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Adipose Tissue Complexities in Dyslipidemias

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Abstract

Adipose tissue is the largest organ in the human body and, in excess, contributes to dyslipidemias and the dysregulation of other vascular and metabolic processes. Adipose tissue is heterogeneous, comprised of several cell types based on morphology, cellular age, and endocrine and paracrine function. Adipose tissue depots are also regional, primarily due to sex differences and genetic variation. Adipose tissue is also characterized as subcutaneous vs. visceral. In addition, fatty deposits exist outside of adipose tissue, such as those surrounding the heart, or as infiltration of skeletal muscle. This review focuses on adipose tissue and its contribution to dyslipidemias. Dyslipidemias are defined as circulating blood lipid levels that are too high or altered. Lipids include both traditional and nontraditional species. Leaving aside traditional definitions, adipose tissue contributes to dyslipidemias in a myriad of ways. To address a small portion of this topic, we reviewed (a) adipose tissue location and cell types, (b) body composition, (c) endocrine adipose, (d) the fat-brain axis, and (e) genetic susceptibility. The influence of these complex aspects of adipose tissue on dyslipidemias and human health, illustrating that, once again, that adipose tissue is a quintessential, multifunctional tissue of the human body, will be summarized.

Keywords: adipose tissue, adipocyte, body weight, body mass index, lipidomics, obesity, leptin, APOE, endocrine, brain

1. Introduction

The World Health Organization (WHO) reports that by 2050, 20% of the world's population will be age 60 years and older [1]. Correspondingly, cardio- and cerebrovascular diseases are the top 10 most common causes of death [2]. Ischemic heart disease is first, followed by stroke (second); Alzheimer's disease (fifth), the disease of the latest life; and type 2 diabetes (T2D, sixth). Vascular diseases comprise four of the top 10 causes of death because of their association with pandemic obesity [2].

Adipose tissue (AT) is the largest organ in the human body. Adiposity (amount of AT) is often classified as overweight and obese using body mass index (BMI, kg/m^2) or Waist Circumference (WC). Over the life course and with aging, BMI is dynamic and evolves in relation to physical growth, puberty, reproductive status, as well as nutritional health and adequacy. The life course evolution of BMI represents an evolutionary metabolism. As such, potential relationships between BMI and accompanying vascular risk factors, such as blood lipid levels, change over the life course and in association with disease. BMI and central adiposity cut points for overweight and obesity as well as for hyperlipidemias (the most common form of

clinical dyslipidemia) are those associated with mortality and later-life outcomes. See **Tables 1** and **2** for common definitions of these cut points.

Epidemiologic studies exploring the natural history of vascular phenotypes show that levels of body weight, BMI, and blood lipids increase throughout adult life and decline with aging and later-life diseases [3–6]. This is practically illustrated by comparing mid- versus later-life risk scores for late-onset dementia. Obesity and hyperlipidemia are components of mid-life risk scores, but not of later-life risk scores [7–10]. This is often referred to as the “obesity paradox.” This contradictory combination of higher disease risk associated with higher mid-life vascular risk and declining vascular phenotypes in the years immediately preceding and at the time of later-onset diseases and death requires further understanding but has very practical implications (**Figure 1**). Lower blood lipid levels and/or rigorous control of blood lipid levels may not be advantageous during the latest life [11]. In addition, genetic

Disease risk* relative to normal BMI and WC						
	BMI (kg/m ²)	Obesity class	Women ≤88 cm	Women >88 cm ⁺	Men ≤102 cm	Men >102 cm ⁺
Underweight	<18.5					
Normal	18.5–24.9					
Overweight	25.0–29.9		Increased	High	Increased	High
Obesity	30.0–34.9	1	High	Very high	High	Very high
	35.0–39.9	2	Very high	Very high	Very high	Very high
Extreme obesity	≥40	3	Extremely high	Extremely high	Extremely high	Extremely high

*Disease risk for T2D, hypertension, and cardiovascular disease.
⁺Increased Waist Circumference is a marker for increased risk, even in adults of normal weight.

Table 1.

Classification of overweight and obesity by Body Mass Index and Waist Circumference and disease* risk based on anthropometric estimates of adipose tissue [108–111].

mg/dl	Interpretation
LDL cholesterol	
<100	Optimal
100–129	Near optimal/above normal
130–159	Borderline high
160–189	High
≥190	Very high
Total cholesterol	
<200	Desirable
200–239	Borderline high
≥240	High
HDL cholesterol	
<40	Low
≥60	High

The National Cholesterol Education Program ATP III Guidelines [112].

Table 2.

