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Sex dimorphism and depot differences in adipose tissue function

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Abstract

Obesity, characterized by excessive adiposity, is a risk factor for many metabolic pathologies, such as Type 2 Diabetes mellitus (T2DM). Numerous studies have shown that adipose tissue distribution may be a greater predictor of metabolic health. Upper-body fat (visceral and subcutaneous abdominal) is commonly associated with the unfavorable complications of obesity, while lower-body fat (gluteal-femoral) may be protective. Current research investigations are focused on analyzing the metabolic properties of adipose tissue, in order to better understand the mechanisms that regulate fat distribution in both men and women. This review will highlight the adipose tissue depot- and sex- dependent differences in white adipose tissue function, including adipogenesis, adipose tissue developmental patterning, the storage and release of fatty acids, and secretory function.

Keywords

Adipocyte; Adipose Tissue; Adipogenesis; Fat Distribution; Lipolysis; Fatty Acid Uptake; Adipokine

1. Introduction

Adipocytes are highly specialized cells that form and store fat in adipose tissue and play a major role in energy homeostasis in vertebrate organisms. Obesity results from an energy surplus and is characterized by an increased storage of lipid and expansion of adipose tissue. Obesity modifies the endocrine and metabolic functions of adipose tissue and is a risk factor for many other metabolic diseases, including Type 2 diabetes (T2DM), cardiovascular disease (CVD), atherosclerosis, and hypertension. No longer recognized as just a lipid-storage depot, white adipose tissue (WAT) has additional properties, including insulin sensitivity and secretory function, that contribute to the pathogenesis of obesity and T2DM (reviewed in [1]). Hence, it is well-established that WAT can significantly impact metabolic health, as its development and function greatly influence whole-body metabolism.

Though overall excessive adiposity is associated with serious co-morbidities, the distribution of body fat has been shown to be a stronger predictor of health risk [2–8]. Numerous studies have described differential correlations of WAT depots and metabolic risk in humans,

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presumably due to intrinsic differences in function of the adipose tissue [9–13]. The two types of WAT, visceral (VAT) and subcutaneous (SAT), are defined by location, and the mechanisms and developmental signals that account for each depot's unique characteristics are steadily emerging. In human subjects, VAT is usually represented by the omental depot (although it also includes the mesenteric fat) and by the perigonadal depot (parametrial and epididymal fat pad) in rodents; while SAT is represented by the abdominal, gluteal and femoral depots in humans and by the inguinal fat pad in rodents. Studies have revealed that central/abdominal (subcutaneous upper body and visceral) fat deposition correlate with an increased susceptibility for metabolic complications [14–18], while gluteal-femoral (lower body) adipose tissue is associated with reduced metabolic risk and may be protective against the adverse health effects of obesity in both sexes [16, 19–23](reviewed in [24]). Current investigations are focused on elucidating the mechanisms, adipose tissue- secreted factors, and developmental signals that account for regional differences in WAT development and function. It is important to note that the developmental origin of white and brown adipose tissue is distinct (reviewed in [25, 26]), and the physiological role of brown fat in human body weight regulation and obesity-associated metabolic complications is controversial and has not been elucidated (reviewed in [27]). This review will provide an overview of the depot- and sex- dependent differences in important functions of white adipose tissue, such as adipogenesis, expression of developmental patterning transcription factors, the storage and release of fatty acids, and secretory function.

2. Sex Differences in Fat Distribution

Sex differences in adipose tissue distribution are well-supported by many literature findings and are associated with whole body metabolic health. Women generally have higher adiposity relative to men throughout the entire lifespan [28, 29]. However, men often have more adipose tissue distributed in the central or abdominal region ('android' or 'apple' phenotype), which carries a much greater risk for metabolic disorders [30](reviewed in [31] and [32]). In contrast, women are characterized by less VAT and more SAT [30, 33–35], especially in the lower body ('gynoid' or 'pear' phenotype) [36, 37]. Likewise, though women can also possess the upper-body obese phenotype, the reduced metabolic disease risk in women has been attributed to the propensity to store body fat in the SAT depot, particularly in the gluteal-femoral region. Though the factors and mechanisms that govern this sexual dimorphism are not elucidated, these characteristic android and gynoid fat distribution patterns in men and women appear as early as puberty (reviewed in [38]). Therefore, evidence suggests that this distribution may be predominantly sex hormone-dependent [39] (reviewed in [40]).

Sex steroids are endogenous modulators of adipose tissue development and function, and may also influence, in part, the distribution of SAT versus VAT depots (reviewed in [41]), although little is known about the cellular and molecular mechanisms of this regulation. In menopausal women, who have a decline in circulating estrogen levels [42–46], visceral adiposity increases, resulting from a shift towards a central/android body fat distribution. Postmenopausal women were shown to have a much greater increase in VAT volume as compared to premenopausal women [47, 48]. Furthermore, women who received hormone replacement therapy (HRT) had lower waist circumferences and VAT than those who did not receive therapy [49–51]. Collectively, these studies suggest that estrogen may modulate WAT distribution by effectively reducing central adiposity in humans. Likewise, the deposition of fat in the gluteal-femoral SAT depots in women versus deposition in the VAT in men may be related to the higher level of estrogen in premenopausal women compared to men (reviewed in [52]).

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Androgens may also have depot- and gender- specific effects on adipose tissue distribution. In men, as testosterone declines with age [53] and in polycystic ovary syndrome (PCOS) women, often characterized by a hyper-androgenic state [54, 55] (reviewed in [56]), there is an increase in VAT. Testosterone therapy in aging men decreased visceral fat mass and increased lean muscle mass [57, 58]. In women, testosterone levels correlated positively with significantly increased abdominal fat [59, 60]. In addition, obese postmenopausal women treated with testosterone developed significantly increased visceral fat [61, 62].

Numerous studies have demonstrated that both SAT and VAT in men and women express sex steroid receptors, notably the estrogen (ERα, ERβ and its variants, and G protein-coupled ER) and androgen (AR) receptors [63–66]. There is also limited evidence to support regional and sex differences in the expression of sex hormone receptors. ERβ1 expression (mRNA and protein) was much reduced in VAT (intraabdominal) compared to SAT, whereas the expression of ERβ4 and ERβ5 mRNA levels were significantly higher in gluteal SAT compared to abdominal SAT in both men and women, with higher ERβ mRNA levels in women compared with men [67]. Recent findings by Gavin et al. support these results, as their analyses demonstrate that abdominal SAT contained more ERα protein compared to gluteal, and gluteal SAT contained more ERβ protein when compared to abdominal SAT from overweight premenopausal women collected during the follicular phase of the menstrual cycle [68]. Importantly, the waist-to hip ratio negatively correlates with the gluteal ERβ protein abundance and positively with the ERα/ ERβ ratio, indicating that ERs play a role in modulating regional fat distribution. In addition, ERα and ERβ have been reported to mediate distinct, depot-specific actions [66, 67, 69]. Estrogens *in vitro* up-regulate the expression of both ERα and ERβ mRNA in subcutaneous adipocytes from women, but only the ERα in subcutaneous and visceral adipocytes from men [66, 67, 69]. In addition, though the ERα subtype was present in preadipocytes, estrogens *in vitro* regulated the ER activity in differentiated but not in confluent preadipocytes, suggesting that the ER becomes functional during the course of adipogenesis [66, 67, 69]. Investigations utilizing knockout models have also yielded novel information regarding the specific roles for estrogen, as well as ERα and ERβ, in the maintenance of WAT lipid and glucose homeostasis [70–73](reviewed in [74]). Hence, these studies provide evidence that estrogen may modulate fat accumulation in a depot- specific manner via the differential expression of ERs within WAT.

