Journal of the American College of Cardiology
© 2011 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 57, No. 25, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.02.038

STATE-OF-THE-ART PAPER

Adiposopathy

Is "Sick Fat" a Cardiovascular Disease?

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Being overweight or obese is a worldwide epidemic. Adiposity can cause fat mass–related cardiovascular disease (CVD). Adiposity may also cause adipocyte and adipose tissue anatomic and functional abnormalities, termed adiposopathy (adipose-opathy) or "sick fat," that result in endocrine and immune derangements. Adiposopathy may directly contribute to CVD through pericardiac and perivascular effects on the myocardium and blood vessels. Adiposopathy may also indirectly contribute to CVD through promoting or worsening major CVD risk factors such as type 2 diabetes mellitus, high blood pressure, and dyslipidemia. Despite CVD being the most common cause of mortality among overweight individuals, the pathophysiologic relationship between adiposity and CVD is often thought mysterious, as evidenced by "obesity paradoxes." Underlying this uncertainty are suggestions that excessive body fat does not always increase the risk of CVD and, in some cases, may actually decrease such risks. These paradoxical findings are made less paradoxical when the pathogenic potential of excessive body fat is assessed based on adipose tissue dysfunction rather than simply on increased fat mass alone. This introductory review 1) provides a brief historical perspective of the pathogenic potential of adipose tissue; 2) describes the relationships between adipose tissue (histology, embryology, and adipogenesis) and cardiovascular medicine; 3) outlines the anatomic, functional, endocrine, and immune manifestations of adiposopathy; and 4) describes the importance of cross talk and/or interactions of adipose tissue with other body tissues. Finally, this review describes how "sick fat" helps account for various clinical obesity/cardiovascular paradoxes, supporting adiposopathy as a cardiovascular disease. (J Am Coll Cardiol 2011;57:2461–73)

Adiposity is excessive adipose tissue. Those with adiposity are characterized as being overweight or obese. Obesity is described as an independent risk factor for cardiovascular disease (CVD) (1). Adiposity is pathological to the cardiovascular system through excessive fat-mass mechanisms and through adipocyte and adipose tissue dysfunction (2) (Table 1, Fig. 1) Adiposopathy (or "sick fat") is defined as pathologic adipose tissue anatomic/functional disturbances promoted by positive caloric balance in genetically and environmentally susceptible individuals that result in adverse endocrine and immune responses that may directly promote CVD, and may cause or worsen metabolic disease. Because many of these metabolic diseases are major CVD risk factors (e.g., type 2 diabetes mellitus [T2DM], high blood pressure, and dyslipidemia), adiposopathy also indirectly increases CVD risk (3–6) (Table 2, Fig. 1) This review examines the relationship between pathogenic adipose tissue, CVD, and CVD risk factors.

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Manuscript received December 28, 2010; revised manuscript received February 16, 2011, accepted February 22, 2011.

Adiposopathy: A Historical Perspective

Despite the known relationship between adiposity and metabolic disease (5), perceptions have lagged for decades in acknowledging the pathologic potential of adipose tissue. As early as the 1940s, reports described visceral adiposity as increasing the risk of metabolic disease and CVD in men (7). Reports from subsequent decades also supported the pathogenic potential of adipose tissue (8,9), and identified excessive adipocyte hypertrophy as promoting metabolic disease (10,11). However, as late as the 1980s, the relationship between adiposity and metabolic disease remained elusive, as evidenced by the haunting term *syndrome X*,

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Abbreviations and Acronyms

BMI = body mass index

CVD = cardiovascular disease

ECM = extracellular matrix

ER = endoplasmic reticulum

PPAR = peroxisome proliferator-activated receptor

SAT = subcutaneous adipose tissue

T2DM = type 2 diabetes mellitus

VAT = visceral adipose tissue

which was not only cryptic in its wording, but also confusing because it represented only 1 of about 20 terms describing a similar relationship (3,12). Ultimately, the term *metabolic syndrome* was generally agreed upon to describe a common clustering of CVD risk factors that included increased waist circumference as a diagnostic criterion. Even then, different international scientific organizations had different diagnostic criteria for the metabolic syndrome (13–15). Furthermore, in 2005, the American Diabetes Association and the European Association for the Study of Diabetes issued a joint statement questioning the clinical utility of the term metabolic syndrome (16). Among reasons for the skepticism of this term were 1) metabolic syndrome did not reflect a unified, pathophysiologic process leading to clustering of metabolic disorders; 2) the diagnostic criteria was predominantly based on U.S. and European data, which did not necessarily apply to other populations (e.g., Asians) (3); 3) and the diagnosis of the metabolic syndrome did not appear to be a better predictor of future metabolic disease than the assessment of its individual components (17).

In the early to mid-2000s, concurrent with debates involving metabolic syndrome (18,19), was the undercurrent of mounting evidence supporting ("confirming") the metabolic components of the metabolic syndrome as being due to an underlying, unified pathophysiologic process (20). Decades of research supported adipose tissue pathology as relevant to a "common soil" hypothesis (21). These findings were consistent with the National Education Program, Adult Treatment Panel III guidelines in which an increased waist circumference (a surrogate for subcutaneous abdominal and visceral adipose tissue) was the only organ-associated, anatomic diagnostic criteria for metabolic syndrome (with other metabolic syndrome components being elevated glucose levels, high blood pressure, hypertriglyceridemia, and reduced high-density lipoprotein cholesterol levels) (22). Furthermore, although the National Education Program, Adult Treatment Panel III deemed ≥3 of any of these 5 components as diagnostic for metabolic syndrome, the International Diabetes Federation further validated the importance of pathogenic adipose tissue by designating increased waist circumference/central obesity as the only 1 of 5 criteria required for the diagnosis of metabolic syndrome (23), which then must be accompanied by other metabolic abnormalities.