Lipid cut points for adults based on blood levels of traditionally measured lipids.

background related to vascular risk such as APOEε4 allele possession, which encodes for a protein on the surface of lipoproteins and influences lipid metabolism and vascular health, has also been associated with late-onset dementia and mortality [12].

The vascular and metabolic complexity and ubiquity of AT demand a more expansive definition of dyslipidemia. Herein the multiple potential contributions of a complex, heterogeneous AT to dyslipidemia phenotypes and human health are described. Dyslipidemias are considered expansively and defined as circulating blood lipid levels that are too high or too low, where lipids refer to more than those listed in **Table 2**. AT contributions to dyslipidemia phenotypes relate to (a) AT location and cell types, (b) body composition, (c) endocrine adipose, (d) the fat-brain axis, and (e) genetic susceptibility (**Figure 2**). This review illustrates that AT is a quintessential, multifunctional tissue of the human body.

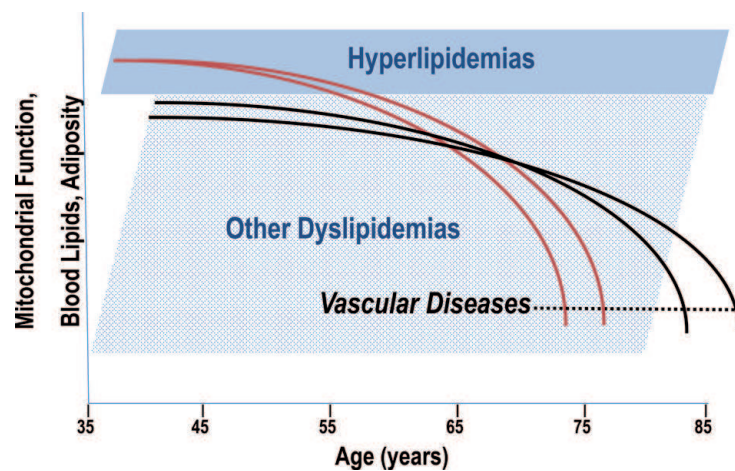


Figure 1.
 The biological declines that accompany dyslipidemias.

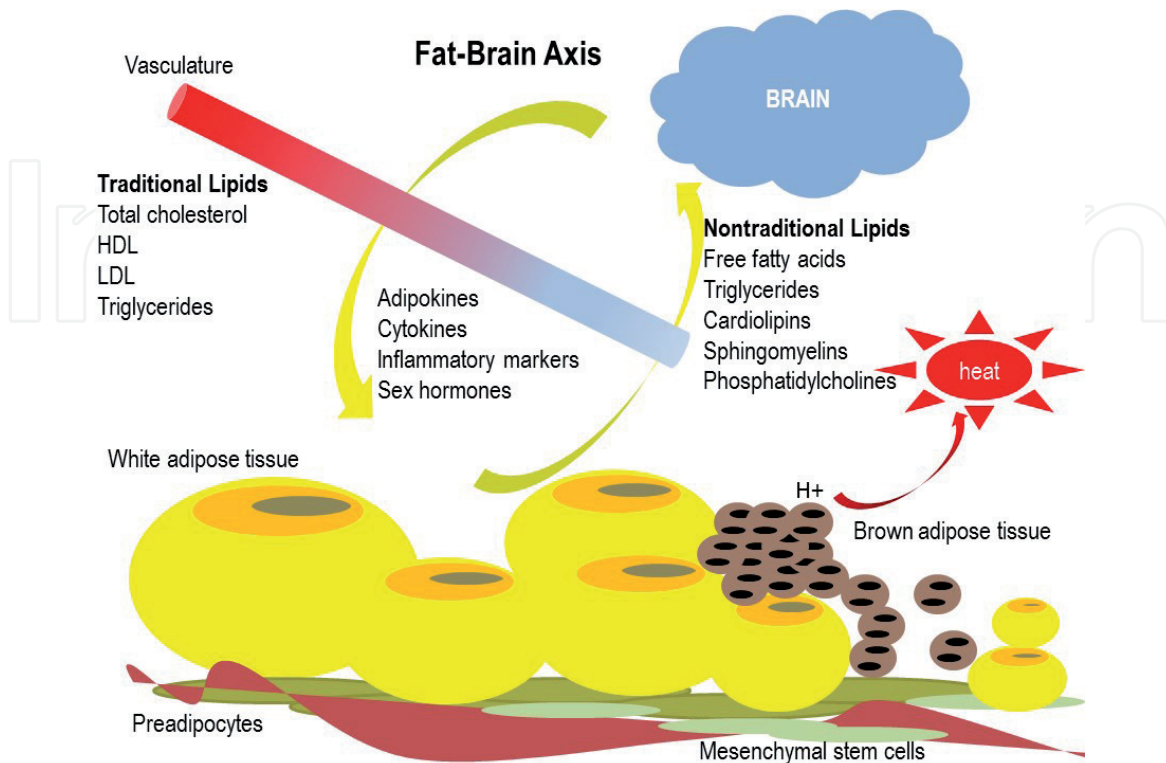


Figure 2.
 The heterogeneity of adipose tissue and its dynamic state due to different and evolving cell populations, proportions of WAT/BAT, energetics, and dyslipidemias.

