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Sex Differences in Adipose Tissue Function

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INTRODUCTION

Women have consistently been found to have higher levels of total body adiposity than men.[1] Women preferentially deposit fat subcutaneously with greater accumulation in the gluteofemoral region. This distribution of fat may provide a buffer for fat storage during periods of positive energy balance and improve glucose metabolism, partially protecting against the development of type 2 diabetes in premenopausal women.[2] In contrast, men tend to accumulate fat in the abdominal region, in the visceral compartment, where it contributes to an increased risk for metabolic disease.[3] These differences in total lipid storage may have evolved to favor the energy needs of reproduction and lactation in women and suggest fundamental differences in the handling of metabolic fuels by the two sexes. Although these sex-based differences in fat distribution could be related to genetics, the fact that these differences first appear at the onset of puberty and become less pronounced after the menopause in women or in association with declining testosterone levels in men suggest that sex steroids play a central role.[4] Studies done in human participants with sex steroid insufficiency occurring naturally or by pharmacologic suppression with our without hormone replacement support this idea. Specifically, although the increase in total fat mass seen in women with the menopausal transition is due in part to advancing age, fat redistribution away from peripheral subcutaneous depots to visceral depots seems to be specifically related to estrogen deficiency.[5] Women who receive post-menopausal hormone therapy see an age-adjusted decrease in visceral fat.[6] Men with Klinefelter syndrome not on testosterone replacement therapy have increased levels of total body fat that decreases with

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DISCLOSURE

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testosterone replacement, although hormone replacement therapy is associated with an increase in intra-abdominal fat content.[7] Studies done in transsexual individuals using gender-affirming hormone therapy show that estrogen use by male-to-female transsexuals is associated with in an increase in total body fat with relatively less fat accumulating in the visceral depot. In contrast, administration of testosterone to female-to-male transsexual individuals results in a reduction in subcutaneous fat area on MRI with a modest increase in visceral fat area.[8,9] The importance of sex steroids in adipose tissue metabolism and regional adiposity has been studied in vitro using isolated adipocytes, in studies of animals after gonadectomy with or without hormone replacement, and in studies of mice with genetic manipulations of relevant hormone signaling systems.[10] Although energy intake and energy expenditure, including energy expended in habitual physical activity, play critical roles in determining differences in total body adiposity between men and women, even these variables seem to be subject to regulation by sex steroids.[11,12] Taken together, these studies strongly support a central role of sex steroids in modifying regional adipose tissue biology, although the details of how these hormones regulate fat mass and distribution are complex.

HOW DOES ONE FAT DEPOT EXPAND RELATIVE TO OTHERS?

The mechanisms determining body fat patterning are not completely understood. Fig. 1 outlines some of the mechanisms that could be involved in the relative expansion of one adipose tissue depot relative to another. The generation of new fat cells (adipogenesis) is necessary across the lifespan to both accommodate expansion of the adipose tissue organ owing to energy surplus, and to maintain the regular turnover of the adipocyte pool, which occurs at a rate of approximately 10% per year.[13] When responding to energy surplus, adipose tissue can expand by hypertrophy (increase in cell size) or hyperplasia (increase in cell number). The role of each of these processes in adipose tissue expansion seems to differ by depot (hypertrophy being characteristic of the abdominal depot and hyperplasia of femoral[14]) and sex (hypertrophy characteristic of adipose tissue in men and hyperplasia in women[15]), although baseline adipocyte size when weight gain occurs is also of importance.[14] Rates of apoptosis of mature adipocytes also affect the total number of adipocytes in a particular depot. Limitations of current methods for measuring adipocyte production and death in vivo in humans has impeded research in this area, although the use of the stable isotope deuterium (^{2}H) labeling technique has made in vivo studies possible.[16,17]

Changes in the size of an adipose tissue depot through hypertrophy also depends on the net delivery of lipid (uptake of free fatty acids [FFA], dietary fat, or very low-density lipoprotein [VLDL]) and lipogenesis as balanced against the loss of lipid through lipolysis (basal or hormone stimulated) and fat oxidation. Extensive studies of the effects of sex steroids on these processes have been performed in an effort to understand the sexual dimorphism in regional adiposity.