It was through decades of adipose tissue scientific research and the acknowledgment of the importance of central adiposity by major scientific organizations that the term *adiposopathy* arose (3). Cardiomyopathy describes the pathologic enlargement of heart cells and the heart organ, which results in anatomic/functional abnormalities leading to adverse clinical consequences. Similarly, adiposopathy describes the pathogenic enlargement of fat cells and fat tissue, which results in anatomic/functional abnormalities leading to adverse clinical consequences, including the most common metabolic diseases encountered in clinical practice (e.g., T2DM, high blood pressure, dyslipidemia) (24). Given that adipose tissue has no less potential for disease than any other body organ, the term adiposopathy is intended to identify adipose tissue organ pathology similar to the "opathies" of multiple other body organs (6). From a clinician standpoint, recognizing the pathogenic potential of adipose tissue may afford a clearer rationale toward recommending weight reduction to overweight patients. In other words, discussing how fat weight gain causes fat to become "sick" and how losing body weight causes fat to become more "healthy" might prove to be more productive than discussing the individual diagnostic components defining the metabolic syndrome (6).

Adipose Tissue Histology, Anatomy, Embryology, and Adipogenesis

As with other body organs, adipose tissue anatomy and functionality are interrelated. The reported histological composition of adipose tissue is dependent on 1) individual characteristics, such as age, race, sex, genetics, environment, caloric balance, ingested food content, and physical activity; 2) the origin or location of the adipose tissue being analyzed;

Table 1 Examples of Adiposity and Adiposopathy Disorders Related to Cardiovascular Disease

Adiposity-related*
Sleep apnea
Thromboembolic events
Increased blood volume
Increased cardiac output
Atrial enlargement
Ventricular dilation
Electrocardiogram abnormalities: increased heart rate, increased PR interval, increased QRS interval, decreased QRS voltage (although sometimes increased), increased QTc interval, abnormal signal-averaged electrocardiogram late potentials, ST–T-wave abnormalities, left-axis deviation, criteria for left ventricular hypertrophy, flattening of the T waves (inferolateral leads), left atrial abnormalities, and false positive criteria for inferior myocardial infarction
Adiposopathy-related*
Type 2 diabetes mellitus
High blood pressure
Dyslipidemia
Metabolic syndrome
Atherosclerosis
Cardiomyopathy ("fatty heart")

*In some cases, the listed disorders may have both adiposity and adiposopathy-related components.

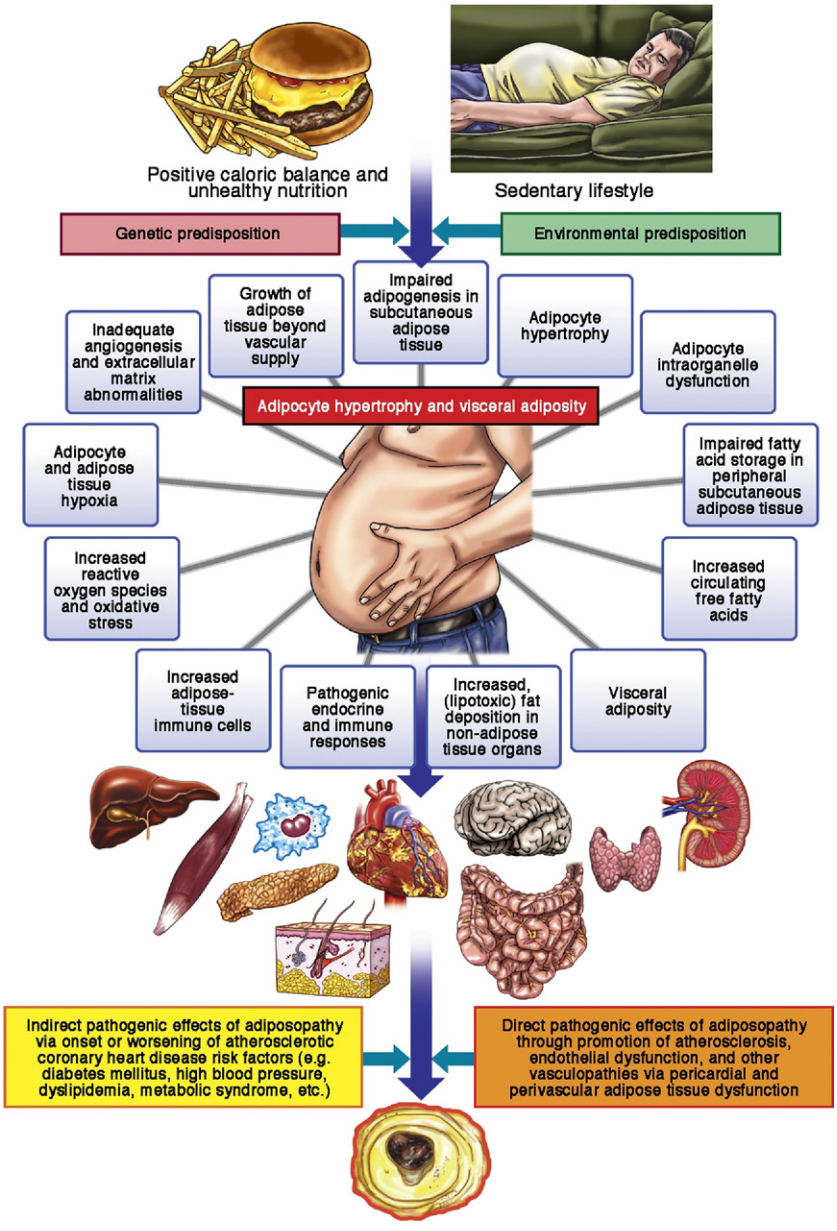

Figure 1 **Adiposopathy: Simplified Relationship Between Pathogenic Adipose Tissue and Cardiovascular Disease**

