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Etiology and Pathophysiology

Subcutaneous and visceral adipose tissue: structural and functional differences

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Summary

Obesity is a heterogeneous disorder. Obese individuals vary in their body fat distribution, their metabolic profile and degree of associated cardiovascular and metabolic risk. Abdominal obesity carries greater risk of developing diabetes and future cardiovascular events than peripheral or gluteofemoral obesity. There are differences between adipose tissue present in subcutaneous areas (SCAT) and visceral adipose tissue (VAT) present in the abdominal cavity. These include anatomical, cellular, molecular, physiological, clinical and prognostic differences. Anatomically, VAT is present mainly in the mesentery and omentum, and drains directly through the portal circulaion to the liver. VAT compared with SCAT is more cellular, vascular, innervated and contains a larger number of inflammatory and immune cells, lesser preadipocyte differentiating capacity and a greater percentage of large adipocytes. There are more glucocorticoid and androgen receptors in VAT than in SCAT. VAT adipocytes are more metabolically active, more sensitive to lipolysis and more insulin-resistant than SCAT adipocytes. VAT has a greater capacity to generate free fatty acids and to uptake glucose than SCAT and is more sensitive to adrenergic stimulation, while SCAT is more avid in absorption of circulating free fatty acids and triglycerides. VAT carries a greater prediction of mortality than SCAT.

Keywords: Adipokines, adipose tissue, fatty acids, obesity.

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Aim of this review

- provides a better understanding of the structure and function of adipose tissue as it relates to its distribution in subcutaneous and visceral areas;
- describe the heterogenous nature of obesity and the important differences between visceral and subcutaneous adiposity;
- introduces the reader to modern basic science information related to adipocyte physiology such as molecular biology of adipose tissue, insulin resistance and regional fat metabolism.

Introduction

It has been recognized for more than 60 years (1) that the cardiovascular risk of obesity and increased body weight are related more to body fat distribution rather than total body fat. Individuals with upper abdominal, central or android obesity are at a greater risk than those with gluteofemoral, peripheral or gynoid obesity. Fat present around abdominal viscera in mesentery and omentum, known as visceral fat, is different from that present in subcutaneous areas (subcutaneous fat). The type of fat cells (adipocytes), their endocrine function, lipolytic activity,

response to insulin and other hormones differ between subcutaneous adipose tissue (SCAT) and visceral adipose tissue (VAT). Inflammatory cells (macrophages) are more prevalent in visceral compared with subcutaneous fat (2,3). However this was not found by all investigators (4).

Subcutaneous fat accumulation represents the normal physiological buffer for excess energy intake (high-caloric diet) with limited energy expenditure (physical inactivity). It acts as a metabolic sink where excess free fatty acids (FFAs) and glycerol are stored as triglycerides (TGs) in adipocytes (5). When the storage capacity of SCAT is exceeded or its ability to generate new adipocytes is impaired because of either genetic predisposition or stresses (physiological and mental stress), fat begins to accumulate in areas outside the subcutaneous tissue – the natural store house for energy. Chronic stress leads to elevated cortesol levels that may lead to accumulation of VAT (6).

The anatomical and physiological differences between VAT and SCAT help explain the increased metabolic and cardiovascular risks associated with abdominal obesity. It is important to mention that the sequences proposed are being hypothetical.

Anatomical differences

The main areas for subcutaneous fat deposition are the femerogluteal regions, back and anterior abdominal wall. About 80% of all body fat is in the subcutaneous area (7,8). The abdominal fat is present in two main depots: subcutaneous and intra-abdominal.

Intra-abdominal fat

Visceral fat accounts for up to 10–20% of total fat in men and 5–8% in women (7). The amount of visceral fat increases with age in both genders (7).

Portal drainage

Because of its anatomical position, visceral fat venous blood is drained directly to the liver through the portal vein. This contrasts with subcutaneous fat where venous drainage is through systemic veins. The portal drainage of visceral fat provides direct hepatic access to FFAs and adipokines secreted by visceral adipocytes. Adipokines activate hepatic immune mechanisms with production of inflammatory mediators such as C-reactive protein (CRP) (9,10).

Cellular differences

Structure of adipose tissue

The adipose tissue is made of a large number of adipocytes, other non-fat cells, connective tissue matrix, vascular and neural tissues. The non-adipocytes cellular component includes inflammatory cells (macrophages), immune cells, preadipocytes and fibroblasts.

