

Perspectives in Diabetes

The Perils of Portliness

Causes and Consequences of Visceral Adiposity

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Although an individual's total fat mass predicts morbidities such as coronary artery disease and diabetes, the anatomical distribution of adipose tissue is a strong and independent predictor of such adverse health outcomes. Thus, obese individuals with most of their fat stored in visceral adipose depots generally suffer greater adverse metabolic consequences than similarly overweight subjects with fat stored predominantly in subcutaneous sites. A fuller understanding of the biology of central obesity will require information regarding the genetic and environmental determinants of human fat topography and of the molecular mechanisms linking visceral adiposity to degenerative metabolic and vascular disease. Here we attempt to summarize the growing body of data relevant to these key areas and, in particular, to illustrate how recent advances in adipocyte biology are providing the basis for new pathophysiological insights. *Diabetes* 49:883-888, 2000

Obesity is a growing public health problem in developed and developing countries (1). Credit for the first formal recognition that particular distributions of human body fat may be associated with metabolic disease is generally given to French physician Jean Vague (2), who published a series of papers during the 1950s reporting that upper-body (android) obesity was more frequently found in individuals suffering from diabetes, gout, and atherosclerosis than lower-body (gynoid) obesity. Subsequently, numerous large epidemiological studies have

confirmed these initial clinic-based observations. Upper-body obesity, most commonly observed in males and measured by an increase in the waist-to-hip ratio (WHR), has been shown to be an important predictor for increased morbidity and mortality from coronary heart disease, certain cancers, and diabetes (3-8). It is also closely associated with glucose intolerance, hyperinsulinemia, hypertriglyceridemia, and other features of the so-called syndrome X (i.e., raised blood pressure, decreased levels of HDLs, and increased levels of VLDLs) (6,9). In contrast, individuals with comparable amounts of fat stored in the femoral or gluteal depots (lower-body obesity) have a much lower risk of morbidity from these metabolic disturbances. Upper-body fat includes the visceral and abdominal subcutaneous depots. The visceral fat depot is contained within the body cavity, surrounding the internal organs, and is composed of the mesenteric and the greater and lesser omental depots. Each of these depots is separate and distinct but, for the purposes of this article, is defined as visceral. Visceral depots represent ~20 and 6% of total body fat in men and women, respectively (10,11). The abdominal subcutaneous fat depot is situated immediately below the skin in the abdominal region. In the lower body, all adipose depots are subcutaneous; the 2 largest sites of storage are in the gluteal and femoral regions.

Although the WHR encompasses both intra-abdominal (visceral) and abdominal subcutaneous adipose depots, more detailed studies using computed tomography (CT) or magnetic resonance imaging (MRI) scans of the abdomen suggest that it is the visceral component that is most closely linked to adverse outcomes (12,13). Additionally, the selective reduction of visceral adiposity through diet and exercise is accompanied by improvements in intermediary metabolism (13) and a reduction in risk factors for coronary heart disease (14). Indirect support for the idea that increased visceral adipose tissue leads to systemic insulin resistance was provided in a recent study by Albu et al. (15). Visceral adipose tissue of African-American and Caucasian women was measured by CT and MRI, and a reduction in the antilipolytic effect of insulin was significantly correlated with visceral adipose tissue area but not with subcutaneous adipose tissue area or with WHR. However, the authors were unable to conclude whether this correlation was due to a reduction in insulin sensitivity in visceral adipocytes or a resistance to the antilipolytic effects of insulin in subcutaneous adipocytes, which may lead to increased fat storage in visceral depots. More compelling evidence for the deleterious effects of adipose storage

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CT, computed tomography; FFA, free fatty acid; IR, insulin receptor; IRS, insulin receptor substrate; LPL, lipoprotein lipase; MRI, magnetic resonance imaging; PAI-1, plasminogen activator inhibitor 1; PPAR- γ , peroxisome proliferator-activated receptor- γ ; TNF- α , tumor necrosis factor- α ; TZD, thiazolidinedione; WHR, waist-to-hip ratio.

in visceral depots was provided by a recent study in rats. When the visceral fat pads of obese Sprague-Dawley rats were surgically removed, there was a marked improvement in hepatic insulin sensitivity and reduction in hepatic glucose production in the animals (16).

