REVIEW ARTICLE

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Reassessing Human Adipose Tissue

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Adipose tissue is an underappreciated and misunderstood organ. Capable of more than doubling in mass and then returning to baseline,[1] white adipose tissue (WAT) continues to play an essential role in the development of humans. WAT efficiently stores sufficient energy to free us from constantly seeking food, permitting us to devote our physical and mental efforts toward building civilization. Brown adipose tissue (BAT) consumes glucose and triglycerides, generating heat. An organ designed for nonshivering thermogenesis, BAT has enabled mammals to thrive in the current Cenozoic era. Once thought to be physiologically irrelevant in adult humans, long-term activation of BAT has been hypothesized to contribute to wide-ranging health benefits in tissues as diverse as the gastrointestinal, cardiovascular, and musculoskeletal systems.[2] Highlighting the developments from the past 5 to 10 years, this review discusses the two principal facets of human adipose tissue: its functional roles related to triglyceride storage, as well as its excess in obesity, and its far-reaching, complementary physiological roles in the endocrine system.

Structure and Distribution of Adipose-Tissue Depots

Too many people are confident that they know what fat is: an undesired body appendage that they strive to reduce over their entire lives. For those who struggle to lose weight, fat is often a source of misery, not marvel. Among medical professionals, it had been disregarded to the extent that fat has merited little attention in curricula and does not even feature in atlases of anatomy. Fortunately, the past three decades have witnessed a revolution in our understanding of and perspective on this tissue.[3] Fat is not one entity; it is a collection of related but different anatomical and functional adipose-tissue depots.[4,5] Derived principally from the mesoderm,[6] human WAT begins to develop in the second trimester of pregnancy, and by birth, both visceral and subcutaneous depots are well established. BAT first arises during the late second trimester and protects newborns from cold as they develop the ability to shiver. In lean adults, the entire WAT depot ranges from 20 to 30 kg in women (30 to 40% of total body mass) and 10 to 20 kg in men (15 to 25% of total body mass).[7]

Fat mass can be estimated rapidly and in many persons with the use of inexpensive methods such as skinfold calipers, waist circumference, or body-mass index (BMI). Assessments are more accurate with bioimpedance analysis and dual-energy x-ray absorptiometry, and very precise calculations may be accomplished by means of computed tomography (CT) and magnetic resonance imaging (MRI).[8] The relative amounts and distribution of adult human BAT are predictably influenced by allometric scaling. Adult mice, a common model for studies of vertebrate physiology, weigh 20 to 50 g, and BAT is 2 to 5% of their body mass. Humans are three orders of magnitude larger, so our lower ratio of surface area to volume and greater insulation from muscle and WAT reduce the need for BAT thermogenesis.

The distribution of adult human BAT is also much more restricted, found only in certain anatomical depots in the neck, shoulders, posterior thorax, and abdomen.[9] A unifying feature is that these depots drain directly into the systemic circulation and may lead to more rapid distribution of warmed blood to the rest of the body.

Quantification of active BAT is challenging and relies on whole-body, noninvasive imaging with the use of either positron-emission tomography–CT or MRI.[10] The maximum detectable BAT mass in humans appears to be approximately 1 kg, and in adults 20 to 50 years of age, it ranges from 50 to 500 g, or 0.1 to 0.5% of total body mass, and 0.2 to 3.0% of total adipose tissue mass.[9] The amount of BAT also varies according to sex, and it has an inverse association with age and BMI.[11] As discussed below, how much further BAT mass can be increased in humans and whether a larger proportion could affect energy balance or metabolic health remain to be determined.

Fat tissue plays a central role in energy distribution. All food eaten by mammals consists of just three macronutrients: carbohydrates, proteins, and fats. Even though individual meals can have widely varying proportions of these three fuels, the human body is capable of metabolic flexibility, which is the ability of mitochondria to alter their substrate preference for fat as compared with carbohydrate oxidation.[12] Recent research has shown that dysfunctional mitochondria lead to insulin resistance in skeletal muscle, not because of impaired flexibility in response to substrate availability but because of an overall decrease in substrate oxidation.[12] Therefore, overfeeding of any one of the macronutrients — carbohydrates, proteins, or fats — ultimately leads to a positive energy balance and weight gain.[13] The contribution of macronutrient composition to energy expenditure and the development of obesity and metabolic disease is an area of active debate.[14] The primary function of WAT is to store energy in the form of triglycerides, yet there are substantial, clinically relevant physiological differences among the various WAT depots.[15] Metabolic health risks are therefore due at least as much to the location of excess triglyceride storage as to the overall fat mass of the body.[16] WAT is commonly separated into visceral fat and subcutaneous fat, which confer negative and neutral or positive metabolic effects, respectively.[17] Visceral fat can be divided into multiple distinct regions with different metabolic risks. The locations of the WAT and BAT depots[18-24] are shown in Figure 1.

On the basis of microscopic anatomy and cell physiology, it is more appropriate to refer to fat as adipose tissue because it is composed of multiple distinct cell types. There are the adipocytes themselves but also the stromal vascular fraction — fibroblasts, blood and blood vessels, macrophages and other immune cells, and nerve tissue. Relatively recent forms of technology involving single-cell and single-nucleus RNA sequencing, which are becoming an integral part of mapping tissues and their complexity, have identified numerous cell subtypes that play critical roles in regulating adipogenesis, thermogenesis, and interorgan communication.[25] In addition, the various proteins and proteoglycans in the extracellular matrix play an active role in the function of both WAT and BAT.[16,26]

Many features of adipose-tissue depots, such as location, size, and metabolic behavior, are influenced by genetic background and sex.[27] Beyond that, adipose tissue is a dynamic organ. The widely held belief that humans are born with all the fat cells they will ever have, which are capable only of enlarging or shrinking, is now understood to be incorrect. Innovative use of isotopic labeling has enabled researchers to measure new adipogenesis. These studies showed that adipogenesis continues throughout life, with a median turnover rate of 8% per year, indicating an entire replacement of the adipocytes in the body every 15 years.[28] For perspective, this rate is similar to that of osteocytes and faster than the turnover of many cardiomyocytes.[29] Adipocyte precursor cells, known as preadipocytes, are present in the stromal vascular fraction and perivascular tissue, which are capable of self-renewal.[30] Growth of the adipocytes comes both from hypertrophy, the enlargement of cell size, and hyperplasia, the increase in cell number.[31] The balance among hypertrophy, hyperplasia, fibrosis, and lipolysis in both visceral and subcutaneous WAT is associated with different risks for progression to physiological dysfunction.[32] The newfound diversity and capability have led to the recognition that mammalian adipose tissue is a "polychromatic" organ. In addition to white and brown, there are distinct thermogenic adipocytes, termed "beige/brite,"

