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Sex and Sex Steroids: Impact on the Kinetics of Fatty Acids Underlying Body Shape

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Abstract

Adult humans have a remarkable sexual dimorphism in body shape. Men tend to store relatively more fat in the upper body whereas women store more fat in the lower body. We do not have a complete understanding of the mechanisms underlying these differences, but we know that people who preferentially store abdominal fat are at greater risk of metabolic disease. It is also known that the changes in sex steroid concentrations during puberty and again with advancing age are accompanied by changes in body fat distribution. The objective of this review is to describe what has been learned regarding the mechanisms underlying changes in regional body fat distribution that occur as a result of changes in sex hormones and to delineate effects of sex steroids in modulating body composition.

Keywords

aging; body fat distribution; lipid metabolism; sex dimorphism; sex steroid hormones

1. Introduction

Not everyone is created equal when it comes to body shape and obesity. There is a wide range of fat distribution, with some people accumulating fat preferentially in their upper body (also known as android obesity) and others developing a predominant lower body fat distribution (gynoid obesity). These shape differences provide significant clues to health risks as humans with an upper body/android fat distribution are at greater risk for metabolic diseases, including hypertension, dyslipidemia and type 2 diabetes - all cardiovascular risk factors - than those with a lower body/gynoid fat distribution (1).

We do not currently have a complete understanding as to why some people are android shaped and others are gynoid shaped, although the sex differences in body fat distribution that develop during puberty suggest that gonadal steroids play an important role. Most males have little leg fat relative to upper body fat and most females have ample lower body fat

stores and limited visceral fat. These shifts in body fat distribution during puberty are preceded by changes in sex steroid production, and may shift again with menopause in women and aging in men. Though there has been considerable interest in the role of brown adipose tissue (BAT) in obesity development/prevention, we do not know of any data indicating that BAT contributes to the sexual dimorphism of fat distribution. The focus of our review will be on the contribution of fat metabolism to the sex-related differences in white adipose tissue distribution. The objective of this review is to describe what has been learned regarding the mechanisms underlying changes in regional body fat distribution that occur as a result of changes in sex hormones and to delineate effects of sex steroids in modulating body composition. Although several studies have contributed towards answering this question from different perspectives, the focus of this review will be to examine the contribution of fatty acid metabolism in body fat distribution.

2. Regional adipose tissue depots defined

We and others have observed large variations in body fat, ranging from less than 5% and up to 60% of body weight. In addition, substantial regional differences in white adipose tissue deposition can occur. The regulation of lipolysis, fat storage and, by inference, adipocyte cellular characteristics, varies substantially by anatomical location (2-4). Below we provide an overview of white adipose tissue depots that have been shown to be functionally distinct.

The majority of fat in most adults is found beneath the skin, i.e. subcutaneous adipose tissue (SAT). For convenience sake we have further divided SAT into upper and lower body regions. We have typically defined lower body SAT as the adipose tissue caudal to the inguinal ligament anteriorly and the ileac crest inferiorly, which includes gluteal, subcutaneous leg fat and (unfortunately because of the greater difficulty in quantifying) intramuscular fat. Visceral adipose tissue (VAT) (also known as intraperitoneal fat) includes the omental mesenteric depots, both of which drain into the portal vein and thus can preferentially affect hepatic metabolism (5). Upper body subcutaneous fat – all non-intra-abdominal, non-lower body fat, is likewise heterogeneous. It includes deep and superficial abdominal fat, head and neck fat, as well as breast fat in women. In lean men VAT typically constitutes ~ 10% of total body fat mass whereas in women it is ~ 5% of body fat. (6). Other, smaller fat depots include epicardial/pericardial fat (around the heart).

3. Importance of regional body composition to death and disease risk

Excess adiposity is a risk factor of all-cause mortality regardless of the presence of the usual metabolic abnormalities (7). An upper body fat distribution clearly increases the risk for metabolic disease to an even greater extent irrespective of BMI (8). Jean Vague was the first to report the relationship between “android” obesity and diabetes (9). Since that report numerous studies have confirmed the relationship between central adiposity and risk of diabetes (10, 11), cardiovascular disease risk and events (12, 13), hypertension (14), sleep apnea (15), cancer (16) and overall mortality rates (17); men and women in the highest quintile of measured WC are reported to have almost twice the mortality rates than those in the lower quintiles.

