Journal of Obesity & Metabolic Syndrome 2024;33:275-288
https://doi.org/10.7570/jomes24013

Review

jomes
pISSN 2508-6235
eISSN 2508-7576

Understanding Adipose Tissue Dysfunction

Matthias Blüher[1,2,*]

[1]*Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum München at the University of Leipzig and University Hospital Leipzig, Leipzig;* [2]*Medical Department III—Endocrinology, Nephrology, Rheumatology, University of Leipzig Medical Center, Leipzig, Germany*

Diseases affecting adipose tissue (AT) function include obesity, lipodystrophy, and lipedema, among others. Both a lack of and excess AT are associated with increased risk for developing diseases including type 2 diabetes mellitus, hypertension, obstructive sleep apnea, and some types of cancer. However, individual risk of developing cardiometabolic and other 'obesity-related' diseases is not entirely determined by fat mass. Rather than excess fat accumulation, AT dysfunction may represent the mechanistic link between obesity and comorbid diseases. There are people who remain metabolically healthy despite obesity, whereas people with normal weight or very low subcutaneous AT mass may develop typically obesity-related diseases. AT dysfunction is characterized by adipocyte hypertrophy, impaired subcutaneous AT expandability (ectopic fat deposition), hypoxia, a variety of stress, inflammatory processes, and the release of proinflammatory, diabetogenic, and atherogenic signals. Genetic and environmental factors might contribute to AT heterogeneity either alone or via interaction with intrinsic biological factors. However, many questions remain regarding the mechanisms of AT dysfunction initiation and whether and how it could be reversed. Do AT signatures define clinically relevant subtypes of obesity? Is the cellular composition of AT associated with variation in obesity phenotypes? What roles do environmental compounds play in the manifestation of AT dysfunction? Answers to these and other questions may explain AT disease mechanisms and help to define strategies for improving AT health. This review focuses on recent advances in our understanding of AT biology.

Key words: Obesity, Adipocytes, Lipodystrophy, Lipedema, Adipose tissue, Inflammation, Adipokines

Received April 25, 2024
Reviewed June 8, 2024
Accepted December 16, 2024

*Corresponding author
Matthias Blüher

https://orcid.org/0000-0003-0208-2065

Helmholtz Institute for Metabolic, Obesity and Vascular Research (HI-MAG) of the Helmholtz Zentrum München at the University of Leipzig and University Hospital Leipzig, Philipp-Rosenthal-Str. 27, D-04103 Leipzig, Germany
Tel: +49-341-9715984
Fax: +49-341-9722929
E-mail: bluma@medizin.uni-leipzig.de

INTRODUCTION

Obesity and abdominal fat distribution are major health burdens of modern societies.[1-5] Excessive accumulation of body fat induces metabolic abnormalities and diseases, including insulin resistance, prediabetes, type 2 diabetes mellitus (T2DM), dyslipidemia (high triglyceride and low high-density lipoprotein cholesterol (HDL-C) circulating concentrations), gout, and metabolic dysfunction-associated fatty liver disease, among others. With increasing body mass index (BMI), the risk of developing T2DM progressively increases.[6] On the other hand, very low or lack of subcutaneous body fat may lead to similar metabolic and cardiovascular outcomes as obesity.[7,8] People with very low total body fat due to lipodystrophy have a prevalence of T2DM that is similar to those with BMI > 40 kg/m^2, data from the Leipzig Obesity BioBank (LOBB)[9] suggest (Fig. 1). Human lipodystrophy is an example that obesity-related metabolic diseases might be the result of an inability of subcutaneous adipose tissue (AT) to adequately expand upon a chronic positive energy balance.[10-12] Recently, it has been observed that people living with human immunodeficiency virus (HIV) disease experience changes in AT mass and fat depot composition before and after initiating antiretroviral therapy that include regional AT loss (lipoatrophy), gain (lipohypertrophy), or mixed lipodystrophy.[13] Another disease that primarily affects AT is lipedema. Lipedema is a painful subcutaneous AT disease that is characterized by adipocyte hypertrophy, altered immune cell recruitment, and fibrosis in the affected areas.[14]

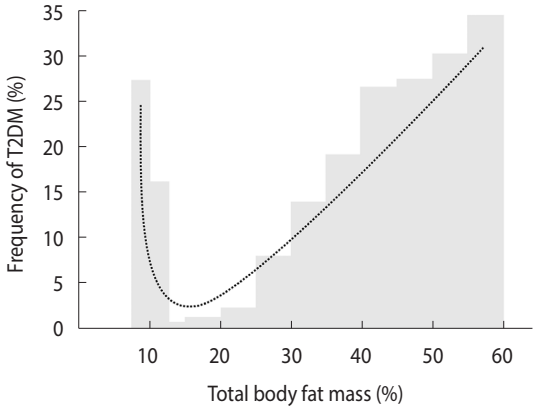

Figure 1. Relationship between body fat mass and frequency of type 2 diabetes mellitus (T2DM). Background data were extracted from 1,650 participants of the Leipzig Obesity BioBank[9] that represent a wide range of age (18 to 96 years), body mass index (16 to 92 kg/m^2), and body fat mass (7.5% to 60%) from among people with lipodystrophy to morbid obesity.[14] For categories of 2.5% or 5% body fat mass groups, the prevalence T2DM is displayed. The j-curved extrapolated line does not represent the exact mathematical relationship, but the hypothetical curve suggests that both severely low fat mass in people with lipodystrophy and obesity are associated with a higher risk of developing T2DM.

Although obesity is by far the most prevalent disease associated with AT dysfunction,[4] a better understanding of the initiating factors and mechanisms of this condition and their relation to impaired function and distribution of the adipose organ is needed.[2,10,15]

In this review, an overview of the current understanding of AT dysfunction causes and consequences is provided, because insights into AT dysfunction-related disease mechanisms will facilitate the development of strategies to improve metabolic health.

NORMAL ADIPOSE TISSUE FUNCTION

Adipose tissue physiology

AT has several important physiologic functions: it contributes to energy homeostasis as the main organ for energy storage, it provides insulation for the body, and plays roles in thermoregulation and mechanical organ protection.[16-21] During periods of fasting and prolonged starvation, AT releases lipids to serve as energy for the body.[16,17] In this context, AT possesses a remarkable capacity to expand and shrink as a result of different external and systemic cues that include food intake, nutrition status, and temperature, among others.[22] Importantly, in addition to white adipocytes, brown and beige (or brite) adipocytes contribute to the central role of AT in systemic thermoregulation and energy homeostasis in humans.[23-25] White adipocytes of white AT comprise >95% of adipose mass, while brown adipocytes represent approximately 1%–2% of fat and beige or brite are interspersed within white AT and can transform into brown-like adipocytes in response to cold exposure or adrenergic stimulation. White adipocytes are mainly responsible for AT expansion in obesity. In contrast, brown and beige adipocytes have multilocular droplets and high mitochondrial density to dissipate heat through uncoupled respiration. In humans, AT dysfunction has mainly been described in white AT, but impaired function also exists in brown fat, but this has primarily been observed in rodent models. However, the focus of this review is on white adipocytes and AT dysfunction in humans.

