Perspectives in Diabetes
The Perils of Portliness
Causes and Consequences of Visceral Adiposity

Carl T. Montague and Stephen O'Rahilly

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**

O besity 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

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, 11β-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), adipsin (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 thrombolyis, 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 pardox." TZDs potently enhance insulin sensitivity in humans and are therefore useful antidiabetic agents. However, they potently 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.

REFERENCES

1. Seidell JC: Time trends in obesity: an epidemiological perspective. *Horm Metab Res* 29:155–158, 1997
2. Vague J: The degree of masculine differentiation of obesities, a factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. *Am J Clin Nutr* 4:20–34, 1956
3. Krotkiewski M, Bjorntorp P, Sjostrom L, Smith U: Impact of obesity on metabolism in men and women: importance of regional adipose tissue distribution. *J Clin Invest* 72:1150–1162, 1983
4. Ohlson L, Larsson B, Svardsudd K, Welin L, Eriksson H, Wilhelmsen L, Bjorntorp P, Tibblin G: The influence of body fat distribution on the incidence of diabetes mellitus. *Diabetes* 34:1055–1058, 1985
5. Lapidus L, Bengtsson C, Larsson B, Pennert K, Rybo E, Sjostrom L: Distribution of adipose tissue and risk of cardiovascular disease and death: a 12 year follow up of participants in the population study of women in Gothenburg, Sweden. *Br Med J* 289:1257–1261, 1984
6. Kissebah AH, Vydelingum N, Murray M, Evans DJ, Hartz AJ, Kalkhoff RK, Adams PW: Relation of body fat distribution to metabolic complications of obesity. *J Clin Endocrinol Metab* 54:254–260, 1982
7. Gillum RF: The association of body fat distribution with hypertension, hypertensive heart disease, coronary heart disease, diabetes and cardiovascular risk factors in men and women aged 18–79 years. *J Chronic Dis* 40:421–428, 1987
8. Kannel WB, Cupples LA, Ramaswami R, Stokes J, Kreger BE, Higgins M: Regional obesity and risk of cardiovascular disease: the Framingham study. *J Clin Epidemiol* 44:183–190, 1991
9. Evans DJ, Murray R, Kissebah AH: Relationship between skeletal muscle insulin resistance, insulin-mediated glucose disposal, and insulin binding: effects of obesity and body fat topography. *J Clin Invest* 74:1515–1525, 1984
10. Ross R, Leger L, Morris D, de Guise J, Guardo R: Quantification of adipose tissue by MRI: relationship with anthropometric variables. *J Appl Physiol* 72:787–795, 1992
11. Ross R, Shaw KD, Rissanen J, Martel Y, de Guise J, Avruch L: Adipose tissue

distribution measured by magnetic resonance imaging in obese women. *Am J Clin Nutr* 57:470–475, 1993

12. Peiris AN, Hennes MI, Evans DJ, Wilson CR, Lee MB, Kissebah AH: Relationship of anthropometric measurements of body fat distribution to metabolic profile in premenopausal women. *Acta Med Scand Suppl* 723:179–188, 1988

13. Fujioka S, Matsuzawa Y, Tokunaga K, Kawamoto T, Kobatake T, Keno Y, Kotani K, Yoshida S, Tarui S: Improvement of glucose and lipid metabolism associated with selective reduction of intra-abdominal visceral fat in premenopausal women with visceral fat obesity. *Int J Obes* 15:853–859, 1990

14. Riches FM, Watts GF, Hua J, Stewart GR, Naoumova RP, Barrett PHR: Reduction in visceral adipose tissue is associated with improvement in apolipoprotein B-100 metabolism in obese men. *J Clin Endocrinol Metab* 84:2854–2861, 1999

15. Albu JB, Curi M, Shur M, Murphy L, Matthews DE, Pi-Sunyer FX: Systemic resistance to the antilipolytic effect of insulin in black and white women with visceral obesity. *Am J Physiol* 277:E551–E560, 1999

16. Barzilai N, She L, Liu B-Q, Vuguin P, Cohen P, Wang J, Rossetti L: Surgical removal of visceral fat reverses hepatic insulin resistance. *Diabetes* 48:94–98, 1999

17. Comuzzie A, Allison D: The search for human obesity genes. *Science* 280:1374–1377, 1998

18. Bouchard C, Rice T, Lemieux S, Despres J-P, Perusse L, Rao DC: Major gene for abdominal visceral fat area in the Quebec Family Study. *Int J Obes* 20:420–427, 1996