4. The role of sex in body fat distribution

The differences between adult men and women in body fat and body fat distribution are so distinctive that it is almost possible to distinguish between them by body fat and body fat distribution provided they are matched for BMI. Healthy, modestly active/sedentary women with BMI's 20-25 kg/m² very often have 25-35% body fat, whereas men of the same BMI have 10-20% body fat; highly athletic women and men can have less body fat (18). Moreover, men have a greater propensity to store fat in VAT than women. Computed tomography (CT) scans of the abdomen have shown that men have higher VAT even after correction for total body fat mass (19). In addition, increases in total fat mass in men is associated with greater increases in VAT than comparable increases in body fat in women (19). The mechanisms underlying the differences in body fat distribution between men and women are not completely understood. However, throughout the lifetime, shifts in body fat correspond with shifts in sex hormones such as during puberty (20) or menopause (21); suggesting a major role of sex hormones in determining body fat distribution.

5. Sex steroids and shifts in regional body fat distribution

5.1 Decreases in sex steroids leads to shifts in regional body fat distribution

Age-related declines in sex steroids correspond to shifts in regional body fat distribution towards a more central fat distribution in both men and women (22, 23). During and after the menopausal transition, when female sex steroids (estrogen and progesterone) decrease, greater accumulation of abdominal fat occurs (22). Over 3 years, early postmenopausal women experienced an increase in total fat mass of ~5 kg and an increase in trunk fat of ~3 kg (24). This finding was consistent with that of another 5 year prospective study where indicators of upper body obesity increase during the menopausal transition (25). The increase in upper body adiposity in postmenopausal women appears to be independent of total fat mass as postmenopausal matched to premenopausal women for fat mass had greater trunk:leg fat (26). When postmenopausal women were divided into "young" and "old" groups, trunk:leg fat was not different despite more total fat in the old group (26). This finding supports a dominant effect of menopausal status over age on body fat distribution.

Although men do not undergo such abrupt changes in sex steroid concentrations with aging, older men have lower testosterone concentrations than younger men (23, 27, 28). Lower testosterone concentrations in aging men have been associated with increases in total body fat accumulation (29, 30). However, the effect of testosterone on body fat and body fat distribution is unclear. Fat gain itself can result in partial suppression of the hypothalamic-pituitary-gonadal axis in men and substantial weight loss, such as after bariatric surgery, can return testosterone concentrations to normal. This suggests that some of the fall in testosterone with aging may be due to age-related increases in adiposity. However, some studies have found that age-related hypogonadism in men is accompanied by increases in visceral adiposity (29) whereas in other studies increases in abdominal SAT rather than VAT were observed (31, 32). Hypogonadism resulting from castration in males has been shown to a markedly gynoid fat pattern (33). Thus, it is sometimes difficult to distinguish between obesity-related suppression of the hypothalamic-pituitary-gonadal axis and a pathological central hypogonadism that results in fat gain (primary hypogonadism is easily

diagnosed on the basis of elevated FSH and LH). One clue is that obesity-independent central hypogonadism in men will result in increasing total fat deposition whereas preferential gain of VAT appears to associate strongly to obesity-related (weight loss responsive) hypogonadism.

5.2 Increases in sex steroids leads to shifts in regional body fat distribution

During puberty increases in estradiol in females are associated with the development of a gynoid body fat pattern (34). Similarly, there is evidence that hormone replacement therapy (HRT) during menopause prevents the menopause-associated shifts towards central fat distribution in women (21, 24, 35-38). The long term effects of HRT on body fat distribution are supported by Ahtiainen et al (39) who studied monozygotic twin pairs discordant for HRT. They found that the twin that used HRT had significantly lower total body and abdominal fat compared to the twin that did not use HRT (39). There are however, studies reporting no effect of HRT on weight gain and body fat distribution (40, 41). Kritz-Silverstein and Barrett-Connor (41) saw that weight gain and central obesity was not associated with intermittent or continuous HRT use over a period of 15 years or more. However, women who used HRT were at significantly lower risk of mortality than untreated women thus, potentially biasing the results (41). Despite these studies, there is stronger evidence supporting an effect of estrogen on fat partitioning than not. The effect of estrogen on body fat distribution is more clearly observed in male to female transsexuals where estrogen treatment increased total and, in particular, lower body SAT (42).

