the femoral artery, femoral vein and hepatic vein. By measuring blood flow to the leg and the splanchnic bed with dye dilution techniques, it was possible to calculate rates of FFA uptake and release across the leg and splanchnic bed. Because we also measured systemic FFA release, knowledge of the simultaneous FFA release from the leg and splanchnic bed allowed us, by subtraction, to assess the contribution of upper-body non-splanchnic (subcutaneous) adipose tissue to a systemic FFA release.

In vivo studies of regional FFA metabolism

Some of the initial studies were performed to determine the regional contributions of the leg, splanchnic and upper-body subcutaneous tissues to basal (overnight postabsorptive) FFA release in non-obese men and women (Figure 3)[8]. The significant differences in the proportions of body fat present in the gluteofemoral and visceral regions between men and women led us to suspect that there would also be regional differences in the proportions of FFA originating from the leg and splanchnic bed in men and women. However, there was no difference between the regional contribution of the different adipose tissue beds to systemic FFA release. Upper-body subcutaneous fat contributed the vast majority of FFA release in both lean men and lean women under overnight postabsorptive circumstances. Of note, adipose tissue in the leg was found to be less lipolytically active than upper-body subcutaneous adipose tissue in both lean men and lean women. This is consistent with *in vitro* studies of adipocyte lipolysis.

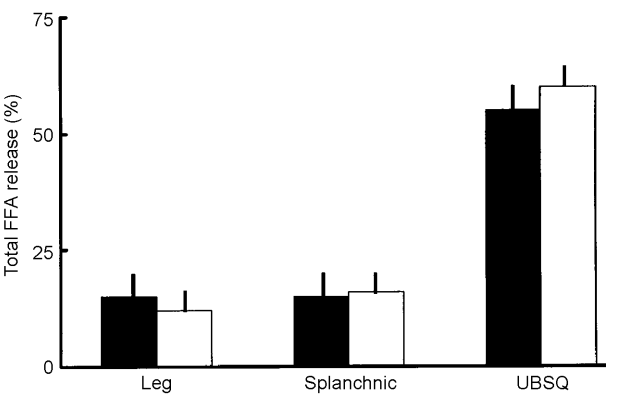

Figure 3 **Mean±SEM of the percentage of FFA release from leg, splanchnic bed, and upper-body subcutaneous (UBSQ) fat from lean women (■) and lean men (□)** [Source: Jensen and Johnson, 1996 from Ref 8]

Other studies were performed to examine whether there are regional differences in basal FFA release between lean women and obese women with an upper-body or lower-body fat phenotype. Because of the strong correlation between visceral adiposity and adverse health consequences, and because upper-body obesity is known to be associated with elevated FFA concentrations and release rate, we anticipated that the excess FFA release found in upper-body obesity would originate from the splanchnic bed. Instead, we found that upper-body subcutaneous fat was the source of the excess FFA in overnight postabsorptive upper-body obese women (Figure 4)[9]. It was also evident that greater leg fat mass did not result in greater leg FFA release in either obesity phenotype. It appeared that leg adipose tissue lipolysis was downregulated such that absolute FFA release was maintained at 'non-obese' levels despite almost two-fold greater leg fat mass. The same was true for upper-body subcutaneous fat in lower-body obese women; FFA release was equal to that observed in non-obese women despite much greater fat mass.

In summary, despite significant differences in the relative amounts of visceral fat between men and women, and between upper-body and lower-body obesity, we found either no difference in the regional contributions to basal FFA release (men versus women) or 'excess' coming from upper-body subcutaneous fat (upper-body obese versus lower-body obese). We note, however, that some workers believe that the overnight postabsorptive period may not be the only interval important for metabolic health.

Indeed, the most significant and consistent abnormality of lipolysis in visceral obesity seems to be abnormal suppression of FFA release during the postprandial period[17], due almost certainly to an attenuated suppression of lipolysis by insulin[6]. Consequently, we examined regional FFA release in the postprandial period and in response to euglycaemic hyperinsulinaemia. Systemic hyperinsulinaemia, whether created using the euglycaemic hyperinsulinaemic clamp technique or by meal ingestion, results in tremendous suppression of FFA release in non-obese men and women[7,18]. Using the former approach, we found a significant increase in the relative contribution of the splanchnic bed to systemic FFA release[18], suggesting that visceral fat may be an important contributor to excess FFA availability in viscerally obese individuals. We also examined the regional contribution of body fat to FFA release under meal-suppressed conditions in lean men and lean women[7,13]. Again, a somewhat greater relative contribution of the splanchnic bed to systemic FFA availability was noted, although this was in the context of marked (60–85%) suppression of lipolysis[7,13]. Of interest, despite the fact that lean men have a greater proportion of their body fat in the visceral compartment, they did not display consistently a greater relative splanchnic release of FFA in the postprandial period[7,13]. Additional studies were therefore pursued to assess the relative contributions of upper-body subcutaneous fat, leg fat and splanchnic fat to meal-suppressed FFA release in upper-body obese and lower-body obese women. The reasoning was that greater discrepancies in visceral fatness would allow identification of excess splanchnic FFA release in the postprandial period. Consistent with our previous observation[17], upper-body obese women had high postprandial FFA concentrations and FFA release rates from adipose tissue[10]. Despite our deliberate selection bias, however, the entire excess of FFA release was found to occur from the upper-body subcutaneous bed, not from the splanchnic bed[10]. In summary, despite the significantly greater visceral fat in upper-body obese compared with lower-body obese women, this did not translate into greater postprandial FFA release from the splanchnic bed in upper-body obesity.