AT produces and secretes adipokines and exosomes, which are involved in the regulation of appetite, satiety, locomotor activity, reproductive function, and insulin action.[18]

Cellular composition of adipose tissue

AT has remarkable plasticity, displaying adipocyte transdifferentiation from white to brown phenotypes during chronic cold exposure, physical exercise, lactation, and obesity.[16]

High-fat feeding and other metabolic stressors cause marked changes in AT morphology, function, and even cellular composition.[26,27] Although adipocytes represent the main parenchymal cell type, AT is composed of several different cells including preadipocyte, fibroblast, endothelial, and immune cells, among others. Recently, several human AT single-cell-resolution atlases have been reported.[27-34] Adipocytes, which vary in size by up to 20-fold, are fragile, and have a high lipid load, present unique challenges to single-cell RNA-sequencing, but have been included in recent atlases that utilized spatial and/or single-nucleus transcriptomics. Using single-cell-resolution approaches, these studies identified spatial arrangements and differential insulin responsiveness of adipocytes,[29] adipogenic potential of distinct progenitor cells,[30] adipocyte regulation of thermogenesis,[31] plasticity of mouse AT in response to diet-induced obesity,[32] associations between specific AT cell types and metabolic states,[27,28] as well as commonalities and differences across species and dietary conditions.[27] Interestingly, AT atlases noted some fat depot differences in cellular composition, but mainly emphasized

Table 1. Cell clusters of human adipose tissue with key marker genes

Cell population	Key marker genes[27,28]
Adipocytes	ADIPOQ, PLIN
Adipose stem and progenitor cells	PDGFRA
Fibroblast and adipogenic progenitor cells	CD55, PI16
Mesothelial cells	MSLN
Endothelial cells	JAM2
Lymphatic endothelial cells	PROX1
Pericytes	STEAP4
Smooth muscle cells	MYOCD
Macrophages	MAFB
Monocytes	CYBB
Dendritic cells	FLT3
Mast cells	CPA3
Neutrophil cells	CSF3R
B cells	MS4A1
NK cells	KLRD1
T cells	IL7R
Endometrial cells	PRLR

Clusters of cells have been identified in human visceral, omental, and subcutaneous adipose tissue by single nuclei and single-cell RNA-sequencing approaches.[27-34] Higher-resolution maps identified more than 60 subpopulations of adipocytes, fibroblast and adipogenic progenitors, and vascular and immune cells.[28]

commonalities in cell composition between subcutaneous and visceral AT.[27-34] In humans, adipocyte number is determined during childhood and adolescence, and is maintained in adults even after substantial weight loss.[35] Despite data providing novel cellular and even spatial resolution of AT gene expression, the variation in gene expression signatures among fat depots and their distinct functions remain poorly understood.

Using the sophisticated bioinformatics approach CELL-type Expression-specific integration for Complex Traits (CELLECT)[36] that integrates scRNA-seq and sNuc-seq data with data from genome wide association studies, Emont et al.[27] sought to identify distinct cell populations that may reflect the risk of developing obesity-related diseases or conditions (Table 1). Surprisingly, there was no cellular correlate of BMI variation, but there was a significant association between B and T lymphocytes and natural killer (NK) cells in AT with autoimmune type 1 diabetes mellitus.[27] Adipocyte phenotype was associated with waist to hip ratio as a surrogate for abdominal fat deposition even after adjustments to BMI.[27] In a subsequent comprehensive meta-analysis of publicly available and newly-generated single-cell, single-nucleus, and spatial transcriptomic data from human subcutaneous, omental, and perivascular AT, Massier et al.[28] identified cell-cell interactions as well as relationships between specific cell subtypes (including those in the adipocyte fraction) as well as insulin resistance, dyslipidemia, adipocyte volume, and lipolysis with long-term weight changes. To validate these intriguing insights from cross-sectional studies of AT cellular composition, longitudinal and interventional approaches (e.g., before and after pronounced weight loss upon bariatric surgery) are required. Taken together, recent sNuc-seq data from human (and mouse) AT suggest associations between distinct cell types, fat distribution and metabolic states beyond BMI.

SIGNS AND SYMPTOMS OF ADIPOSE TISSUE DYSFUNCTION

According to the World Health Organization, obesity is defined as 'abnormal or excessive fat accumulation that presents a risk to health.'[37] However, high-fat accumulation alone is not sufficient to explain the heterogeneity in the individual risk of adiposity-induced metabolic dysfunction.[4,38,39] People with obesity that is characterized by predominantly upper body (abdominal subcutaneous and intra-abdominal visceral), intrahepatic, intramyocelluar, and pancreatic fat deposition are at higher risk of developing T2DM than those with a lower body, gluteofemoral fat deposition.[18,40] Predominantly gluteofemoral fat accumulation—a phenotype more frequently observed in premenopausal women, is associated with lower triglyceride and higher HDL-C serum concentrations, improved insulin sensitivity, lower fasting blood glucose and insulin concentrations and decreased risk of T2DM independent of BMI.[41]

In addition to the health- or disease-promoting aspects of fat deposition, a deeper look into AT from animal models of obesity and humans with or without cardiometabolic diseases led to the notion that AT function may contribute to a multitude of diseases through distinct AT-based alterations.[18-22] Although the mechanisms initiating AT dysfunction are not entirely understood, a chronic positive energy balance with weight gain, increased nutrient flux into AT, impaired subcutaneous expandability, and secretion of chemoattractant molecules, as well as extrinsic factors such as toxins (e.g., alcohol in acquired lipodystrophy)[42] or environmental compound exposure and bioaccumulation[43] may initiate this process (Fig. 2).

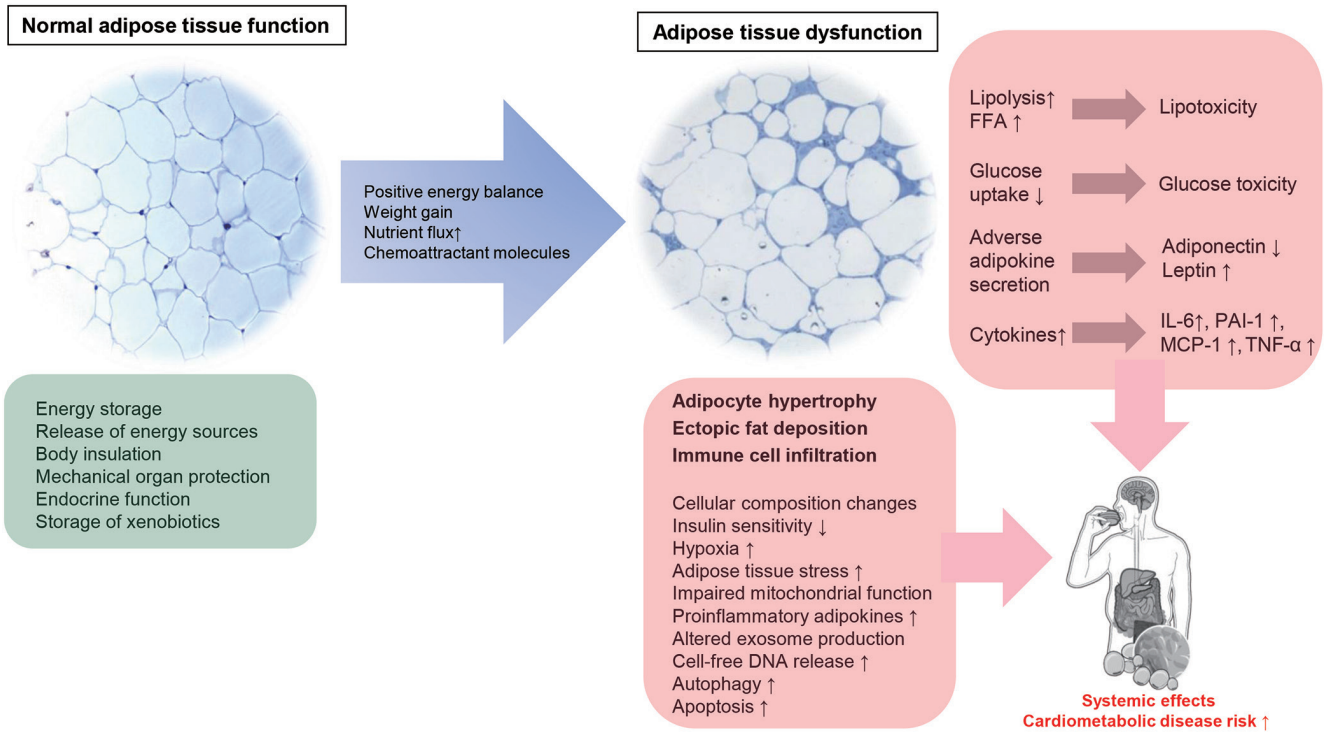

Figure 2. Transition from normal to impaired adipose tissue (AT) function and adverse systemic outcomes. AT serves important functions including energy storage, release of metabolites, body insulation, mechanical organ protection, endocrine secretion, and storage of xenobiotics under normal conditions. With a chronic positive energy balance and body weight gain, AT expands due to increased nutrient flux. Adipocytes primarily respond to the higher demand for energy storage by increasing their size (adipocyte hypertrophy). Adipocyte hypertrophy contributes to hypoxia, cellular and tissue stress, altered exosome production and release, and increased production of proinflammatory cytokines (including tumor necrosis factor-α [TNF-α], interleukin [IL]-1β, monocyte chemoattractant protein-1, chemerin, progranulin, plasminogen activator inhibitor-1 [PAI-1]), as well as activation of autophagy and apoptosis (mainly in visceral depots) and increased release of cell-free DNA. AT dysfunction is characterized by altered cellular composition including an increased number of immune cells. Symptoms of AT dysfunction include adipocyte hypertrophy, ectopic AT deposition, and immune cell infiltration of AT. Through different mechanisms including increased lipolysis, higher free fatty acid (FFA) release from AT, reduced glucose uptake, and increased secretion of diabetogenic, atherogenic, and proinflammatory signals, AT dysfunction is linked to endorgan damage. MCP-1, monocyte-chemotactic-protein-1.