2. Adipose tissue location and cell types

AT consists of multiple cell types exhibiting multiple cellular phenotypes depending on parent cell type and location of deposition [13]. In mammals, body fat compartments include total fat, subcutaneous fat, and internal fat, which is comprised of visceral (within chest, abdomen, and pelvis), nonvisceral (intramuscular, perimuscular), and other fat (e.g., lipomas) [14]. In addition, extra-adipose fatty acid deposits, such as those surrounding the internal organs, including the heart, have profound effects on disease susceptibility and occurrence [15]. Triglyceride deposits in the pancreas have been linked to alterations in insulin secretion; and epicardial fat has been linked to coronary heart disease [15]. While obese levels of BMI are correlated with the amount of these extra-adipose fatty acid deposits, BMI is not a sensitive indicator of their influence on human health and disease, part of which is local alterations in lipid metabolism [15].

AT cells, adipocytes, originate from multipotent mesenchymal stem cell populations (MSCs) in the bone marrow [16]. After initial determination steps, differentiation into a variety of cell types including osteoblasts, myocytes, and chondrocytes may occur [17]. AT-derived stem cells (ADSCs) also differentiate into non-mesenchymal cells (hepatocytes, neurons, pancreatic cells, endothelial cells, and cardiomyocytes) [18]. Characterization of diverse adipocyte populations enhances the understanding of the role of AT in lipid metabolism. Adipocytes differentially secrete hormones and cytokines based on the location of AT or triglyceride deposits; thus location is important for function [19, 20]. The ubiquity of AT and triglyceride deposits throughout the mammalian body and the corresponding autocrine, paracrine, and endocrine effects evidence the importance of the regulatory roles of AT.

AT quality and functionality may be more relevant for vascular and cardiometabolic risk than the total amount of AT [21]. In response to energy surplus, there may be a maladaptive AT expansion in consequent obesity. The significance of this expansion is local and systemic. In response to local excess, hypoxia, dysregulated adipokine secretion, and impaired mitochondrial function may occur. Overtaxed adipocytes release fatty acids and pro-inflammatory factors into the circulation. Subsequent systemic effects include leptin and insulin resistance, altered lipid and glucose metabolism, hypertension, end-organ fat accumulation (e.g., nonalcoholic fatty liver disease), the metabolic syndrome, pro-inflammatory and pro-thrombotic states, and endothelial dysfunction, all of which provide mechanisms for observed associations between obesity and cardio- and cerebrovascular diseases [21, 22]. Specific associations have been observed for dyslipidemias. For example, hypercholesterolemia has been associated with pro-inflammatory macrophage subpopulations in visceral adipose tissue (VAT), while BMI had a prominent effect in white adipose tissue (WAT) only [23].

2.1 White adipose tissue versus brown adipose tissue

There are generally two visual presentations of AT - WAT and brown adipose tissue (BAT) [17, 24]. WAT is characterized by its “white” color, due to a large, lipid-filled cell body. BAT, filled with mitochondria, presents as brown. Several later-onset diseases are characterized by mitochondrial/respiratory chain dysfunction, which emphasizes the potential importance of BAT. Brain and skeletal muscles are the tissues most affected by mitochondrial disorders because they exhibit the highest rates of aerobic metabolism [27, 28]. For example, mitochondria accumulate amyloid-beta, a key protein in Alzheimer’s disease [25] that in the brain leads to cellular dysfunction. Brain is comprised of 60% fat [26], yet not AT.

In addition, while not typically containing a large amount of fat, with aging, mitochondria-rich skeletal muscle is infiltrated with extra-AT and triglyceride deposits, leading to a condition called sarcopenia, and contributing to a type of dyslipidemia [29].

WAT and BAT originate from two different stem cell populations in bone marrow. BAT plays an important role, not only in neonatal but in human adult physiology [30].

2.1.1 White adipose tissue

WAT is the predominant AT in mammals. During embryonic development, it arises from lateral plate mesoderm, which forms the underlying stroma or supportive connective tissue. The stroma is highly vascularized and contains progenitor cells that give rise to mature adipocytes. Preadipocytes are immature fat cells that have not yet accumulated lipid. Fully differentiated adipocytes contain lipid in the form of triglyceride when provided with the appropriate nutrients (e.g., glucose) and hormones (e.g., insulin and leptin) [31]. WAT is a storage tissue for fatty acids and other compounds, for example, fat-soluble vitamins [32] and organochlorine pesticides [33].