DO GENETIC FACTORS INFLUENCE HUMAN FAT DISTRIBUTION?

A substantial body of evidence points to the existence of genetic determinants of human fat mass (17). Although derived from a smaller number of studies, there is equally compelling evidence for the influence of heredity on human fat distribution. The Quebec Family Study used CT scanning to measure abdominal visceral fat area in 382 men and women from 100 families. Segregation analysis suggested that 51% of the adjusted variance in abdominal visceral fat size was likely to be determined by a single gene, with a further 21% determined by a multifactorial component (18). More than 60% of the variance in intra-abdominal fat mass was accounted for by heritable factors, and this estimate dropped by only 10% after adjustment for total fat mass. Similar degrees of heritability have been reported in studies using WHR and/or subcutaneous skin-fold thicknesses to assess fat distribution (19). Particularly strong support for the notion that genetic factors can determine fat distribution comes from the twin overfeeding studies of Bouchard et al. (19). Six pairs of monozygotic twins were overfed for 22 days and regional fat deposition was analyzed using CT scanning. Consequently, 75% of the variance in the site of fat deposition was found between, and only 25% within, the pairs of twins.

The most important determinant of fat distribution is sex, with males being typified by central and females by peripheral fat distribution. The assertion that the effect of sex is, at least in part, mediated by the sex-hormone milieu is supported by the reciprocal changes in fat distribution that occur in male-to-female and female-to-male transsexuals (20,21). However, even within the sexes, genetic factors demonstrably play a role in the determination of fat distribution.

Thus, there is good evidence that **1**) genetic factors influence human fat distribution, and **2**) the genetic determinants

are likely to be substantially different from those determining fat mass per se. Even though a number of monogenic causes of human obesity have been described in the past 4 years (22–27) and genome-wide studies in obese families are showing promising and consistent linkages (17), there has been little concrete progress in the identification of genetic variants involved in the determination of fat distribution. One exception is the rare autosomal dominant Dunnigan-Kobberling syndrome. In this disorder, patients develop progressive atrophy of fat tissue on limbs and trunk but retain fat in the visceral cavity and around the face and neck. The disorder is associated with severe insulin resistance, diabetes, and hyperlipidemia. Surprisingly, mutations in the nuclear envelope protein Lamin A have recently been found in several kindred groups with this syndrome. Intriguingly, mutations at 2 specific sites appear to be uniquely linked to this syndrome, whereas mutations elsewhere in this gene are associated with Emory-Dreyfuss muscular dystrophy or familial cardiomyopathy. Why these specific mutations in this apparently structural protein result in site-selective loss of adipose tissue remains mysterious: This is obviously an important area for future research (28,29)

HOW IS EXCESS VISCERAL ADIPOSE TISSUE LINKED TO DEGENERATIVE METABOLIC DISEASE?

The epidemiological evidence linking visceral adiposity with diabetes and other aspects of syndrome X is unequivocal. What pathophysiological mechanisms might result in this association? The following 3 possible explanations for this link come to mind: **1**) central obesity is not in itself pathological but is simply a marker for some underlying genetic/environmental mix that itself leads to disease—the “common soil” theory; **2**) visceral fat is uniquely deleterious because of its anatomical site with its direct venous drainage to the liver; and **3**) some intrinsic properties of visceral adipocytes (Table 1) make the expansion of this depot particularly dangerous. It is important to stress, however, that these explanations are not mutually exclusive.