Sex-specific adipose tissue distribution may also result from the secretion of sex hormones from adipose tissue in a depot-specific manner. Though other tissues account for the majority of sex hormones in circulation, adipose tissue can also contribute a substantial amount of circulating estrogen and testosterone (reviewed in [75, 76]). Furthermore, human WAT depots possess the enzymes and intermediates necessary for sex hormone synthesis in a depot-specific manner (reviewed in [77, 78]). Collectively, these data suggest that both circulating and local adipose tissue production of sex hormones may have important effects on adipose tissue distribution (reviewed in [79]). Further studies are necessary to elucidate the regional effects of sex-steroid hormones in adipose tissue. Determining the expression of steroidogenic metabolizing enzymes and ERs in upper- and lower-body WAT and testing the effects of treatment with sex steroids on the cellular dynamic properties of preadipocytes in both sexes will further advance our understanding of the contribution of sex hormones to WAT metabolism.

3. Adipogenesis

3A. Definition

Although most development occurs during prenatal and early postnatal life (reviewed in [80]), WAT retains the ability to expand during adult life, especially to accommodate energy

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surplus. Adipose tissue expansion (adipogenesis) occurs in two ways- by increase of existing adipocytes' size (hypertrophy) or by recruiting new fat cells (hyperplasia). The mechanisms that influence the pattern of expansion via hypertrophy and/or hyperplasia have not been elucidated, as individuals vary by the predominant depot-dependent cellular mechanisms that are involved. Preliminary evidence in rodents suggests that VAT (perigonadal) expands predominantly by adipocyte hypertrophy, while SAT (inguinal) by adipocyte hyperplasia following exposure to a high-fat diet [81]. Findings from Tchoukalova et al. have shown that SAT expansion in response to overfeeding resulted in higher adipocyte hypertrophy in the upper-body (abdominal) SAT depot, relative to femoral SAT depot, which had increased hyperplasia [82]. Indeed, adipocyte morphology is significant, as increased adipocyte size correlates with higher metabolic risk [83–85].

Accumulating evidence in human subjects suggests that obesity complications result from the inability of SAT to expand and safely store lipids, which leads to ectopic deposition in other tissues, lipotoxicity, and insulin resistance (reviewed in [86–90]). We have shown that the number of small, early-differentiated adipocytes, isolated from the stromal-vascular fraction (SVF) in SAT depots of normal weight men and women, correlates positively with subcutaneous adiposity (particularly in the femoral SAT), and negatively with the visceral fat accumulation [91]. These data indicate that the abundance of adipocytes in the SAT depots is an important predictor for SAT expendability. The aforementioned studies highlight the importance of proliferative adipocyte precursor cells that are capable of undergoing differentiation to supply new, mature adipocytes, in order to support the expansion of SAT, prevent the accumulation of fat in VAT, and maintain healthy adipose dynamics. Therefore, to safely accommodate metabolic demands, an adipocyte precursor pool is thought to remain present and undergo a constant cell turnover in WAT during adult life. Studies by Spalding et al. suggest that approximately 10% of the body's adipocytes are regenerated each year [92]. In addition, adipocyte number can increase during the development of obesity in adulthood, despite a higher rate of apoptosis (cell death) [93]. Although the term adipogenesis refers to the proliferation and differentiation of adipocyte precursor cells, the apoptosis of adipocytes and their precursors is an important regulator of adipocyte cellularity and is, thus, also mentioned in this section.

3B. Methods for Assessment of Adipogenesis

Very few *in vivo* data is available regarding the mechanisms that modulate the commitment of adipocyte precursor cells to the preadipocyte, as well as the processes that control the formation of new adipocytes in human WAT. The established approaches to assess adipogenesis in WAT depots involve observing the changes in adipocyte size and/or number or analyzing fat cell size distribution, accompanied by the expression profiles of proteins or genes involved in adipogenesis [94, 95]. Alternative methods include functional assays and immunohistochemistry to determine adipocyte differentiation, proliferation, and susceptibility to apoptosis, using preadipocyte cell lines or primary adipose-derived stem cell cultures (reviewed in [96, 97]). These techniques have been invaluable in providing data regarding various facets of adipogenesis and in identifying proteins or pathways that regulate adipogenesis. However, these *in vitro* techniques show limited snapshots of select mechanisms of adipogenesis and cannot provide an integrative evaluation of adipogenesis within the natural microenvironment of the adipose tissue.

Additional studies designed to overcome these limitations have been performed by investigators using animal models, in which adipocyte size-distribution analyses were taken at the end of high-fat dietary interventions with gradually increasing durations to show the dynamics of adipocyte cellularity with weight gain, using a cross-sectional design [93] or obtained longitudinally by serial biopsies of inguinal WAT depots [98]. Collectively, these

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studies suggest an oscillatory pattern of adipose tissue remodeling, involving simultaneous and repetitive cycles of hyperplasia, hypertrophy, and hypoplasia (decreased adipocyte number), presumably reflecting proliferation and differentiation of adipocyte precursor cells, development of mature adipocytes, and apoptosis, respectively. Interestingly, the rate of enlargement of adipocytes (hypertrophy) is proportional to the difference between the lipid load and the storage capacity of adipocytes [98], which may also depend on both the number and metabolic properties of the adipocytes. These findings correlate with other studies, which suggest that the adipose morphology of SAT may be related to adipocyte turnover [99], as subjects with hypertrophy generated 70% less adipocytes per year than those with hyperplasia. Frequent cycling, however, may promote replicative senescence of adipocyte progenitor cells and impairment of their adipogenic function [100]. Though these approaches could yield valuable information, they are not applicable to study human subjects due to the ethical consideration of their invasiveness.

Recently, Spalding and colleagues introduced an innovative method to study adipocyte turnover in humans by measuring the incorporation of ^{14}C derived from above ground nuclear bomb tests in adipocyte DNA [92]. Though the lipid turnover rates calculated by this method are reliable, the ^{14}C-labeling method involves the retrospective analysis over a long period of time (years). However, an additional method, which employs labeling of DNA of adipocytes and the SVF with the stable isotope deuterium (^{2}H) over a short period of time (months), offers an advantage to study *in vivo* adipogenesis [101]. Our laboratory has refined this method in a rat model by purifying the isolated adipocytes and adipocyte progenitor cells (short-time culturing of SVF) [102]. Importantly, this method provides an advantage over the *in vitro* techniques for assessment of adipogenesis, as it provides an integrative evaluation of adipogenesis within the natural microenvironment of the adipose tissue, which can also be utilized for intervention studies due to the shorter duration of time. Overall, this method has valuable implications to assess cell turnover in adipose tissue [103]; however, the effectiveness of this method to study human adipogenesis and adipocyte cell turnover *in vivo* remains to be validated.

3C. Depot- Differences in Adipogenesis

While numerous studies have investigated regional differences in adipose tissue metabolism, few have examined depot-specific differences in adipocyte differentiation [104–107]. WAT depots possess significant differences in adipogenesis, as the proliferation and differentiation of both human and rodent primary preadipocytes have been shown to be influenced by the anatomic location of the depot, as well as aging, gender, and metabolic health [82, 89, 108–118]. While the differences in adipogenesis and its regulation in SAT and VAT depots have been extensively studied [104, 105, 119], studies comparing adipogenesis between upper-body and lower-body subcutaneous depots are sparse [82, 106]. Early studies using thymidine incorporation into fat cell DNA reported increased proliferation in the visceral (parametrial and retroperitoneal depots) preadipocytes of high fat diet-fed rats [120]. Additional studies in rodents indicated that SAT (inguinal) adipocyte progenitors in rodents are more abundant and have significantly increased proliferation as compared to VAT (perigonadal) adipocyte progenitors in response to high-fat diet [81]. Notably, recent studies by Macotela et al. that highlight the intrinsic differences of VAT(epididymal) versus SAT (inguinal) preadipocyte pools in mice reveal that precursor cells from VAT display less differentiation capacity, and VAT has a decreased percentage of preadipocytes following high fat diet, with subsequent increase in other stromovascular cells (i.e. macrophages). They also demonstrate that preadipocytes from VAT highly express anti-adipogenic factors, as opposed to preadipocytes from SAT, which show higher expression of pro-adipogenic genes [121]. This decrease in the preadipocyte pool may be partially attributed to increased cell death of adipocyte precursor cells in VAT, as increased susceptibility to apoptotic

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stimuli of VAT (vs. abdominal SAT) preadipocytes have been reported in human subjects [122, 123]. Early human studies from the Kirkland laboratory revealed that preadipocytes from abdominal SAT accumulated more lipids and had higher differentiation capacity and levels of adipocyte markers compared to preadipocytes from VAT in obese subjects [119]. Other studies performed in primary cultures showed that the proliferation capacity of preadipocytes from abdominal SAT precursor cells was higher than in VAT (omental) cells in obese individuals [105]. Overall, the reduced proliferation and differentiation capacity of visceral preadipocytes may account for the increased hypertropy of existent adipocytes and the metabolic abnormalities associated with VAT.