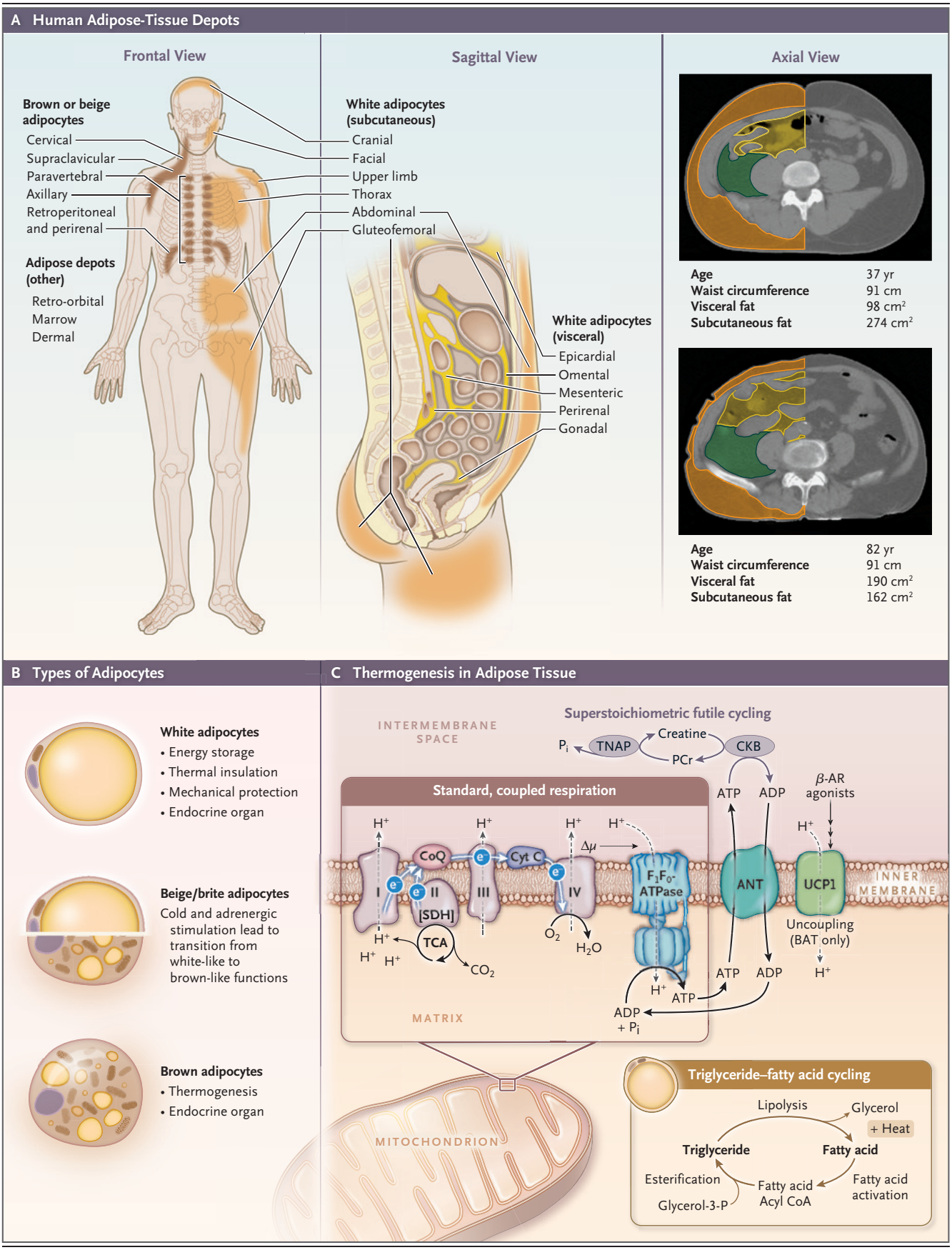


Figure 1 (facing page). Human Adipose Tissues.
Panel A shows the principal human adipose-tissue depots from the frontal (left) and sagittal (center) planes. Brown or beige depots are shown in brown, subcutaneous white fat in orange, and visceral white fat in yellow. Panel A also shows CT scans, with axial views of the abdomen (right), in two men with the same waist circumference but different partitioning of the adipose-tissue depots. Orange indicates subcutaneous fat, green retroperitoneal visceral fat, and yellow mesenteric visceral fat. The volumes of fat refer to the sum of both the left and right sides of the body.[20] Panel B shows the three principal types of adipocytes and their known physiological roles. Panel C shows the molecular mechanisms for thermogenesis in the adipose tissue. The upper diagram on the left shows the tricarboxylic acid (TCA) cycle and its interaction with the electron transport chain (ETC), composed of coenzyme Q (CoQ), cytochrome C (Cyt C), and complexes I through IV. In all cells with mitochondria, these two systems generate a proton-based (H^+) electrochemical gradient ($\Delta\mu$) that enables the cells to generate ATP through F_1F_0-ATPase. In brown and beige/brite adipocytes, stimulation of β-adrenergic (β-AR) signaling activates tissue-specific uncoupling protein 1 (UCP1), which dissipates the electrochemical gradient and uncouples TCA and the ETC from ATP production. Instead, there is an increase in the rates of the associated exergonic reactions of TCA and the ETC, which generates heat.[23] Other thermogenic processes include hydrolysis of ETC-generated ATP when the mitochondrial adenine nucleotide translocator (ANT) shuttles ATP from the mitochondrial matrix into the intermembrane space, where mitochondrial creatine kinase B (CKB) catalyzes the conversion of creatine to phosphocreatine, which is then hydrolyzed by tissue-nonspecific alkaline phosphatase (TNAP), generating heat through superstoichiometric futile cycling. The mitochondrial inner membrane also uses succinate dehydrogenase (SDH), part of ETC complex II and one of the enzymes of the TCA cycle, to oxidize succinate and produce reactive oxygen species that drive thermogenic respiration.[22] BAT denotes brown adipose tissue, e^- electron, PCr phosphocreatine, and P_i inorganic phosphate. The lower diagram shows triglyceride–fatty acid futile cycling, seen in white adipose tissue.[23,24] CoA denotes coenzyme A.

which have features of both white and brown adipocytes, and pink adipocytes in breast tissue,[33,34] as well as fat in the bone marrow and dermis, each with a distinct physiological role.[35,36]

FUNCTION AND COMMUNICATION

WAT has three commonly understood and related macroscopic functions. It stores food calories, creates a layer of thermal insulation, and provides mechanical protection, which is important for resisting infection and injury.[37] Insulin is the principal driver of fuel absorption and storage, with adipose tissue responsible for 5% of insulin-mediated glucose uptake in adults who are lean and 20% in those who are obese.[38] Until three decades ago, these physiological roles were all that most people considered when thinking about WAT, but the discoveries of white adipocyte–derived hormones such as leptin and adiponectin made clear that WAT is also an endocrine organ[39-43] (Fig. 2). Beyond these hormones, adipocytes and the other resident cell types produce dozens of other adipokines that affect local and distant physiology, such as proinflammatory tumor necrosis factor α (TNF-α), monocyte chemotactic protein 1, and the sex hormone estrogen.[44] WAT as a mesodermal organ communicates its functional status at the autocrine, paracrine, and endocrine levels. For example, pregnancy requires a sufficient long-term supply of energy, and WAT is essential for the proper function of the reproductive system, which includes the secretion of regulatory and sex hormones and lactation. Too little WAT, as seen in anorexia nervosa and lipodystrophies, interrupts menstruation.[45] Too much WAT leads to early puberty.[46] WAT also uses interorgan signaling to coordinate the storage and consumption of nutrients with the liver and skeletal muscle.[47]

The discovery of leptin three decades ago[48] heralded a new era in obesity medicine but not as originally anticipated. Leptin does not induce satiety, but low leptin levels signal low energy stores and starvation. People with obesity have leptin resistance such that exogenous administration does not lead to appetite suppression or weight loss, except in persons with congenital leptin deficiency, which is extremely rare. Various studies of the effects of leptin have led to new insights regarding the control of food intake by the hypothalamus and other brain regions.