Most likely, impaired adipocyte function is caused by a combination of genetic, behavioral, and environmental factors that are not entirely understood. The hallmarks of AT dysfunction can be summarized as size (adipocyte hypertrophy), site (ectopic fat deposition), and 'cytes' (immune cell infiltration) (Fig. 2).

The inability of AT to expand by recruiting new (healthy) adipocytes may activate a sequence of pathological mechanisms including cellular insulin resistance and increased lipolytic capacity, intracellular accumulation of toxic molecules, activation of stress pathways, visceral (ectopic) fat accumulation, changes in cellular and intracellular matrix composition, increased number of immune cells within AT, increased autophagy and apoptosis, fibrosis, alterations in gene and protein expression patterns.[21] As a result of impaired subcutaneous AT expandability, adipocytes become larger (size: adipocyte hypertrophy), excess nutrients are more frequently stored in ectopic depots (sites), and AT releases signals (e.g., hormones, cells, and metabolites) resulting in a proinflammatory, diabetogenic, and atherogenic serum profile (Fig. 2). These adverse signals may contribute to inflammation of AT ('cytes') and secondary organ damage in target tissues such as the liver, brain, endothelium, vasculature, endocrine organs, and skeletal muscle.

CAUSES (MECHANISMS/MOLECULAR PLAYERS/PATHWAYS) OF ADIPOSE TISSUE DYSFUNCTION

Adipose tissue stress and mitochondrial dysfunction

Adipocyte hypertrophy, AT hypoxia, advanced glycation prod-

ucts, xenobiotics, toxins, lipopolysaccharides, and endogenous lipids, as well as cell debris after damage, apoptosis, or local necrosis may activate stress-sensing pathways in different AT cells.[44,45] Several stimuli can activate nuclear factor κB (NF-κB) and IκB kinase-β (IKKβ) via receptor-mediated pathways.[44] In addition to the classical cytokine receptor activation such as tumor necrosis factor-α, Toll-like receptors, and receptors for advanced glycation end products, intracellular stress including reactive oxygen species, endoplasmatic reticulum stress, ceramide, and different protein kinase C isoforms can also activate NF-κB and IKKβ.[46]

The first studies on the biological processes that initiate AT dysfunction and contribute to obesity-related metabolic impairment were conducted in mouse models.[18] Impaired AT function could be the result of adipocyte hypoxia caused by inadequate oxygen delivery under conditions of increased adipocyte oxygen demand such as obesity.[47,48] Hypoxia may directly cause AT fibrosis by stimulating AT fibrogenesis and AT immune cell infiltration via secretion of chemotactic factors.[49,50] Another consequence of AT dysfunction that may result from AT hypoxia is the suppression of AT branched-chain amino acid catabolism, subsequently increasing plasma branched-chain amino acid concentrations.[51,52]

These mechanisms of AT dysfunction in animal models of obesity could be translated into human conditions of obesity and AT dysfunction. In human AT dysfunction, decreased interstitial AT partial pressure of oxygen,[53] increased rates of fibrogenesis and expression of genes involved in extracellular matrix (ECM) formation,[54] production of exosomes that can induce insulin resistance,[55,56] and alterations in expression of genes involved in branched-chain amino acid catabolism[53] have been validated. Interestingly, activation of AT stress seems to contribute to the distinction between insulin-sensitive versus insulin-resistant metabolically healthy obesity in people that were matched for age, sex, BMI, and fat mass.[57-61]

Data from animal models and humans suggest that obesity is associated with impaired mitochondrial function in AT.[22] Mitochondrial oxidative phosphorylation (OXPHOS) and biogenesis in human subcutaneous AT are compromised under conditions of obesity and hyperglycemia or diabetic obese and diabetic states.[62-64] Interestingly, the reduction of mitochondria function in AT does not seem to be primarily regulated by inherited factors. For example, in monozygotic twin pairs discordant for BMI, AT mitochondrial biogenesis and OXPHOS are downregulated as a function of obesity and the extent of metabolic dysregulation.[65,66] On the other hand, treatment with peroxisome proliferator-activated receptor γ (PPARγ) agonists or structured exercise programs with subsequent improvements in insulin sensitivity enhance mitochondrial biogenesis and OXPHOS in AT.[67-69] In addition, improved AT mitochondrial function may be associated with weight loss.[70,71] In this context, genes that control mitochondrial function (e.g., OXPHOS, citric acid cycle, and free fatty acid oxidation pathways) show significantly higher expression in subcutaneous AT after weight loss induced by diet interventions[71] or bariatric surgery.[70] Despite these lines of evidence, whether impaired mitochondrial function is a cause or consequence of AT dysfunction remains unclear.[18]

Genetic studies in mice indicate a causal link between reduced mitochondrial function in adipocytes and the development of insulin resistance.[72] Mice with an AT-specific knockout of the mitochondrial transcription factor A exhibit AT inflammation, increased adipocyte apoptosis and whole body insulin resistance.[73] Deletion PPARγ coactivator 1α (PGC1α) in adipocytes causes reduced mitochondrial biogenesis in subcutaneous AT and systemic insulin resistance,[74] whereas increased AT mitochondrial function protects against the development of AT dysfunction and immune cell infiltration.[45,75] Indeed transgenic overexpression of the mitochondrial protein that contains a NEET (Asn-Glu-Glu-Thr) sequence (mitoNEET) significantly improved AT function and caused beneficial effects on insulin sensitivity at the systemic level in mice despite adiposity.[45,75] In summary, there are several lines of experimental and human evidence supporting that mitochondrial function is associated with normal AT function and that reduced mitochondrial mass and/or function is an indicator of AT malfunction.[18]

Fibrosis of adipose tissue

In the past decade, there has been growing evidence that human AT fibrosis is a symptom and hallmark of pathologically altered AT morphology and function.[76-78] Bel Lassen et al.[77] recently created a fibrosis score of adipose tissue (FAT score) that integrates perilobular and pericellular fibrosis and represents a simple semiquantitative evaluation of human subcutaneous fat fibrosis. Using this FAT score, people with obesity and AT fibrosis exhibit less weight loss after bariatric surgery compared to people without evidence for AT

fibrosis.[77] AT fibrosis maybe considered an end stage of AT dysfunction that is initiated by alterations of the ECM, which is somewhat analogous to liver pathologies. The ECM is an important component sof the plasticity of AT, because it is essential for structural support, mechanical stability, and cell signaling and function.[78] In obesity with AT dysfunction, the tightly regulated balance between ECM synthesis and degradation malfunctions in a way that prevents the plasticity and function of different cell types in AT.[78,79] Recently, it has been suggested that in subtypes of obesity, adipocyte size in visceral depots and fibrosis parameters are interrelated and reflected by circulating microRNA.[58] Interestingly, AT fibrosis persists after weight loss and further enhances AT dysfunction if weight is regained.[77,78] Obesity can induce alterations in AT ECM composition and deposition as well as the presence of thicker and more aligned collagen fibers and ECM stiffness.[76,80] The levels of several matrix metalloproteinases and their tissue inhibitors of metalloproteinases are regulated in response to obesity.[80,81]