Adiposopathy is promoted by unhealthy nutrition and a sedentary lifestyle in genetically and environmentally predisposed individuals. With impaired adipogenesis of peripheral, subcutaneous adipose tissue during positive caloric balance, existing fat cells may hypertrophy, circulating free fatty acids may increase, and lipids may be deposited in nonadipose tissue organs (e.g., liver, muscle, possibly pancreas) resulting in lipotoxicity. Adiposopathic endocrine and immune responses may be directly pathogenic to the cardiovascular system or otherwise interact with other body systems. If not mitigated by these other body organs, adiposopathy may indirectly cause or promote major atherosclerotic risk factors (type 2 diabetes mellitus, high blood pressure, or dyslipidemia). Figure illustration by Craig Skaggs.

and 3) the techniques by which analyses are performed (e.g., aspiration or excisional biopsy) (25).

Adipocytes typically constitute the majority of adipose tissue cellular content. Fat-containing adipocytes constitute, by far, most of the adipose tissue volume. Adipocytes are surrounded by fibrous connective tissue, collagen, nerves, and blood vessels (1). Adipose tissue's supporting framework contains "stromal vascular fraction" cells, which include mesenchymal cells, fibroblasts, preadipocytes, endothelial precursor cells, smooth muscle cells, blood cells, and immune cells.

Adipose tissue–associated mesenchymal cells are especially applicable to cardiovascular medicine because cardiovascular and adipose tissue cells share a common lineage. After fertilization of the ovum and mitotic divisions of the zygote, the subsequent pluripotent stem cells give rise to

Table 2 Adiposopathy ("Sick Fat"): Summary of Causality and Examples of Anatomic, Pathophysiological, and Clinical Manifestations*

Causes of adiposopathy
Positive caloric balance
Sedentary lifestyle
Genetic predisposition
Environmental causes
Anatomic manifestations of adiposopathy
Adipocyte hypertrophy
Visceral, pericardial, perivascular, and other periorgan adiposity
Growth of adipose tissue beyond its vascular supply
Increased number of adipose tissue immune cells
"Ectopic fat deposition" in other body organs
Pathophysiological manifestations of adiposopathy
Impaired adipogenesis
Pathological adipocyte organelle dysfunction
Increased circulating free fatty acids
Pathogenic adipose tissue endocrine responses (e.g., increased leptin, increased tumor necrosis factor-alpha, decreased adiponectin, and increased mineralocorticoids)
Pathogenic adipose tissue immune responses (e.g., increased proinflammatory responses through increased tumor necrosis factor-alpha and decreased anti-inflammatory responses through decreased adiponectin)
Pathogenic interactions or pathogenic cross talk with other body organs (e.g., liver, muscle, and central nervous system)
Clinical manifestations of adiposopathy
Hyperglycemia
High blood pressure
Dyslipidemia
Metabolic syndrome
Atherosclerosis
Fatty liver
Hyperandrogenemia in women
Hypoandrogenemia in men
Cancer

*Adiposity can result in both fat-mass pathology and fat dysfunctional abnormalities resulting in adiposopathy.

endoderm, ectoderm, and mesoderm (Fig. 2). The mesoderm may differentiate into hematopoietic tissue, kidney, and sex organs, as well as mesenchymal stem cells (Fig. 2). Mesenchymal stem cells may differentiate into skeletal myoblasts, osteoblasts, chondroblasts, tenoblasts, marrow stromal cells, neuron-like cells, and importantly, into cardiomyocytes, angiocytes, and adipocytes (26). Thus, adipose tissue is a rich, nonembryonic source of mesenchymal cells (27) whose relative ease in accessibility and capacity for differentiating into heart and blood vessel cells have medical applications to CVD regenerative medicine, tissue engineering, and cell replacement therapies and represents a potential therapeutic modality to repair post-ischemic or infarcted heart tissue (28).

Beyond cardiovascular and adipose cells having common stem cell origins, once mesenchymal stem cells are committed to adipocyte formation, adipogenesis itself has relevance to CVD. Previously, adipogenesis was thought to cease early in life, resulting in a fixed number of adipocytes that predestined individuals to be lean or obese. However, fat-cell turnover is now known to be a dynamic process by which mesenchymal stem cells undergo lineage commitment, pre-adipocyte proliferation, growth arrest, and terminal differentiation into mature adipocytes. The number of adipocytes is therefore dependent on the balance between adipogenesis and apoptosis (29,30), with some suggesting that approximately 10% of fat cells are renewed annually at all adult ages and at all levels of body mass index (BMI) (31).

This has clinical implications because during positive caloric balance, adipocytes normally undergo initial hypertrophy, which elicits cellular signaling for the recruitment, proliferation, and differentiation of new fat cells. If adipogenesis proceeds unencumbered in peripheral subcutaneous adipose tissue, then adiposity may not cause demonstrable adipose tissue dysfunction or adverse metabolic consequences. Conversely, if adipogenesis is impaired, then the lack of adipocytes to adequately proliferate (or differentiate) may be pathophysiologically analogous to a relative lack of adipocytes, sometimes described as representing an acquired lipodystrophy (32). The lack of excess energy storage in new fat cells due to inadequate adipogenesis may cause existing fat cells to undergo excessive hypertrophy, causing adipocyte dysfunction and pathogenic adipocyte and adipose tissue endocrine and immune responses (2) (Tables 3 and 4).