Adiponectin regulates glucose and lipid metabolism and promotes a metabolic profile that is antiatherogenic, antiinflammatory, and insulin-sensitizing.[49] Advances in understanding adipose tissue as an endocrine organ have been supported by the identification of non–peptide-signaling species that have local and systemic effects. Bioactive lipids such as 12,13-dihydroxy-9Z-octadecenoic acid (12,13-diHOME) and 12-hydroxyeicosapentaenoic acid (12-HEPE) are released by BAT and stimulate glucose and fatty acid uptake in BAT and muscle, thereby support-

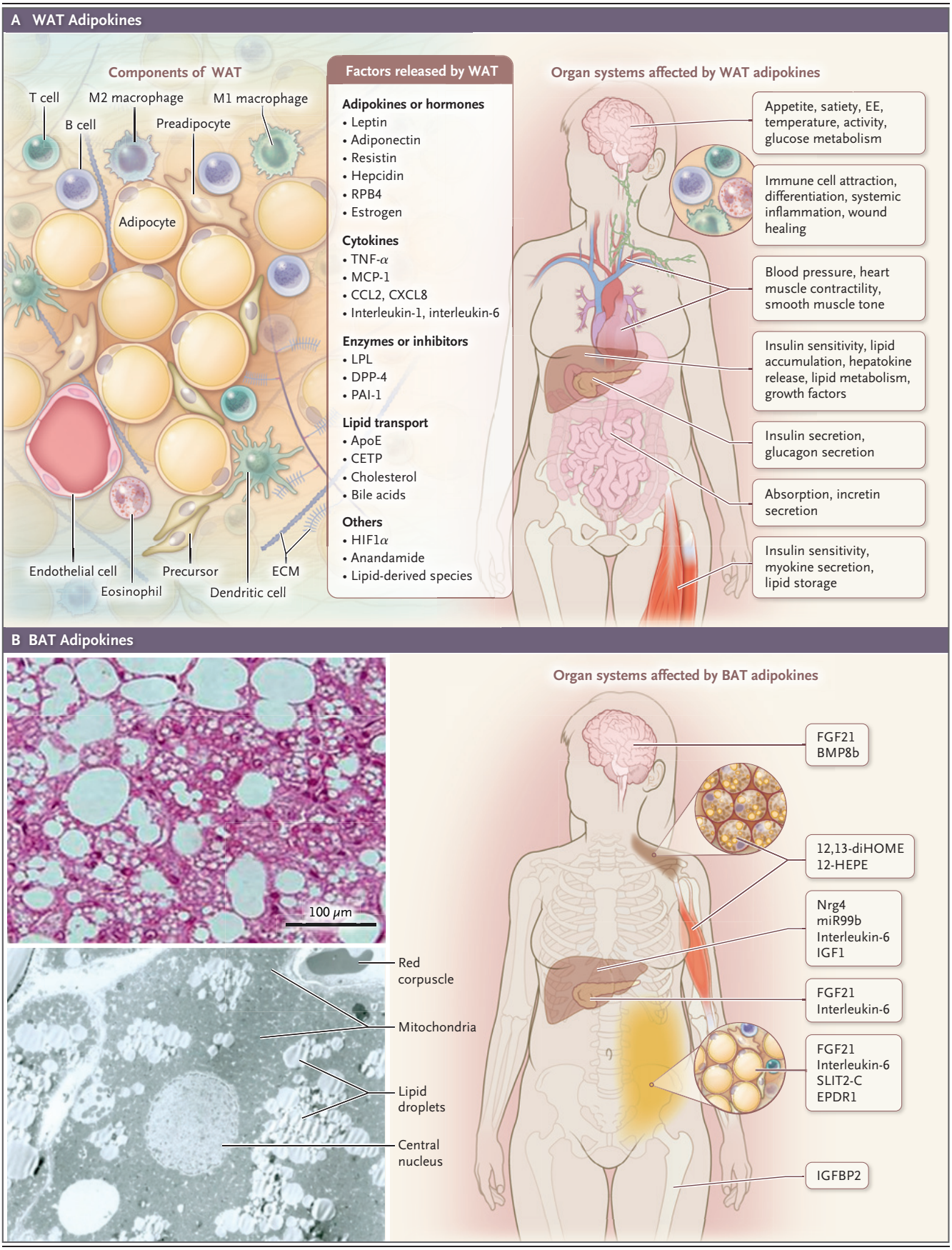


Figure 2 (facing page). White and Brown Adipokines.
Panel A lists the categories of factors released by white adipose tissue (WAT) as mediators of its autocrine, paracrine, and endocrine signaling. At left is a depiction of the various cell types and components of WAT. On the right are the organ systems affected by WAT adipokines. In Panel B, the top image on the left is brown adipose tissue (BAT) collected from a depot near the longus colli muscle in the neck and stained with hematoxylin and eosin.[42] The bottom image, a transmission electron micrograph of a brown adipocyte, shows the densely packed mitochondria responsible for thermogenesis, as wells as lipid droplets, the central nucleus, and a red corpuscle.[43] On the right are the organs affected by the listed BAT adipokines.[39,40] ApoE denotes apolipoprotein E, BMP8b bone morphogenetic protein 8b, CCL2 C-C motif chemokine ligand 2, CETP cholesteryl ester transfer protein, CXCL8 C-X-C motif chemokine ligand 8, 12,13-diHOME 12,13-dihydroxy-9Z-octadecenoic acid, DPP-4 dipeptidyl peptidase 4, ECM extracellular matrix, EE energy expenditure, EPDR1 ependymin-related protein 1, FGF21 fibroblast growth factor 21, 12-HEPE 12-hydroxyeicosapentaenoic acid, HIF1α hypoxia-inducible factor 1α, IGF1 insulin-like growth factor 1, IGFBP2 insulin-like growth factor–binding protein 2, LPL lipoprotein lipase, MCP-1 monocyte chemoattractant protein 1, miR99b microRNA 99b, Nrg4 neuregulin 4, PAI-1 plasminogen activator inhibitor 1, RBP4 retinol-binding protein 4, SLIT2-C SLIT2 C-terminal protein, and TNF-α tumor necrosis factor α.