19. Bouchard C, Després J-P, Mauriége P: Genetic and nongenetic determinants of regional fat distribution. *Endocr Rev* 34:72–93, 1993

20. Vague J, Meignen JM, Negrin JF: Effects of testosterone and estrogens on deltoid and trochanter adipocytes in two cases of transsexualism. *Horm Metab Res* 16:380–381, 1984

21. Elbers JM, Asscheman H, Seidell JC, Megens JA, Gooren LJ: Long-term testosterone administration increases visceral fat in female to male transsexuals. *J Clin Endocrinol Metab* 82:2044–2047, 1997

22. Montague CT, Farooqi IS, Whitehead JP, Soos MA, Rau H, Wareham NJ, Sewter CP, Digby JE, Mohammed SN, Hurst JA, Cheetham CH, Early AR, Barnett AH, Prins JB, O'Rahilly S: Congenital leptin deficiency is associated with severe early-onset obesity in humans. *Nature* 387:903–908, 1997

23. Clement K, Vaisse C, Lahlou N, Cabrol S, Pelloux V, Cassuto D, Gourmelen M, Dina C, Chambaz J, Lacorte J, Basdevant A, Bougneres P, Lebouc Y, Froguel P, Guygrand B: A mutation in the human leptin receptor gene causes obesity and pituitary dysfunction. *Nature* 392:398–401, 1998

24. Jackson RS, Creemers JWM, Ohagi S, Raffin-Sanson M-L, Sanders L, Montague CT, Hutton JC, O'Rahilly S: Obesity and impaired prohormone processing associated with mutations in the prohormone convertase 1 gene. *Nat Genet* 16:303–306, 1997

25. Krude H, Biebermann H, Luck W, Horn R, Brabant G, Gruters A: Severe early-onset obesity, adrenal insufficiency and red hair pigmentation caused by POMC mutations in humans. *Nat Genet* 19:155–157, 1998

26. Yeo G, Farooqi I, Aminian S, Halsall D, Stanhope R, O'Rahilly S: A frameshift mutation in MC4R associated with dominantly inherited human obesity. *Nat Genet* 20:111–112, 1998

27. Ristow M, Mullerwieland D, Pfeiffer A, Krone W, Kahn C: Obesity associated with a mutation in a genetic regulator of adipocyte differentiation. *N Engl J Med* 339:953–959, 1998

28. Cao H, Hegele RA: Nuclear lamin A/C R482Q mutation in Canadian kindreds with Dunnigan-type familial partial lipodystrophy. *Hum Mol Gen* 9:109–112, 2000

29. Shackleton S, Lloyd DJ, Jackson SNJ, Evans R, Niermeijer MF, Singh BM, Schmidt H, Brabant G, Kumar S, Durrington PN, Gregory S, O'Rahilly S, Trembath RC: LMNA, encoding lamin A/C, is mutated in partial lipodystrophy. *Nat Genet* 24:153–156, 2000

30. Moller D, Chang P, Yaspelkis B, Flier J, Wallberg-Henriksson H, Ivy J: Transgenic mice with muscle-specific insulin resistance develop increased adiposity, impaired glucose tolerance, and dyslipidemia. *Endocrinology* 137:2397–2405, 1996

31. Bruning J, Michael MD, Winnay J, Hayashi T, Horsch D, Accili D, Goodyear LJ, Kahn CJ: A muscle-specific insulin receptor knockout exhibits features of the metabolic syndrome of NIDDM without altering glucose tolerance. *Mol Cell* 2:559–569, 1998

32. Schwartz M, Boyko E, Kahn S, Ravussin E, Bogardus C: Reduced insulin secretion: an independent predictor of body weight gain. *J Clin Endocrinol Metab* 80:1571–1576, 1995

33. Kissebah AH, Krakower GR: Regional adiposity and morbidity. *Physiol Rev* 74:761–811, 1994

34. Nagy K, Levy J, Grunberger G: High-fat feeding induces tissue-specific alteration in proportion of activated insulin receptors in rats. *Acta Endocrinol* 122:361–368, 1990

35. Hennes MMI, Shrago E, Kissebah AH: Receptor and postreceptor effects of free fatty acids (FFA) on hepatocyte insulin dynamics. *Int J Obes* 14:831–841, 1990

36. Jensen M: Health consequences of fat distribution. *Horm Res* 48:88–92, 1997

37. Rebuffé-Scrive M, Andersson B, Olbe L, Björntorp P: Metabolism of adipose tissue in intraabdominal depots of nonobese men and women. *Metabolism* 38:453–458, 1989