Although targeting tissue fibrosis may have significant health benefits that may include improving AT health, no anti-fibrotic therapies have been approved by the U.S. Food and Drug Administration.[78] However, there have been promising developments in several drug candidates that target AT ECM remodeling.[78] Despite the fact that AT fibrosis and inflammation are regulated by distinct mechanisms,[81] targeting macrophages that play a role in the onset and progression of both obesity-related AT inflammation and fibrosis may represent a promising therapeutic strategy.[82] In the early phases of drug development, some anti-inflammatory agents have been shown to prevent macrophage infiltration into AT and might also alter the macrophage phenotype towards an anti-inflammatory subset.[83] We need a better understanding of the precise mechanisms, causative factors, and targets of AT fibrosis development to cultivate pharmacotherapies that specifically prevent AT fibrosis.[78]

Role of environmental compound accumulation in adipose tissue dysfunction

The global increase in obesity prevalence is associated with changes in behavior and lifestyle, but also the wide use of chemicals in agriculture (e.g., pesticides), for food preservation and packaging (e.g., plasticizers), and in cosmetics and other aspects of daily life.[43,84,85] Because genetic variation may only account for approximately 50% of obesity inheritance, behavior and environmental factors may play an important role as drivers of obesity at the societal and individual level. Although it is difficult to assess exposure to potentially obesogenic environmental compounds, measuring bioaccumulation of lipophilic xenobiotics in human AT may provide an estimate. In this context, we recently examined visceral and subcutaneous AT biopsies from donors of the LOBB[9] to test the hypothesis that storage of distinct environmental chemicals correlates with parameters of body shape and AT function.[49] We found that specific environmental chemicals are significantly associated with AT dysfunction measures including adipocyte hypertrophy, local AT and systemic inflammation, as well as variation in fat distribution even in people with normal body weight (Fig. 3).[43] Interestingly, we observed neither a correlation of several environmental compounds with obesity nor a fat depot-specific accumulation of these compounds. However, in accordance with previous data[86,87] on the abundance of persistent organic pollutants in serum and AT, we found associations between certain xenobiotics in AT and parameters of insulin sensitivity as well as fasting and chronic hyperglycemia.[49] Taken together, AT bioaccumulation of distinct environmental compounds that may directly act on AT processes via estrogen receptors[88] and PPARγ[89] may contribute to impaired AT function and may further link AT dysfunction to systemic glucose metabolism.

There is an unmet need for mechanistic studies testing the hypothesis that specific environmental compounds or exposure to a mixture of chemicals may contribute to the regulation of fat distribution, AT function, and cardiometabolic diseases.

CONSEQUENCES OF ADIPOSE TISSUE DYSFUNCTION

Adipose tissue signatures as predictors of obesity subtypes

In clinical practice, it is a frequent observation that human obesity consists of heterogeneous phenotypes. Subtypes of obesity include monogenic, childhood-onset, syndromic, and forms of obesity that vary in the extent of how medical, functional, and psychological traits are affected.[4,10,39,57,90-92] A better stratification of obesity subphenotypes may help to prioritize treatment strategies and to identify those people who may benefit the most from weight loss interventions. In this context, the Edmonton Obesity Staging System

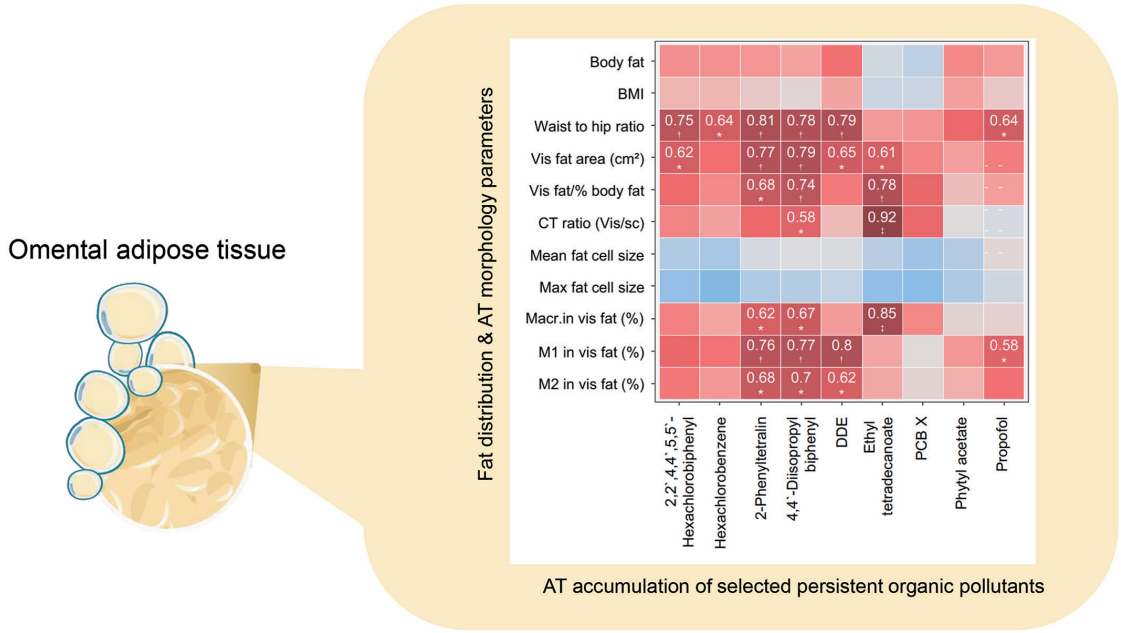

Figure 3. Adipose tissue (AT) distribution and morphology parameters in relation to persistent organic pollution concentration. Association of omental AT bioaccumulation of persistent organic pollutants with anthropometric and AT morphology parameters in 13 lean subjects (body mass index [BMI] <25 kg/m^2). Values in tiles are Pearson's correlation coefficients. Adapted from Rolle-Kampczyk et al.,[43] with permission from Elsevier. *P<0.05; †P<0.01; ‡P<0.001. CT, computed tomography; vis, visceral; sc, subcutaneous; Macr, macrophage; M1, M1 macrophages; M2, M2 macrophages; DDE, dichlorodiphenyldichloroethane; PCB X, polychlorinated biphenyl X.

considers the severity of obesity based on the number and extent of obesity-related comorbidities rather than BMI classification, and may identify people with obesity who are at highest mortality risk.[92] On the other hand, there are individuals with obesity that do not develop premature obesity-related cardiometabolic diseases.[10] People with metabolically healthy obesity seem to be protected against AT dysfunction[10,57] and exhibit lower morbidity and mortality risks attributable to obesity.[92] In order to identify factors underlying metabolically healthy obesity, we recently compared pairs of people with obesity without manifest metabolic comorbidities and cardiovascular risk factors which have been matched for age, sex and BMI into groups of insulin-sensitive or insulin-resistant obesity.[10] Interestingly, patients with insulin-resistant obesity had a significantly higher number of macrophages in visceral AT than those with insulin-sensitive obesity, suggesting that the association between AT inflammation and insulin resistance is not primarily related to fat mass or BMI.[10] Consistent with our data, another independent study identified visceral AT inflammation as the most significant correlate of metabolically unhealthy obesity.[93] As another indicator for distinct obesity subtypes, people with obesity who undergo bariatric surgery exhibit different responses with regard to weight loss, but also T2DM (Fig. 4) and the risk of early weight regain. We hypothesized that there is an obesogenic memory in AT that contributes to these different effects.[94] In the context of a two-step bariatric surgery strategy with an initial sleeve gastrectomy followed by Roux-en-Y gastric bypass surgery, we investigated AT histology and gene expression signatures and found two distinct directions of responses to weight loss characterized by remission (n=68) or reoccurrence (n=32) of T2DM 2 years after the initial step surgery (Fig. 4).[94] These observations suggest an obesogenic memory that may be related to the inability of AT to return to normal function after significant weight loss.[18] However, the exact mechanisms of AT obesogenic memory remain unclear. Based on these observations and data, we are currently searching for obesity subphenotypes in the LOBB[9] using artificial intelligence methods that integrate AT gene expression signatures at the whole-tissue and single-nuclei level with genetics and proteomics information. Recent examples from newly identified subtypes of T2DM and prediabetes suggest that novel technologies and deeper phenotyping have the potential to define potentially clinical relevant phenotypes that may guide treatment