ing ongoing thermogenesis.[50] BAT also releases exosomal microRNAs that can regulate gene expression in other tissues such as the liver.[51]

WAT and, more recently, BAT have been identified as integral and regulatable components of lipoprotein and bile acid metabolism. Triglyceride-rich lipoproteins, in the form of chylomicrons from a meal, and liver-derived very-low-density lipoprotein deliver their lipid payloads to WAT and BAT. Studies in rodents have shown that prolonged BAT activation leads to changes in liver cholesterol homeostasis, bile acid metabolism, and the composition of the microbiome.[52] More than a decade after the discovery of BAT as a functional tissue in adult humans,[53] there is nascent evidence suggesting that BAT activation may also lower the risk of atherosclerosis and drive the consumption of glucose and lipids by skeletal muscle.[54]

Both WAT and BAT participate in immunomodulation, the suppression and activation of the immune system, and each tissue releases its distinct profile of mediators of the complement system.[41] Obesity leads to WAT-derived proinflammatory cytokines such as TNF-α, interleukin-1β, interleukin-6, and interferon-γ. These compounds activate and recruit macrophages, which can increase from less than 10% to nearly 40% of the total number of cells in adipose tissue.[55] Dendritic cells and B cells join to induce the expansion of CD4 and CD8 T cells. One important consequence of the resulting adipocyte insulin resistance and macrophage activation is increased fatty acid release, which ultimately drives hepatic gluconeogenesis and hyperglycemia.[56] In contrast, BAT is particularly resistant to obesity-induced inflammation,[57] and in rodent models, BAT has been found to express high levels of programmed death ligand 1, which reduce T-cell activation[58] and may improve insulin sensitivity.

OBESITY AS A COMPLICATION OF TOO MUCH WAT

The overweight and obesity pandemics affect more than 70% of the U.S. population[59] and are projected to increase in prevalence over the next 30 years.[60] In parallel, there has been a rise in obesity-related conditions such as type 2 diabetes, precocious puberty, cardiovascular disease, and several cancers.[61] Even more troubling is the observation that the rates of obesity are increasing much faster among children than among adults and that obese children are more likely to become obese adults at high risk for severe health complications (Fig. 3).[62] Adequate responses to the clinical and societal sequelae of these trends require a more accurate understanding of the specific effects of the different WAT and BAT depots. Current assessments across adult and pediatric populations often use BMI exclusively, which, at minimum, requires adjustments for age, sex, and genetic and ethnic backgrounds.[63] BMI cannot provide information about WAT distribution or the predispositions of specific depots for their distinctive pathophysiology or the likelihood of a response to targeted therapies. Going forward, it will be particularly important to conduct large studies of epidemiologic trends that go beyond BMI and incorporate other estimates of the distribution of WAT depots, including waist circumference,[64] in order to better understand the role of WAT distribution in obesity-related metabolic disease.

Although it is correct to attribute the increas-

A

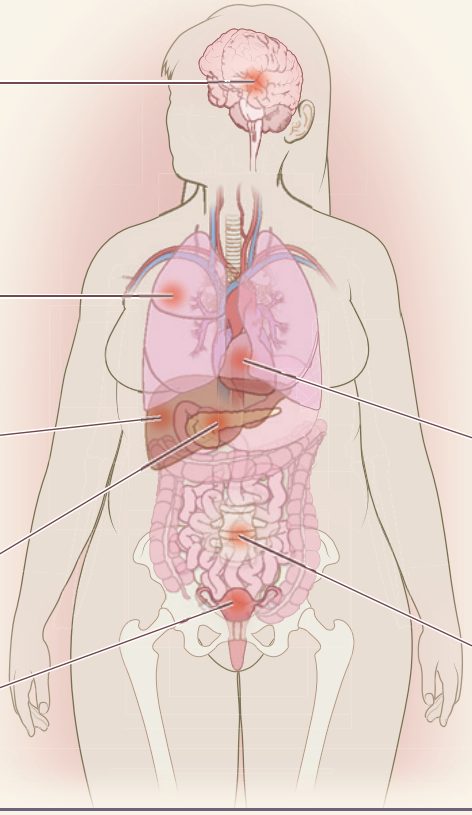
Neuropsychosocial
- Stroke
- Cataracts
- Depression
- Idiopathic intracranial hypertension
- Pseudotumor cerebri

Pulmonary
- Obstructive sleep apnea
- Pulmonary embolism
- Pulmonary hypertension

Gastrointestinal
- NAFLD and NASH
- Gallbladder disease
- Pancreatitis

Endocrine
Type 2 diabetes

Reproductive
- Abnormal menses
- Infertility
- PCOS
- Male hypogonadism



Oncologic
Cancer of the breast, uterus, ovary, esophagus, stomach, colon or rectum, liver, gallbladder, pancreas, kidney, thyroid, and meninges and multiple myeloma

Immunologic
- Chronic inflammation
- Heightened susceptibility to infection (e.g., Covid-19)

Cardiovascular
- Coronary heart disease
- Hypertension
- Dyslipidemia
- Thrombosis
- Phlebitis
- Edema of the legs and feet

Musculoskeletal
- Lower back pain
- Vertebral disc degeneration
- Osteoarthritis
- Gout

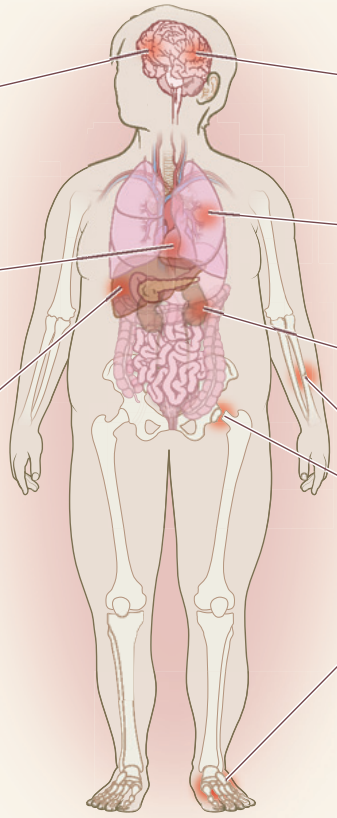
B

Psychosocial
- Depression
- Eating disorders
- Poor self-esteem

Cardiovascular
- Dyslipidemia
- Hypertension
- Coagulopathy
- Chronic inflammation
- Endothelial dysfunction

Gastrointestinal
- Gallstones
- NAFLD and NASH

Endocrine
- Type 2 diabetes
- Precocious puberty
- PCOS
- Male hypogonadism



Neurologic
Pseudotumor cerebri

Pulmonary
- Sleep apnea
- Asthma
- Exercise intolerance

Renal
Glomerulopathy

Musculoskeletal
- Forearm fracture
- Slipped capital femoral epiphysis
- Flat feet