Not all WAT cells are the same. “Healthy” WAT adipocytes are relatively small and have a high capacity for mitochondrial oxidative phosphorylation, which generates ATP, the cell’s aerobic currency. They are also characterized by more efficient cycling of triacylglycerol molecules and fatty acids and de novo lipogenesis. These intrinsic metabolic features of healthy WAT benefit locally and systemically [34].

Unhealthy WAT is attributed to excess or insufficient lipid storage in WAT droplets, which is associated with dyslipidemia, insulin resistance, and increased risk for T2D [35]. WAT adipocyte proteins control adipocyte lipid storage and limit lipid spillover and lipotoxic effects thought to contribute to disease [35]. For example, Caspase-2 is a WAT protein that is associated with abdominal fat accumulation, dyslipidemia, hyperproliferation, and “browning” of adipose [22]. “Overworked” adipocytes are more likely to release fatty acids and pro-inflammatory factors into the circulation that promote organ fat accumulation, insulin resistance, and the metabolic syndrome. Obesity is associated with both hypertrophy and hyperplasia of adipocytes, AT inflammation, impaired extracellular matrix remodeling, fibrosis, and altered secretion of adipokines [36]. These observations illustrate the potential for tissue or regional level dyslipidemias as a result of the changes in the structural, molecular, and metabolic integrity of the adipocyte.

2.1.2 Brown adipose tissue

In contrast to the developmental origins of WAT, mesenchymal stem cells from the paraxial mesoderm give rise to BAT. BAT is identifiable because it expresses the uncoupling protein 1 (UCP1). Myocytes (skeletal muscle cells) are also derived from paraxial mesoderm. Both UCP1-expressing BAT and myocytes express Myf5 (Myf5+) [17], thus further differentiating them from WAT, which are Myf5-. It has been traditionally thought that most BAT disappears fairly quickly with aging; however a significant amount of BAT is present in adults, particularly in paracervical and supraclavicular AT [37], as well as surrounding the kidney and along large blood vessels [38]. At least two types of BAT exist. Myf5+ brown fat is classical brown fat and exists in the aforementioned locations. Myf5- BAT is interspersed in WAT and may sometimes be referred to as “beige” adipose [17, 39].

A notable feature of BAT is an uncoupling of oxidative phosphorylation in response to cold temperatures and other factors that activate the sympathetic nervous system [40]. Free fatty acids are transferred to the mitochondria where

they are broken down by two carbon units and undergo β -oxidation. However, UCP1 uncouples oxidation and phosphorylation, leading to futile cycling, adaptive thermogenesis, and the release of energy as heat (instead of ATP) [28].

Using 18F-FDG-PET/CT, it has been observed that women have more BAT mass and activity [41] and that there is proportionately more BAT among older women. However, parallel to later-life body weight and BMI decline, both BAT mass and activity decrease with age, perhaps to a greater extent among men [41]. Seemingly paradoxical, yet as expected, is that amount of BAT is inversely related to BMI during adulthood [42]. Both mass and glucose uptake activity of 18F-FDG-PET/CT-detected BAT decrease with increasing outdoor temperature, age, and BMI [42]. BAT is suggested to be protective for obesity due to its role in adaptive adrenergic thermogenesis [30].

2.1.3 White adipose tissue and brown adipose tissue in aging

Questions that remain are: How are WAT and BAT related to usual aging and aging-related dyslipidemias? How do WAT and BAT relate to observed declines in BMI and blood cholesterol levels with aging? Mitochondrial disorders are common among aging-related diseases [21, 43] and may be exacerbated by BAT. Aging is also associated with a decrease in subcutaneous fat and increase in VAT (located around internal organs). The ratio of BAT to WAT also appears to increase, such that the amount of BAT is inversely correlated with BMI in the elderly [44]. Perhaps there is an evolving proportion of BAT/WAT over the life course that favors anti-obesity and anti-dyslipidemias in mid-life and, among some, accelerated BMI decline in late life, as a result of dysregulated adaptive thermogenesis. There is a paucity of literature linking AT directly to the variety of dyslipidemias that occur with usual aging.

Some data suggest that specific dietary fatty acids are protective for atypical accumulations of body fat, systemic low-grade inflammation, dyslipidemias, and insulin resistance [34]. For example, “healthy adipocytes” are induced in the WAT of obese mice in response to dietary omega-3 polyunsaturated fatty acids (omega-3 PUFAs), especially when combined with other “lifestyle” interventions, for example, moderate calorie restriction. It is unclear whether this relies on the activation of BAT and/or the induction of brite/beige adipocytes in WAT [34].