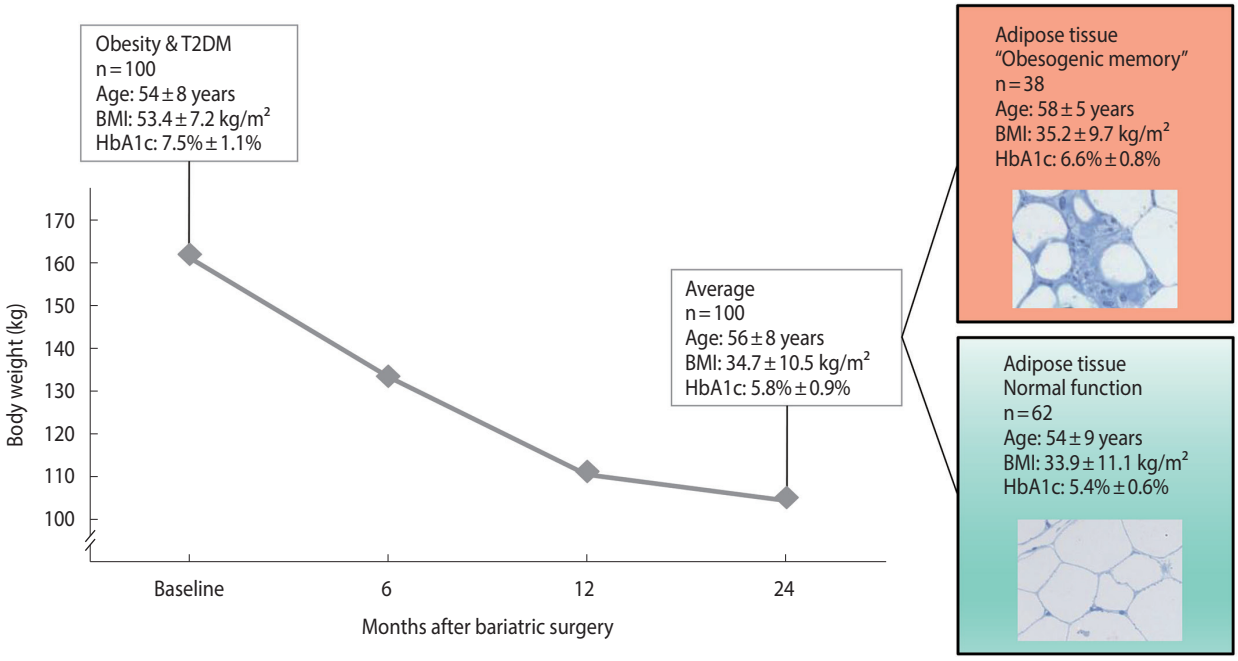

Figure 4. Obesogenic memory in a subgroup of patients from the Leipzig Obesity Biobank with obesity and type 2 diabetes mellitus (T2DM) undergoing bariatric surgery (n = 100). In the context of a two-step bariatric surgery procedure with an initial sleeve gastrectomy (baseline) and a Roux-en-Y gastric bypass surgery (up to 24 months), we investigated adipose tissue (AT) histology and gene expression signatures as described in Schmitz et al.[94] We found two distinct directions of responses to weight loss characterized by remission (n = 68) or reoccurrence (n = 32) of T2DM 2 years after the initial surgery. Mechanisms for sustained or delayed obesogenic memory specifically in AT remain unclear. Average age, body mass index (BMI), and glycosylated hemoglobin (HbA1c) are shown at baseline and at approximately 2 years after significant average weight loss. AT signatures but not BMI or age was associated with T2DM remission. The figure displays data included into a previous original publication by the author's research group.[94]

in the future.[95-97]

Recently, Yang et al.[98] identified the existence of two patterns of unexplained human phenotypic variation via multi-dimensional analysis of monozygotic phenotypically discordant twins. One phenotype is characterized by increased fat mass with only a modest reduction of lean mass, the other phenotype exhibits clinical outcomes linked to insulinemia, coordinated increases in fat and lean mass across the body, and decreased neuronatin and increased histone deacetylase-responsive gene signatures.[98] This study provides an example that stratification of disease phenotypes using novel multi-dimensional approaches has the potential to identify phenotypically and molecularly distinct types of obesity.[98]

Altered signals link adipose tissue dysfunction to endorgan damage

After the discovery that AT is an active endocrine organ,[99-101] it became clear that adipokines play specific roles in the regulation of appetite and satiety, immune response and inflammation, glucose and lipid metabolism, insulin sensitivity, hypertension, vascular growth and function, atherosclerosis development, bone development, growth, and other biological processes.[18-21,99-104] Altered secretion of adipokines (e.g., leptin and adiponectin), cytokines (e.g., monocyte chemoattractant protein-1, chemerin, and interleukin-6), metabolites (fatty acids), exosomes,[105] and immune cells, among others, is a symptom of AT dysfunction. An adverse, diabetogenic, proinflammatory, and atherogenic adipokine secretion pattern links obesity and AT dysfunction (including conditions like lipodystrophy) to obesity-related cardiometabolic diseases.[20] Therefore, adipokines are considered both as biomarkers for AT dysfunction and as tools for the prevention and treatment of obesity-related diseases.[18,103,106,107] Changes in adipokine production under conditions of AT dysfunction dramatically change AT communication with organs including the brain, pancreas, liver, skeletal muscle, heart, vasculature, immune system, and distant fat depots.[102,104] Indeed, adipokines regulate physiological functions of several organs and in states of AT dysfunction adipokines have disease-modifying

effects contributing to endorgan damage and pathological outcomes.[107]

Altered adipokine secretion upon AT dysfunction may affect periphery-brain cross-talk. For example, leptin regulates appetite, satiety, and locomotor activity. AT dysfunction and fatty liver diseases are closely interconnected. Adipokine secretion and changes in metabolite release may contribute to fat accumulation in the liver and liver insulin resistance.[104] As an example, leptin may improve hepatic steatosis via indirect effects and directly via hepatic activation of adenosine monophosphate-activated protein kinase (AMPK).[108] Adiponectin affects liver metabolism through its receptors and suppresses hepatic glucose output via phosphorylation of AMPK in addition to lowering hepatic proinflammatory ceramides and inhibiting the fibrogenic effects of transforming growth factor-β.[109] Among signals released from brown fat, neuregulin 4 (NRG4) has been suggested to link the activation of brown adipose tissue (BAT) with protection against diet-induced obesity, insulin resistance, and hepatic steatosis.[110] NRG4 was shown to directly reduce lipogenesis in hepatocytes, and could indirectly activate BAT via sympathetic neurons or via inducing brown adipocyte-like signatures in white adipocytes in a paracrine manner.[111]

Adipsin/complement factor D controls alternative activation of the complement system and reduces hepatic gluconeogenesis and inflammation in mouse models for diabetes.[112] Adipsin expression changes in AT dysfunction may exert relevant effects on impaired ß-cell function.[112] In addition to adipokines and altered metabolite release from dysfunctional AT, adipose-secreted exosomes might provide new treatment targets and markers to distinguish subtypes of obesity that vary in the degree of associated metabolic alterations. Extracellular vesicles contain bioactive molecules such as miRNAs and adipokines and contribute to interorgan cross-talk.[105] Exosomes may have the advantages of higher stability, ability to be stored for longer periods, and easily controlled dosing compared to other biological therapeutics.[103]

Taken together, adipokines are candidates for future pharmacological treatment strategies.[107] Metreleptin is already used as a pharmacotherapy in individuals with congenital leptin deficiency and lipodystrophies.[107] Novel adipokine-related treatment strategies may offer exciting new opportunities in a spectrum of diseases caused or modified by AT dysfunction.