Adipocytes

Adipocytes constitute the main cellular component of adipose tissue and are the chief storage depots of the energy in form of TG droplets. New smaller adipocytes act as a sink or powerful buffers, which avidly absorb FFAs and TGs in the postprandial period. As adipocytes grow larger, they become dysfunctional. Large adipocytes are insulin-resistant, hyperlipolytic and resistant to anti-lipolytic effect of insulin. VAT contains greater number of large adipocytes in contrast to SCAT, which contains the small adipocytes. Small adipocytes are more insulin-sensitive and have high avidity for FFAs and TGs uptake, preventing their deposition in non-adipose tissue (10,11).

Vascularity and innervation

Visceral adipose tissue is characterized by being more vascular, rich in blood supply and more heavily innervated than SCAT.

Molecular differences

- Receptors: adipose tissue cells are provided by receptors that are activated by three types of signals (i) Chemical signals in form of the circulating endocrine hormones that reach adipocytes through bloodstream; (ii) Chemical signals of biologically active molecules (adipokines) that are generated locally in adipose tissue and activate the neighbouring fat tissue cells through paracrine mechanisms and (iii) Nervous signals in form of the nerve impulses originating in the central nervous system and activating specific adrenergic receptors in fat tissue e.g. β_3-adrenergic receptors and α_2-adrenergic receptors.
- Adipokines: adipose tissue is capable of synthesizing a number of peptides, proteins and cytokines. These biologically active molecules are known as adipokines. Over 50 adipokines have already been identified (12).

Adipose tissue receptors

There are regional variations in the adipose tissue receptors density, affinity and signal transduction.

Glucocorticoid receptors

Glucocorticoid receptors are involved in metabolic regulation and distribution of body fat (13). They show regional variation in density with elevated concentrations in VAT (14).

Androgen receptors

Androgen receptors have higher density in VAT adipocytes than in adipocytes isolated form SCAT (5). After middle age in men, with decline in testosterone, more fat is deposited in VAT stores, and SCAT tends to decrease after age of 50 years (15).

Oestrogen receptors

Oestrogen receptors are expressed in human adipose tissue (16) and show regional variation in density with gender differences and greater binding capacity in SCAT (17). Oestrogen promotes the accumulation of peripheral gluteofemoral SCAT, which may be protective. Deficiency of oestrogens contribute to increase in VAT in postmenopausal women (5,15).

Adrenergic receptors

Abdominal visceral adipocytes, compared with subcutaneous abdominal or femoral adipose cells, are more sensitive to catecholamine-induced lipolysis and less sensitive to α_2-adrenergic receptor-dependent inhibition of lipolysis (18,19).

Increased β_3-adrenoreceptor sensitivity and α_2-adrenergic receptor sensitivity to catecholamine stimulation is present in VAT compared with SCAT (20). Level of β_3-adrenoreceptors is higher in VAT (21).

Adipokines and modern adipocyte physiology

Mature adipocytes act as an active endocrine and paracrine organ and through a communication network with other tissue, sympathetic nervous system and brain can influence appetite, energy balance, immunity, insulin sensitivity, angiogenesis, blood pressure, lipid metabolism and homeostasis. Adipocytes contribute to the raised pro-inflammatory state in obesity and diabetes. They are capable of synthesizing pro-inflammatory and anti-inflammatory proteins. They secrete monocyte chemoattract protein-1 that can induce macrophages infiltration and activation in adipose tissue. Macrophages are important source of inflammatory cytokines such as tumour necrosis factor (TNF)-α and IL-6. New discoveries have demonstrated the diversity of adipokines (12,22–24) including classical cytokines, growth factors, protein involved in vascular haemostasis, glucose haemostasis, angiogenesis and acute phase responses. Six adipokines were newly identified as secretary products of omental adipose tissue (25): three chemokines (growth-related oncogen factor, RANTES, macrophage inflammatory protein-1B), one interlukin (IL-7), one tissue inhibitor of metalloproteinases (TIMP-), and one growth factor (thrombopoietin). The following is a summary of functions of some important adipokines.

Leptin

- Signals the status of energy stores and its secretion can reduce appetite and increase energy expenditure.
- Development of vasculature (angiogenesis).
- Production of red blood cells (haemotopoisesis).
- Immunity.
- Induce proliferation and migration of vascular smooth muscle cells.
- Enhance platelet aggregation and arterial thrombosis.
- Obesity is associated with elevated leptin levels. Leptin is a sensitive marker for predicting cardiovascular risk and metabolic syndrome.