Figure 3 (facing page). Complications of Obesity.
Complications of obesity and diseases associated with it are shown in adults[61] (Panel A) and children[62] (Panel B). Covid-19 denotes coronavirus disease 2019, GERD gastroesophageal reflux disease, NAFLD nonalcoholic fatty liver disease, NASH nonalcoholic steatohepatitis, and PCOS polycystic ovary syndrome.

ing rates of obesity to excessive triglyceride storage in WAT, that picture is too simplistic and impedes the development of treatment strategies. Since the start of the obesity pandemic in the 1970s, the principal contributing causes and their individual influence remain unknown. The roles of portion sizes, specific food classes, particular ingredients, and changes in patterns of activity are being investigated.[65] Concomitantly, it is useful to conceptualize obesity as a disease of the brain that is manifested as an excess of WAT and dysfunctional BAT. Studies have shown the pernicious cycles that accelerate the development of obesity once a person has begun to gain weight.[66] The hypothalamic region of the brain is of increasing interest because it integrates multiple physiological signals from the body, transmits them to different brain regions, and coordinates the regulation of diverse processes, including body temperature and feeding. Studies in rodents have mapped the neuronal pathways that interpret signals from feeding and from the WAT itself regarding its mass and then integrate those signals into homeostatic and hedonic messages, which interpret the availability of energy stores and the emotional meaning of specific foods, respectively.[67] Besides the WAT, obesity also disrupts the ability of the hypothalamus to stimulate BAT energy expenditure.[67] Obesity cannot be viewed simply as a failure of willpower. Instead, it is a complex interplay among hundreds of genes, socioeconomic demands, and personal decision making that ultimately leads to a long-term increase in average caloric intake over energy expenditure.[68]

Connections among obesity, its metabolic complications, and genetic influences have become more established through genomewide association studies. These large-scale global population studies have identified new genetic loci in the central nervous system, indicating a potentially genetic component of aspects of lifestyle, as well as insulin resistance, linking central obesity to metabolic dysregulation and, ultimately, the risk of cardiovascular disease.[69] However, it is critical to appreciate the distinction between the heritability of obesity and the effect of any one gene. Genetic influences on obesity are substantial, up to 70% on the basis of studies involving populations of predominantly European origin,[70,71] but this strong effect should not be misinterpreted to mean that there is a single "fat gene." Currently, only 20% of the entire phenotypic variation in obesity can be explained by the thousands of loci identified so far.[72] Adding further complexity is the effect of epigenetics — heritable yet reversible changes in gene function that do not involve the DNA code itself. Obesity and even dietary components can have profound phenotypic effects.[73] Efforts are now being focused on how the mechanisms by which the genes and the associated physiological pathways affect short- and long-term energy imbalances and the subsequent health complications.

How does excess adipose tissue lead to disease? Like no other cells, white adipocytes are adept at enlarging and can swell from a diameter of 30 to 40 μm to more than 100 μm, an increase in volume by a factor of more than 10. Starting in early adulthood, lean U.S. adults spend the next decades challenging their adipocytes by gaining on average 0.5 kg (1.1 lb) per year, with even higher weight increases among the overweight and obese,[74] putting an enormous demand on the WAT depots to store triglycerides by the fifth and sixth decades of life.[75]

Anatomical location and genetics largely determine the proportional increase in adipocyte size and number and the physiological responses. For example, people whose subcutaneous depots maintain smaller adipocytes have fewer metabolic complications.[31] Furthermore, in people who are genetically predisposed to impaired catecholamine-mediated lipolysis, white adipocytes become very large,[32] a situation exacerbated by a genetic inability to recruit new adipocytes.[76] As obesity progresses, preadipocyte differentiation becomes dysfunctional, leading to reduced insulin signaling, glucose uptake, and adiponectin release by the mature adipocytes.[77,78] Ultimately, hypertrophic WAT growth and expansion restrict the ability of oxygen to diffuse from the capillaries into the adipocytes.[77] This hypoxia constitutes a biologic red alert for the cells, altering

the expression of more than 1000 genes and triggering a series of interconnected responses that ultimately lead to local resistance to both insulin and adrenergic signaling, increased inflammation, and cellular damage. Failure of the adipose tissue to continue expanding leads to overflow and subsequent deposition of triglycerides throughout the body, with ectopic accumulation in the liver and skeletal muscle. The extent of this lipotoxicity is an important determinant of the development of metabolic dysregulation, type 2 diabetes, and cardiovascular disease.[79]

This milieu leads to immune-system dysfunction and is thought to contribute to increased morbidity and mortality from infectious disease, currently highlighted by the worrisome epidemiologic reports about people with obesity and coronavirus disease 2019.[80] Obesity is also associated with an increased risk of many types of cancer, including cancer of the breast, uterus, ovary, esophagus, stomach, colon or rectum, liver, gallbladder, pancreas, kidney, thyroid, and meninges, as well as multiple myeloma,[81] but the precise mechanisms are currently unclear. Three causative agents identified so far are hyperinsulinemia, factors released during chronic inflammation, and increased estrogen production. Given the scope of disorders, the question that arises is whether excess stored triglycerides are ever benign. A metabolically healthy obese phenotype has been postulated, which has been associated with several aspects of adipocyte function, such as the release of specific adipokines.[82] Whether obese persons who are metabolically healthy are nevertheless on an inexorable path toward metabolic disease remains to be determined.[83]

TREATMENTS FOR OVERWEIGHT AND OBESITY

There are three ways to achieve a net negative energy balance: reduce food consumption, reduce nutrient absorption, and increase energy expenditure. All three ultimately converge on the common goal of reducing WAT triglyceride content. Pharmacotherapy aimed at these different pathways has been extensively reviewed.[84] Several treatments currently approved by the Food and Drug Administration for the treatment of obesity directly involve adipose tissues. For example, glucagon-like peptide 1 receptor agonists such as liraglutide cause weight loss by means of appetite inhibition and are even more effective with exercise,[85] yet their beneficial effects may also be mediated by stimulation of WAT lipolysis and BAT thermogenesis.[86] Potential new therapies focusing on adipose tissue include bimagrumab, an inhibitor of the activin type II receptor, which reduces WAT mass while increasing the growth of skeletal muscle.[87] The most effective approach to weight loss that also results in metabolic improvements is bariatric surgery.[88] Although these operations reduce the complications of obesity through multiple mechanisms, much of the effectiveness is due to the profound loss of WAT mass.[89] Current studies are determining the mechanisms by which weight loss is achieved, the long-term adverse effects, and the durability of the various surgical interventions.