CONCLUSION

AT dysfunction, which is characterized by increased abdominal, intra-abdominal, liver, and ectopic fat distribution, adipocyte hypertrophy and a disease-promoting adipokine secretion pattern, links AT-related diseases like obesity and lipodystrophy to cardiometabolic diseases. Altered adipokine profiles, AT inflammation, and the release of metabolites may provide a mechanistic link between obesity diseases. A better understanding of the mechanisms responsible for AT dysfunction can lead to novel therapeutic interventions for obesity-related diseases. Alterations in AT dysfunction include immune cell infiltration into (visceral) AT, fibrosis, and the production of exosomes that can impair systemic insulin sensitivity. Our understanding of the secreted factors that cause impaired organ health continues to improve, but questions remain about the alterations in AT communication that lead to irreversible endorgan damage. In addition, factors that regulate AT function via brain, autonomous nervous system, liver, and muscle cross-talk need to be elucidated. To date, there are no specific therapies targeting AT dysfunction, although therapeutic weight loss, exercise, and healthier eating patterns can ameliorate or normalize AT function. Therefore, understanding the mechanisms of AT dysfunction and targeting them may hold opportunities to improve the health of people with obesity, lipodystrophy, and lipedema.

CONFLICTS OF INTEREST

Matthias Blüher received honoraria as a consultant and speaker from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Daiichi-Sankyo, Lilly, Novo Nordisk, Novartis, Pfizer, and Sanofi.

REFERENCES

1. GBD 2021 US Burden of Disease and Forecasting Collaborators. Burden of disease scenarios by state in the USA, 2022-50: a forecasting analysis for the Global Burden of Disease Study 2021. Lancet 2024;404:2341-70.
2. Busetto L, Dicker D, Frühbeck G, Halford JC, Sbraccia P, Yumuk V, et al. A new framework for the diagnosis, staging

and management of obesity in adults. Nat Med 2024;30:2395-9.
3. Jeong SM, Jung JH, Yang YS, Kim W, Cho IY, Lee YB, et al. 2023 Obesity fact sheet: prevalence of obesity and abdominal obesity in adults, adolescents, and children in Korea from 2012 to 2021. J Obes Metab Syndr 2024;33:27-35.
4. Blüher M. Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 2019;15:288-98.
5. Kang E, Hong YH, Kim J, Chung S, Kim KK, Haam JH, et al. Obesity in children and adolescents: 2022 update of clinical practice guidelines for obesity by the Korean Society for the Study of Obesity. J Obes Metab Syndr 2024;33:11-9.
6. Colditz GA, Willett WC, Rotnitzky A, Manson JE. Weight gain as a risk factor for clinical diabetes mellitus in women. Ann Intern Med 1995;122:481-6.
7. Robbins AL, Savage DB. The genetics of lipid storage and human lipodystrophies. Trends Mol Med 2015;21:433-8.
8. Lim K, Haider A, Adams C, Sleigh A, Savage DB. Lipodistrophy: a paradigm for understanding the consequences of "overloading" adipose tissue. Physiol Rev 2021;101:907-93.
9. Leipzig Obesity BioBank [Internet]. Helmholtz Munich; 2024 [cited 2024 Dec 20]. Available from: https://www.helmholtz-munich.de/en/hi-mag/cohort/leipzig-obesity-bio-bank-lobb
10. Blüher M. Metabolically healthy obesity. Endocr Rev 2020;41:bnaa004.
11. Sun K, Kusminski CM, Scherer PE. Adipose tissue remodeling and obesity. J Clin Invest 2011;121:2094-101.
12. Ghaben AL, Scherer PE. Adipogenesis and metabolic health. Nat Rev Mol Cell Biol 2019;20:242-58.
13. Ramirez Bustamante CE, Agarwal N, Cox AR, Hartig SM, Lake JE, Balasubramanyam A. Adipose tissue dysfunction and energy balance paradigms in people living with HIV. Endocr Rev 2024;45:190-209.
14. Kruppa P, Gohlke S, Łapiński K, Garcia-Carrizo F, Soultoukis GA, Infanger M, et al. Lipedema stage affects adipocyte hypertrophy, subcutaneous adipose tissue inflammation and interstitial fibrosis. Front Immunol 2023;14:1223264.
15. Meister BM, Hong SG, Shin J, Rath M, Sayoc J, Park JY. Healthy versus unhealthy adipose tissue expansion: the role of exercise. J Obes Metab Syndr 2022;31:37-50.
16. Cinti S. The adipose organ at a glance. Dis Model Mech 2012;5:588-94.
17. Arner P, Rydén M. Human white adipose tissue: a highly dynamic metabolic organ. J Intern Med 2022;291:611-21.
18. Klein S, Gastaldelli A, Yki-Järvinen H, Scherer PE. Why does obesity cause diabetes? Cell Metab 2022;34:11-20.
19. Blüher M. Adipose tissue inflammation: a cause or consequence of obesity-related insulin resistance? Clin Sci (Lond) 2016;130:1603-14.
20. Hagberg CE, Spalding KL. White adipocyte dysfunction and obesity-associated pathologies in humans. Nat Rev Mol Cell Biol 2024;25:270-89.
21. Blüher M. Adipose tissue dysfunction contributes to obesity related metabolic diseases. Best Pract Res Clin Endocrinol Metab 2013;27:163-77.
22. Chouchani ET, Kajimura S. Metabolic adaptation and maladaptation in adipose tissue. Nat Metab 2019;1:189-200.
23. Kajimura S, Spiegelman BM, Seale P. Brown and beige fat: physiological roles beyond heat generation. Cell Metab 2015;22:546-59.
24. Cypess AM. Does activating brown fat contribute to important metabolic benefits in humans? Yes! J Clin Invest 2023;133:e175282.
25. Waldén TB, Hansen IR, Timmons JA, Cannon B, Nedergaard J. Recruited vs. nonrecruited molecular signatures of brown, "brite," and white adipose tissues. Am J Physiol Endocrinol Metab 2012;302:E19-31.
26. Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell 2014;156:20-44.
27. Emont MP, Jacobs C, Essene AL, Pant D, Tenen D, Colleluori G, et al. A single-cell atlas of human and mouse white adipose tissue. Nature 2022;603:926-33.
28. Massier L, Jalkanen J, Elmastas M, Zhong J, Wang T, Nono Nankam PA, et al. An integrated single cell and spatial transcriptomic map of human white adipose tissue. Nat Commun 2023;14:1438.
29. Bäckdahl J, Franzén L, Massier L, Li Q, Jalkanen J, Gao H, et al. Spatial mapping reveals human adipocyte subpopulations with distinct sensitivities to insulin. Cell Metab 2021;