The concept of adipocyte hypertrophy during positive caloric balance representing a failure of adipocytes to adequately proliferate (32) is supported by findings that T2DM is associated with a decrease in adipogenic gene expression (34) and that T2DM patients have larger adipocyte size but decreased adipocyte cellularity compared with obese patients without T2DM (35). In short, if during positive caloric balance, any stage of the adipogenic processes is impaired (recruitment, proliferation [36] or differentiation [35,37,38]), then this may lead to pathologic adipose tissue endocrine and immune responses that contribute to metabolic disease, particularly in individuals who are genetically or environmentally predisposed (2) (Fig. 1).

Fat Depots

The clinical importance of adiposity is not only how fat is stored (i.e., adipocyte proliferation vs. adipocyte hypertrophy), but also where fat is stored. Visceral adipose tissue (VAT) may be more metabolically active than subcutaneous adipose tissue (SAT), and these depots inherently differ in processes involving lipolysis/lipogenesis, expression of adipocyte receptors, and differ in the secretion of adipokines/cytokines, enzymes, hormones, immune molecules, proteins, and other factors (2). Derangements in adipose tissue endocrine and immune processes contribute to metabolic disease (4).

Fat depots other than VAT have pathogenic potential (39,40). Pericardial, subcutaneous abdominal, perimuscular, perivascular, orbital, and paraosseal fat depots also have lipolytic and inflammatory activities (2). Pericardial and perivascu-

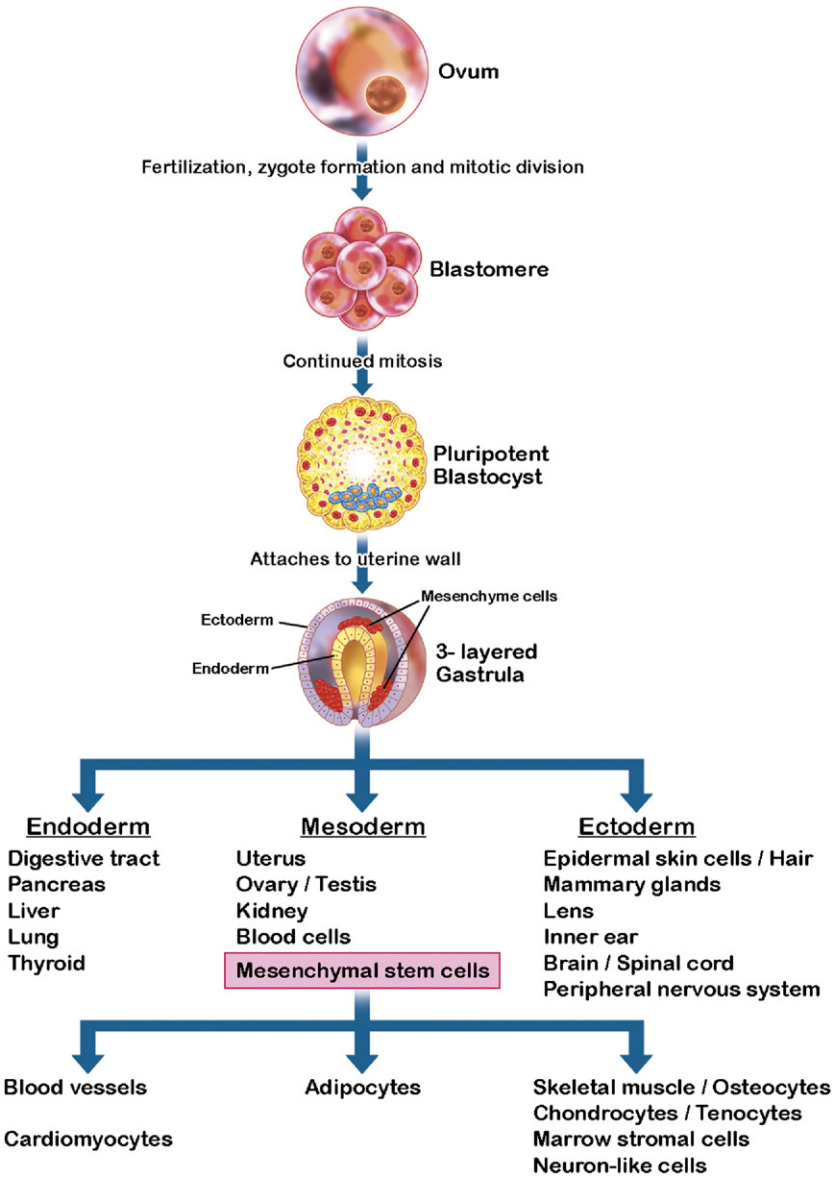

Figure 2 **Simplified Diagram of the Common Embryonic Origin of Heart, Blood Vessels, and Adipose Tissue**

Through the formation of mesenchymal stem cells, cardiomyocytes, angiocytes, and adipocytes share a common genetic lineage. Figure illustration by Craig Skaggs.

lar adiposopathy may have direct pathogenic effects on the myocardium, coronary arteries, and peripheral vessels via dysregulated local secretion of vasoactive and inflammatory factors that may contribute to atheroma instability and other cardiovascular pathophysiology (41–45). Pericardial adiposity is strongly associated with coronary atherosclerosis in African Americans with T2DM, which may contribute to ethnic disparities in atherosclerosis susceptibility (46). Finally, although often assumed that atherosclerosis is exclusively an intraluminal, subendothelial, lipid-mediated process, pathogenic pericardial and perivascular adipose tissue may directly contribute to atherosclerosis through an "outside to inside" inflammatory atherogenic model (41–43), which is again supported by the strong association between pericardial adipose tissue and coronary artery calcification (47).