ADIPOCYTE PRODUCTION AND TURNOVER

Sex Differences in Adipogenesis

Adipose tissue in males is characterized by more adipocyte hypertrophy, whereas females demonstrate more hyperplasia.[14,15] Tchoukalova and coworkers[14] found that women had a

greater fraction of stromal vascular cells that were early differentiated adipocytes compared with men, particularly in the femoral depot.[18] They additionally found a tendency for preadipocytes from the femoral region of women to be less susceptible to apoptosis compared with subcutaneous abdominal preadipocytes. Additionally, in vivo studies in overweight and obese premenopausal women suggest that subcutaneous femoral adipose tissue has a higher capacity for adipogenesis compared with abdominal adipose tissue.[19]

Effects of Estrogen and Testosterone on Adipocyte Development

Estrogen—Human adipocyte precursors exposed to estradiol (E_2) in culture consistently demonstrate increased replication and proliferation.[20] This effect is mediated by estrogen receptors and varies with the estrogen receptor content of the adipose tissue being studied. In vivo data also support the notion that estrogen promotes adipocyte precursor proliferation in both visceral and gluteofemoral regions.[18] This finding is consistent with the overall effects of estrogen to promote adipose tissue accumulation. However, the effects are complex, with evidence also showing E_2 to be a negative regulator of adipogenesis.[21,22] The effect of E_2 seems to depend on the stage of adipocyte development considered. Estrogens seem to be more effective in promoting the proliferation of adipocyte precursors in women compared with men, although this sex difference is not observed in vitro suggesting an important role for features of the local adipose tissue environment that have yet to be defined.[23,24]

Testosterone—Androgens seem to have a more consistent effect on adipocyte development than estrogens. In vivo and in vitro studies demonstrate decreased preadipocyte proliferation in testosterone replete conditions and testosterone incubation seems to inhibit commitment and differentiation of adipocyte precursors from men.[25–27] These results are consistent with the overall effect of testosterone to reduce adipose tissue proliferation. These effects are mediated through androgen receptors and downstream effects on IGF-1 and PPAR-γ2. Recent data suggest that the suppressive effects of testosterone on preadipocyte differentiation may depend on intermediate effects on macrophage polarization.[28]

Although androgens have been implicated as having an important role altering adipocyte development, increases in fat mass in male murine and human models of disruption of estrogen signaling and estrogen deficiency implicate estrogens in mediating some effects of androgens on fat after their aromatization to E_2.[29–31]

Bone Marrow-Derived Adipocytes

Recent evidence suggests that some adipocyte precursors come from the bone marrow in both rodents and humans.[32] These precursor cells seem to be preferentially directed toward visceral adipose tissue depots. In rodents, ovariectomy results in an increase in bone marrow-derived adipocytes in gonadal (visceral) fat as compared with control animals and this increase was prevented with estrogen replacement.[33]

Brown Adipose Tissue

Although controversial, there is increasing interest in the possible role of brown adipose tissue (BAT) in weight regulation in humans. There is evidence that sex steroids play a role in the function of BAT.[12] In both rodents and humans, females have more BAT activity than

males.[34,35] Experimental studies support the notion that estrogens promote UCP1 expression, whereas testosterone decreases it.[36] In female rats, ovariectomy result in a reduction in UCP1 expression that is restored with estrogen treatment.[37]

Potential Effects of Follicle-Stimulating Hormone

As women transition through menopause, E_2 levels decrease and follicle-stimulating hormone increases. A recent study by Liu and colleagues[38] found that administration of an antibody to follicle-stimulating hormone that blocked the interaction of the hormone with its cognate receptor protected both male and female mice against high fat diet induced obesity. A similar effect was observed in mice that were genetically modified to not express the cognate receptor of follicle-stimulating hormone. In these studies, there was an increase total energy expenditure and UCP1 expression and evidence for "beiging" of white adipose tissue. It is not clear why food intake did not increase in response to increased energy expenditure, but these results raise the question as to whether some of the increase in visceral adipose tissue observed in postmenopausal women could be due in part to increases in follicle-stimulating hormone and not solely due to decreases in E_2.[39]