Accumulating evidence suggests that preadipocyte number and cellularity may depend on the metabolic state of the individual. Isakson et al. demonstrated impaired differentiation of preadipocytes from abdominal SAT in obese individuals, when compared to lean [87]. More recent reports showed that abdominal SAT has increased proliferation of adipocyte precursors in increasing obese conditions [124]. Collectively, these findings suggest that the preadipocytes in the abdominal SAT depot of obese individuals have the capacity to proliferate, in response to metabolic demand, but lack the ability to differentiate. Conversely, other studies indicate that the preadipocyte numbers were lower in obese women as compared to lean [88]. However, these observations could be attributed to greater recruitment of preadipocytes to adipogenesis or greater preadipocyte apoptosis.

Recent findings demonstrate that humans with morbid obesity, with corresponding excessive WAT development, had decreased adipocyte precursors in abdominal SAT, compared to individuals with moderate obesity [125]. This decrease was accompanied by smaller mean adipocyte diameter and a marked increase in the expression of adipogenic markers, which suggests increased differentiation of new preadipocytes and subsequent depletion of the adipocyte progenitor pool. Indeed, recent compelling data reported decreased replicative potential, premature cellular senescence, and loss of the differentiation potential of VAT preadipocytes from patients with morbid obesity compared to lean individuals [100]. Likewise, other findings have shown that although thiazolidinediones stimulate adipogenesis, its chronic administration decreases the adipogenic potential of adipocyte progenitor cells in WAT [126]. Hence, depot-specific differences in adipocyte progenitor abundance and proliferation may influence whether a fat depot expands by hypertrophy or hyperplasia, and thus could also have important implications on the development of metabolic disease. Collectively, the aforementioned studies demonstrate that, compared to VAT preadipocytes, the SAT preadipocytes have higher proliferation and differentiation, but are less prone to apoptosis. This suggests the existence of an adipocyte precursor pool with a higher efficiency for adipogenesis that may contribute to a higher contribution of hyperplasia in SAT than VAT in conditions of obesity.

Though the aforementioned data collectively indicate that SAT depots contain a greater number of functional adipocyte progenitors as compared to VAT depots, these findings are inconclusive; as additional analyses of the adipose cellularity of lower-body depots are necessary. Limited investigations indicate that preadipocytes from abdominal SAT of obese women differentiate less readily and are more susceptible to apoptosis as compared to the femoral SAT depot [88]. These results support previous reports in primary cultures showing that abdominal SAT preadipocyte differentiation inversely correlates with increased obesity and central adiposity [127]. Thus, the stromavascular fraction (SVF) of abdominal SAT fat tissue from centrally obese individuals might contain more preadipocytes with impaired differentiation potential compared to femoral SAT. This provides evidence that VAT and abdominal SAT may share similar properties, as previously shown [128].

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3D. Sex- Differences in Adipogenesis

Limited studies depict sexual dimorphism in adipogenesis. Cross-sectional comparisons of adipocyte morphology and adipogenesis in abdominal and femoral SAT depots in men and premenopausal women with normal weight show larger femoral vs. abdominal SAT adipocyte size in both sexes, but more abundant small adipocytes (aP2^{+}CD68^{-} population in the SVF) in women than in men, especially in the femoral depot [91, 129]. Interestingly, femoral adipocytes differentiate less than abdominal SAT *in vitro* but are more resistant to tumor necrosis factor alpha (TNFα)-induced apoptosis, suggesting reduced turnover and utilization of the preadipocyte pool in lower- vs. upper-body fat in women [91]. Thus, it appears that a contribution by microenvironmental factors and the existence of a high abundance of small adipocytes, rather than the inherent dynamic properties of preadipocytes, may explain the higher percent of lower-body SAT in women with normal weight.

With accumulation of adipose tissue in obesity, the number of adipocytes increases in women but not in men [129] (Table 1). While adipocyte size increases in both sexes, the rate of the adipocyte hypertrophy is higher in men than in women, particularly in the lower-body fat. Cross-sectional comparisons of adipocyte morphology and adipogenesis in abdominal SAT and VAT depots in pre- and postmenopausal women reveals adipocyte hypertrophy in both depots but hyperplasia only in the abdominal SAT depot [130]) (Table 1). Although such comparisons have not been done solely in men, the findings of reduced adipogenic capability of VAT preadipocytes compared to abdominal SAT preadipocytes in studies of obese men and women combined and the larger visceral fat accumulation in men [91, 131] suggest greater contribution of adipocyte hypertrophy to the VAT expansion in men than in women.

Because sex hormones are known regulators of WAT function, there is increasing evidence for the effects of sex steroids on preadipocyte kinetics. For example, testosterone supplementation inhibits the commitment of pluripotent mesenchymal stem cells to the adipogenic lineage, while promoting myogenesis [132]. Furthermore, testosterone impairs adipogenesis of 3T3-L1 preadipocytes, via interaction of the androgen-receptor complex with β-catenin in the *Wnt* signaling pathway [133]. Estrogen stimulates preadipocyte proliferation [134], via non-genomic mechanisms involving MAPK-dependent and *c-fos* signaling pathways [135]. The mitogenic effect of estrogen is demonstrated in both abdominal SAT and VAT preadipocytes; but women are more responsive than men [136]. Estrogen increases adipogenesis via transcriptional up-regulation of PPARγ and IGFR1 genes in ovariectomised animals only [137]. Progestins stimulate preadipocyte differentiation by increasing the gene expression of adipocyte determination and differentiation 1/sterol regulatory element-binding protein 1 (ADD1/SREBP1) transcription factor, which in turn up-regulates the transcription of the lipogenic enzyme fatty acid synthase (FAS) [138]. More importantly, the transcription of cytochrome P450, one of the components of aromatase, is higher in the femoral than in the abdominal region SAT [139, 140]. In addition, an analysis of the global gene expression in the VAT (perigonadal) fat pads in male vs. female mice found that members of the cytochrome 450 superfamily, including aromatase cytochrome P450 (product of the Cyp 19 gene), and hydroxysteroid dehydrogenases are among the sexually dimorphic genes [140].

Women have fluctuations in their levels of sex hormones, which can be modulated by the menopausal status, the use of contraceptives in premenopausal women, or the receipt of HRT in peri- or post-menopausal women. Therefore, these factors must be considered when formulating a study design to effectively analyze WAT, as sex hormones are effectors of adipose metabolism. Nevertheless, the aforementioned studies included women that took contraceptives [91] and postmenopausal women [130], and additional analyses excluding these women did not change the main results or conclusions of the study.