Common soil. It is possible that visceral adiposity and metabolic disorders are not themselves causally linked, but that

TABLE 1
Differences in biochemical properties between adipose cells from visceral and subcutaneous adipose depots

Factor	Regional difference	Reference
Leptin mRNA and protein	Sc > visceral	43, 58, 60
TZD-stimulated preadipocyte differentiation	Sc > visceral	70
Lipolytic response to catecholamines	Visceral > Sc	37
Antilipolytic effect of insulin	Sc > visceral	41, 42
11β-HSD1 activity	Visceral > Sc	47
β ₁ and β ₂ -Adrenergic receptor binding and mRNA	Visceral > Sc	38, 39
Dexamethasone-induced increase in LPL	Visceral > Sc	45
α ₂ -Adrenergic receptor agonist inhibition of cAMP	Sc > visceral	40
Insulin receptor affinity	Sc > visceral	42
IRS-1 protein expression	Sc > visceral	42
Insulin receptor (exon 11 deleted)	Visceral > Sc	43
Glucocorticoid receptor mRNA	Visceral > Sc	46
cIAP2 mRNA	Visceral > Sc	66
Androgen receptor mRNA	Visceral > Sc	50
IRS-1 protein	Sc > visceral	42
PAI-1 protein	Visceral > Sc	63

Sc, subcutaneous.

the genetic and environmental factors that lead to insulin resistance, diabetes, and dyslipidemia also coincidentally lead to visceral adiposity. Of note in this regard are the reports that mice with muscle-specific insulin resistance, generated either through a skeletal muscle-specific dominant-negative insulin receptor transgene (30) or by myocyte-specific gene targeting of the insulin receptor (31), develop increased adiposity, with a largely central distribution. This suggests the possibility that inherited muscle-based insulin resistance in humans could lead to both diabetes and central obesity. Conversely, Schwartz et al. (32) have reported that a low insulin secretory response to glucose predicts not only the later development of diabetes but also the development of increased visceral fat mass.

Anatomical site. One potential reason for the particularly deleterious effects of visceral obesity may simply relate to its anatomical site and pattern of venous drainage. Visceral adipose tissue drains via the portal venous system, and thus the liver will be exposed to the full and undiluted repertoire of metabolites and secretory products produced by these fat depots. Because substrate delivery is a major determinant of both hepatic gluconeogenesis and VLDL synthesis (33), an increased volume of visceral adipose tissue, releasing more free fatty acids (FFAs), glycerol, and lactate, would be expected to have a major influence on these hepatic processes. There is evidence that exposure of the liver to high concentrations of FFAs can induce changes in insulin signaling, which would promote hepatic insulin resistance. In rats, high-fat feeding has been demonstrated to stimulate tyrosine-kinase activity, and reduce autophosphorylation of the β -subunit of the insulin receptor in liver and muscle (34). In addition, *in vitro* exposure of isolated hepatocytes to FFAs caused a dose-dependent decrease in cell-surface insulin receptor binding (35) along with diminished receptor-mediated internalization and degradation (33).

In addition, the decrease in insulin action in the liver may lead to decreased inhibition of hepatic glucose output. Hepatic gluconeogenesis may be further elevated by the increased availability of glycerol as a result of fatty acid oxidation.

Regional differences in adipocyte biology. The traditional view of the adipocyte has treated that cell type as a rather passive vessel concerned simply with the storage of excess calories as lipid when energy balance is positive and the release of FFAs for use elsewhere in the body when energy balance is negative. More recently, the adipocyte has been rediscovered as a much more active participant in physiological homeostasis through its regulated production of hormones and cytokines, which act in autocrine, paracrine, and endocrine modes. This characterization is accompanied by increasing evidence that not all fat cells are the same. A decade ago, it was demonstrated that brown and white adipocytes have markedly different properties; only recently has attention been focused on the heterogeneity of white adipocytes. Some profound differences are seen between white adipocytes of visceral and subcutaneous fat depots, and it seems increasingly likely that these special properties of visceral fat cells may contribute to the adverse consequences of visceral obesity.