LIPID METABOLISM

Upper body (subcutaneous and visceral) and lower body fat depots show distinct properties in the uptake of fatty acids derived from circulating triglycerides (Tg) and FFA as well as the rates and net amounts of the release of FFA through lipolysis. Investigators have hypothesized that differences in the rate of lipid uptake and release may be responsible for the depot-specific characteristics of adipose tissue. A large number of studies over the last 30 years have examined these pathways. The results of these studies have not always been consistent nor have they supported the importance of a single pathway in explaining the observed differences in body fat distribution. Studies in this area face a number of design challenges. The processes under study are dynamic and differences in the pathways studied may be most relevant under specific circumstances (eg, during puberty, during exercise, or after overfeeding). Direct studies of visceral fat metabolism in humans are quite difficult and obtaining samples of adipose tissue from this depot in humans is rare. Data can be expressed per gram of fat, which is relevant for understanding the cellular mechanisms, or at a whole depot level, which may be more relevant for whole body metabolism. In vitro studies can provide control of experimental conditions, but may remove relevant local effectors present in vivo (e.g., local levels of estrogen or cortisol,[40,41] local sympathetic nerve activity,[42] or local adenosine levels). A number of reviews have highlighted the results of these studies.[11,23,43] What emerges is a picture of great complexity, but one where sex and sex steroids clearly play important roles.

The Uptake and Storage of Triglyceride-Derived Fatty Acids

Dietary fat is an important source of the lipid stored in adipose tissue. The rate-limiting step in the uptake of dietary fat carried in chylomicron particles (and VLDL) is thought to be lipoprotein lipase (LPL) that is made by and acts locally in adipose tissue (ATLPL). ATLPL content is increased by insulin and so, ideally, measures would be taken in both fasted and fed states. The uptake of dietary fat by adipose tissue has been examined using test meals

that contain a dietary fat tracer. Tissues can then be sampled at some interval after ingestion. The specific results may depend on what time point is selected because lipid within adipose tissue is constantly turning over. Sex hormones may have a role in modulating LPL expression and activity as well as direct Tg-derived fatty acid uptake.

Sex differences in the uptake and storage of triglyceride-derived fatty acids—

Meal fat studies in rats[44] and humans[45] have not shown marked sex based differences in the uptake of dietary fat by adipose tissue. Several of these studies find more dietary fat being stored in the upper body as compared with the lower body fat in both sexes.[46,47] However, when participants were overfed a high-fat meal, women stored more fat in lower body adipose tissue as compared with men.[48] Furthermore, women with lower body obesity stored more dietary fat per gram of adipose tissue in the gluteal as compared with the abdominal region, whereas men with upper body obesity stored less dietary fat in subcutaneous depots as compared with women.[49]

Effects of estrogens and testosterone on the uptake and storage of triglyceride-derived fatty acids

Estrogen: Santosa and Jensen[50] found that dietary fat uptake was greater in the femoral depot in premenopausal women as compared with postmenopausal, although no group differences in ATLPL were evident. In a different study, estrogen decreased LPL and Tg accumulation in cultured adipocytes.[51] These investigators were unable to find an estrogen response element in the LPL gene and thus concluded that the effect was indirect. Yamaguchi and coworkers[52] found that ATLPL varied systematically across the estrous cycle in female rats. This variation was attributed to differences in plasma insulin concentrations during some phases of the estrous cycle and estrogen concentration in others.[52] Eckel[53] reported that ATLPL is higher in gluteofemoral fat as compared with abdominal subcutaneous fat in premenopausal women. Rebuffe-Scrive and associates[54] found that femoral ATLPL increased markedly in postmenopausal women after treatment with E_2 and progesterone. The results of these studies generally support the idea that estrogen favors the storage of dietary fat in lower body adipose tissue depots.

Testosterone: Rebuffé-Scrive and coworkers[55] administered androgens to normal young men and found increases in abdominal ATLPL. Subsequently, this group measured the uptake of a dietary fat tracer by abdominal and femoral fat in men receiving androgens. They found supplemental androgens did not alter ATLPL or fat uptake in femoral fat, but reduced both in abdominal fat.[46] Santosa and coworkers acutely suppressed testosterone production in normal men with the gonadotropin-releasing hormone agonist Lupron. Participants were then studied before and after testosterone replacement. They found that testosterone deficiency was associated with increases in LPL in both the fasting and fed states, as well as increased uptake of dietary fat.[7] Rynders and colleagues[56] studied healthy young men once after suppression of testosterone and E_2 levels with a gonadotropin-releasing hormone antagonist and an aromatase inhibitor and again after testosterone add back. They found the low testosterone/estrogen condition was associated with greater lower body up-take of a dietary fat tracer. Blouin and colleagues[26] found that LPL production by adipose tissue explants declined after exposure to testosterone. Taken together, these findings are consistent

with the idea that testosterone decreases the expansion of subcutaneous fat but promotes abdominal obesity by decreasing the delivery of Tg-derived fatty acid to lower body fat depots.