Extracellular Matrix Remodeling, Angiogenesis, and Hypoxia

In addition to how fat is stored and where fat is stored, other determinants of the pathogenic potential of expanding adipose tissue include the interdependent physiologic processes of angiogenesis and extracellular matrix (ECM) remodeling (2). If an increase in fat storage results in excessive adipocyte enlargement, then adipocyte hypertrophy may contribute to intracellular hypoxia (48,49). Addi-

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Table 3 Adipose Tissue as an Endocrine Organ: Adipocytes and Adipose Tissue Produce Factors Actively Involved in Metabolic Processes Important for Human Health*

Angiogenesis
Adipogenesis
Extracellular matrix dissolution and reformation
Lipogenesis
Growth factor production
Glucose metabolism
Production of factors associated with the renin-angiotensin system
Lipid metabolism
Enzyme production
Hormone production
Steroid metabolism
Immune response
Hemostasis
Element binding
Adipose tissue has receptors for traditional peptides and glycoprotein hormones, receptors for nuclear hormones, other nuclear receptors, receptors for cytokines or adipokines with cytokine-like activity, receptors for growth factors, catecholamine receptors, and other receptors.

Data from Bays et al. (2) and Bays et al. (33). *Disruption of adipose tissue endocrine function may contribute to metabolic disease.

tionally, when fat accumulation outpaces angiogenesis, then a relative lack of blood flow may result in both cellular and adipose tissue hypoxia (49,50). As with other body tissues (e.g., heart), cellular and tissue adipose hypoxia contributes to cellular and organ dysfunction (51), contributes to pro-inflammatory responses, and all may contribute to the onset or worsening of metabolic disease (52). For example, if periadipose ECM remodeling is impaired due to relative hypoxia or other adipocyte dysfunction, then further fat storage may be physically limited, resulting in increased circulating free fatty acids and lipotoxicity. Furthermore, hypoxia-driven inflammation may promote ECM instability (53), and excessive synthesis of ECM components may impose long-term interference with cell–cell contact and adipogenic signaling mechanisms, and thus persistent adverse cellular responses even after weight loss (54).

Free Fatty Acids and Lipotoxicity

If during positive caloric balance, adipocytes are unable to store excess energy (mostly in the form of triglycerides), then circulating free fatty acids are increased, causing pathologic disruption of nonadipose tissue organs, such as the liver, muscle, pancreas, and blood vessels. Potential adverse metabolic consequences of lipotoxicity (55) include abnormalities of glucose and lipid metabolism (5,56), and high blood pressure (57).

Although VAT is most recognized as a contributor to metabolic disease, the majority of circulating free fatty acids actually originates from SAT, mainly because SAT is the largest fat depot, constituting ~80% or more of total body fat. Even within large vessel drainage of VAT (which sometimes constitutes ~20% of body fat), the majority of free fatty acids in the portal system may originate within SAT (38,58), which may contribute to lipotoxic effects on the liver, with adverse clinical consequences such as hyperglycemia and dyslipidemia (4). So while VAT is generally considered among the most pathogenic fat depots (2,59,60), if SAT fat storage is limited or impaired during positive caloric balance and if SAT net free fatty acid release is increased into the circulation, then this SAT dysfunction may adversely affect nonhepatic organs (59,60), resulting in lipotoxicity to muscle (causing insulin resistance) and the pancreas (possibly reducing insulin secretion) (2,61,62).

Adipose Tissue as an Active Endocrine and Immune Organ

Excessive adipocyte hypertrophy disrupts the normal physiological function of fat-cell organelles (causing adipocytes to become "sick"), as evidenced by increased markers of intracellular endoplasmic reticulum (ER) stress and mitochondrial dysfunction (49,63,64). The ER is a network of interconnected tubules, vesicles, and cisternae that, among other functions, produce protein and lipids and transport proteins and carbohydrates necessary for normal cellular function. Increased markers of adipocyte ER stress are associated with inflammation, cellular dysfunction, and metabolic disease (65). Mitochondria are membrane-enclosed organelles that contain enzymes responsible for

Table 4 Adipose Tissue as an Immune Organ: Adipocytes and Adipose Tissue Produce Factors Actively Involved in Immunological Processes Important for Human Health*

Pro-inflammatory adipose tissue factors
Factors with cytokine activity include adipsin, IL-1B, IL-6, IL-8, IL-17D, IL-18, leptin, MCSF-1, MCP-1, MMIF, resistin, tumor necrosis factor-alpha, RANTES, VASPIN
Acute phase response proteins include AGP, ceruloplasmin, C-reactive protein, haptoglobin, IL-1RA, lipocalins, metallothionein, pentraxin-3, PAI-1, and serum amyloid A
Proteins of the alternative complement system include adipsin, ASP, complement C3 and B
Chemotactic/chemoattractants for immune cells include eotaxin, interferon inducible protein, MCSF-1, MCP-1, MMIF, RANTES, resistin, stromal-derived factor 1, VAP-1, and VCAM-1
Eicosanoids/prostaglandins such as prostaglandin E_2
Anti-inflammatory adipose tissue factors
Adiponectin
Annexin-1
IL-6 and -10
Transforming growth factor-beta
Bone morphogenic factor
Nitric oxide
IL-1 receptor antagonist

*Adipose inflammatory factors are produced by adipocytes and adipose tissue-associated macrophages. An increase in adipose tissue inflammatory response and a decrease in anti-inflammatory response may contribute to metabolic disease.

AGP = alpha-1 acid glycoprotein; ASP = acylation-stimulating protein; IL = interleukin; MCP = monocyte chemoattractant protein; MCSF = macrophage colony-stimulating factor; MMIF = macrophage migration inhibitory factor; PAI = plasminogen activator inhibitor; RANTES = regulated on activation, normal T-cell expressed and secreted; VAP = vascular adhesion protein; VASPIN = visceral adipose tissue–derived serpin; VCAM = vascular cell adhesion molecule.

transforming nutrients into cellular energy through the production of adenosine triphosphate. Increased markers of adipocyte mitochondrial stress are associated with obesity, insulin resistance, and T2DM (66).