33:1869-82.
30. Palani NP, Horvath C, Timshel PN, Folkertsma P, Grønning AG, Henriksen TI, et al. Adipogenic and SWAT cells separate from a common progenitor in human brown and white adipose depots. Nat Metab 2023;5:996-1013.
31. Sun W, Dong H, Balaz M, Slyper M, Drokhlyansky E, Colleluori G, et al. snRNA-seq reveals a subpopulation of adipocytes that regulates thermogenesis. Nature 2020;587:98-102.
32. Sárvári AK, Van Hauwaert EL, Markussen LK, Gammelmark E, Marcher AB, Ebbesen MF, et al. Plasticity of epididymal adipose tissue in response to diet-induced obesity at single-nucleus resolution. Cell Metab 2021;33:437-53.
33. Vijay J, Gauthier MF, Biswell RL, Louiselle DA, Johnston JJ, Cheung WA, et al. Single-cell analysis of human adipose tissue identifies depot and disease specific cell types. Nat Metab 2020;2:97-109.
34. Hinte LC, Castellano-Castillo D, Ghosh A, Melrose K, Gasser E, Noé F, et al. Adipose tissue retains an epigenetic memory of obesity after weight loss. Nature 2024;636:457-65.
35. Arner P, Bernard S, Salehpour M, Possnert G, Liebl J, Steier P, et al. Dynamics of human adipose lipid turnover in health and metabolic disease. Nature 2011;478:110-3.
36. Timshel PN, Thompson JJ, Pers TH. Genetic mapping of etiologic brain cell types for obesity. Elife 2020;9:e55851.
37. World Health Organization. Obesity and overweight [Internet]. WHO; 2024 [cited 2024 Dec 20]. Available from: https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight
38. Klein S, Wadden T, Sugerman HJ. AGA technical review on obesity. Gastroenterology 2002;123:882-932.
39. Klein S, Fontana L, Young VL, Coggan AR, Kilo C, Patterson BW, et al. Absence of an effect of liposuction on insulin action and risk factors for coronary heart disease. N Engl J Med 2004;350:2549-57.
40. Blüher M, Laufs U. New concepts for body shape-related cardiovascular risk: role of fat distribution and adipose tissue function. Eur Heart J 2019;40:2856-8.
41. Manolopoulos KN, Karpe F, Frayn KN. Gluteofemoral body fat as a determinant of metabolic health. Int J Obes (Lond) 2010;34:949-59.
42. Vantyghem MC, Balavoine AS, Douillard C, Defrance F, Dieudonne L, Mouton F, et al. How to diagnose a lipodystrophy syndrome. Ann Endocrinol (Paris) 2012;73:170-89.
43. Rolle-Kampczyk U, Gebauer S, Haange SB, Schubert K, Kern M, Moulla Y, et al. Accumulation of distinct persistent organic pollutants is associated with adipose tissue inflammation. Sci Total Environ 2020;748:142458.
44. Rudich A, Kanety H, Bashan N. Adipose stress-sensing kinases: linking obesity to malfunction. Trends Endocrinol Metab 2007;18:291-9.
45. Kusminski CM, Holland WL, Sun K, Park J, Spurgin SB, Lin Y, et al. MitoNEET-driven alterations in adipocyte mitochondrial activity reveal a crucial adaptive process that preserves insulin sensitivity in obesity. Nat Med 2012;18:1539-49.
46. Shoelson SE, Lee J, Goldfine AB. Inflammation and insulin resistance. J Clin Invest 2006;116:1793-801.
47. Seo JB, Riopel M, Cabrales P, Huh JY, Bandyopadhyay GK, Andreyev AY, et al. Knockdown of Ant2 reduces adipocyte hypoxia and improves insulin resistance in obesity. Nat Metab 2019;1:86-97.
48. Sun K, Wernstedt Asterholm I, Kusminski CM, Bueno AC, Wang ZV, Pollard JW, et al. Dichotomous effects of VEGF-A on adipose tissue dysfunction. Proc Natl Acad Sci U S A 2012;109:5874-9.
49. Halberg N, Khan T, Trujillo ME, Wernstedt-Asterholm I, Attie AD, Sherwani S, et al. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. Mol Cell Biol 2009;29:4467-83.
50. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW Jr. Obesity is associated with macrophage accumulation in adipose tissue. J Clin Invest 2003;112:1796-808.
51. Lo KA, Labadorf A, Kennedy NJ, Han MS, Yap YS, Matthews B, et al. Analysis of in vitro insulin-resistance models and their physiological relevance to in vivo diet-induced adipose insulin resistance. Cell Rep 2013;5:259-70.
52. Haufe S, Witt H, Engeli S, Kaminski J, Utz W, Fuhrmann JC, et al. Branched-chain and aromatic amino acids, insulin resistance and liver specific ectopic fat storage in overweight to

obese subjects. Nutr Metab Cardiovasc Dis 2016;26:637-42.
53. Cifarelli V, Beeman SC, Smith GI, Yoshino J, Morozov D, Beals JW, et al. Decreased adipose tissue oxygenation associates with insulin resistance in individuals with obesity. J Clin Invest 2020;130:6688-99.
54. Beals JW, Smith GI, Shankaran M, Fuchs A, Schweitzer GG, Yoshino J, et al. Increased adipose tissue fibrogenesis, not impaired expandability, is associated with nonalcoholic fatty liver disease. Hepatology 2021;74:1287-99.
55. Fuchs A, Samovski D, Smith GI, Cifarelli V, Farabi SS, Yoshino J, et al. Associations among adipose tissue immunology, inflammation, exosomes and insulin sensitivity in people with obesity and nonalcoholic fatty liver disease. Gastroenterology 2021;161:968-81.
56. Akbar N, Azzimato V, Choudhury RP, Aouadi M. Extracellular vesicles in metabolic disease. Diabetologia 2019;62:2179-87.
57. Klöting N, Fasshauer M, Dietrich A, Kovacs P, Schön MR, Kern M, et al. Insulin-sensitive obesity. Am J Physiol Endocrinol Metab 2010;299:E506-15.
58. Pincu Y, Makarenkov N, Tsitrina AA, Rosengarten-Levine M, Haim Y, Yoel U, et al. Visceral adipocyte size links obesity with dysmetabolism more than fibrosis, and both can be estimated by circulating miRNAs. Obesity (Silver Spring) 2023;31:2986-97.
59. Mulhem A, Moulla Y, Klöting N, Ebert T, Tönjes A, Fasshauer M, et al. Circulating cell adhesion molecules in metabolically healthy obesity. Int J Obes (Lond) 2021;45:331-6.
60. Maixner N, Pecht T, Haim Y, Chalifa-Caspi V, Goldstein N, Tarnovscki T, et al. A TRAIL-TL1A paracrine network involving adipocytes, macrophages, and lymphocytes induces adipose tissue dysfunction downstream of E2F1 in human obesity. Diabetes 2020;69:2310-23.
61. Goldstein N, Kezerle Y, Gepner Y, Haim Y, Pecht T, Gazit R, et al. Higher mast cell accumulation in human adipose tissues defines clinically favorable obesity sub-phenotypes. Cells 2020;9:1508.
62. Schöttl T, Kappler L, Fromme T, Klingenspor M. Limited OXPHOS capacity in white adipocytes is a hallmark of obesity in laboratory mice irrespective of the glucose tolerance status. Mol Metab 2015;4:631-42.
63. Yin X, Lanza IR, Swain JM, Sarr MG, Nair KS, Jensen MD. Adipocyte mitochondrial function is reduced in human obesity independent of fat cell size. J Clin Endocrinol Metab 2014;99:E209-16.
64. Choo HJ, Kim JH, Kwon OB, Lee CS, Mun JY, Han SS, et al. Mitochondria are impaired in the adipocytes of type 2 diabetic mice. Diabetologia 2006;49:784-91.
65. Heinonen S, Muniandy M, Buzkova J, Mardinoglu A, Rodríguez A, Frühbeck G, et al. Mitochondria-related transcriptional signature is downregulated in adipocytes in obesity: a study of young healthy MZ twins. Diabetologia 2017;60:169-81.
66. Heinonen S, Buzkova J, Muniandy M, Kaksonen R, Ollikainen M, Ismail K, et al. Impaired mitochondrial biogenesis in adipose tissue in acquired obesity. Diabetes 2015;64:3135-45.
67. Ohno H, Shinoda K, Spiegelman BM, Kajimura S. PPARγ agonists induce a white-to-brown fat conversion through stabilization of PRDM16 protein. Cell Metab 2012;15:395-404.
68. Trevellin E, Scorzeto M, Olivieri M, Granzotto M, Valerio A, Tedesco L, et al. Exercise training induces mitochondrial biogenesis and glucose uptake in subcutaneous adipose tissue through eNOS-dependent mechanisms. Diabetes 2014;63:2800-11.
69. Wilson-Fritch L, Nicoloro S, Chouinard M, Lazar MA, Chui PC, Leszyk J, et al. Mitochondrial remodeling in adipose tissue associated with obesity and treatment with rosiglitazone. J Clin Invest 2004;114:1281-9.
70. Mardinoglu A, Heiker JT, Gärtner D, Björnson E, Schön MR, Flehmig G, et al. Extensive weight loss reveals distinct gene expression changes in human subcutaneous and visceral adipose tissue. Sci Rep 2015;5:14841.
71. Jokinen R, Rinnankoski-Tuikka R, Kaye S, Saarinen L, Heinonen S, Myöhänen M, et al. Adipose tissue mitochondrial capacity associates with long-term weight loss success. Int J Obes (Lond) 2018;42:817-25.
72. Kang GS, Jo HJ, Lee YR, Oh T, Park HJ, Ahn GO. Sensing the oxygen and temperature in the adipose tissues: who's sensing what? Exp Mol Med 2023;55:2300-7.