Adiponectin

- Anti-atherogenic: inhibits expression of adhesion molecules and vascular smooth muscle cells proliferation and suppresses transformation of macrophages to foam cells. It induces the production of important anti-inflammatory factors such as IL-10.
- Anti-diabetic: increases insulin sensitivity and decreases hepatic glucose output. It increases fatty acid oxidation.
- Adiponectin is decreased in abdominal obesity.

IL-6

- Proatherogenic: increase vascular inflammation.
- Prodiabetic: decrease insulin signalling.
- Major regulator of hepatic CRP production.
- IL-6 is increased is abdominal obesity; 30% of circulating IL-6 originates from adipose tissue.

TNF-α

- Proatherogenic: increase vascular inflammation (activates transcription factor nuclear factor-κ B).
- Prodiabetic: decrease insulin sensitivity and insulin signalling.
- TNF-α is increased in abdominal obesity.

CRP

- Proatherogenic: increase vascular inflammation.
- Correlates with metabolic syndrome.
- Prodiabetic: predict development of diabetes.
- CRP is increased in abdominal obesity.

Plasminogen activator inhibitor-1 (PAI-1)

- Proatherogenic: increase atherothrombotic risk, increase thrombosis function.

Interactions between adipokines

Tumour necrosis factor-α and interlukins increase leptin gene expression and circulating leptin levels (26,27). TNF-α contributes to obesity-related hyperliptonemia by regulating leptin release from adipocytes (26). PAI-1 production was significantly correlated with that of TNF-α, emphasizing a possible local contribution of TNF-α in the

regulation of PAI-1 production by human adipose tissue (28). Adiponectin has been shown to inhibit the TNF-α-induced changes in monocyte adhesion molecule expression and in the endothelial inflammatory response (29). Interlukins and TNF-α are potent inhibitors of adiponectin expression and secretion in human white adipose tissue (30).

There are differences between VAT and SCAT regarding the capacity to synthesize and release adipokines.

Leptin. Leptin expression and levels increase as the size of adipose tissue TG stores increase (24,26). Subcutaneous fat depot is the major source of leptin (7).

Adiponectin. Adiponectin is expressed more in VAT than SCAT (5,31). There is significant negative correlation between body weight and plasma adiponectin level.

Pro-inflammatory cytokines – TNF-α, CRP and IL-6. VAT is more infiltrated with inflammatory cells and is more capable of generating those proteins than SCAT (4,32,33). Abdominal obesity increases levels of inflammatory markers. CRP levels were significantly related to waist circumference (WC) and VAT (34,35). Compared with SCAT, VAT was more highly associated with monocyte chemoattract protein-1 (35).

Angiotensinogen. Adipose tissue constitutes the most important source of angiotensinogen after the liver (7). Angiotensinogen is expressed more in VAT than SCAT (36,37).

Plasminogen activator inhibitors-1. In obesity, PAI-1 levels are increased. PAI-1 is expressed more in VAT than SCAT. Omental adipose tissue secretes PAI-1 than does SCAT (38).

Physiological and metabolic differences

Insulin resistance

Adipocytes from VAT are more insulin-resistant than SCAT adipocytes (39,40). Smaller adipocytes tend to be more insulin-sensitive; large adipocytes become insulin-resistant (41,42). Amount of visceral fat is an important factor associated with variations in insulin sensitivity (10,11,43).

Insulin resistance prevents glucose and more fat from entering the cell and becoming preferentially oxidized. Subjects with visceral abdominal obesity, when compared with those with peripheral obesity, had lower glucose disposal, glucose oxidation and greater lipid oxidation.

Insulin resistance may be one of the most important factors linking abdominal visceral adiposity to cardiovascular risk.