3. Adipose tissue and body composition

Sex-specific changes in body composition over the life course may lead to profound changes in metabolic feedback loops between the brain and AT, gut, and other peripheral locations. Altered metabolic states may occur as compensatory or to promote or accelerate other aging processes.

With aging, the proportion of fat-to-fat free mass (FFM) increases. Sometimes these changes are accompanied by changes in body weight or BMI, but not necessarily. FFM represents the mass of the organism without fat and is comprised of chemical components, amino acids, water, and minerals. FFM includes the metabolically active mass of cellular elements in the body, which is primarily muscle, organ tissue, and other tissue cells. Resting metabolism occurs in the FFM, which varies by tissue; and FFM depletion occurs in conditions such as cancer, HIV/AIDS, and dementia as well as with age. While there is a decrease in resting metabolic rate (RMR) with decreasing FFM as one ages [45], this decrease does not correspond to changes in body composition nor does it reflect in which body tissues this decrease

occurs. It has been hypothesized that a reduction in RMR is due to a combination of decreases in mass and cellular fractions of organs and tissues. It has been shown that increasing age is related to decreasing mass of the brain, kidney, liver, and spleen [46].

4. Endocrine adipose tissue

As aforementioned, AT is measured clinically in several ways. Common clinical and epidemiologic measures include anthropometry, such as BMI, WC, and Waist-to-Hip Ratio (WHR). In addition, are whole and regional body imaging. While the imaging gold standard is Magnetic Resonance Imaging (MRI) or Computed Tomography (CT), Dual X-Ray Absorptiometry (DXA) is also used, as is Bioelectrical Impedance Analysis (BIA). However, given the higher costs of body imaging techniques, peripheral blood-based biomarkers, such as adipokines including leptin, and free fatty acids, measured using lipidomics technologies, are of increasing importance.

Over 600 secretory proteins are attributed to AT [47]. AT is the source of a variety of hormones and cytokines, such as leptin, adiponectin, pro-inflammatory cytokines, and components of complement and the renin-angiotensin system (RAS) [48–50]. A classic example of the endocrine function of AT is its role in female reproductive health. Hypotheses related to a critical percentage of body adiposity for the initiation of menarche in females, such as the Frisch hypothesis, were first reported in 1973 [51]. In addition, AT is the primary source of bioactive estrogen (as estrone, E1) in postmenopausal women via aromatase [52]. AT-derived sex hormones also link adiposity and changes in adiposity to the occurrence of dyslipidemias. For example, aromatase knockout mice exhibit elevated circulating levels of leptin and cholesterol concomitant with lower estrogen levels than wild-type controls [53]. The metabolic implications of AT are wide ranging, and knowledge related to this phenomenon is far from complete.

Changes in body composition over the adult life and corresponding influences on dyslipidemias are not yet fully characterized. Declines in both BMI and blood cholesterol levels [3, 54] occur with aging; however there is a relative lack of published studies on changes over time, across populations and with lipid-lowering treatments. One may speculate that the changes in adiposity observed in aging correspond directly to changes in blood levels of AT metabolites, including FFA, and traditionally measured lipids [33]. There may be important temporal, acute changes occurring that are not easily understood when using cross-sectional analyses depending on chronological and biological age. The complexity of AT endocrinology and related systems is well-illustrated by the range of medications used for vascular diseases of old age. Several of these medications differentially influence body weight [11, 55] and subsequent blood lipid levels. In addition, studies of adults with cerebral small vessel disease or HIV-related adiposity syndromes allow continued evaluation of the aforementioned, co-occurring factors and partitioning out of different adiposity pathways [49, 56, 57]. AT contributions to dyslipidemias may be apparent across any body weight or BMI, with or without the use of lipid-lowering agents.

Hormones and cytokines produced by AT such as leptin and adiponectin are involved in the regulation and dysregulation of nutrient utilization, as well as inflammation, endothelial dysfunction, hypertension, and atherogenesis [58]. In addition, combinations of hormones, such as insulin and leptin, interact in various

processes such as nutrient utilization to augment effects. Two AT hormones, leptin and adiponectin, are described here as well as a discussion of lipidomics approaches. **Table 3** contains several selected examples of adipokines that may be associated with dyslipidemias.