Lipolysis and Free Fatty Acid Release

Lipid is lost from adipose tissue through oxidation but, more important, through lipolysis resulting in the liberation of FFAs to fuel tissues and organs. Rates of lipolysis are decreased by insulin after feeding and increased by catecholamines in the fasted state and during exercise. It has long been thought that the products of visceral adipose tissue lipolysis preferentially go to the liver,[57] where they may promote VLDL synthesis and perhaps insulin resistance. It is important to note that although this finding is true in well-fed individuals, FFAs provide energy for hepatic gluconeogenesis and substrate for ketogenesis in malnourished individuals. This finding may be relevant given that the metabolic regulatory systems seem to prioritize fat storage in the visceral depot in men (why not women?).

Sex differences in lipolysis and free fatty acid release—If differences in the rate of lipolysis were the cause of differences in total body adiposity and regional fat distribution in men and women, one might think that lipolysis would be lower in women than in men and lower in regions that accumulate fat in both sexes. This is not what studies have shown. Whole body rates of lipolysis are similar in men and women and women suppress lipolysis in response to insulin to a greater extent than men.[58] In addition, women have higher rates of nonoxidative FFA disposal as compared with men.[59] Lipolysis in upper body fat is suppressed less by insulin in men than women, a result that is the opposite of what one would predict. On a whole body level, women with upper body obesity have higher rates of basal lipolysis than women with lower body obesity or lean controls, but are less responsive to the lipolytic stimulatory effects of catecholamines.[60] Lower body fat is also less responsive to stimulation by catecholamines compared with upper body fat in women.[61] Women have higher rates of lipolysis during exercise, which is associated with a greater reliance on fat oxidation as compared with men when exercising at an equivalent workload.[62] This finding seems to be due to sex-based differences in the sensitivity to α2-adrenergic antilipolytic activation.[63]

Effects of estrogen and testosterone on lipolysis and free fatty acid release

Estrogen: The effects of estrogens on lipolysis are complicated. Most in vivo studies in postmenopausal women demonstrate a suppressive effect of E_2 treatment on basal lipolysis.[64–66] This antilipolytic action of estrogen could be mediated by an increase in α2-adrenergic receptors[67] or improved insulin-mediated suppression of lipolysis.[68] Acute E_2 treatment also seems to inhibit catecholamine stimulated lipolysis in femoral subcutaneous adipose tissue,[65] whereas chronic E_2 treatment decreases norepinephrine stimulated lipolysis in the abdominal subcutaneous adipose tissue.[69] However, studies in premenopausal women find lipolysis does not vary with alterations in E_2 over the menstrual cycle[70,71] and that chronic oral contraceptive use actually increases submaximal exercise stimulated lipolysis.[70] Local perfusion of E_2 into subcutaneous adipose tissue of premenopausal women does not alter basal lipolysis, but results in a depot-specific effect on maximally stimulated lipolysis,

blunting lipolysis in the gluteal region, but potentiating it in the abdominal region.[72] Thus, the role of estrogens in regulating lipolysis varies between studies of premenopausal and postmenopausal women, adipose depots, basal or stimulated conditions, and chronic (genomic) or acute (nongenomic) exposures.

Testosterone: Studies of male rodents in the late 1980s and early 1990s demonstrated a role for testosterone in the regulation of lipolysis. A study of castrated hamsters before and after testosterone supplementation found that basal and catecholamine-stimulated rates of lipolysis were decreased in the testosterone-deficient state and were restored by testosterone treatment.[73] A similar study in rats found that only stimulated, but not basal, lipolysis was altered by testosterone status.[74,75] In contrast, in studies of preadipocytes isolated from a mix of men and women of varying age and body mass index, in vitro testosterone exposure decreased both the lipolytic response to catecholamines and the expression of hormone-sensitive lipase in cells from the subcutaneous but not visceral depot.[76] In another set of studies in elderly men, testosterone supplementation did not alter systemic rates of basal lipolysis,[77] postprandial lipolysis, or responses of lipolysis to insulin.[78]

In summary, studies on the sex-based differences in lipolysis and the effects of sex steroids on the regulation of lipolysis are conflicting and suggest that differences in lipolysis are likely involved in, but do not play the primary role in determining adipose tissue distribution in women and men.