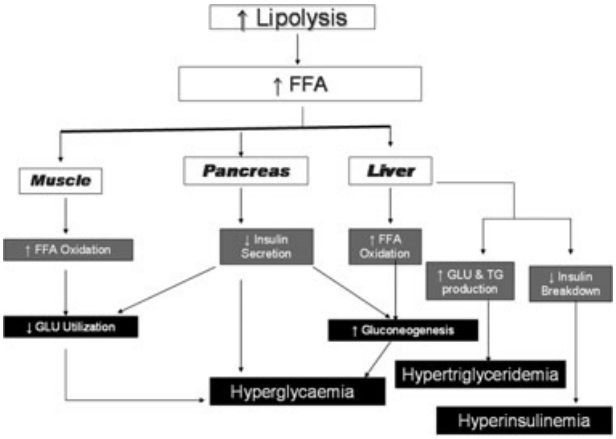

Figure 1 Adverse effects of increased lipolysis and FFA mobilization. FFAs, free fatty acids; TG, triglyceride.

Rate of lipolysis – free fatty acids and glycerol release

Visceral adipocytes are more metabolically active and have a greater lipolytic activity than SCAT adipocytes (44,45). VAT is more susceptible to the catecholamine-induced lipolysis and less to the anti-lipolytic action of insulin.

Free fatty acids induce insulin resistance. In the liver, insulin inhibits gluconeogenesis and glycogenlysis and stimulates glycogen formation. Actions that limit hepatic glucose production are shown in Fig. 1.

The degree of FFA suppression following meal ingestion differs between abdominally and peripherally obese persons. FFAs release is greater in the abdominally obese individuals (5).

Glucose uptake

Visceral adipose tissue has higher rate of insulin-stimulated glucose uptake compared with SCAT adipocytes.

Absorption of circulating free fatty acids and triglycerides

Small adipocytes in SCAT have a high avidity for FFAs and TG uptake. The new, small, more insulin-sensitive adipocytes act as a sink or powerful 'buffers', avidly absorbing circulating FFAs and TGs in the postprandial period (5,8). SCAT cells may act as a buffer or sink for circulating FFAs and TGs, but once they reach their capacity they loose their protective benefit, fat begins to accumulate in tissues not suited for lipid storage (5) (Fig. 2). SCAT in abdominal wall has higher uptake of TGs and larger FFA release per kilograms than does femoral fat (10,43).

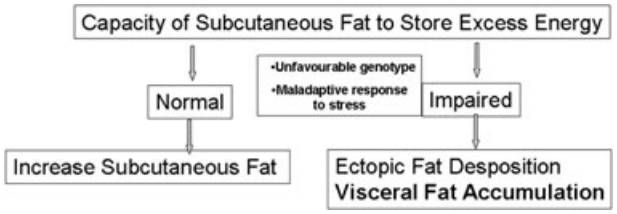

Figure 2 Energy surplus results in accumulation of triglycerides in adipocytes at subcutaneous adipose tissue, which acts as a metabolic sink. When capacity of subcutaneous fat is exceeded or if it is impaired, fat will accumulate in areas outside the subcutaneous compartment.

Clinical and prognostic differences

Metabolic risks

Visceral fat accumulation is associated with tendency to hyperglycaemia, hyperinsulinemia, hypertriglyceridemia, impaired glucose tolerance, increased apolipoproteins B-rich lipoproteins, which are features of the insulin resistance syndrome. Increased risk of developing diabetes is greater in individuals with excess VAT (42,45,46). Individuals with high levels of VAT area had higher mean plasma cholesterol and TG levels and lower high-density lipoprotein cholesterol values (47).

Metabolic syndrome

An increased body WC is considered now to be a prerequisite of the metabolic syndrome.

Visceral obesity, like hyperinsulinemia and insulin resistance, not only accompanies but antedates the components of the metabolic syndrome (45,48).

Elevated arterial blood pressure that is one of the components of the metabolic syndrome was explained by insulin resistance and compensating hyperinsulinemia in viscerally obese individuals (49–51). Central obesity can induce the development of hypertension through increased activity of adipose tissue renin-angiotensin-aldosterone system, sympathetic activation and other mechanisms closely connected with insulin resistance.

Vascular risk and cardiovascular events

Visceral fat quantified as waist size has been identified as an independent risk factor for cardiovascular disease, hypertension and stroke (46,52). Excess VAT has the potential to cause hypercoagulability because of increased secretion of PAI-1. Increased WC when accompanied by increased TG leads to increased risk of coronary heart disease (53,54).

Abdominal obesity correlates closely with other measures of atherosclerosis such as intima–media thickness (55). Peripheral arterial disease also has been correlated to VAT, but not to total body fat in elderly subjects (56). Subjects with abdominal obesity were reported to have greater risk of having an abnormal albumin excretion rate (57). Microalbuminuria signifies enhanced cardiovascular risk. Hyperinsulinemia, associated with visceral obesity, is a predictor of coronary artery disease (58).