There is also the direct approach of removing adipose tissue, but as intimated above, resecting the wrong adipose-tissue depot could worsen the metabolic effect. Noncosmetic liposuction of subcutaneous fat does not lead to long-term weight loss or improved health.[90] Also, it is essential to retain at least a modicum of adipose tissue. The lipodystrophic syndromes associated with human immunodeficiency virus infection and medications used to treat it, as well as more rare genetic syndromes, have shown that too little WAT leads to lipotoxic metabolic dysfunction and leptin-deficient reproductive dysfunction.[91,92] In certain circumstances, it is even beneficial to increase adipose tissue mass. Thiazolidinediones are medications that treat diabetes by activating the nuclear receptor PPAR-γ (peroxisome proliferator–activated receptor γ) and increasing the number of smaller and more insulin-responsive adipocytes that can more safely store triglycerides.[93] By inducing hyperplasia instead of hypertrophy, thiazolidinediones lead to a paradoxical improvement in a patient's metabolic profile while increasing adipocyte mass.

Could long-term BAT activation help treat obesity or related metabolic diseases? In rodents, the answer is unequivocally yes,[94] but in humans, the answer has yet to be determined. As already discussed, humans have proportionally less BAT than smaller mammals, but contemporary humans may have even less BAT than is required to support their physiological and

metabolic needs. BAT mass dramatically decreases with increased ambient temperatures,[95] and aging also appears to induce BAT atrophy,[96] raising the possibility that contemporary humans who create a thermoneutral environment are artificially lowering their BAT mass and its contribution to energy balance and metabolic health. Even the limited BAT present in adults appears to have a substantial clinical effect, because retrospective and prospective studies show an inverse association between BAT activity and BMI.[97] In addition, a recent study showed that persons with BAT had healthier blood glucose, triglyceride, and high-density lipoprotein levels than persons without BAT.[2] Those with BAT had a lower prevalence of cardiometabolic diseases such as type 2 diabetes, dyslipidemia, coronary artery disease, cerebrovascular disease, congestive heart failure, and hypertension.

Clinical trials are necessary to determine the outcomes from long-term BAT activation, given that studies in rodents suggest that activating BAT could lead to compensatory food intake[98] or the opposite, suppression of appetite.[99] Initial prospective clinical studies have shown that long-term treatment with β3-adrenergic receptor agonists increases BAT mass and browning of WAT and is associated with improvements in insulin sensitivity and cardiometabolic risk factors.[100]

CONCLUSIONS

The riskiest approach to human adipose tissue is to dismiss its importance. WAT lies at the heart of the obesity pandemic, and its response to excess calories has an effect on every organ system, with profound effects on morbidity and mortality worldwide. The past decade, and particularly the past 5 years, has seen an explosive growth in our understanding of adipose tissue, with work that recognizes human WAT and BAT as organs that have anatomical, functional, and genetic diversity. Going forward, fat will ideally be appreciated for what it is, a polychromatic tissue, which is as relevant and influential as other organs for sustaining human health.

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REFERENCES

1. Carlsson LMS, Sjöholm K, Jacobson P, et al. Life expectancy after bariatric surgery in the Swedish Obese Subjects study. N Engl J Med 2020;383:1535-43.
2. Becher T, Palanisamy S, Kramer DJ, et al. Brown adipose tissue is associated with cardiometabolic health. Nat Med 2021;27:58-65.
3. Rosen ED, Spiegelman BM. What we talk about when we talk about fat. Cell 2014;156:20-44.
4. Zwick RK, Guerrero-Juarez CF, Horsley V, Plikus MV. Anatomical, physiological, and functional diversity of adipose tissue. Cell Metab 2018;27:68-83.
5. Kahn CR, Wang G, Lee KY. Altered adipose tissue and adipocyte function in the pathogenesis of metabolic syndrome. J Clin Invest 2019;129:3990-4000.
6. Berry DC, Stenesen D, Zeve D, Graff JM. The developmental origins of adipose tissue. Development 2013;140:3939-49.
7. Gallagher D, Heymsfield SB, Heo M, Jebb SA, Murgatroyd PR, Sakamoto Y. Healthy percentage body fat ranges: an approach for developing guidelines based on body mass index. Am J Clin Nutr 2000;72:694-701.
8. Borga M, West J, Bell JD, et al. Advanced body composition assessment: from body mass index to body composition profiling. J Investig Med 2018;66:1-9.
9. Leitner BP, Huang S, Brychta RJ, et al. Mapping of human brown adipose tissue in lean and obese young men. Proc Natl Acad Sci U S A 2017;114:8649-54.
10. Fraum TJ, Crandall JP, Ludwig DR, et al. Repeatability of quantitative brown adipose tissue imaging metrics on positron emission tomography with ^{18}F-fluorodeoxyglucose in humans. Cell Metab 2019;30(1):212-224.e4.
11. Pfannenberg C, Werner MK, Ripkens S, et al. Impact of age on the relationships of brown adipose tissue with sex and adiposity in humans. Diabetes 2010;59:1789-93.
12. Song JD, Alves TC, Befroy DE, et al. Dissociation of muscle insulin resistance from alterations in mitochondrial substrate preference. Cell Metab 2020;32(5):726-735.e5.
13. Hall KD. Predicting metabolic adaptation, body weight change, and energy intake in humans. Am J Physiol Endocrinol Metab 2010;298(3):E449-E466.
14. Atkinson RL, Macdonald IA. Editors' comments on the contributions from Dr Hall and colleagues and Dr Ludwig and colleagues. Int J Obes (Lond) 2019;43:2349.
15. Lenz M, Arts ICW, Peeters RLM, de Kok TM, Ertaylan G. Adipose tissue in health and disease through the lens of its building blocks. Sci Rep 2020;10:10433.
16. Lee JJ, Pedley A, Therkelsen KE, et al. Upper body subcutaneous fat is associated with cardiometabolic risk factors. Am J Med 2017;130(8):958-966.e1.
17. Lee M-J, Wu Y, Fried SK. Adipose tissue heterogeneity: implication of depot differences in adipose tissue for obesity complications. Mol Aspects Med 2013;34:1-11.
18. Jespersen NZ, Feizi A, Andersen ES, et al. Heterogeneity in the perirenal region of humans suggests presence of dormant brown adipose tissue that contains brown fat precursor cells. Mol Metab 2019;24:30-43.
19. Rodríguez A, Becerril S, Hernández-Pardos AW, Frühbeck G. Adipose tissue depot differences in adipokines and effects on skeletal and cardiac muscle. Curr Opin Pharmacol 2020;52:1-8.
20. Kuk JL, Saunders TJ, Davidson LE, Ross R. Age-related changes in total and