Metabolic properties. *In vivo* studies in humans, using isotopically labeled dietary fat administered to patients undergoing elective surgery, have clearly demonstrated a substantially higher turnover of triglyceride in upper-body compared

with lower-body fat depots (36). Consistent with this observation is a range of studies examining the metabolic properties of isolated visceral fat cells. In comparison to subcutaneously derived adipocytes, visceral fat cells show higher rates of catecholamine-induced lipolysis (37), express higher numbers of β_1 - and β_2 -adrenergic receptor (38,39), and are less responsive to the cAMP-lowering effects of α_2 -adrenergic receptor agonists (40). Thus, visceral adipocytes appear to have a more active lipolytic program. In concert with these characteristics, antilipolytic signaling mechanisms appear to be less active in visceral fat cells. Thus, visceral adipocytes are less responsive to the antilipolytic effect of insulin than are subcutaneous fat cells (41,42). This finding may relate to differences in insulin receptor (IR) affinity (42), in particular, the preponderance of the lower-affinity exon 11 minus isoform of the IR in visceral fat (43). In addition, reduced insulin receptor substrate (IRS)-1 protein expression in visceral compared with subcutaneous adipocytes may provide a further explanation of the reduced responsiveness of omental adipocytes to insulin (IRS-1) (42).

Steroid responsiveness and interconversion. It has long been known that both sex steroids and glucocorticoids can profoundly alter human fat distribution. However, the effects of steroids are complex. For example, testosterone administration to hypogonadal males reverses visceral adiposity, whereas it promotes visceral adiposity in females (21,44). Studies of the regional variation in expression of steroid receptors and interconverting enzymes in fat cells are beginning to provide a molecular explanation for some of these effects.

Activation of glucocorticoid receptors in adipocytes causes an increase in lipoprotein lipase (LPL) expression and enhances triglyceride storage (45). Visceral adipocytes express higher numbers of glucocorticoid receptors (46) and show the expected increase in LPL responsiveness to glucocorticoid (45). More recently, profound differences in the enzyme regulating intracellular conversion of inactive cortisone to active cortisol have been demonstrated between visceral and subcutaneous fat. Thus, 11 β -hydroxysteroid dehydrogenase-1 oxo-reductase activity (47) is very high in visceral adipose tissue and barely detectable in subcutaneous sites. Therefore, it is likely that the visceral fat depot actively contributes to the production of high local concentrations of cortisol.

The effects of sex steroids on human adipocytes are complex and poorly understood. Estrogen appears to enhance LPL activity (48) and testosterone to decrease it (49). Androgen receptors appear to be consistently higher in visceral than in subcutaneous fat in both males and females (50). However, it is difficult to reconcile these observations with the diametrically opposed effects of testosterone administration to hypogonadal males versus normal females, respectively. Estrogen receptors appear to be more highly expressed in male subcutaneous versus visceral adipocytes, but no such site-specific differences have been reported in female adipose depots (51).

Production of hormones, cytokines, and polypeptides. The list of secretory products of adipocytes is extensive and includes leptin (52), tumor necrosis factor- α (TNF- α) (53), interleukin-6 (54), adiponectin (55), complement factor C3 (56), angiotensinogen, and plasminogen activator inhibitor 1 (PAI-1) (57). A number of these products have been demonstrated to be secreted in a depot-related manner.

Leptin is a recently characterized adipocyte-derived peptide hormone that is involved in the control of fat mass through

actions in the hypothalamus and elsewhere. Leptin mRNA levels are markedly higher in subcutaneous than visceral adipocytes (43,58). Consistent with this finding, circulating levels of leptin show a higher degree of correlation with subcutaneous adiposity than with visceral adiposity (59), and leptin secretion is greater from subcutaneous than from visceral fat tissue (60). Thus, fat stored in the subcutaneous adipose depots may make a greater contribution to the pool of circulating leptin, and thus have a greater effect on the regulation of appetite, than an equivalent amount of fat stored in the visceral adipose depots. If, as seems possible, leptin has additional insulin-sensitizing effects on skeletal muscle and other tissues (61,62), then the diminished leptin increment seen when fat mass is accrued in the visceral areas may, at least in part, contribute to the association between central obesity and insulin resistance.