4.1 Leptin

Leptin is a 16 kDa protein hormone discovered in 1994. While deemed to be the putative obesity hormone in the mid-1990s [59], with effects possibly mediated by an impaired BBB [60], it did not become the answer to the current obesity epidemic as originally hoped. The amount of AT is positively related to blood leptin levels, as AT is the major source of this hormone [61, 62]. The Prospective Study of Women in Gothenburg, Sweden, shows mid-life correlations of $r = 0.67$ and late-life correlations of $r = 0.61$ between BMI and blood leptin levels [6]. Similar BMI-leptin correlations are also observed in “at-risk” populations such as women with HIV infection and cerebral small vessel disease (unpublished observations).

Adipose tissue secretory product	Function
Adiponectin	Insulin sensitizer; circulating levels inversely correlated to dyslipidemias, insulin resistance, metabolic syndrome, obesity, T2D, and cardiovascular diseases [49, 50, 113]
Chemerin	Regulates adipogenesis and mature adipocyte metabolism; elevated in obesity, dyslipidemia, T2D, and osteoporosis; a marker of inflammation and metabolic syndrome [114]
Hepatocyte growth factor (HGF)	Angiogenic and mitogenic effects; linked to vascular diseases; elevated in obese adults and adolescents [115, 116]
Interleukin (IL)-6	Pro-inflammatory, upregulated in obesity, can exacerbate CVD and metabolic syndrome [113]
Leptin	Regulates body weight via decreasing appetite and increasing sympathetic nervous activity [49, 50, 117, 118]
Neuregulin 4	Regulates energy metabolism; associated with BMI, WHR, triglycerides, and other metabolites; secreted from brown/beige AT [119–121]
Nerve growth factor (NGF)	Correlated with waist-to-hip ratio (WHR); associated with NGF and leptin, T2D, cardiovascular disease, and stroke [122]
Omentin-1	Associated with VAT, dyslipidemia, metabolic syndrome, T2D, and cardiovascular disease; inhibits the inflammatory response and improves insulin resistance; vasodilatory [123]
Plasminogen activator inhibitor-1 (PAI-1)	Associated with central obesity; mediates fibrinolysis; crosses an intact blood-brain barrier [124, 125]
Progranulin	Higher in obesity, insulin resistance, T2D, fatty liver disease; associated with inflammation, growth-promotion, and neuroprotection [126]
Resistin	Pro-inflammatory; produced in response to pro-inflammatory cytokines [113, 127]
Retinol-binding protein (RBP)	Elevated in obesity; implicated in insulin resistance; associated with triglyceride and small HDL levels [128, 129]
Tumor necrosis factor (TNF)- α	Pro-inflammatory; upregulated in obesity; exacerbates cardiovascular disease and metabolic syndrome [113]

Table 3. Examples of adipose tissue secretory products and their functions that may be disrupted in dyslipidemias.

Classical functions of leptin include signaling inadequate energy stores through the regulation of food intake, regulation of energy expenditure, improving insulin sensitivity, facilitating lipolysis, inhibiting lipogenesis, and reducing intracellular lipids [63]. In addition, leptin plays a permissive role in neuroendocrine immune function [63]. In obesity, there occurs a phenomenon called “leptin resistance.” Analogous to insulin resistance, leptin resistance implies decreased tissue sensitivity to leptin, which leads to dyslipidemia [64]. In contrast, leptin replacement therapy (metreleptin) is used to treat lipodystrophy syndromes characterized by a loss of AT that also leads to dyslipidemia [65].

Understanding interactions between leptin and insulin in the brain may weave together the interrelationship of adiposity and T2D. T2D is also associated with dyslipidemias. Not only leptin, as aforementioned, but insulin interacts directly with hypothalamic nuclei, and it appears that both are involved in the manifestation of insulin resistance. The pro-opiomelanocortin (POMC) neurons in the hypothalamus express both leptin and insulin receptors and regulate energy balance and glucose homeostasis. Experimental mouse models lacking both leptin and insulin receptors in POMC neurons display systemic insulin resistance, which is distinct from what occurs with the single deletion of either receptor. These mice also show alterations in sex hormone levels that reduce fertility. Thus, direct actions of both insulin and leptin on POMC neurons appear to be required to maintain normal glucose homeostasis and reproductive function [66] and will therefore influence blood lipid levels and AT-related FFA metabolism. It has also been proposed that cross talk between leptin and insulin occurs within a network of cells rather than within individual POMC neurons [67].

In relation to AT, it has been shown in mouse models that leptin regulates body weight via decreasing appetite and increasing sympathetic nervous activity. This, in turn, increases energy expenditure in interscapular BAT [68], and correspondingly there is an increase in BAT temperature. Neurons in the dorsomedial hypothalamus appear to mediate this thermogenic response to hyperleptinemia in obese mice, and a functional melanocortin system is not required. Because the sympathetic nervous system contributes in regulating blood pressure, heart rate, and hepatic glucose production, selective leptin resistance may be a crucial mechanism linking adiposity, BAT, and dyslipidemias [64, 69].