Among the adverse consequences of adiposity-induced "sick fat" (5,6) is a disruption of physiological endocrine (6) and immune function (39), which, in turn, contributes to metabolic disease (2,67–69). The mechanisms by which adiposopathic endocrine and immune responses contribute to T2DM, high blood pressure, dyslipidemia, and other metabolic disorders (4,5), and mechanisms explaining how nutrition, physical activity, drug therapies, and bariatric surgical interventions improve metabolic disease (33,70–74) are beyond the scope of this discussion. Nonetheless, Tables 3 and 4 list examples of adipose tissue endocrine and immune functions whose disruption may contribute to metabolic disease.

Adipose Tissue Cross Talk and Interactions With Other Body Organs

A misconception of an adipocentric paradigm is that it fails to account for the pathophysiological role of nonadipose organs. Although adipocyte and adipose tissue dysfunction are often etiologic, adiposopathy alone does not cause or worsen metabolic disease. Instead, the clinical consequences of "sick fat" depend on how adipose tissue interacts or undergoes "cross talk" with other body organs such as the liver, muscle, pancreas, as well as organs of the cardiovascular, endocrine, immune, nervous, genitourinary, gastrointestinal, integumentary, and other body systems (5).

T2DM, high blood pressure, and dyslipidemia often have defined causes (3) (Table 5). However, the exact "cause" of most instances of these metabolic diseases are ill defined. What is well defined is that the prevalence of these major cardiovascular risk factors markedly increase with increasing body weight (5). The accumulation of adipose tissue (adiposity) and dysfunctional adipose tissue (adiposopathy) contributes to most, if not all, cardiometabolic risk factors (75). Recognizing the pathogenic potential of adipose tissue not only helps describe the relationship between adiposity and metabolic disease, but also provides a scientific foundation as to why treatment of adiposopathy often improves metabolic disease (73). This concept also helps validate the "emerging concept is that the development of anti-obesity agents must not only reduce fat mass (adiposity) but must also correct fat dysfunction (adiposopathy)" (76).

Table 5 Examples of Diseases Other Than Adiposopathy That Cause Common Metabolic Diseases

Type 2 diabetes mellitus
Hemochromatosis
Chronic pancreatitis
Hypercortisolism
Excessive growth hormone
Genetic syndromes of insulin resistance
Genetic syndromes of decreased pancreatic function
High blood pressure
Pheochromocytoma
Primary hyperaldosteronism
Hypercortisolism
Hyperthyroidism
Renal artery stenosis
Various kidney diseases
Familial or genetic syndromes
Dyslipidemia
Untreated hypothyroidism
Poorly controlled diabetes mellitus
Certain types of liver or kidney diseases
Genetic dyslipidemias

In but 1 example, adiposopathy increases circulating free fatty acids. If the liver and muscle are "inflexible" (limited) in their ability to metabolize increased free fatty acid influx, then this may cause "lipotoxic" intraorgan and intracellular accumulation of lipid metabolites (e.g., fatty acyl coenzyme A, diacylglycerol, ceramide), which contributes to insulin resistance (2,55). The pancreas and arterial tissues maybe adversely affected as well, possibly causing beta-cell dysfunction and accelerated atherosclerosis, respectively (55,77). In fact, "inflexible" intraorgan triglyceride concentration may distinguish obese individuals in whom metabolic abnormalities develop from obese individuals in whom none develop (78).

Conversely, if organs such as the liver are able to overcome lipotoxicity through inherent hyperflexibility or through the use of therapeutic agents such as peroxisome proliferator-activated receptor (PPAR) gamma agonists (2,55), then the onset or worsening of metabolic disease may be mitigated. Some investigators suggest that if adiposity occurs without intraorgan (e.g., intrahepatic) fatty infiltration, then the onset or worsening of metabolic disease may be averted (79). They conclude that 1) the characteristics of adipose tissue are more important than the amount of body fat in determining the risk of obesity-related metabolic disease; 2) insulin resistance is associated with increased fat-cell size, increased adipose tissue lipolytic activity, adipose tissue inflammatory cell infiltration, adipose tissue hypoxia, and adipose tissue ER stress; and 3) the accumulation of ectopic fat in other organs, particularly the liver, might be a marker of adipose tissue pathology (79), as might occur in patients with adiposopathic responses to positive caloric balance.

Adiposopathy and Aging

Irrespective of age, adiposopathy increases the prevalence of metabolic disease and CVD risk factors (80,81). However, adiposopathy and aging share analogous pathophysiologies. From a cellular standpoint, both adiposopathy and aging can increase markers of intracellular ER stress and mitochondrial dysfunction (49,63–66,82–84), and both are associated with impaired adipogenesis (2,85). From a clinical standpoint, both adiposopathy and aging: 1) are risk factors for CVD, T2DM, high blood pressure, and dyslipidemia;

2) promote endocrinopathies, such as increased free fatty acids (86) and reduced testosterone levels in men (87,88); and 3) both may promote immunopathies such as increased C-reactive protein (2,89). When stratified based on age and BMI, the relationship between adiposopathy and aging is complex, as evidenced by the variable association of metabolic syndrome components (90). Adverse oxidative reactions are also shared by adiposopathy (91) and aging (92). Oxidation creates unstable oxygen free radicals and other reactive oxygen species that create biomolecular instabilities toxic to cells. If reactive oxygen species production exceeds a biological system's ability to detoxify them, then this "oxidative stress" may contribute to metabolic disease and atherosclerosis (91).