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3E. Summary

Overall, *in vitro* analyses have provided limited, yet very useful information on the processes of adipocyte turnover. Analyzing the various aspects of adipocyte morphology and adipogenesis (Table1) will contribute to a greater understanding of factors that influence depot- and sex-specific WAT expansion. Recent research investigations have integrated the complex dynamics of adipocyte morphology and adipose tissue remodeling in relation to other aspects of WAT function. An overview of the differences in adipose tissue remodeling cycles among depots in men and women that is based on current published data is suggested in Table 1. The general hypothesis is that the high rate of adipocyte hypertrophy and low contribution of hyperplasia in WAT predispose some individuals to increased susceptibility to apoptosis, increased initiation of a local inflammatory response (infiltration of adipose tissue with immune cells and increased secretion of pro-inflammatory molecules by immune cells and adipocyte precursor cells) [141], and gradual impairment of the adipogenic potential of adipocyte precursor cells [100]. In effect, these events shorten the cycles leading to unfavorable increase in their frequency. Taking into account the depot-differences in adipogenesis and adipocyte morphology, it appears that VAT may be more susceptible to this detrimental adipose remodeling than the SAT depots in both sexes. In addition, the more hypertrophic type of WAT expansion in men vs. women and the less available small adipocytes having high lipid storage capacity may cause accelerated adipose tissue remodeling and subsequent adipose dysfunction in men. In contrast, in SAT depots in women, these cycles may be insignificantly affected, and the local inflammation accompanying the adipocyte hypertrophy may be successfully resolved without any unfavorable functional consequences. Because WAT remodeling and metabolism are very complex, future analyses should involve the assessment of adipogenesis *in vivo*, in order to integrate factors within the natural microenvironment of the adipose tissue that are not present *in vitro*.

4. Developmental Programming of Regional Adipose Tissue Function

Transcriptional profiling has revealed limited yet valuable information about potential genetic determinants and intrinsic mechanisms that underlie the depot-specific characteristics of adipose tissue in both men and women. Differences in the expression of developmental genes, many of which are highly conserved transcription factors that act during normal development and remain active in adults, have been reported in the adipose tissue of rodents and humans [142–147]. One large group of developmental genes contain a particular DNA sequence (homeobox) coding for a distinguishable but variable protein domain of approximately 60 amino acids (homeodomain) [148]. Genes encoding proteins with similar sequences within the homeodomain are categorized into eleven classes [148]. One interesting family of 39 members that contains the homeodomain sequence from Class 1 is the HOX genes. They are organized in four clusters of 9–11 genes localized on chromosomes 7 (HOXA), 17 (HOXB), 12 (HOXC), and 2 (HOXD). Genes in the four clusters with similar sequences and position on the locus can be aligned with each other into 13 paralogous group, which are organized along the chromosome in an order that parallels their expression along the anterior-posterior body axis in chronological order [149]. Specifically, 3’ HOX genes in groups 1– 3 are expressed earliest during development and primarily control the rostral body segments, followed by the expression of the central HOX genes in groups 4–8, which control the thoracic portion of the body, and finally by the 5’ Hox genes in groups 9–13 that control the lumbo-sacral region. This approach, defined as spatial and temporal co-linearity, enables the HOX genes to convey regional body patterning. Other families of homeodomain proteins, found to be expressed in adipose tissue include Irx (iroquois), hedgehog (Hh), engrailed (En) genes, paired related homeobox (Prrx), Meis homeobox 1 (Meis), pre-B-cell leukemia homeobox I (Pbx), PBX/knotted homeobox

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(Pknox), short stature homeobox (Shox), and others. T-box (TBX) genes are a family of genes encoding transcription factors that are different from the homeodomain proteins, but also regulate a variety of developmental processes and are expressed in adipose tissue.

4A. Depot-dependent differences in the expression of developmental genes

Studies comparing SAT (inguinal in mice and abdominal SAT in humans) and VAT (epididymal in mice and omental in humans) reveal that adipose tissue from VAT express higher levels of HOXA5 and HOXC8, whereas SAT has higher levels of HOXA10, SHOX2, and EN1, in both mice and humans [104, 142–144]. Conversely, TBX15 and Sfrp2 were higher in SAT vs. VAT in mice, but higher in VAT vs. SAT in humans [144]. In addition, microarray analyses identify that gluteal SAT, adipocytes and the SVF express higher levels of HOXA2, HOXA3, HOXA4, HOXA5, HOXA9, HOXB7, HOXB8, HOXC8, and IRX2, but lower levels of HOXA10, HOXC13, and PBX15 compared to those from the abdominal SAT site [146, 147]. Notably, depot-specific variations in gene expression are also observed in preadipocytes [104, 144]. In addition, select developmental genes, TBX15 and HOXA5, demonstrate changes in expression that correlate with levels of obesity (body mass index) and fat distribution (waist-to-hip ratio) [144]. More extensive gene expression analyses reveal that homeobox genes and other pregnancy-associated factors, are distinct between fat cell progenitors of both rodent and human adipose tissue depots [104, 150, 151]. The observed differences in gene expression appear to be intrinsic and persist through *in vitro* culture and differentiation; hence, the microenvironment does not appear to be an influence. Furthermore, the results from the aforementioned experiments by Tchkonia et al. highlighting the differences in lipid accumulation and differentiation capacity of abdominal SAT versus VAT preadipocytes [119] were *ass*ocia*ted* with distinct patterns of gene expression and conserved over multiple cell generations [145]. Collectively, these data suggest that WAT depots originate from different precursor cells, whose function is presumably controlled by genes involved in development and pattern specification.

Questions arise as to the regulatory mechanisms that drive the homeobox gene expression. Recently, several hormones and their cognate receptors that influence adipogenesis have been shown to regulate select homeobox gene expression. For example, retinoic acid has a well-characterized role in the commitment of mouse embryonic stem cells to the adipocyte lineage [152]. Interestingly, PBX1 has been shown to be induced after following treatment with retinoic acid suggesting its involvement in mediating the retinoic acid action [152]. A siRNA-mediated silencing of PBX1 expression in multipotent adipose derived stem cells (hMADs) demonstrates that PBX1 may play a role in human adipogenesis by maintaining the proliferation of adipocyte precursors and preventing their commitment to the adipocyte lineage [152]. Recently, the expression of PBX1 and PBX3 has been shown to be higher in abdominal SAT compared to gluteal depots [146]. Taken together, these data suggest that the depot-specific differences in preadipocyte pools are established during development.

4B. Sex-dependent differences in the expression of developmental genes

Sex differences in the expression of homeobox genes have also been observed in adipose tissue. Gesta et al. reports that there is higher expression of the HOXC9 gene in SAT than in VAT in males, but not in females [144]. Genome-wide association studies (GWAS) and meta-analyses of GWAS have also identified novel sexually-dimorphic genetic loci associated with upper- or lower-body fat distribution [153, 154], including five genes *(RSPO3, TBX15, ITPR2, WARS2* and *STAB1)* that are differentially expressed between abdominal and gluteal SAT [153]. These studies provide evidence for sexual dimorphism in the associations of certain genetic loci as effectors of adipose tissue distribution. Sex differences in epigenetic regulation by environmental and/or hormonal factors have been reported in both rodents and humans and greatly contribute to adipose tissue distribution

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[155]. Polymorphisms in the estrogen receptor α gene are also associated with body fat distribution in women [156, 157].

A recent transcriptional study of the homeobox genes in abdominal and gluteal SAT depots in men with abdominal obesity (WHR 0.91) and premenopausal women with more peripheral fat distribution (WHR 0.82) show that the expression of HOXC13 and HOXB8 in the gluteal depot is higher in females than in males, whereas the expression of the HOXA2 gene is higher in males compared to females [146]. The expression of the homeobox gene cofactors PBX1, PBX3, and MEIS 1 is higher in abdominal SAT compared to the gluteal depots only in male subjects [146]. Sex hormones, including estrogen, progesterone, and testosterone, have also been described to regulate homeobox gene expression and mediate diverse functions in both developing and adult tissues (reviewed in [158]). These data further support the notion that the apparent differences in adipose tissue function between obese males and females may be mediated by sex hormones via downstream regulation of homeobox gene transcription.