It is widely appreciated that testosterone increases muscle mass (43-46), however the effects of testosterone on fat mass and distribution are less clear. During puberty in boys the increases in serum testosterone concentrations are associated with decreases in percent body fat and a relative increase in abdominal SAT (47). This cross-sectional data was expanded upon by findings that testosterone treatment of adolescents with delayed puberty decreased body fat (48). As men age the shifts in body fat distribution may be partially rescued with testosterone replacement. Restoration of testosterone to physiological levels in hypogonadal men has been observed to decrease total body and abdominal fat mass in several (43, 46, 49-53) but not (54) all studies. In general, the body of evidence indicates that increasing testosterone concentrations in men leads to decreases in total body fat mass. However, whether testosterone supplementation decreases abdominal SAT or VAT remains unclear. Some investigators have reported reductions in upper body SAT (46, 50, 51, 53, 55), whereas others showed decreases in VAT (45, 49). The varying doses of testosterone used in these studies could have contributed to the observed differences in changes in total and regional adiposity. A dose-response study by Woodhouse et al (56) showed that change in total body fat mass was inversely correlated ($r=-0.49$) with testosterone dose; men in the 2 lowest doses gained fat whereas men receiving the highest dose experienced a decrease in fat mass (56). Increases in thigh SAT, abdominal SAT, and VAT was also observed at the lowest dose and the largest decreases were shown with the highest dose of testosterone (56). Thus, testosterone appears to play a significant role in determining regional body fat distribution in men.

6. Importance of Adipose Tissue Fatty acid (FA) metabolism

A principle function of adipose tissue depots is to store and release FA in response to changes in energy balance. The balance between storage and release rates of fatty acids will determine whether the depot will increase or decrease in size. Adipose tissue lipolysis releases free fatty acids (FFA) and glycerol and is under delicate hormonal control. Insulin is the primary hormone that inhibits release of FFA. There is a very wide dynamic range of lipolysis regulation by insulin (57) and different adipose depots have different insulin responses (58). Under fasting and exercise conditions there is very little fatty acid storage and a considerable amount of fatty acid release via lipolysis. When energy needs are met following consumption of a meal, circulating chylomicron-triglyceride fatty acids are stored via a lipoprotein lipase (LPL) dependent pathway. Endothelial LPL can hydrolyze chylomicron TAG and very low density lipoprotein (VLDL)-TAG, allowing the fatty acids to enter the adjacent tissues. The FA may be taken up locally or “spillover” into systemic circulation. A less appreciated pathway of adipose tissue FA storage occurs via the direct re-uptake of FFA from the systemic circulation independent of the LPL mechanism. Some of the FFA released as a result of adipose tissue lipolysis, thought mainly to supply fuel to lean tissues for fat oxidation, are taken up and stored in distant adipocytes. We have referred to this process as direct adipose tissue FFA storage. Both FFA released by LPL and by lipolysis can cross the adipocyte membrane via passive (flip flop) or protein facilitated diffusion (59). We have examined the role of some of the proteins involved in the eventual storage of these FFA as triglycerides. Acyl CoA synthetase (ACS), diacylglycerol acyltransferase (DGAT), and fatty acid transport protein (CD36) are key proteins that act in concert at different levels of FFA storage. CD36 is a ubiquitous cell surface glycoprotein involved in the binding and plasma membrane transport of FFA (60, 61). ACS activates long chain FFA through acylation (62) and DGAT is the enzyme involved in the final step of triglyceride storage esterifying FFA to diglycerides (63). Each of these proteins involved in FFA storage have been examined in the context of sex steroids.

7. The role of lipid metabolism in the sexual dimorphism of regional fat distribution

Although other factors, such as the gain or loss of lean tissue, impact body composition, this review will focus on studies that examine the contributions of FA metabolism in determining regional body composition. A sufficient number of studies have been conducted to expand our understanding of how the variation in body fat distribution in men and women relate to systemic and regional fatty acid metabolism. Based on the results of these studies, we have regional FFA metabolism over a 24 hour period in a normal weight man and woman (Table 1). Moreover, the sexual dimorphism in adiposity along with differences in fat metabolism found in men and women allude to a compelling role of sex steroids in determining regional fat distribution. Several studies have examined the effects of sex steroid suppression and/or supplementation on fat metabolism.