regional fat distribution. Ageing Res Rev 2009;8:339-48.
21. Sun Y, Rahbani JF, Jedrychowski MP, et al. Mitochondrial TNAP controls thermogenesis by hydrolysis of phosphocreatine. Nature 2021;593:580-5.
22. Mills EL, Pierce KA, Jedrychowski MP, et al. Accumulation of succinate controls activation of adipose tissue thermogenesis. Nature 2018;560:102-6.
23. Chen KY, Brychta RJ, Abdul Sater Z, et al. Opportunities and challenges in the therapeutic activation of human energy expenditure and thermogenesis to manage obesity. J Biol Chem 2020;295:1926-42.
24. Blondin DP, Nielsen S, Kuipers EN, et al. Human brown adipocyte thermogenesis is driven by β2-AR stimulation. Cell Metab 2020;32(2):287-300.e7.
25. Sun W, Dong H, Balaz M, et al. snRNA-seq reveals a subpopulation of adipocytes that regulates thermogenesis. Nature 2020;587:98-102.
26. Corvera S. Cellular heterogeneity in adipose tissues. Annu Rev Physiol 2021;83:257-78.
27. Bouchard C. Genetics of obesity: what we have learned over decades of research. Obesity (Silver Spring) 2021;29:802-20.
28. Spalding KL, Arner E, Westermark PO, et al. Dynamics of fat cell turnover in humans. Nature 2008;453:783-7.
29. Sender R, Milo R. The distribution of cellular turnover in the human body. Nat Med 2021;27:45-8.
30. Greenhill C. Identification of thermogenic adipocyte lineages. Nat Rev Endocrinol 2021;17:319.
31. Hammarstedt A, Gogg S, Hedjazifar S, Nerstedt A, Smith U. Impaired adipogenesis and dysfunctional adipose tissue in human hypertrophic obesity. Physiol Rev 2018;98:1911-41.
32. Arner P, Andersson DP, Bäckdahl J, Dahlman I, Rydén M. Weight gain and impaired glucose metabolism in women are predicted by inefficient subcutaneous fat cell lipolysis. Cell Metab 2018;28(1):45-54.e3.
33. Cinti S. Adipose organ development and remodeling. Compr Physiol 2018;8:1357-431.
34. Cannon B, de Jong JMA, Fischer AW, Nedergaard J, Petrovic N. Human brown adipose tissue: classical brown rather than brite/beige? Exp Physiol 2020;105:1191-200.
35. Kruglikov IL, Scherer PE. Dermal adipocytes: from irrelevance to metabolic targets? Trends Endocrinol Metab 2016;27:1-10.
36. Horowitz MC, Berry R, Holtrup B, et al. Bone marrow adipocytes. Adipocyte 2017;6:193-204.
37. Trayhurn P, Beattie JH. Physiological role of adipose tissue: white adipose tissue as an endocrine and secretory organ. Proc Nutr Soc 2001;60:329-39.
38. Honka M-J, Latva-Rasku A, Bucci M, et al. Insulin-stimulated glucose uptake in skeletal muscle, adipose tissue and liver: a positron emission tomography study. Eur J Endocrinol 2018;178:523-31.
39. Villarroya J, Cereijo R, Gavaldà-Navarro A, Peyrou M, Giralt M, Villarroya F. New insights into the secretory functions of brown adipose tissue. J Endocrinol 2019;243(2):R19-R27.
40. Scheele C, Wolfrum C. Brown adipose crosstalk in tissue plasticity and human metabolism. Endocr Rev 2020;41:53-65.
41. Deshmukh AS, Peijs L, Beaudry JL, et al. Proteomics-based comparative mapping of the secretomes of human brown and white adipocytes reveals EPDR1 as a novel batokine. Cell Metab 2019;30(5):963-975.e7.
42. Cypess AM, White AP, Vernochet C, et al. Anatomical localization, gene expression profiling and functional characterization of adult human neck brown fat. Nat Med 2013;19:635-9.
43. Cypess AM, Doyle AN, Sass CA, et al. Quantification of human and rodent brown adipose tissue function using 99mTc-methoxyisobutylisonitrile SPECT/CT and 18F-FDG PET/CT. J Nucl Med 2013;54:1896-901.
44. Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004;89:2548-56.
45. Boutari C, Pappas PD, Mintziori G, et al. The effect of underweight on female and male reproduction. Metabolism 2020;107:154229.
46. Kansra AR, Lakkunarajah S, Jay MS. Childhood and adolescent obesity: a review. Front Pediatr 2021;8:581461.
47. Ahima RS, Lazar MA. Adipokines and the peripheral and neural control of energy balance. Mol Endocrinol 2008;22:1023-31.
48. 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.
49. Iwabu M, Okada-Iwabu M, Yamauchi T, Kadowaki T. Adiponectin/AdipoR research and its implications for lifestyle-related diseases. Front Cardiovasc Med 2019;6:116.
50. Leiria LO, Tseng Y-H. Lipidomics of brown and white adipose tissue: implications for energy metabolism. Biochim Biophys Acta Mol Cell Biol Lipids 2020;1865:158788.
51. Thomou T, Mori MA, Dreyfuss JM, et al. Adipose-derived circulating miRNAs regulate gene expression in other tissues. Nature 2017;542:450-5.
52. Worthmann A, John C, Rühlemann MC, et al. Cold-induced conversion of cholesterol to bile acids in mice shapes the gut microbiome and promotes adaptive thermogenesis. Nat Med 2017;23:839-49.
53. Cohen P, Kajimura S. The cellular and functional complexity of thermogenic fat. Nat Rev Mol Cell Biol 2021;22:393-409.
54. Worthmann A, Schlein C, Berbée JFP, Rensen PCN, Heeren J, Bartelt A. Effects of pharmacological thermogenic adipocyte activation on metabolism and atherosclerotic plaque regression. Nutrients 2019;11:463.
55. 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.
56. Perry RJ, Camporez JG, Kursawe R, et al. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. Cell 2015;160:745-58.
57. Fitzgibbons TP, Kogan S, Aouadi M, Hendricks GM, Straubhaar J, Czech MP. Similarity of mouse perivascular and brown adipose tissues and their resistance to diet-induced inflammation. Am J Physiol Heart Circ Physiol 2011;301(4):H1425-H1437.
58. Ingram JR, Dougan M, Rashidian M, et al. PD-L1 is an activation-independent marker of brown adipocytes. Nat Commun 2017;8:647.
59. Fryar CD, Carroll MD, Afful J. Prevalence of overweight, obesity, and severe obesity among adults aged 20 and over: United States, 1960–1962 through 2017–2018. National Center for Health Statistics Health E-Stats, December 2020 (https://www.cdc.gov/nchs/data/hestat/obesity-adult-17-18/overweight-obesity-adults-H.pdf).
60. Wang Y, Beydoun MA, Liang L, Caballero B, Kumanyika SK. Will all Americans become overweight or obese? Estimating the progression and cost of the US obesity epidemic. Obesity (Silver Spring) 2008;16:2323-30.
61. Kastanias P, Mackenzie K, Robinson S, Wang W. Medical complications resulting from severe obesity. In: Sockalingam S, Hawa R, eds. Psychiatric care in severe obesity: an interdisciplinary guide to integrated care. Cham, Switzerland: Springer International Publishing, 2017:49-73.
62. Klish WJ, Skelton JA. Overview of the health consequences of obesity in children and adolescents. Waltham, MA: UpToDate, 2021 (https://www.uptodate.com/contents/overview-of-the-health-consequences-of-obesity-in-children-and-adolescents).
63. Heymsfield SB, Peterson CM, Thomas DM, Heo M, Schuna JM Jr. Why are there race/ethnic differences in adult body mass index–adiposity relationships? A quantitative critical review. Obes Rev 2016;17:262-75.
64. Woolcott OO, Bergman RN. Relative fat mass (RFM) as a new estimator of whole-body fat percentage — a cross-sectional study in American adult individuals. Sci Rep 2018;8:10980.
65. Young LR, Nestle M. The contribution