4C. Summary

Because developmental genes heavily influence cell fate and may regulate the development of WAT in utero, their role in nutritional reprogramming of regional adiposity in both sexes requires further investigation. Given the evidence of their differential expression in adult adipose tissue among depots and between sexes, future studies are warranted to explore the precise role in the regulation of regional WAT expansion and fat distribution. Specific directions are well delineated by Karastergiou and colleagues [159] and include: 1) to validate whether the depot- and sex differences in developmental genes are retained after *ex vivo* culture; 2) to understand the importance of developmental genes in regulating adipogenesis and the functional properties of mature adipocytes; 3) to determine whether other cellular types from the SVF also exhibit depot-dependent differential gene expression and, if so, to understand the subsequent effect on the microenvironment; 4) to investigate whether fat distribution has contributed to the differences in gene expression profiles found between men and women with peripheral fat distribution, by performing additional comparisons between men and women with the same (upper-body) fat distribution phenotype or between women with upper- vs. lower-body fat distribution; and 5) to determine whether depot differences in HOX gene expression contribute to racial differences in fat distribution.

5. Secretory Function

An important property of adipose tissue is the production of secretory factors (adipokines) that mediate local and whole body metabolism via auto-/paracrine and endocrine mechanisms. Adipose tissue expansion, and subsequent remodeling, is often associated with altered adipokine production. Several WAT-derived factors have been investigated and shown to modulate numerous physiological systems. Notably, many adipokines are also up-regulated in obesity and promote inflammatory responses, insulin resistance, and other metabolic complications (reviewed in [160]). Evidence suggests that variances in adipokine secretion may partly contribute to the differential metabolic risks that are associated with fat distribution, notably the protective properties of lower body WAT (reviewed in [24]).

Leptin, an adipocyte-secreted factor, was shown to be predominantly expressed by isolated subcutaneous adipocytes as opposed to omental adipocytes, particularly in women [161, 162]. *In vivo* human studies demonstrate that secreted levels of leptin are higher in femoral SAT than abdominal SAT [163]. Another metabolically favorable adipokine, adiponectin, was shown to be positively associated with femoral SAT and gluteal fat mass [164, 165] and

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negatively associated with VAT [166]. Interestingly, levels of both leptin and adiponectin are higher in women [167–171].

Other adipokines have been shown to be highly regulated in obesity/T2DM and may contribute to metabolic dysfunction. Retinol-binding protein 4 (RBP4), a protein released from adipocytes and associated with obesity and insulin resistance, is preferentially produced by VAT and is a marker of intra-abdominal adipose tissue expansion [172]. Plasminogen activator inhibitor 1 (PAI1), an inhibitor of fibrinolysis, is strongly up-regulated in VAT depots, and plasma levels correlate with trunk fat mass in obesity [173], suggesting a plausible link between obesity and thrombotic disorders [174].

5A. Novel Adipokines

In recent years, several novel adipokines have been identified and are at the forefront of scientific research to elucidate their roles in human metabolism and disease. Here, we present the current state of the knowledge of selected adipokines (summarized in Table 3).

Dipeptidyl peptidase (DPP)-4—Protein expression of dipeptidyl peptidase (DPP)-4, a novel adipokine previously studied for its role in the incretin system, is substantially elevated in VAT compared with SAT of obese individuals [175]. The main cellular source of DPP4 secretion is differentiated adipocytes, with a lesser contribution from SVF cells and macrophages. DPP4 mediates insulin resistance, as this adipokine decreases insulin action in adipocytes via decreased insulin-stimulated Akt phosphorylation. Serum levels of DPP4 are also elevated in obese subjects, compared to subjects with normal weight, and are highly associated with abdominal SAT adipocyte hypertrophy, insulin resistance, and other components of the metabolic syndrome.

Chemerin—Chemerin, also known as retinoic acid receptor responder 2 (RARRES2) or tazarotene-induced gene 2 (TIG2), is another recently discovered adipocytokine that may influence adipose tissue development, inflammation, and glucose homeostasis [176]. It is synthesized as an inactive precursor, prochemerin, which is converted to its active form through C-terminal cleavage by serine proteases, especially during inflammatory conditions. Chemerin signals through the G-protein coupled seven transmembrane receptors ChemR23 (CMKLR1) [177]) and G protein-coupled receptor 1 (GPR1) [178]). Evidence also suggests that chemerin binds to the C-C chemokine receptor-like 2 (CCLR2), which seems to increase its local concentration and facilitate its presentation to ChemR23 on adjacent cells [179, 180]). CMKLR1$^{-/-}$ mice exhibit decreased adipose tissue TNFα and IL-6 mRNA, but are glucose intolerant compared with wild-type mice due decreased glucose-stimulated insulin secretion and glucose uptake in skeletal muscle and WAT [181]. Both adipocytes [182] and fibroblasts [183] produce chemerin. Adipocyte hypertrophy and the inflammatory microenvironment in adipose tissue enhance chemerin synthesis, as judged by its increased secretion in response to free fatty acids, lipopolysaccharide, and interleukin-1beta [184, 185]. Chemerin acts like a chemokine in that it induces leukocyte migration and increases macrophage adhesion to VCAM-1 and fibronectin [186], and thereby potentiating local inflammation. In contrast, it also exerts potent anti-inflammatory effects on activated macrophages by promoting phagocytosis [187]. It is not clear whether these dual actions are elicited by different chemerin variants; hence, these effects require further analysis and validation.

Obese subjects with metabolic syndrome have elevated levels of circulating and gluteal SAT-secreted chemerin [188]. In addition, circulating chemerin levels are positively correlated with VAT accumulation [189] and low circulating estradiol concentrations [190]. Moreover, measurements of the chemerin expression in paired abdominal SAT and VAT

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samples in patients with severe obesity reveal higher levels in VAT than in abdominal SAT in men, but the opposite is observed in women. Interestingly, women with PCOS show a pattern similar to men, suggesting a role of androgens in the sexual dimorphism in adipose tissue-derived chemerin secretory function [191]. Similar sex- and adipose tissue depot-specific differences in chemerin mRNA expression levels are also reported by Alfadda A et al. [192], with expression significantly higher in women than men and in abdominal SAT than VAT. Interestingly, they show a significant negative correlation between chemerin mRNA expression in abdominal SAT and circulating chemerin levels, which in this study are associated with obesity markers but not with markers of insulin resistance. Apparently, the auto-/paracrine and endocrine mechanisms of chemerin that regulate adipose tissue function and glucose homeostasis is depot-specific. Further studies of the chemerin transduction pathways in different adipose tissue depots are warranted to unravel these distinct mechanisms.

Lipocalin 2—Lipocalin 2 (also known as neutrophil gelatinase-associated lipocalin and 24p3) belongs to the lipocalin protein superfamily (reviewed in [193]). Lipocalins bind and transport lipophilic substances such as retinoids, arachidonic acid and steroids but the high-affinity endogenous ligands of lipocalin 2 are unknown. Circulating lipocalin 2 levels are positively associated with adiposity, but metabolic endotoxemia and consumption of saturated fat may influence their levels [194]. Involvement of this and possibly other factors could explain the variable lipocalin-2 levels in the circulation of women with PCOS, an insulin resistant state, that are found to be reduced [195], normal [196], or increased [197] compared to healthy women. Likewise, lipocalin 2-deficiency in mice is reported to either improve [198] or impair [199] insulin sensitivity compared with control littermates in the context of diet-induced obesity. The expression of lipocalin 2 in adipose tissue increases with obesity by inflammatory stimuli [200–204]. There are sex-and depot-dependent differences in the expression of lipocalin 2 that resemble those of chemerin; i.e. men have higher expression of in VAT than in abdominal SAT, whereas women showed the opposite [191]. Further studies are needed to understand how these differences contribute to the distinct regional adipose tissue function and whole body glucose homeostasis.

Glypican-4 (Gpc4)—The cell surface proteoglycan glypican-4 (Gpc4) was shown to be released primarily by adipocytes, following a proteolytic cleavage of the GPI anchor by lipases, such as the insulin-regulated glycosylphosphatidylinositol-specific phospholipase D (GPLD1). Glypican-4 expression is higher in abdominal SAT versus VAT depots in humans with normal weight [205]. Conversely, with increasing body mass index (BMI) and waste-to-hip ratio (WHR), Gpc4 mRNA levels in abdominal SAT decrease while those in VAT increase, reaching the highest abundance in overweight and obese individuals [206]. In women, serum Gpc4 levels continuously increase from the lean to the obese phenotype. While in men, serum Gpc4 increases from the lean to overweight phenotype, but in obese men, Gpc4 levels decrease to those observed in lean men, possibly due greater reduction of GPLD1 activity as a result of enhanced insulin resistance [206]. Overall, circulating Gpc4 levels positively correlate with increasing BMI and insulin resistance, and additional experiments depict glypican-4 as a novel adipogenesis-promoting and insulin-sensitizing adipose-derived factor [206].