73. Vernochet C, Damilano F, Mourier A, Bezy O, Mori MA, Smyth G, et al. Adipose tissue mitochondrial dysfunction triggers a lipodystrophic syndrome with insulin resistance, hepatosteatosis, and cardiovascular complications. FASEB J 2014;28:4408-19.
74. Kleiner S, Mepani RJ, Laznik D, Ye L, Jurczak MJ, Jornayvaz FR, et al. Development of insulin resistance in mice lacking PGC-1α in adipose tissues. Proc Natl Acad Sci U S A 2012; 109:9635-40.
75. Kusminski CM, Park J, Scherer PE. MitoNEET-mediated effects on browning of white adipose tissue. Nat Commun 2014;5:3962.
76. Divoux A, Tordjman J, Lacasa D, Veyrie N, Hugol D, Aissat A, et al. Fibrosis in human adipose tissue: composition, distribution, and link with lipid metabolism and fat mass loss. Diabetes 2010;59:2817-25.
77. Bel Lassen P, Charlotte F, Liu Y, Bedossa P, Le Naour G, Tordjman J, et al. The FAT score, a fibrosis score of adipose tissue: predicting weight-loss outcome after gastric bypass. J Clin Endocrinol Metab 2017;102:2443-53.
78. Gliniak CM, Pedersen L, Scherer PE. Adipose tissue fibrosis: the unwanted houseguest invited by obesity. J Endocrinol 2023;259:e230180.
79. Pincu Y, Yoel U, Haim Y, Makarenkov N, Maixner N, Shaco-Levy R, et al. Assessing obesity-related adipose tissue disease (OrAD) to improve precision medicine for patients living with obesity. Front Endocrinol (Lausanne) 2022;13:860799.
80. Mariman EC, Wang P. Adipocyte extracellular matrix composition, dynamics and role in obesity. Cell Mol Life Sci 2010; 67:1277-92.
81. Lin D, Chun TH, Kang L. Adipose extracellular matrix remodelling in obesity and insulin resistance. Biochem Pharmacol 2016;119:8-16.
82. McVicker BL, Bennett RG. Novel anti-fibrotic therapies. Front Pharmacol 2017;8:318.
83. Li X, Ren Y, Chang K, Wu W, Griffiths HR, Lu S, et al. Adipose tissue macrophages as potential targets for obesity and metabolic diseases. Front Immunol 2023;14:1153915.
84. Le Magueresse-Battistoni B, Vidal H, Naville D. Environmental pollutants and metabolic disorders: the multi-exposure scenario of life. Front Endocrinol (Lausanne) 2018;9:582.
85. Swinburn BA, Sacks G, Hall KD, McPherson K, Finegood DT, Moodie ML, et al. The global obesity pandemic: shaped by global drivers and local environments. Lancet 2011;378: 804-14.
86. Pestana D, Faria G, Sá C, Fernandes VC, Teixeira D, Norberto S, et al. Persistent organic pollutant levels in human visceral and subcutaneous adipose tissue in obese individuals: depot differences and dysmetabolism implications. Environ Res 2014;133:170-7.
87. Müllerová D, Kopecký J. White adipose tissue: storage and effector site for environmental pollutants. Physiol Res 2007; 56:375-82.
88. McLachlan JA. Environmental signaling: from environmental estrogens to endocrine-disrupting chemicals and beyond. Andrology 2016;4:684-94.
89. Desvergne B, Feige JN, Casals-Casas C. PPAR-mediated activity of phthalates: a link to the obesity epidemic? Mol Cell Endocrinol 2009;304:43-8.
90. Farooqi S, O'Rahilly S. Genetics of obesity in humans. Endocr Rev 2006;27:710-18.
91. Farooqi IS, Keogh JM, Yeo GS, Lank EJ, Cheetham T, O'Rahilly S. Clinical spectrum of obesity and mutations in the melanocortin 4 receptor gene. N Engl J Med 2003;348:1085-95.
92. Kuk JL, Ardern CI, Church TS, Sharma AM, Padwal R, Sui X, et al. Edmonton Obesity Staging System: association with weight history and mortality risk. Appl Physiol Nutr Metab 2011;36:570-6.
93. Hardy OT, Perugini RA, Nicoloro SM, Gallagher-Dorval K, Puri V, Straubhaar J, et al. Body mass index-independent inflammation in omental adipose tissue associated with insulin resistance in morbid obesity. Surg Obes Relat Dis 2011;7: 60-7.
94. Schmitz J, Evers N, Awazawa M, Nicholls HT, Brönneke HS, Dietrich A, et al. Obesogenic memory can confer long-term increases in adipose tissue but not liver inflammation and insulin resistance after weight loss. Mol Metab 2016;5:328-39.
95. Ahlqvist E, Storm P, Käräjämäki A, Martinell M, Dorkhan M, Carlsson A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster

analysis of six variables. Lancet Diabetes Endocrinol 2018;6:361-9.
96. Wagner R, Heni M, Tabák AG, Machann J, Schick F, Randrianarisoa E, et al. Pathophysiology-based subphenotyping of individuals at elevated risk for type 2 diabetes. Nat Med 2021;27:49-57.
97. Fritsche A, Wagner R, Heni M, Kantartzis K, Machann J, Schick F, et al. Different effects of lifestyle intervention in high- and low-risk prediabetes: results of the Randomized Controlled Prediabetes Lifestyle Intervention Study (PLIS). Diabetes 2021;70:2785-95.
98. Yang CH, Fagnocchi L, Apostle S, Wegert V, Casaní-Galdón S, Landgraf K, et al. Independent phenotypic plasticity axes define distinct obesity sub-types. Nat Metab 2022;4:1150-65.
99. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman JM. Positional cloning of the mouse obese gene and its human homologue. Nature 1994;372:425-32.
100. Cook KS, Min HY, Johnson D, Chaplinsky RJ, Flier JS, Hunt CR, et al. Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve. Science 1987;237:402-5.
101. Scherer PE, Williams S, Fogliano M, Baldini G, Lodish HF. A novel serum protein similar to C1q, produced exclusively in adipocytes. J Biol Chem 1995;270:26746-9.
102. Würfel M, Blüher M, Stumvoll M, Ebert T, Kovacs P, Tönjes A, et al. Adipokines as clinically relevant therapeutic targets in obesity. Biomedicines 2023;11:1427.
103. Fasshauer M, Blüher M. Adipokines in health and disease. Trends Pharmacol Sci 2015;36:461-70.
104. Gilani A, Stoll L, Homan EA, Lo JC. Adipose signals regulating distal organ health and disease. Diabetes 2024;73:169-77.
105. Rome S. Muscle and adipose tissue communicate with extracellular vesicles. Int J Mol Sci 2022;23:7052.
106. Müller TD, Blüher M, Tschöp MH, DiMarchi RD. Anti-obesity drug discovery: advances and challenges. Nat Rev Drug Discov 2022;21:201-23.
107. Blüher M. Adipokines: removing road blocks to obesity and diabetes therapy. Mol Metab 2014;3:230-40.
108. Marra F, Bertolani C. Adipokines in liver diseases. Hepatology 2009;50:957-69.
109. Holland WL, Miller RA, Wang ZV, Sun K, Barth BM, Bui HH, et al. Receptor-mediated activation of ceramidase activity initiates the pleiotropic actions of adiponectin. Nat Med 2011;17:55-63.
110. Blüher M. Neuregulin 4: a "hotline" between brown fat and liver. Obesity (Silver Spring) 2019;27:1555-7.
111. Wang GX, Zhao XY, Meng ZX, Kern M, Dietrich A, Chen Z, et al. The brown fat-enriched secreted factor Nrg4 preserves metabolic homeostasis through attenuation of hepatic lipogenesis. Nat Med 2014;20:1436-43.
112. Lo JC, Ljubicic S, Leibiger B, Kern M, Leibiger IB, Moede T, et al. Adipsin is an adipokine that improves β cell function in diabetes. Cell 2014;158:41-53.