Adiposopathy as a Conceptual Resolution of the Obesity Paradox

Various obesity paradoxes are described when increased body fat mass does not increase morbidity or mortality, when a decrease in excessive body fat does not improve patient health, or when an increase in body fat mass actually reduces morbidity or mortality. Many of these apparent clinical contradictions are mitigated if the pathogenic potential of excess adipose tissue is assessed not solely by adiposity, but also by adiposopathy.

Not all obesity paradoxes are due to adiposopathy (93). However, many obesity paradoxes are less paradoxical if adipose tissue is accepted as being more than an inert storage organ. For example, not all overweight patients develop metabolic disease and not all patients with metabolic disease are overweight (5). This paradox is best explained when understanding that fat weight gain most often contributes to the onset or worsening of metabolic disease when accompanied by pathogenic adipocyte and adipose tissue anatomic, endocrine, and immune responses in genetically and environmentally susceptible patients (2,4,5,39,94). This also helps explain paradoxical populations described as "metabolically healthy, but obese" (95), "metabolically obese, normal weight" (95), and the increased risk of T2DM among Pima Indians (2,96). Adiposopathy also helps explain the otherwise curious (paradoxical) use of "ectopic fat" to describe excessive fat deposition in any body organ, including increased fat deposition in fat depots (e.g., visceral adipose tissue) (55,73,97), and helps identify when adiposity or obesity might best be considered a disease (6,98,99).

Cardiovascular risk paradox. The susceptibility to adiposopathy provides an explanation for the high prevalence of T2DM, the metabolic syndrome, and CVD among Asians, particularly those from the South and East Asian subcontinent (2,3). Asian Indians have an increased adipocyte size, fewer adipocytes (100,101), increased visceral adiposity (102), increased circulating free fatty acids (103), increased leptin levels (103,104), increased pro-inflammatory factors (e.g., increased C-reactive protein levels) (105), and decreased anti-inflammatory factors (e.g., decreased adiponectin) (103,104), which lead to increased insulin resistance (103) and increased CVD risk (106). Genetic susceptibility helps account for the common clinical finding that many patients of Asian descent have metabolic disease, even when not markedly overweight (100). This has prompted international organizations to suggest that Asians should have different cutoff points for the determination of overweight and obesity (107).

Similarly, adiposopathy helps explain why, for the same age and weight, men have higher rate of CVD compared with women. During positive caloric balance, men often expand lower body fat through the more pathogenic process of adipocyte hypertrophy, whereas women typically undergo the less pathogenic process of adipocyte hyperplasia (108). Furthermore, men often store excessive fat in an "android" or "apple" (i.e., visceral) distribution, whereas women often store fat in a "gynoid" or "pear" (i.e., peripheral subcutaneous) distribution. These differences in adipose tissue expansion and fat depot accumulation may help explain the sex paradox (109), in which, when corrected for various demographic factors (such as age), men have higher CVD risk than women (2,7,29,110).

Finally, it is clinically relevant that not all body fat gain worsens cardiovascular risk or risk factors. Benign multiple symmetrical lipomatosis is manifest by increased fat accumulation in the SAT regions of the arms, legs, shoulders, and neck. Despite adiposity, typically glucose or lipid disorders do not develop in patients, a finding most likely due to increased proliferation of small adipocytes in SAT and the increased secretion of anti-inflammatory adipokines, such as adiponectin (111).

Cardiovascular event and cardiac procedure paradox. Modestly overweight individuals may live longer than those who weigh less (112), possibly because patients with reduced body weight often have illnesses with high mortality (e.g., chronic heart disease, cancer) (113). However, studies have consistently suggested that modestly overweight patients have reduced morbidities and mortality after diagnosis of CVD, after experiencing a CVD event, and/or after undergoing CVD procedures (114–122).

This CVD paradox may be risk factor dependent. Regarding the CVD risk factor of sedentary lifestyle, overweight and obese men may have increased longevity only if they are physically fit (123). Cigarette smoking reduces body weight, but is a major CVD risk factor. CVD patients who smoke have an increase in all-cause mortality compared with those who quit smoking (124), especially if they have chronic lung disease, which would tend to further decrease body weight (117). Thus, despite lower body weight in cigarette smokers, their CVD risk is increased. Patients with chronic heart failure may have no survival benefit with obesity if they have the major CVD risk factor of T2DM (125). Most CVD patients have "normal" or only modest elevations in cholesterol (another CVD risk factor) (126), yet have a high prevalence of other adiposopathy-associated

CVD risk factors (127). But, although the CVD associated with the adiposopathy-related CVD risk factors may be more frequent, the morbidity and mortality associated with nonadiposopathy-related CVD pathology may be more clinically adverse. In other words, many patients with genetic dyslipidemias (e.g., familial hypercholesterolemia) are not overweight, yet have a disproportionately high rate of premature cardiovascular morbidity and mortality. Thus, although adiposopathy-induced CVD may be more common, the morbidity and mortality with nonadiposopathy-induced CVD may be much worse. Finally, mortality among those with CVD is directly associated with central obesity and inversely associated with BMI (128). Given that central or visceral adiposity is an anatomic manifestation of "sick fat," this supports the concept that adiposopathy may be a more rational treatment target than adiposity alone (129).

Yet another potential explanation of the CVD risk/obesity paradox is that establishing an independent relationship between adiposity and CVD is challenging because of the confounding effects of covariants, comorbidities, and concomitant drug treatments (130). Due to adiposity-related illnesses, overweight patients may receive more frequent medical care and have greater access to global preventive care, which may reduce morbidity and mortality. Many overweight patients have metabolic diseases that prompt treatment with metabolic drug treatments proven to reduce CVD morbidity and, in some cases, treatments proven to reduce cardiac and overall mortality (131). For example, the extent to which reducing hyperglycemia in T2DM reduces atherosclerotic cardiovascular events is unclear (5). However, patients with T2DM are not only treated with glucose-lowering therapies, but often aggressively treated with antihypertensive, lipid-altering, and even antithrombotic therapies that conceivably reduce cardiovascular morbidity and mortality relative to matched nonoverweight patients without T2DM, many of whom may not be treated with such agents.