38. Hellmér J, Marcus C, Sonnenfeld T, Arner P: Mechanisms for differences in lipolysis between human subcutaneous and omental fat cells. *J Clin Endocrinol Metab* 75:15–20, 1992

39. Arner P, Hellstrom L, Wahrenberg H, Bronnegard M: Beta-adrenoceptor expression in human fat cells from different regions. *J Clin Invest* 86:1595–1600, 1990

40. Vikman H-L, Savola J-M, Raasmaja A, Ohisalo JJ: α2A-Adrenergic regulation of cyclic AMP accumulation and lipolysis in human omental and subcutaneous adipocytes. *Int J Obes* 20:185–189, 1996

41. Bolinder J, Kager L, Ostman J, Arner P: Differences at the receptor and postreceptor levels between human omental and subcutaneous adipose tissue in the action of insulin on lipolysis. *Diabetes* 32:117–123, 1983

42. Zierath J, Livingston J, Thorne A, Bolinder J, Reynisdottir S, Lonnqvist F, Arner P: Regional difference in insulin inhibition of non-esterified fatty acid release from human adipocytes: relation to insulin receptor phosphorylation and intracellular signalling through the insulin receptor substrate-1 pathway. *Diabetologia* 41:1343–1354, 1998

43. Lefebvre A-M, Laville M, Vega N, Riou JP, van Gaal L, Auwerx J, Vidal H: Depot-specific differences in adipose tissue gene expression in lean and obese subjects. *Diabetes* 47:98–103, 1998

44. Marin P, Lönn L, Andersson B, Odén B, Olbe L, Bengtsson B-A, Björntorp P: Assimilation of triglycerides in subcutaneous and intraabdominal adipose tissue *in vivo* in men: effects of testosterone. *J Clin Endocrinol Metab* 81:1018–1022, 1996

45. Fried SK, Russell CD, Grauso NL, Brolin RE: Lipoprotein lipase regulation by insulin and glucocorticoid in subcutaneous and omental adipose tissues of obese women and men. *J Clin Invest* 92:2191–2198, 1993

46. Rebuffé-Scrive M, Bronnegard M, Nilsson A, Eldh J, Gustafsson J-A, Bjorntorp P: Steroid hormone receptors in human adipose tissues. *J Clin Endocrinol Metab* 71:1215–1219, 1990

47. Bujalska IJ, Kumar S, Stewart PM: Does central obesity reflect "Cushing's disease of the omentum"? *Lancet* 349:1210–1213, 1997

48. Rebuffé-Scrive M, Lönnroth P, Màrin P, Wesslau C, Björntorp P, Smith U: Regional adipose tissue metabolism in men and postmenopausal women. *Int J Obes* 11:347–355, 1987

49. Màrin P, Odén B, Björntorp P: Assimilation and mobilization of triglycerides in subcutaneous abdominal and femoral adipose tissue *in vivo* in men: effects of androgens. *J Clin Endocrinol Metab* 80:239–243, 1995

50. Dieudonne M, Pecquery R, Boumediene A, Leneveu M, Giudicelli Y: Androgen receptors in human preadipocytes and adipocytes: regional specificities and regulation by sex steroids. *Am J Physiol* 274:C1645–C1652, 1998

51. Pedersen SB, Hanses PS, Lund S, Andersen PH, Odgaard A, Richelsen B: Identification of oestrogen receptors and oestrogen receptor mRNA in human adipose tissue. *Eur J Clin Invest* 26:262–269, 1996

52. Zhang Y, Proenca R, Maffei M, Barone M, Leopold L, Friedman J: Positional cloning of the mouse obese gene and its human homologue. *Nature* 372:425–432, 1994

53. Hotamisligil GS, Shargill NS, Spiegelman BM: Adipose expression of tumour necrosis factor-α: direct role in obesity-linked insulin resistance. *Science* 259:87–91, 1993

54. Fried S, Bunkin D, Greenberg A: Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *J Clin Endocrinol* 83:847–850, 1998

55. Cook KC, Min HY, Johnson D, Chaplinsky RJ, Flier JS, Hunt CR, Spiegelman BM: Adipsin: a circulating serine protease homolog secreted by adipose tissue and sciatic nerve. *Science* 237:402–404, 1987

56. Saleh J, Summers L, Cianflone K, Fielding B, Sniderman A, Frayn K: Coordinated release of acylation stimulating protein (ASP) and triacylglycerol clearance by human adipose tissue in vivo in the postprandial period. *J Lipid Res* 39:884–891, 1998