Omentin—Omentin is another new adipocytokine that is secreted mainly by stromavascular cells [207]. Circulating omentin levels are reduced in subjects with obesity and T2DM compared with lean subjects [208–210] and lower omentin mRNA levels in gluteal adipose depot have been reported in obese subjects with metabolic syndrome [188]. Omentin gene expression is higher in VAT than in abdominal SAT [191, 211] in both men and women, despite the putative androgen response elements in its promoter region

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suggesting that other factors may be involved in the regulation [191]. A recent study finds sex as one of the determinants of circulating omentin concentrations, and low testosterone concentrations are related to higher omentin levels [190]. Omentin increases glucose uptake by human adipocytes *in vitro* through enhanced protein kinase B (AKT) phosphorylation and insulin signal transduction [210]. It also exerts antiinflammatory effects by inhibiting TNFα-induced expression of adhesion molecules in endothelial and vascular smooth muscle cells [212, 213]. These data suggest that omentin may play a positive role to reduce inflammation and increase insulin sensitivity, but its clinical relevance needs to be confirmed in future studies.

Secreted frizzled-related proteins (SFRPs)—A family of five secreted frizzled-related proteins, termed SFRP1–5, has been implicated in the regulation of adipogenesis. They share significant homology with the Frizzled receptors and bind to wingless-type (Wnt) ligands, interfering with the Wnt/β-catenin signaling [214], which exerts adipogenesis-inhibitory action by reducing the expression of pro-adipogenic transcription factors [215]. SFRP1 and SFRP 4 mRNA is up-regulated during adipogenic differentiation, suggesting a proadipogenic role [216, 217]. A comprehensive assessment of all five SFRP proteins in abdominal SAT and VAT depots from lean and obese people in a study by Ehrlund A et al. [218] shows that distinctive members of the SFRP family exhibit different depot-dependent expression patterns as a function of obesity. Specifically, SFRP1 decreases in abdominal SAT but is unchanged in VAT, whereas SFRP2–4 is up-regulated, more noticeably in the VAT depot, and SFRP5 does not change in either depot. SFRP1 in abdominal SAT is negatively associated with BMI and insulin resistance via reducing the secretion of the proinflammatory cytokines and increasing the release of adiponectin. SFRP2–4 mRNA levels in both abdominal depots show opposite relationships, but the mechanisms are unknown. Notably, SFRP1, SFRP2 and SFRP4 are secreted by abdominal SAT explants but not SFRP5, raising speculation about its contribution to the SFRP5 in circulation. Furthermore, the reports on the role of circulating SFRP5 in obesity-related insulin resistance are inconsistent. Some observations in animals and humans show that the levels decline with obesity [219, 220], while others report opposite findings [221, 222]. It is of interest to note that one study finds higher plasma SFRP5 levels in females compared to males, suggesting possible sex-specific regulation. Additional studies are needed to elucidate the role of SFRP2–5 in the adipose tissue function, obesity, and metabolic health.

Vaspin—Vaspin (visceral adipose tissue–derived serine protease inhibitor, serpinA12), is another adipokine associated with insulin-sensitizing effects. In human studies, the vaspin mRNA levels are not detectable in persons with normal weight and in some obese subjects with insulin resistance. However, vaspin expression is induced in VAT and/or SAT of overweight and obese individuals [223]. Administration of vaspin to mice with dietary-induced obesity ameliorates insulin resistance, in part, through normalizing the altered expression of genes relevant to insulin resistance, including leptin, resistin, TNFα, glucose transporter 4, and adiponectin [224]. Some studies suggest that the induction of vaspin gene expression in human adipose tissue may be a compensatory mechanism associated with obesity and insulin resistance. The vaspin mRNA levels vary between VAT and SAT depots, but its regulation appears to be depot specific. Its expression in VAT is strongly predicted by percent body fat whereas insulin sensitivity predicts the SAT vaspin mRNA levels. Interestingly, although no sex-differences are observed for the vaspin expression in adipose tissue, sexual dimorphism has been reported for circulating levels, which were shown to be higher in women [225, 226].

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5B. Summary

Overall, there is limited knowledge about the roles of functionally divergent WAT depots in human adipokine production. Nevertheless, many adipokines have been shown to be differentially expressed and secreted, as a function of adipocyte morphology, between WAT depots, specifically abdominal SAT and VAT. Likewise, the relationship between circulating levels of adipokines, their secretion from WAT depots, as well as their endocrine effects, have been heavily evaluated to understand their contribution to the development of obesity and related metabolic disorders. It is important to discern whether these adipokines appear as a compensatory reaction to increased metabolic distress, i.e. adipocyte hypertrophy, in an effort to undergo normal adipose tissue remodeling, or if they have a pathogenic role leading to WAT metabolic dysfunction. Accordingly, select adipokines may exert dual pro- or anti-inflammatory or insulin resistant or insulin sensitive effects, relative to the adipocyte characteristics and WAT remodeling paradigms. A speculative summary of the depot- and sex-dependent differences in novel adipokine production is presented in Table 2. Overall, cytokines that decrease adipocyte insulin resistance and show pro-inflammatory actions, including DPP4, chemerin, and lipocalin 2, appear to be produced more in VAT than SAT depots and more in men than in women. This may result from their secretion from hypertrophic adipocytes, macrophages, and/or adipocyte precursor cells in a more inflammatory state, reflecting a WAT remodeling pattern more frequent in VAT depots and in men (Table 1). While adipokines with insulin sensitizing and/or anti-inflammatory properties, such as Gpc4, omentin, and certain SFRPs, seem to increase mostly in the VAT (more in women than men), in an attempt to ameliorate or resolve the local inflammation, and increase much less or decrease in abdominal SAT (less in women than men). Of note, vaspin, is not detected in many subjects but may also be expressed as part of a compensatory mechanism in response to the development of insulin resistance. Importantly, although the expression of adipokines in lower-body SAT has not been analyzed, we speculate that sex differences in the production will be highly significant, considering the differences in adipocyte cellularity between the two SAT depots between the sexes (Table 1). Further studies of the adipokine expression in upper- and lower-body depots using longitudinal designs will be necessary to test these hypotheses. Likewise, the characterization of sex- and depot-differences in the expression and secretion of the numerous novel adipokines (reviewed in [193, 227]) will provide further insight into the paracrine and endocrine function of adipose tissue depots and the relationship to energy homeostasis and metabolic health.

6. Lipid Metabolism

A critical function of adipose tissue is the storage and release of triglycerides (TGs) to provide energy in the form of fatty acids, to be utilized during exercise, fasting, or starvation. Important factors in adipose tissue fatty acid metabolism are the rate of TG storage, primarily via lipoprotein lipase activity, and the rate of lipolysis, which is potently regulated by insulin (fed state) and catecholamines (fasted state) and results in the liberation of free fatty acids (FFAs) as fuel to tissues and organs. Likewise, evidence suggests that upper-body (subcutaneous and visceral) and lower-body fat depots show distinct properties in the rates and amounts of lipolysis and fatty acid uptake, and variations in these factors may be responsible for the depot-specific characteristics of adipose tissue.