Sex Differences in the Uptake and Storage of Free Fatty Acid

For many years, the role that the direct uptake of FFA by adipose tissue plays in net lipid uptake was felt to be negligible. However, Jensen and colleagues[79,80] demonstrated experimentally that indeed direct uptake of FFA was a significant contributor to the overall lipid supply of adipose tissue. It is less clear whether this pathway is entirely independent of or linked to the pathway that delivers lipid from Tg-rich lipoproteins.[79] Direct uptake and storage of circulating FFA is significantly greater in the subcutaneous fat of women as compared with men.[80] Furthermore, direct uptake of FFA is greater in abdominal fat as compared with femoral fat in men, but this regional difference was not observed in women. A study of more than 80 participants confirmed the greater uptake of FFA in the subcutaneous fat of women as compared with men and showed alignment of regional FFA uptake with differences in regional adiposity with women having greater uptake of FFA in lower body fat depots and men in upper body fat.[81] FFA uptake also correlated with circulating FFA concentrations. In summary, whole body and regional direct uptake of FFA correlates with sex-based differences in whole body and regional fat accumulation.

SEX DIFFERENCES IN PRODUCTS SECRETED BY ADIPOSE TISSUE

Adipose tissue is not only a site for energy storage and liberation, but also serves an important role in the secretion of cytokines and adipokines. These secreted factors act locally and systemically to mediate a range of physiologic functions, including but not limited to insulin sensitivity, energy intake, inflammation, and blood pressure.[82] Here we discuss two important adipokines, leptin and adiponectin.

Leptin

Leptin is secreted by adipose tissue with circulating levels generally proportional to total fat mass. Because women have higher levels of adiposity than men, they also have higher circulating levels of leptin. However, many but not all[83,84] studies show that the higher level of leptin in women is maintained even after correcting for total body fat. Some of the sex-based differences in leptin concentration may be in part due to the fact that the relationship between percent body fat and leptin concentration is not linear but logarithmic.[85] Differences in leptin concentration between males and females are most pronounced during puberty when leptin seems to be important in sexual maturation.[86] There is evidence that subcutaneous adipose tissue produces more leptin per gram of fat than intra-abdominal fat.[87] Because girls and women have more subcutaneous fat relative to visceral fat than men, this factor could explain the sex-based difference. In one study, correcting for regional fat distribution indeed eliminated sex-based differences in leptin concentrations.[88] Other studies have found correlations with estrogen concentration directly. The importance of estrogen is suggested by the fact that leptin levels corrected for the increase in adiposity at puberty[89] and decrease with the menopause.[90]

Adiponectin

Adiponectin is a factor secreted by adipose tissue that is associated with improved insulin sensitivity. It also is associated with a decreased risk of cardiovascular disease. In contrast with leptin, adiponectin levels are inversely related to fat mass. Interestingly, adiponectin levels are actually higher in adult females as compared with males,[83] with an inverse correlation with visceral adipose tissue in women only.[91] The sex-based difference develops during puberty when adiponectin levels decrease dramatically in boys.[92] During this period, fat mass increases in females and decreases in males. These changes in fat mass would predict decreasing adiponectin levels in females and increasing levels in males, but the opposite is observed. In the one study that measured sex steroids, testosterone levels were inversely correlated with adiponectin levels.[93] Consistent with these data, androgen receptor-null mice have high levels of adiponectin and are insulin sensitive.[94] Low levels of adiponectin secretion from adipose tissue may in part underlie the relatively greater risk of type 2 diabetes in males.

SUMMARY

Differences in the amount and distribution of body fat between men and women are the result of a large number of complex yet coordinated adjustments to basic aspects of adipocyte biology resulting in reduced total fat but relatively more visceral fat in men and greater total fat with more subcutaneous gluteofemoral fat in women. Although we focus on the potential effects of these differences on health, the broad effects of sex steroids on adipose function suggest that lipid metabolism is fundamentally different in men as compared with women. Visceral fat, the relatively preferred site for fat accumulation in men, delivers at least some of its products of hydrolysis to the liver, supporting gluconeogenesis and ketogenesis in states of undernutrition or providing substrate for VLDL Tg synthesis in states of full nutrition. VLDL Tg is available to tissues as a source of fuel based on the hormonal regulation of LPL in that tissue by insulin and catecholamines. Conversely,

subcutaneous fat releases its products of hydrolysis into the systemic circulation where these FFA are available to all tissues and their uptake is less subject to regulation by hormones. The fact that sex steroids alter so many processes in adipocyte function suggests that sex differences in lipid metabolism are important for supporting normal sex-specific functions. The implications of these differences in adipose tissue function extend to glucose and protein metabolism as well as nutrient sensing and appetite. Many questions remain, but it may be useful to try to develop a whole body model of sex differences in fuel metabolism that can be a foundation for future studies of both normal metabolism and disease risk and treatment. Understanding sex differences in adipose tissue metabolism and function may be a good place to start.