4.2 Adiponectin

Adiponectin (also known as ACRP30) is an effective insulin sensitizer; circulating levels are inversely correlated to dyslipidemias, insulin resistance, metabolic syndrome, obesity, T2D, and cardiovascular diseases. These observations, as for leptin, appear consistent cross-culturally. Adiponectin exists as complex multimeric isoforms comprised of high molecular weight (HMW), hexamers, and trimers [70]. HMW adiponectin or HMW adiponectin/total adiponectin may be better indicators of insulin sensitivity than total adiponectin in obesity, T2D, and cardiovascular disease [70]. Adiponectin is produced not only by AT but by numerous other tissues including the brain. BMI is inversely related to circulating adiponectin. The Prospective Study of Women in Gothenburg, Sweden, shows late-life correlations of $r = -0.29$, between BMI and blood adiponectin levels (unpublished). Similar correlations are observed in women with HIV infection and in adults with cerebral small vessel disease (unpublished observations). In addition, since adiponectin is a VAT marker and only moderately correlated with BMI, it may not be associated in a similar fashion with lipid metabolism when compared to BMI or other anthropometric measures [71]. Interestingly, the adiponectin/leptin ratio has been proposed as a better indicator of AT dysfunction and cardiometabolic risk [72].

4.3 Lipidomics

Lipidomics platforms comprised of mass spectrometry/gas chromatography are used to discriminate among levels of obesity and to identify dyslipidemias characterized by nontraditional lipid biomarkers. These alternative lipid species may be associated with obesity-related chronic diseases as well as for accumulation of excess AT [73–75]. For example, obesity, independent of genetic influences, has been related to [1] increases in lysophosphatidylcholines and lipids observed in pro-inflammatory and pro-atherogenic conditions and [2] decreases in other phospholipids, which are known to have antioxidant properties [76]. Certain conditions characterized by lipodystrophies and/or higher levels of AT, such as HIV infection, facilitate studies of traditionally and nontraditionally defined dyslipidemias and altered energy metabolism [77–79]. Nontraditional blood lipids of importance may include cardiolipins, sphingomyelins, phosphatidylcholines, and nonesterified fatty acids [80]. While the differential bioactivities of these lipids are unknown, mitochondrial dysfunction may underlie some of these differences among disease states and between diseased and healthy states [81, 82].

Cardiolipins (CLs) are an example of a class of lipids that may be informative for obesity, dyslipidemias, and associated diseases. CLs are diphosphatidylglycerol molecules with four acyl groups that can bind four fatty acids. In human circulation, these are usually 18-carbon fatty acids [80% linoleic acid (18:2(*n*–6))] [83]. CLs in the central nervous system contain a wider range of fatty acids including palmitic, stearic (18:0), oleic (18:1), arachidonic (20:0), and docosahexaenoic acids (22:6) (over 100 molecular species); and lymphoblast CLs contain only monoenoic fatty acids. CLs are predominant in the heart (where first discovered), liver, and brain [83]. Individuals with obesity, T2D, or heart failure have elevated levels of serum free fatty acids [84] that promote lipotoxicity of cardiomyocytes [85]; and profound changes in CLs' composition occur in T2D. Since the brain is approximately 60% fat [26] and obesity is associated with later-onset cognitive impairments and dementias [50, 55, 86], perhaps the abundance of these circulating lipid species is of multisystem pathological significance. This multisystem role of CL alterations contributing to mitochondrial dysfunction in particular makes them especially interesting [87].

CLs are mitochondrial membrane phospholipids present mostly in the inner membrane, where they comprise ~20% of the total lipid content [88]. However, CLs are also transferred to the outer mitochondrial membrane and can comprise ~25% of the lipid content at locations where fission and fusion occur. Inner membrane CLs, the site of the electron transport chain, and the electrochemical gradient involved in ATP production [89] are evidence of the likely role of CLs in mitochondrial bioenergetics. CLs are required for optimal functioning of several inner mitochondrial membrane proteins and enzymes [89–94], including those involved in electron transport chain-mediated oxidative phosphorylation and coupled respiration [95]. CLs appear to be an integral component of these proteins and critical for folding, structure, and function. CLs are prone to reactive oxygen species-induced oxidative damage and important during mitochondrial apoptosis [88]. CL oxidation is observed in insulin resistance [96], obesity [97], and nonalcoholic fatty liver disease [98]. Metabolic dysfunction pertaining to CLs in brain mitochondria is suggested in neurodegenerative diseases, including Alzheimer's disease and Parkinson's disease [99]. In Parkinson's disease, for example, α -synuclein seems to form an oligomer that binds to mitochondrial membrane CLs, thereby disrupting integrity and impairing function [100, 101].