6A. Lipolysis and FFA Release from WAT

Numerous findings suggest that there is great heterogeneity in lipolysis between adipose tissue depots of men and women. On average, adipose tissue lipolysis is substantially greater (~40%) in women than in men, even though metabolic health is typically better in women. This is presumably due, in part, to increased fat oxidation and more efficient utilization and

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disposal of FFA in women [228, 229] (reviewed in [230]). Studies have shown that upper-body adipocytes isolated from lean males and females are highly responsive to lipolytic adrenergic stimulation, as compared to lower body adipocytes [231–235]. Importantly, these effects were more pronounced in females. Subsequent *in vivo* studies in lean individuals support these findings, in that catecholamine-induced lipolysis is greater in upper-body than in lower-body SAT depots [236–238]. In addition, both exercise-induced and prolonged fasting-induced lipolytic activity was significantly more marked in abdominal than in gluteal-femoral SAT [239, 240]. Furthermore, in obese women, femoral SAT is less lipolytically active than upper-body fat [14, 241]. A recent study by Gavin et al. demonstrates that premenopausal overweight women perfused with estrogen had an increased lipolytic response in abdominal SAT, while estrogen inhibited lipolysis in gluteal SAT [242]. This study, among others, highlights the role of sex hormones in body fat distribution [243, 244], and suggests that estrogen may be involved in the maintenance of the gynoid body fat distribution in premenopausal women. Additional studies demonstrate that hormone sensitive lipase (HSL), a key enzyme in lipolysis, is differentially expressed between adipose tissue depots (reviewed in [245]), and the rate of action of HSL is higher in the abdominal than the gluteal depot [246]. Importantly, upper-body/visceral adipose tissue lipolysis from both males and upper-body obese females were also shown to be more resistant to the anti-lipolytic effects of insulin when compared to non-obese or lower body obese adults [247–250]. Furthermore, FFA concentrations are much greater in upper-body obese individuals following a meal [14, 251], supporting the notion that upper-body adipocytes are more resistant to the anti-lipolytic effects of insulin. In contrast, lower body adipocytes are more responsive to the anti-lipolytic effects of alpha 2 adrenergic agonists and have lower responses to lipolytic agonists (reviewed in [252]). Collectively, these studies suggest that body fat distribution greatly influences lipolysis, as summarized in Table 4. While the regulation of lipolytic processes in various WAT depots require further investigation, studies suggest that the differential levels of lipolysis, as shown in the above analyses, may be mediated, in part, through a higher expression of lipolytic beta-adrenergic receptors in the upper-body depot [253, 254].

Sex dimorphism is also evident in these analyses, as abdominal SAT in women greatly exceeds the lipolytic effects seen in men; while femoral SAT had an increased lipolytic response in men but not women [238, 239]. Lipolysis was also much greater in women compared to men following prolonged fasting [255]. Conversely, the stimulation of lipolysis in VAT is much higher in men than women [238, 254].

FFAs that are released from stored TGs can be utilized as required between meals and in the starved state; however, excess FFAs can contribute to the adverse metabolic consequences of obesity by ectopic fat accumulation in hepatic and peripheral tissues. Compared with lean women, systemic FFA release in the fasting state is greater in upper-body obese women, due to their higher fat mass [256]. Likewise, lipolysis-induced FFA release is greatly reduced in lower-body obese women, such that the levels are comparable to non-obese women. Studies have demonstrated that lipolysis of VAT increases, relative to visceral fat mass, which results in the release of excess FFAs into the liver via the portal vein in both obese men and women, but more so in obese women [257]. It is well-established that high levels of FFA can mediate insulin resistance in both muscle [258, 259] and liver [260, 261]. Nevertheless, though VAT-derived FFAs play an important role in abnormalities of hepatic function in obese individuals [262–264], VAT may not be a significant contributor of FFAs to peripheral tissues. Hence, upper-body obesity is highly associated with increased FFA release, and abdominal SAT, as opposed to VAT, may be the primary source of excess systemic FFAs in both men and women [14, 241, 248].

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6C. Storage and Uptake of FFA in WAT

The storage of intracellular TGs in adipose tissue derived from FFAs depends on the action of lipoprotein lipase (LPL) by adipocytes, as this is the rate-determining step in the uptake of circulating TG-FFA. Several studies have assessed the depot- and sex-specific regulation of LPL. In early studies, LPL expression and activity was shown to be higher in subcutaneous abdominal than in gluteal adipocytes in non-obese men [265]. Conversely, the activity of LPL was higher in gluteal- femoral adipocytes from non-obese women as compared with the abdominal depot [265, 266]. Additional studies demonstrate that LPL activity is lower in VAT versus abdominal SAT-derived adipocytes isolated from women, but higher in the VAT depot in obese men [235, 267]. Likewise, in non-obese or moderately obese men, LPL expression and activity is higher in visceral than in gluteal adipocytes [235]. Additional evidence demonstrates that testosterone was able to suppress LPL activity in the femoral SAT of men, contributing to abdominal fat accumulation [268], while other findings suggest that testosterone does not affect LPL activity in the thigh [269]. Other studies have also demonstrated the role of sex hormones in modulating LPL activity and expression [270, 271]. Taken together, these variances may be due to both sex-specific differences and the complex post-transcriptional regulation of LPL [272]. Nevertheless, it is likely that LPL expression and activity play a critical role in sex-specific adipose tissue depot development and function.

Depot- and sex-specific differences in the direct uptake of circulating FFA have also been described. Overall, short-term meal-derived FFA uptake was shown to be greater in upper-body abdominal SAT versus lower-body SAT in both lean and obese men and women, with women storing more in SAT than men [269, 273, 274]. One point of consideration is that the *in vivo* rate of FFA uptake in these studies was measured per mass of the entire adipose tissue. Therefore, uptake may be calculated as greater in SAT due to its larger fat mass and actually similar or lower in visceral adipocytes when calculated per cell. Nevertheless, storage of meal-derived fatty acids per gram of adipose tissue lipid following a high fat diet is greatly increased preferentially in the gluteal-femoral SAT of women compared to men [275]. In addition, studies have shown that femoral SAT of women with lower-body obesity more efficiently takes up meal-derived FFAs from circulation [276]. These regional differences were not observed in men; therefore, the aforementioned studies may partially explain sex-dependent body fat distribution, as women typically have more lower-body fat [266]. Conversely, evidence suggests that the uptake of meal-derived FFA in the VAT depot is greater in lean men than women [273, 277]. There are also differences between the upper-body depots, as FFA uptake following a meal was much greater in the VAT than abdominal SAT depot, which was in turn greater than the femoral SAT depot in obese men and women [278]. Furthermore, in men, testosterone induces meal FFA uptake preferentially into abdominal SAT and decreases uptake in VAT [269]. Hence, older men with decreased testosterone develop more VAT.

In the postabsorptive state, lean men are much less efficient at the direct uptake of circulating FFA into the femoral as compared to the abdominal SAT depot; while in obese subjects, direct FFA uptake is increased specifically in the femoral depot of women [279]. Additional studies support these observations, as Koutsari et al. show that women had greater FFA storage than men in both abdominal and femoral SAT in the postabsorptive state [280]. Notably, storage rates were significantly greater in femoral SAT than abdominal SAT in women, whereas the opposite was true in men. The femoral SAT depot of women was also shown to more effectively store FFA during walking conditions, as compared to the abdominal SAT depot and each SAT depot in men [281]. Collectively, these findings suggest that direct adipose tissue FFA storage is significantly greater in women than men.

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Overall, the upper-body abdominal fat depot may participate in the short-term daily FFA handling and uptake the flux of dietary fatty acids (reviewed in [282]), while the lower-body gluteal-femoral depot appears to exert its protective properties in long-term fatty acid storage, especially in women (Table 4). Moreover, the storage capacity of gluteal-femoral WAT may influence the level of abdominal/central adiposity, as supported by a recent study by Hernandez et al. depicting the pattern of fat redistribution fat following liposuction [283]. Though some studies suggest that the depot-differences in the above findings may be attributed to LPL activity [277], additional studies are necessary to evaluate the mechanisms underlying FFA storage in upper- and lower-body depots of men and women. Short- and long-term fatty acid metabolism in both upper- and lower-body depots has not been fully elucidated and requires further analysis.