Finally, adiposity may be associated with enhanced cardiovascular autoreparative potential. Overweight individuals may have greater availability of adipose tissue-associated mesenchymal cells that upon release, could conceivably reduce CVD morbidity. After an acute CVD event, reparative circulating mesenchymal cells (originating from tissues such as adipose tissue, bone marrow, and blood vessels) (Fig. 2) migrate to the injured myocardial site (132,133). In their naïve state, adult stem cells may have a limited reparative benefit in patients with ischemic heart disease. Pre-emptive lineage pre-specification through guided cardiopoiesis may be needed to optimize therapeutic outcomes (134). Adiposity signaling promotes the recruitment of adipocytes from adipose tissue-associate mesenchymal cells (135). Thus, the presence of adiposity may promote an increased number of progenitor cells available for mobilization into the circulation and potentially enhance adipose tissue mesenchymal differentiation into cells more apt to undergo either cardiopoiesis or adipogenesis (i.e., not yet solely committed to adipogenesis). If so, then an increase in the circulatory release of mesenchymal cells during cardiac injury (or possibly cardiac procedures) might have a greater potential for cardiovascular autorepair. Supporting this mechanism is that abnormally expanded fat tissue increases the mobilization of endothelial progenitor cells, which may have a protective effect against vascular atherosclerosis in obese patients (136).

Fat gain and fat loss cardiovascular risk factor paradox. From a cardiovascular treatment standpoint, a paradoxical clinical scenario is adding fat as a means to treat diseases often associated with too much fat (33). PPAR-gamma agonists increase the recruitment, proliferation, and differentiation of functional fat cells in SAT relative to VAT (2,54,70). Increased adipogenesis helps account for how PPAR-gamma agents increase body fat, improve adipocyte function, lower glucose levels in patients with T2DM, reduce heptatic steatosis (55,137), and helps explain how some PPAR gamma agents improve lipid parameters (138) and potentially reduce CVD risk (139).

Adiposopathy also helps explain why not all body fat loss improves cardiovascular risk factors. Inherited lipodystrophy is characterized by a variable lack of body fat and impaired adipose tissue function (e.g., low adiponectin levels and inability to adequately store fat). Because of limited fat storage potential, lipodystrophic patients have high circulating free fatty acids that contribute to lipotoxicity and metabolic disorders such as hyperglycemia and dyslipidemia (2). Lipoatrophic mice have virtually no white adipose tissue and, as a consequence, severe hyperglycemia. Surgically implanting adipose tissue markedly improves hyperglycemia, hyperinsulinemia, and muscle insulin sensitivity (140). Surgical removal of VAT through omentectomy plus adjustable gastric banding may improve glucose metabolism (oral glucose tolerance, insulin sensitivity, and fasting glucose and insulin levels) more than adjustable gastric banding (141). Conversely, liposuction of SAT may not improve CVD risk factors such as hyperglycemia, high blood pressure, and dyslipidemia (142). Finally, antiretroviral therapy sometimes results in human immunodeficiency virus lipodystrophy. Despite weight loss, patients may experience insulin resistance and dyslipidemia, which may be due to the greater loss of SAT relative to VAT (143).

Cardiovascular clinical trial paradox. Adiposopathy may also help explain why overweight patients with elevated markers of inflammation and no major cardiovascular risk factors may, paradoxically, not be "healthy." The JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) trial was a landmark CVD outcome trial of 17,802 "apparently healthy men and women" with low-density lipoprotein cholesterol levels $<$130 mg/dl and high-sensitivity C-reactive protein levels $\geq$2.0 mg/l who were randomized to rosuvastatin 20 mg/day or placebo. The conclusion was that rosuvastatin significantly reduced CVD in "apparently healthy persons

without hyperlipidemia but with elevated high sensitivity C-reactive protein levels" (144). However, baseline median BMI was ~28 kg/m^2 (a BMI ≥25 kg/m^2 is considered overweight; a BMI ≥27 mg/m^2 with comorbidities is a cutoff point to consider weight-loss drug therapy) (145). Also at baseline, metabolic syndrome was present in 41% of study participants. One interpretation of the study results was that elevated C-reactive protein is not only a marker of vascular inflammation, but also plays a direct role in the pathogenesis of atherosclerosis and thrombosis (146,147). An alternative interpretation is that adiposopathy (a "disease") was present at baseline in many study participants, as supported by the high mean BMI, the high percentage of study participants with metabolic syndrome, and the elevated C-reactive protein. The latter is supported by the findings that C-reactive protein may be directly released from adipose tissue (148). Perhaps more importantly, excessive body fat increases adipose tissue release of interleukin-6 (2), which stimulates increased C-reactive protein production from the liver (2,4). It seems plausible that the increased C-reactive protein level found among many JUPITER study participants was significantly due to pathogenic adipose tissue immune responses. Thus, within the adiposopathic paradigm, many of the study participants were not "healthy persons." Many study participants had evidence of adiposopathy, which may directly and indirectly promote CVD. Finally, it is of interest that a reduction in inflammatory markers (e.g., interleukin-6, C-reactive protein) with statins may, in part, be due to statin-induced reductions in adipose tissue inflammation (149,150).

Conclusions

Adiposopathy or "sick fat" is a cardiovascular disease.

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Key Words: adiposity ■ adiposopathy ■ cardiovascular disease ■ metabolic syndrome ■ obesity ■ obesity paradox.