One concern, however, is that the differences between the amount of visceral fat in upper-body obese and lower-body obese women may have been insufficient to detect a difference in suppression of splanchnic FFA release. We therefore performed similar studies comparing patients with type 2 diabetes mellitus, who typically have much greater amounts of visceral fat, with obese controls without diabetes[11]. As expected, visceral fat area in the volunteers with type 2 diabetes was more than double that of non-diabetic controls ($230\pm21\,cm^2$ versus $98\pm21\,cm^2$, respectively; $P<0.001$). During systemic hyperinsulinaemia created by hyperglycaemic-hyperinsulinaemic clamp, the systemic FFA concentrations and release were twice as high in diabetic subjects as in control subjects[11]. Visceral fat area correlated positively with FFA release during hyperinsulinaemia, confirming the relationship between visceral fatness and dysregulation of lipolysis. Despite the much greater visceral fat in the diabetics, the proportion of FFA released

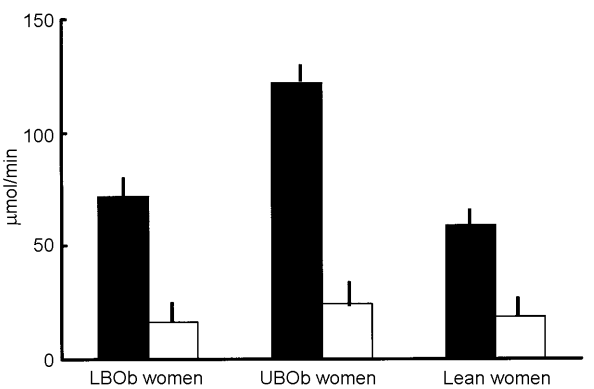

Figure 4 **Palmitate release from upper-body fat (■) versus the splanchnic bed (□) for lower-body obese (LBOb) women, upper-body obese (UBOb) women, and lean women under overnight postabsorptive conditions** [Source: Martin and Jensen, 1991 from Ref 9]

from the splanchnic bed was not different between the two groups, and upper-body subcutaneous fat contributed to the vast majority of FFA release (74–78%) in both groups.

In summary, an upper-body/visceral fat distribution is a strong predictor of both adverse health consequences of obesity—high FFA concentrations and excess FFA release from adipose tissue. By using a combination of physiological research techniques to address this issue, it is now evident that the upper-body subcutaneous adipose tissue depot, rather than visceral fat, is the major contributor to excess systemic FFA availability. Although visceral fat mass correlates with systemic FFA release, especially under insulin-suppressed conditions, it was not the predominant source of FFA release in our studies of regional lipolysis in humans.

These observations suggest either that increased visceral fat is a marker for abnormal regulation of upper-body subcutaneous lipolysis, resulting in high FFA, or that visceral fat exerts adverse metabolic influences via non-FFA mechanisms. These mechanisms include the production of cytokines or other compounds that affect metabolic health.

ADIPOSE TISSUE FATTY ACID STORAGE

Another conclusion that can be drawn from studies of the regulation of regional lipolysis is that regional differences in FFA release do not account for regional differences in fat distribution. Therefore, studies have been initiated to examine the physiology of regional adipose tissue fatty acid uptake. Because the vast majority of the fatty acids stored in adipose tissue originate from dietary fat, studying this aspect of adipose tissue physiology is warranted. The fatty acids present in dietary triglyceride enter the circulation as chylomicrons and are largely cleared by adipose tissue; only a portion of dietary fatty acids are oxidized more directly and immediately. The use of isotopically labelled meal fatty acids to study this issue was originally developed by Björntorp *et al.*[19] and Mårin *et al.*[20,21]. They demonstrated that it is possible to assess the portion of dietary fatty acids stored in different adipose tissue regions by giving a meal containing radiolabelled (^{14}C or ^{3}H) triglycerides and performing adipose tissue biopsies some time later. We recently expanded on their approach by also measuring 24 h integrated dietary fatty acid oxidation combined with regional fat biopsies. This permits a more complete assessment of the portion of the meal stored in different body fat depots. Uptake of meal fatty acid was found to be greater in abdominal subcutaneous adipose tissue than in thigh adipose tissue in both non-obese men and women[5]. Interestingly, despite the significant gender differences in body fat and body fat distribution, there was no difference in the uptake of meal fatty acids into adipose tissue (milligrams of meal fatty acids/gram of adipose tissue lipid) in the 24 h following meal ingestion. We also found that the oxidation of dietary fatty acids over the first 24 h following meal ingestion was not different between men and women (28±1% versus 32±2%, men versus women; *P*=NS).

Women stored a greater proportion of dietary fat in subcutaneous adipose tissue compared with men (38±3% versus 24±3%, women versus men; $P<0.05$)[15], and there was a suggestion that a greater portion of the dietary fat may have been stored in the visceral fat in men compared with women. Of interest, we found that there was not a relationship between adipose tissue LPL activity and meal fatty acid uptake. Consistent with previous reports, LPL activity was almost twice as great in thigh adipose tissue than in abdominal subcutaneous adipose tissue; this was true in both women and men. Despite this, meal fatty acid uptake into thigh adipose tissue was significantly less than abdominal adipose tissue in both genders. Thus, basal LPL activity does not appear to be a good predictor of the ability of adipose tissue to take up and store dietary fatty acids.

We believe that meals containing radiolabelled fatty acids can provide a powerful tool for understanding the regulation of the uptake and storage of adipose tissue lipid. This, combined with studies of regional lipolysis, should provide a more robust understanding of the regulation of adipose tissue in man.

SUMMARY

It is now clear that there are major regional differences in adipose tissue function as regards the uptake and release of fatty acids. Visceral adiposity is a good predictor of abnormal regulation of adipose tissue fuel export, but it is not the source of excess systemic FFA in humans. Regional differences in adipose tissue uptake of fatty acids may be an important determinant of body fat distribution, which in turn appears to predict abnormalities of fatty acid metabolism.

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