7.1 Lipolysis

If sex-differences in body fat distribution were due to sex differences in relative rates of lipolysis we would expect lesser relative rates of leg adipose tissue lipolysis in vivo in women compared with men. Instead, we found that in both men and women leg adipose tissue lipolysis is less than upper body subcutaneous per unit adipose tissue mass. Examined another way, regardless of sex, upper body AT is more lipolytically active than lower body under overnight postabsorptive conditions (64, 65). We also found that insulin is better able to suppress leg than upper body adipose tissue lipolysis in both men and women (58) and that exercise stimulates leg adipose tissue lipolysis equally well in women and men (66). We concluded that regional differences in lipolysis are unlikely to explain the sexual dimorphism seen in body fat distribution.

Unfortunately, there have been no studies of sex steroid effects on regional lipolysis in humans, in vivo. Investigators have studied isolated adipocytes collected from pre- and postmenopausal women as well as men receiving testosterone treatment. They concluded that sex hormones had little effect on lipolysis measured in vitro (67). Because certain doses of testosterone decrease total and abdominal fat mass it is possible this occurs because of increased lipolysis in these regions. Some evidence for this effect has been reported, again using isolated adipocytes (67, 68).

7.2 Meal fatty acid storage

Patterns of meal fatty acid storage only somewhat mirror patterns of regional fat distribution. We found no differences in patterns of meal FA storage in men and women; more meal fatty acids were stored (per g lipid) in upper body SAT than in leg SAT in both groups when consuming isocaloric meals (69-71). However, following consumption of a high calorie, high fat meal, women stored a greater proportion of meal fat in lower body SAT whereas men did not (72). Moreover, when meal fatty acid storage was compared in men and women with different obesity phenotypes, variations in regional meal fat storage were found (73). In lower body obese women, meal FA storage was greater in gluteal than abdominal fat (73), whereas storage was similar in these two depots in upper body obese men and women. We also found that upper body obese men stored a lesser percent of meal fat in subcutaneous fat than either group of women (73). This would be consistent with the concept that meal FA storage may contribute to the sex-differences in regional adiposity.

Few studies have been conducted to examine the effects of estrogen on meal FA storage. We found that postmenopausal had greater meal FA storage than premenopausal women (74). We also found that compared to premenopausal women, meal FA storage in the femoral depot was 2 times greater in postmenopausal women (74). Another study that used LPL as a surrogate for meal FA storage observed that in postmenopausal women treated with estrogen and progesterone LPL activity was higher in femoral vs. abdominal adipocytes (67). These studies indicate that female sex steroids affects meal FA storage in such a way as to promote meal fat storage in lower body fat in women. Why postmenopausal women would thus tend to gain abdominal fat is unclear.

There have been a limited number of studies of the effects of acute or chronic testosterone hormonal manipulation on meal fatty acid metabolism. We found that chronically hypogonadal men stored more meal FA in the femoral region than eugonadal men (75). Whereas meal FA storage (mg per g lipid) in hypogonadal men was similar in the abdominal and femoral region, eugonadal men stored more meal FA in the abdominal than thigh region (75). These patterns of meal fat storage are consistent with what we would expect given the regional differences in fat distribution between hypogonadal and eugonadal men, thus testosterone likely affects regional adiposity at least in part through its effects on regional meal FA storage. Our conclusion is further supported by the finding that 2 years of testosterone treatment of elderly men with below normal testosterone increased meal FA storage in the abdominal compared with femoral adipose tissue (54). Another group reported that although there were no changes in SAT with acute (5 days) testosterone treatment, decreased meal FA storage in VAT occurred (69). In contrast, a study by Marin et al (70) showed baseline differences in meal FA storage where more meal FA was stored in the abdominal vs. femoral depot (70). However, after 9 months of testosterone treatment, these differences in meal FA storage no longer existed (70). This shift was likely because of a significant decrease in meal FA storage in abdominal SAT with T treatment. Potential reasons for this contradictory finding could stem from differences in ages of men between studies, differences in the testosterone treatment period or differences in the timing of biopsies after ingestion of the experimental meal (76).