57. Alessi MC, Peiretti F, Morange P, Henry M, Nalbone G, Juhan-Vague I: Production of plasminogen activator inhibitor 1 by human adipose tissue: possible link between visceral fat accumulation and vascular disease. *Diabetes* 46:860–867, 1997

58. Montague CT, Prins JB, Sanders L, Digby JE, O'Rahilly S: Depot- and sex-specific differences in human leptin mRNA expression. *Diabetes* 46:342–347, 1997

59. Bennett F, Mcfarlane-Anderson N, Wilks R, Luke A, Cooper R, Forrester T: Leptin concentration in women is influenced by regional distribution of adipose tissue. *Am J Clin Nutr* 66:1340–1344, 1997

60. Harmelen VV, Reynisdottir S, Eriksson P, Thorne A, Hoffstedt J, Lonnqvist F, Arner P: Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes* 47:913–917, 1998

61. Rossetti L, Massillon D, Barzilai N, Vuguin P, Chen W, Hawkins M, Wu J, Wang J: Short term effects of leptin on hepatic gluconeogenesis and *in vivo* insulin action. *J Biol Chem* 272:27758–27763, 1997

62. Sivitz W, Walsh S, Morgan D, Thomas M, Haynes W: Effects of leptin on insulin sensitivity in normal rats. *Endocrinology* 138:3395–3401, 1997

63. Shimomura I, Funahashi T, Takahashi M, Maeda K, Kotani K, Nakamura T, Yamashita S, Miura M, Fukuda Y, Takemura K, Tokunaga K, Matsuzawa Y: Enhanced expression of PAI-1 in visceral fat: possible contributor to vascular disease in obesity. *Nat Med* 2:800–803, 1996

64. Eriksson P, Reynisdottir S, Lönnqvist F, Stemme V, Hamsten A, Arner P: Adipose tissue secretion of plasminogen activator inhibitor-1 in non-obese and obese individuals. *Diabetologia* 41:65–71, 1998

65. Niesler C, Siddle K, Prins J: Human preadipocytes display a depot-specific susceptibility to apoptosis. *Diabetes* 47:1365–1368, 1998

66. Montague C, Prins J, Sanders L, Zhang J, Sewter C, Digby J, Byrne C, O'Rahilly S: Depot-related gene expression in human subcutaneous and omental adipocytes. *Diabetes* 47:1384–1391, 1998

67. Hauner H, Wabitsch M, Pfeiffer EF: Differentiation of adipocyte precursor cells from obese and nonobese adult women and from different adipose tissue sites. *Horm Metab Res Suppl* 19:35–39, 1988

68. Tontonoz P, Hu E, Spiegelman BM: Stimulation of adipogenesis in fibroblasts by PPARγ2, a lipid-activated transcription factor. *Cell* 79:1147–1156, 1994

69. Forman BM, Tontonoz P, Chen J, Brun RP, Spiegelman B, Evans RM: 15-Deoxy-12,14-prostaglandin J2 is a ligand for the adipocyte determination factor PPARγ. *Cell* 83:803–812, 1995

70. Adams M, Montague CT, Prins JB, Holder JC, Smith SA, Sanders L, Sewter CP, Digby JE, Lazar MA, Chatterjee VKK, O'Rahilly S: Activators of PPARγ have depot-specific effects on human pre-adipocyte differentiation. *J Clin Invest* 100:3149–3153, 1997

71. Burris T, Pelton P, Zhou L, Osborne M, Cryan E, Demarest K: A novel method for analysis of nuclear receptor function at natural promoters: peroxisome proliferator-activated receptor gamma agonist actions on ap2 gene expression detected using branched DNA messenger RNA quantitation. *Mol Endocrinol* 13:410–417, 1999

72. Kelly I, Han T, Walsh K, Lean M: Effects of a thiazolidinedione compound on body fat and fat distribution of patients with type 2 diabetes. *Diabetes Care* 22:288–293, 1999

73. Mori Y, Murakawa Y, Okada K, Horikoshi H, Yokoyama J, Tajima N, Ikeda Y: Effect of troglitazone on body fat distribution in type 2 diabetic patients. *Diabetes Care* 22:908–912, 1999

74. Yanase T, Yashiro T, Takitani K, Kato S, Taniguchi S, Takayanagi R, Nawata H: Differential expression of PPARγ1 and γ2 isoforms in human adipose tissue. *Biochem Biophys Res Commun* 233:320–324, 1997