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KEY POINTS

- Males have less total body fat, but accumulate a disproportionate amount in the abdominal visceral compartment; women preferentially store fat in the gluteofemoral depot.
- Sex steroids play a central role in these differences by altering developmental and biochemical processes in adipocytes that are, in part, depot specific.
- Effects of sex steroids on adipocytes occur directly through hormone receptors or indirectly by modulating tissue responses to other hormones, including catecholamines and insulin.
- Emerging areas of research include sex differences in the recruitment of brown adipose tissue, disposition of bone marrow-derived adipocyte precursors, and potential independent effects of follicle-stimulating hormone.
- Although these differences have relevance for metabolic disease risk, they may inform us about differences in the priorities of fuel metabolism in men versus women.

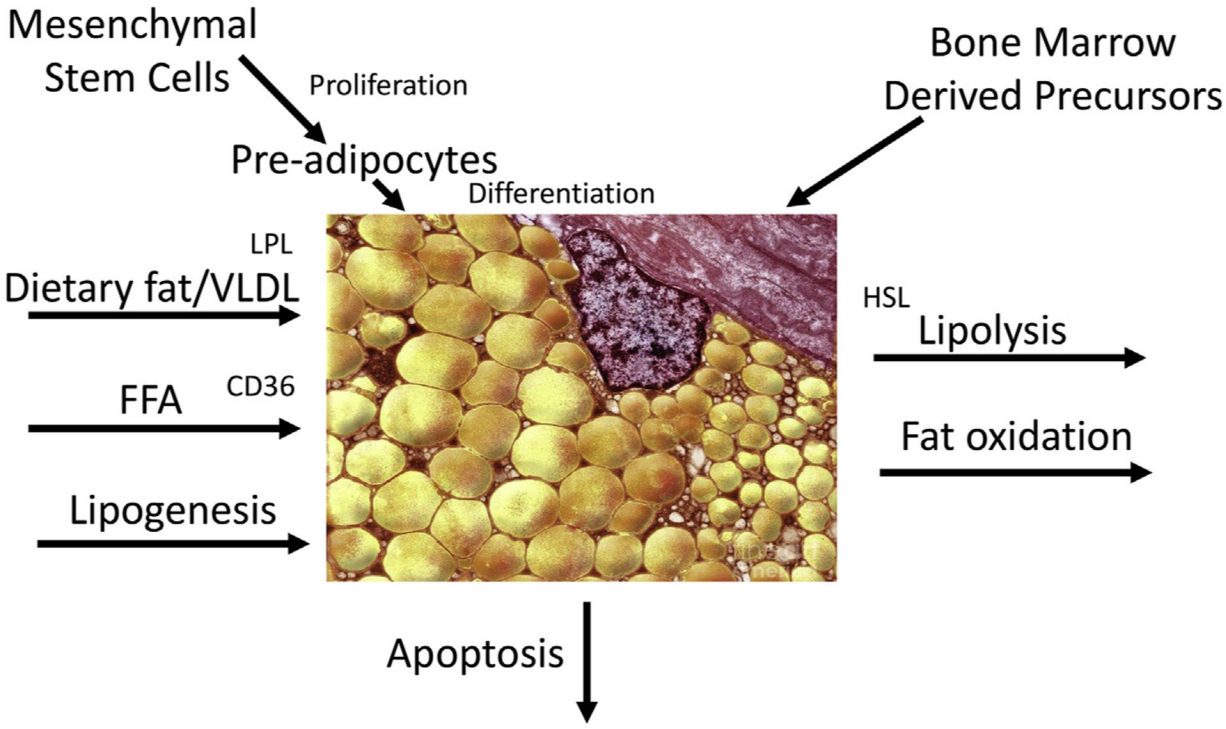

Fig. 1.

Pathways the influence the accumulation of fat in an adipose tissue depot. CD36, cluster of differentiation 36; HSL, hormone-sensitive lipase.