of expanding portion sizes to the US obesity epidemic. Am J Public Health 2002;92:246-9.
66. Shefer G, Marcus Y, Stern N. Is obesity a brain disease? Neurosci Biobehav Rev 2013;37:2489-503.
67. Henningsen JB, Scheele C. Brown adipose tissue: a metabolic regulator in a hypothalamic cross talk? Annu Rev Physiol 2021;83:279-301.
68. Hall KD, Hammond RA, Rahmandad H. Dynamic interplay among homeostatic, hedonic, and cognitive feedback circuits regulating body weight. Am J Public Health 2014;104:1169-75.
69. Shungin D, Winkler TW, Croteau-Chonka DC, et al. New genetic loci link adipose and insulin biology to body fat distribution. Nature 2015;518:187-96.
70. Stunkard AJ, Harris JR, Pedersen NL, McClearn GE. The body-mass index of twins who have been reared apart. N Engl J Med 1990;322:1483-7.
71. Walley AJ, Asher JE, Froguel P. The genetic contribution to non-syndromic human obesity. Nat Rev Genet 2009;10:431-42.
72. Fu J, Hofker M, Wijmenga C. Apple or pear: size and shape matter. Cell Metab 2015;21:507-8.
73. Dhasarathy A, Roemmich JN, Claycombe KJ. Influence of maternal obesity, diet and exercise on epigenetic regulation of adipocytes. Mol Aspects Med 2017;54:37-49.
74. Mozaffarian D, Hao T, Rimm EB, Willett WC, Hu FB. Changes in diet and lifestyle and long-term weight gain in women and men. N Engl J Med 2011;364:2392-404.
75. Richard AJ, White U, Elks CM, Stephens JM. Adipose tissue: physiology to metabolic dysfunction. In: Feingold KR, Anawalt B, Boyce A, et al., eds. Endotext. South Dartmouth, MA: MDText, 2000 (https://www.ncbi.nlm.nih.gov/books/NBK555602/).
76. Dubois SG, Heilbronn LK, Smith SR, Albu JB, Kelley DE, Ravussin E. Decreased expression of adipogenic genes in obese subjects with type 2 diabetes. Obesity (Silver Spring) 2006;14:1543-52.
77. Trayhurn P. Hypoxia and adipose tissue function and dysfunction in obesity. Physiol Rev 2013;93:1-21.
78. Gustafson B, Gogg S, Hedjazifar S, Jenndahl L, Hammarstedt A, Smith U. Inflammation and impaired adipogenesis in hypertrophic obesity in man. Am J Physiol Endocrinol Metab 2009;297(5):E999-E1003.
79. Shulman GI. Ectopic fat in insulin resistance, dyslipidemia, and cardiometabolic disease. N Engl J Med 2014;371:1131-41.
80. Lockhart SM, O'Rahilly S. When two pandemics meet: why is obesity associated with increased COVID-19 mortality? Med (N Y) 2020;1:33-42.
81. Lauby-Secretan B, Scoccianti C, Loomis D, Grosse Y, Bianchini F, Straif K. Body fatness and cancer — viewpoint of the IARC working group. N Engl J Med 2016;375:794-8.
82. Ebert T, Gebhardt C, Scholz M, et al. Relationship between 12 adipocytokines and distinct components of the metabolic syndrome. J Clin Endocrinol Metab 2018;103:1015-23.
83. Blüher M. Metabolically healthy obesity. Endocr Rev 2020;41:405-20.
84. Mehta M, Istfan NW, Apovian CM. Obesity: overview of weight management. Endocr Pract 2021;27:626-35.
85. Lundgren JR, Janus C, Jensen SBK, et al. Healthy weight loss maintenance with exercise, liraglutide, or both combined. N Engl J Med 2021;384:1719-30.
86. Beiroa D, Imbernon M, Gallego R, et al. GLP-1 agonism stimulates brown adipose tissue thermogenesis and browning through hypothalamic AMPK. Diabetes 2014;63:3346-58.
87. Heymsfield SB, Coleman LA, Miller R, et al. Effect of bimagrumab vs placebo on body fat mass among adults with type 2 diabetes and obesity: a phase 2 randomized clinical trial. JAMA Netw Open 2021;4(1):e2033457.
88. Heymsfield SB, Wadden TA. Mechanisms, pathophysiology, and management of obesity. N Engl J Med 2017;376:254-66.
89. Yoshino M, Kayser BD, Yoshino J, et al. Effects of diet versus gastric bypass on metabolic function in diabetes. N Engl J Med 2020;383:721-32.
90. Klein S, Fontana L, Young VL, 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.
91. Torriani M, Srinivasa S, Fitch KV, et al. Dysfunctional subcutaneous fat with reduced dicer and brown adipose tissue gene expression in HIV-infected patients. J Clin Endocrinol Metab 2016;101:1225-34.
92. Brown WV, Garg A, Gorden P, Shamburek R. JCL roundtable: diagnosis and clinical management of lipodystrophy. J Clin Lipidol 2016;10:728-36.
93. Mayerson AB, Hundal RS, Dufour S, et al. The effects of rosiglitazone on insulin sensitivity, lipolysis, and hepatic and skeletal muscle triglyceride content in patients with type 2 diabetes. Diabetes 2002;51:797-802.
94. Cannon B, Nedergaard J. Brown adipose tissue: function and physiological significance. Physiol Rev 2004;84:277-359.
95. Lee P, Smith S, Linderman J, et al. Temperature-acclimated brown adipose tissue modulates insulin sensitivity in humans. Diabetes 2014;63:3686-98.
96. Cypess AM, Lehman S, Williams G, et al. Identification and importance of brown adipose tissue in adult humans. N Engl J Med 2009;360:1509-17.
97. Betz MJ, Enerbäck S. Human brown adipose tissue: what we have learned so far. Diabetes 2015;64:2352-60.
98. Gavrilova O, Marcus-Samuels B, Reitman ML. Lack of responses to a beta3-adrenergic agonist in lipoatrophic A-ZIP/F-1 mice. Diabetes 2000;49:1910-6.
99. Richard JE, López-Ferreras L, Chanclón B, et al. CNS β_3-adrenergic receptor activation regulates feeding behavior, white fat browning, and body weight. Am J Physiol Endocrinol Metab 2017;313(3):E344-E358.
100. O'Mara AE, Johnson JW, Linderman JD, et al. Chronic mirabegron treatment increases human brown fat, HDL cholesterol, and insulin sensitivity. J Clin Invest 2020;130:2209-19.