7. Conclusions

Studies support the hypothesis that regional WAT development and expansion greatly impact metabolic health, as fat in different body locations exhibits distinct features and functional characteristics. Additional evidence also highlights sexual dimorphism in adipose tissue function, and there evidence for a plausible role of sex hormones, especially estrogen, in regional WAT function. Yet, the mechanisms that control the regulation of fat distribution in both males and females are poorly understood. Indeed, the influences of adipose tissue depot- and sex- specific effects on adipocyte function, as well as the relationship to metabolic health are not fully elucidated and warrant further analysis. Numerous studies have described depot-and sex-differences in adipose tissue metabolism, such as adipogenesis, the expression of developmental gene signatures, fatty acid handling, and secretory function. Though many of these analyses have focused on the differences between upper-body SAT and VAT, recent investigations have focused on elucidating the differences between upper-and lower-body WAT metabolism, especially the beneficial effects of gluteal-femoral adiposity.

Investigations have provided limited information on the adipocyte proliferation, differentiation, and remodeling processes that are involved in WAT expansion (Table 1). Much remains to be learned about the factors from the microenvironment that influence adipogenesis in adipose tissue depots in both sexes, and how they subsequently contribute to regional fat distribution and metabolic health.

Various studies have yielded the discovery of novel gene loci that are involved in the regulation of body fat distribution in both males and females. Likewise, analyzing the expression patterns of these sex- and depot- specific genes may also provide clues as to the mechanisms underlying regional fat expansion.

Evidence arising from *in vitro* and *in vivo* studies suggests that the differential regulation of fatty acid release and uptake in SAT and VAT greatly affect their depot-specific metabolic properties (Table 4). Overall, VAT adipocytes in men exhibit higher rates of fatty acid turnover and lipolysis that in women, leading to a greater release of free fatty acids into the circulation. Such differences provide a link between increased VAT and the metabolic risks associated with obesity. Importantly, the long-term storage of fatty acids in the lower-body (gluteal-femoral) depot, preferentially in women, provides a plausible explanation as to the protective properties of this depot from ectopic fat accumulation and metabolic perturbations. Nevertheless, the exact regulatory mechanisms of fatty acid metabolism remain to be elucidated.

With the accumulating evidence for the beneficial role of the femoral WAT depot, it is important to characterize adipokine expression and secretion in both upper- and lower-body

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WAT depots; as it is possible that the gluteal-femoral depot could convey protection through a beneficial adipokine profile. These analyses will facilitate categorizing the importance and beneficence of the known adipokines, but, importantly, include the continued discovery of novel adipokines. In addition, accumulating data suggests that adipokines have paracrine effects on preadipocyte cellular kinetics, as well as mature adipocyte metabolic function or secretion, which demonstrates the multiple effects of adipokines on metabolic health (Table 2).

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Highlights

- Regional fat distribution and sex dimorphism greatly influence metabolic health.
- Developmental genes may contribute to depot- and sex-specific properties of adipose tissue.
- Depot and sex influence adipogenesis, secretory function, and fatty acid handling.

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Table 1

Dynamics of adipocyte characteristics and adipose tissue remodeling with fat gain by depot and sex

Depots		Females			Males		
		Adipocyte size	Adipocyte number	Frequency of fat tissue remodeling*	Adipocyte size	Adipocyte number	Frequency of fat tissue remodeling*
Omental		↑	↔	↑	↑↑↑↑*	↔*	↑↑↑
SAT	Abdominal	↑	↑	↑/↔	↔	↑	↑
	Femoral	↑	↑↑	↔	↑↑↑	↔	↑↑

*Hypothetical interpretations; ↑, increased; ↔, not changed

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Table 2

Notes on depot- and sex differences in the expression of novel adipokines

Molecule	Cellular source(s) in adipose tissue	Auto/paracrine function	Depot-specific effects on mRNA levels	Sex-specific effects on circulating or AT mRNA levels	Effects of obesity
DPP4	Adipocytes-COR$^{(+)}$ size; SVF; Mϕ	↓Insulin signaling in adipocytes	VAT>SAT in obese,		↑Serum DPP4 ↑DPP4 mRNA in VAT, SAT
Chemerin	SVF Adipocytes	Pro-/anti-inflammatory	SAT mRNA COR$^{(-)}$ serum chemerin	M & PCOS-F: VAT>SAT F: SAT>VAT Serum chemerin COR$^{(-)}$ serum estradiol	↑secretion by adipocyte hypertrophy & AT inflammation
Lipocalin 2		Transports lipophilic substances (retinoids, steroids, arachidonic acid)		M & PCOS-F: VAT>SAT F: SAT>VAT SAT mRNA COR$^{(-)}$ serum	↑secretion by AT inflammation Serum levels & relation to insulin sensitivity-varying data
Gpc4	Adipocytes Less by SVF	↑Insulin signaling ↑Adipocyte differentiation	SAT>VAT in lean	Serum Gpc4: F: ↑ continuously with ↑BMI M: ↑ from normal weight, to overweight ↓ in obese	↑VAT, COR$^{(+)}$ BMI, WHR ↓SAT, COR$^{(-)}$ BMI, WHR Serum Gpc4: COR$^{(+)}$ BMI, IR
Omentin	SVF	↑glucose uptake by adipocytes Anti-inflammatory	VAT>SAT	AT mRNA: F=M Serum omentin COR$^{(-)}$ serum testorsterone	↓Circulating & gluteal mRNA Serum omentin: COR$^{(-)}$ MetS
SFRPs	SAT explant secretes SFRP1,−2,−4	↑ adipogenesis SFRP1: antiinflammatory, ↑adiponectin SFRP2–4: inverse to SFRP1		Circulating SFRP5 levels: F>M	SFRP1 mRNA: ↓SAT, ↔VAT SFRP2–4 mRNA: ↑SAT, ↑↑ in VAT Serum SFRP5: varying data
Vaspin	Adipocytes Precursors SVF	↑Glucose uptake by adipocytes Anti-inflammatory ↑Adiponectin	VAT: COR$^{(+)}$ BF SAT: COR$^{(+)}$ IR & WHR	AT mRNA: F=M, Serum vaspin: F>M	No mRNA in AT in lean; ↑compensatory with ↑BF, IR

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Abbreviations: DPP4, dipeptidyl peptidase 4; SV, stroma-vascular; Mφ, macrophages; VAT, visceral adipose tissue; SAT, subcutaneous adipose tissue; $COR^{(+)/(-)}$, positive or negative correlation; PCOS-F, women with polycystic ovarian syndrome; SVF, stromal-vascular fraction; Gpc4, Glypican 4; BMI, body mass index: body weight (kg) : height (cm)2; WHR, waist to hip (circumferences) ratio; F, female(s); M, male(s); TNFα, tumor necrosis factor alpha; SFRPs, a family of five secreted frizzled-related proteins; Wnt, wingless-type ligands; AT, adipose tissue; ↑, increased; ↓, decreased.

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Table 3

Relative alterations in adipokine transcription as a function of regional fat gain in men and women

Depots		Females			Males		
		Pro-inflammatory	**Anti-inflammatory**	**Compensatory anti-inflammatory**	**Pro-inflammatory**	**Anti-inflammatory**	**Compensatory anti-inflammatory**
VAT		↑	↑↑	ND	↑↑↑↑	↑	ND
SAT	Abdominal	↑/↔	↑/↔/↓	+	↑	↓	+/ND
	Femoral[*]	↔	↔	++	↑↑	↓↓	+/ND

[*] Hypothetical interpretations; ND, not detected; ↑, increased; ↓, decreased; ↔, not changed

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Table 4

Schematic of WAT depot- and sex differences in lipid metabolism

Depots		Females			Males		
		WAT depot mass	Lipolysis/FFA release	FFA uptake	WAT depot mass	Lipolysis/FFA release	FFA uptake
	VAT	↓	↑	↑	↑	↑↑	↑
SAT	Abdominal	↑	↑↑	↓	↓	↑	↑
	Gluteal	↑	↓↓	↑↑	↓	↓	↓
	Femoral	↑	↓↓	↑↑	↓	↓	↓