7.3 Direct FFA storage in men and women

More so than meal fatty acid storage, patterns of direct FFA storage correspond to the sexual dimorphism in fat distribution. Specifically, FFA storage in subcutaneous fat is less in men than women, and men store more FFA in abdominal than femoral SAT depots whereas women do not (77). Follow-up studies confirmed these results and noted that FFA storage rates were greater in femoral than abdominal SAT in women (78). In women with varying regional fat distribution, direct storage of FFA also followed regional fat distribution (79). These studies support a role of direct FFA storage as a means of redistributing fatty acids in a manner that appears to influence body shape.

We matched pre and postmenopausal women for age and body composition and found that direct FFA storage was greater in postmenopausal than premenopausal women (74). However, we found no significant regional differences in the storage of FFA between these two groups (74). A closer examination of the key factors involved in FFA storage showed that activity of ACS and DGAT were significantly upregulated in postmenopausal compared to premenopausal women indicating greater potential for FFA storage in postmenopausal women. In a second study we found no differences in the rates of FFA storage between age and body composition match men who were chronically hypogonadal and eugonadal (75). However, activity of ACS was significantly greater in femoral adipose tissue of eugonadal than hypogonadal men. The effects of sex steroids on direct FFA storage remains to be investigated before a conclusion can be drawn.

8. Expert Opinion

The sex-specific variations in body fat distribution appear to be at least partially regulated by sex steroids via effects on FA metabolism specific to certain depots. There is little evidence to support a role for defective lipolysis as a contributor towards fat gain in one depot vs. another in men and women. However, meal fatty acid storage and direct FFA storage do appear to contribute towards these variations in regional adiposity. Future studies are needed to further understand the underlying mechanisms through which sex steroids impact fat distribution.

9. Outlook

Over the next 5-10 years studies will continue to add to our knowledge of how sex steroids contribute towards the sexual dimorphism of body fat distribution. These studies will investigate how specific sex steroids (estrogen vs. progesterone vs. testosterone) affect fat metabolism in a variety of contexts and conditions using tracer and imaging techniques.

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Non-standard abbreviations

ACS	Acyl CoA synthetase
CT	computed tomography
DGAT	diacylglycerol acyltransferase
CD36	fatty acid transport protein
FFA	free fatty acids
HRT	hormone replacement therapy
LPL	lipoprotein lipase
SAT	subcutaneous adipose tissue
VAT	visceral adipose tissue

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10. Highlights

- Perimenopausal decreases in female sex steroids results in greater accumulation of abdominal fat.
- Strong evidence indicates a shift towards a gynoid body fat distribution with increasing estrogen concentrations in women.
- While age-related declines in testosterone concentrations have been associated with increasing adiposity, effects of testosterone on regional shifts in body composition remain murky.
- Several studies indicate decreases in total and abdominal fat mass with increasing testosterone concentrations, though whether the decreases are in visceral or subcutaneous adipose tissue are unclear.
- There is a lack of differences in lipolysis between men and women indicating that lipolysis is not likely to contribute towards the sexual dimorphism of fat distribution.
- Storage of meal fatty acids may partially explain differences in regional fat distribution between men and women.
- Patterns of direct free fatty acid storage correspond to the sexual dimorphism of fat distribution more so than meal fatty acid storage.

Table 1

Regional fatty acid metabolism over a 24 h period in a normal weight man and woman with 15% and 30% body fat, respectively. We assumed that total fat ingestion was 75 g/d and that 8 h of the day was spent postprandial, 14 h of that day was spent post absorptive and 2 h of the day was spent doing physical activity at a level that would affect FA kinetics. For a closer look at the references upon which these calculations are based, please see (3).

Measure	Man			Woman		
	Upper body SAT (g)	Lower body SAT (g)	VAT (g)	Upper body SAT (g)	Lower body SAT (g)	VAT (g)
<i>14 h postabsorptive</i>						
Postabsorptive lipolysis	102	16	17	88	27	11
Direct FFA storage	1.3	0.9	1.9	2.6	2.6	1.9
<i>8 h postprandial</i>						
Postprandial lipolysis	17.6	3.8	6.1	13.2	5.0	3.7
Meal FA storage	3.7	2.9	4.6	5.9	4.4	5.3
Direct FFA storage	0.7	0.4		1.8	1.3	
<i>2 h exercise</i>						
Lipolysis during exercise	18	8.3	3.2	23.3	11	1.9
Direct FFA storage	0.2	0.1		0.3	0.3	