Central obesity is associated with atherothrombotic events (33). It is notable that a major circulating inhibitor of thrombolysis, PAI-1, has been demonstrated to be synthesized and secreted from adipocytes. Interestingly, it was also shown that visceral adipocytes produced considerably more of this peptide than did subcutaneous cells and that the circulating levels of PAI-1 correlated strongly with visceral fat mass (63). These discoveries provide a possible link between central obesity and the thrombotic component of cardiovascular risk. However, further examination may be required to clarify the role of PAI-1 in central obesity, because it has recently been reported that abdominal subcutaneous adipocytes also express and secrete PAI-1 and that the levels of secretion are greatly increased in obese individuals (64). At present, it is unclear whether the apparent divergence between the studies above is related to differences in ethnicity of the patients from whom the samples were obtained.

Adipocyte loss and acquisition. Adipocyte number is regulated both by loss of cells through apoptosis and necrosis and through development of new cells by proliferation and differentiation of the progenitor cells, preadipocytes. There are differences between subcutaneous and visceral fat depots in the rate of apoptosis of preadipocytes in response to stimuli such as TNF- α (65). Additionally, cellular inhibitor of apoptosis-2, a protein that inhibits TNF- α -mediated cell death, was found to be more highly expressed in visceral than subcutaneous adipocytes (66). This suggests that there may be differences in the rates of TNF- α -mediated apoptosis between subcutaneous and visceral adipocytes.

There may also be differences in progenitor cell number and differentiation capacity between adipose depots. Hauner et al. (67) have demonstrated that preadipocytes from the subcutaneous adipose depots have a greater differentiation capacity than those from the visceral depots. The differentiation of preadipocytes into lipid-storing adipocytes is regulated in part by the nuclear hormone receptor, peroxisome proliferator-activated receptor- γ (PPAR- γ) (68). Activation of this receptor by synthetic ligands, such as thiazolidinediones (TZDs), or natural ligands, such as prostaglandin J2 metabolites, leads to stimulation of the differentiation pathway (68,69). Ex vivo studies of human preadipocytes from subcutaneous and visceral adipose depots have demonstrated that TZD-stimulated differentiation is much greater in subcutaneous than visceral preadipocytes (70,71). This may be the mechanism behind the reported observations in humans that treatment with TZDs results in a redistribution of body fat from visceral to subcutaneous depots (72,73).

This site-related sensitivity of preadipocytes to TZDs may provide a possible explanation for the "thiazolidinedione paradox." TZDs potentially enhance insulin sensitivity in humans and are therefore useful antidiabetic agents. However, they potentially promote adipocyte differentiation and often increase total fat mass (73). Because obesity is a major cause of insulin resistance, this presents an apparent paradox. If, however, in humans, TZDs selectively promote adipogenesis in subcutaneous and not in visceral sites, this would encourage the redistribution of body fat away from "dangerous" intra-abdominal sites and toward "safer" subcutaneous ones.

PPAR- γ mRNA expression has been reported to be greater in subcutaneous than visceral adipose tissue in nonobese individuals, but there was no difference in expression between the depots in obese individuals (43). However, 2 other studies that examined PPAR- γ mRNA expression in adipocytes and adipose tissue found no difference in expression between visceral and subcutaneous depots (66,74). It appears likely that the difference in TZD sensitivity between subcutaneous and visceral sites does not simply reflect the relative amounts of PPAR- γ expression.

SUMMARY

The epidemiological relationship between visceral adiposity and degenerative metabolic disease is robust, but causal links have been difficult to establish. Our increasing knowledge of adipocyte biology provides a solid foundation for the identification of molecules that may contribute both to the genetic susceptibility to develop central obesity and to the mediation of the pathological consequences of such obesity. Undoubtedly, diet and physical exercise remain the cornerstones of prevention and treatment in this condition, but when those fail (and they frequently do), pharmacological targeting of molecules involved in this pathophysiological cascade may have a major health impact.

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