5. The fat-brain axis

Mechanisms whereby AT and its secretory products affect peripheral lipid metabolism are centrally coordinated [102]. For example, leptin and adiponectin, peripheral AT signals, interact with hypothalamic nuclei such as the arcuate nucleus. These interactions trigger the release of orexigenic and anorectic peptides from PMC neurons. These peptides exert peripheral effects, modulating food intake, reproduction, water balance, body temperature, and energy balance. In addition, leptin and adiponectin have been shown to enhance synaptic plasticity. This is illustrated in studies of Alzheimer neuropathology, where amyloid is deposited in the areas of the hypothalamus such as the arcuate nucleus, where it potentially interferes with usual physiologic influences of AT and its primary hormones, such as leptin and adiponectin as well as downstream events and feedback loops [49, 50]. The influence of Alzheimer pathology on areas of the brain involved in homeostatic regulation may explain the decline in levels of blood cholesterol and body weight observed in prodromal and overt dementia [11]. In addition, data show that leptin exerts control over hepatic lipid metabolism via the central nervous system and via peripheral nerves. Central regulation of lipid metabolism in WAT and BAT may also contribute to hepatic lipid content indirectly via FFA release and changes in lipoprotein clearance. Impairments in these pathways may contribute to dyslipidemias [102].

6. Genes related to adipose tissue

Given published associations of adiposity with brain outcomes including Alzheimer's Disease (AD) [refs 1, 5, 6, 11, 48–50, 55, 56, 57, 103, 104], understanding the potential role of adiposity- and lipid-related susceptibility genes in AD may provide insights regarding biological underpinnings related to AT. Genes related to AD susceptibility may have a modifying effect on the relationship between AT, dyslipidemias, and aging. Several genes have been identified that link AT and corresponding vascular risk to cognitive decline, AD susceptibility, and pathological processes. APOE and FTO are two of them.

The APOE gene encodes for a protein on the surface of lipoproteins that aids in lipoprotein metabolism [12]. The APOE ϵ 4 allele is a known susceptibility allele for dementia. It also modifies the association between BMI decline, often observed to a great extent among those developing dementia [55], dementia [103], as well as dementia progression [104].

FTO (“fatso”) is an obesity-susceptibility gene and related to T2D. The resulting protein product of FTO appears to be a member of the non-heme dioxygenase (Fe(II)- and 2-oxoglutarate-dependent dioxygenases) superfamily. FTO mRNA is the most abundant in the brain, particularly in hypothalamic nuclei governing energy balance. Levels in the arcuate nucleus are regulated by feeding and fasting [105], thus potentially integrating AT hormones in the fat-brain axis. The influence of lipid type is also modulated by FTO [106].

The existence of susceptibility genes such as APOE and FTO points to the potential role of developmental origins in the life course trajectories of lipids and anthropometric measures of AT, such as BMI, in relation to brain structure and function as well as age- and lipid-related diseases of the brain [107]. Genetic susceptibility and gene-environment interactions, especially over the life course, remain largely unexplored. Stratification of population samples on the basis of these important genotypes lends insight into innate susceptibility-related AT over the life course [103].

7. In conclusion: adipose, a quintessential multifunctional tissue

Understanding the complexity of AT and its role in dyslipidemia in the periphery and its interactions with the brain is paramount to the development of intervention strategies focused on obesity-related exposures, correlates, and outcomes. Issues related to the epidemiology, adipocyte subpopulations, differential energetics, endocrinology, amyloid, and genetics are aspects of adiposity requiring further investigation.

Based on this review, several suggestions can be made for future research. The use of simple anthropometric indicators in epidemiologic studies is somewhat obsolete, particularly for elderly populations. Anthropometric indicators could be replaced by measures reflecting potential biological functions and structures of AT. These measures include traditional and nontraditional lipid species as well as endocrine metabolites of AT that are measurable in peripheral fluids. Whole body imaging is also important. Improving measures of adipocyte subpopulations accompanied by improved methods for biopsying and measuring these important cells and/or their activities in epidemiologic and clinical studies are needed. As adipocytes are produced throughout the life span of mammals, and in response to the changing status of the organism, they may prove to be important gauges and influencers of metabolic health, not only peripherally but centrally for the brain. Therefore, brain imaging measures may be useful as preclinical indicators of susceptibility as well as comprising outcomes associated with the adiposity exposure. Enriching future studies for certain genetic or “at-risk” subgroups may lend additional insights. In time, our appreciation for AT and its complexity will only grow and mature to ultimately improve human health.

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Conflict of interest

The author declares no conflict of interest.

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