Increase in circulating FFAs in abdominal obesity is associated with increase in cardiovascular risk. Elevations in FFA levels promote endothelial dysfunction (50).

Assessment of cardiovascular risk in obese patients from the measurement of body weight may be misleading (59). Only obese individuals characterized by increased VAT show the complications predictive of type 2 diabetes and cardiovascular disease (51). Women generally display a more favourable risk profile than men, and generally lower level of VAT than men. Adjustments for differences in visceral fat between men and women eliminated most of the sex differences in cardiovascular risk factors (60). Peripheral or gluteofemoral fat distribution seems to be protective against atherosclerosis (61–63).

Prediction of mortality

Obesity is associated with increased cardiovascular disease mortality (64,65). Cardiovascular disease death rates are directly related to body mass index in both men and women. Obesity in adulthood is also associated with a striking reduction in life expectancy (66). Abdominal adiposity as measured by WC is a significant predictor of mortality independently of body mass index (67). Visceral fat is a strong, independent predictor of all-cause mortality in men (68).

Effects of weight reduction

Visceral adipose tissue is more sensitive to weight reduction than SCAT (percentage wise) (69). All forms of weight loss affect visceral fat more than subcutaneous fat (70). However, recently Hall and Hallgreen (71) using simple allometric model predicts that increasing weight loss attenuates the preferential loss of VAT vs. SCAT. They concluded that greater weight loss will cause a greater absolute reduction of VAT mass.

Obesity being a chronic low-grade inflammatory state is associated with increased plasma levels of inflammatory markers such CRP. A recent study shows that weight reduction is associated with decrease in CRP level. For every 1 kg of weight loss, CRP levels dip by 0.13 mg L^{-1} (72). Other adipokines also change with weight loss. Extreme weight reduction in obese individuals was associated with an increase in plasma adiponectin concentrations (73).

Future directions

Research is needed on the molecular and cellular mechanisms and signals for adipose tissue. Determination as to which adipocyte factors are most important in promoting metabolic disease will be an important focus for future studies.

Manipulation of adipocyte biology might be a useful therapeutic strategy in metabolic disease. There is a lot of work that remains to be done in the area of adopocytes and adipokines physiology. There are large gaps in our knowledge about the mechanism of action of many adipokines. The existence of additional, yet-unidentified adipocyte-specific factors is highly likely. Prospective cohort trials that use imaging procedures to estimate abdominal and various adipose tissue depots in a precise manner, assess biochemical and metabolic parameters in relation to cardiovascular endpoints are needed.

Racial differences in the accumulation of adipose tissue depots and resulting cardiovascular risk need further investigation.

Abdominal obesity is very common in Middle Eastern countries (74). Women in Egypt and Turkey have the highest proportion of overweight as well as the highest proportion of obesity (75). Ongoing studies are aiming to identify the WC cut-off points that define the threshold of abdominal obesity and an abdominal waist girth. There are racial and genetic variations in body fat distribution that dictates the needs for different thresholds of abdominal obesity among different populations. We are currently correlating in a cross-sectional study (MM Ibrahim *et al.* unpublished observations) the prevalence of a number of cardiovascular risk factors at different levels of WC. The cut-off point based upon this approach is different from the threshold among US, European and Asian men and women.

Conflict of Interest Statement

No conflict of interest was declared.

References

1. Vague J. The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout and uri-calculus disease. *Am J Clin Nutr* 1956; **4**: 20–29.
2. Bruun JM, Lihn AS, Pedersen SB, Richelsen B. Monocyte chemoattractant Protein-1 release is higher in visceral than subcutaneous human adipose tissue (AT): implication of macrophages resident in the AT. *J Clin Endocrinol Metab* 2005; **90**: 2282–2289.
3. Curat CA, Wegner V, Sengenès C, Miranville A, Tonus C, Busse R, Bouloumié A. Macrophages in human visceral adipose tissue: increased accumulation in obesity and a source of resistin and visfatin. *Diabetologia* 2006; **49**: 744–747.
4. Weisberg SP, McCann D, Desai M, Rosenbaum M, Leibel RL, Ferrante AW. Obesity is associated with macrophage accumulation in adipose tissue. *J Clin Invest* 2003; **112**: 1796–1808.
5. Freedland ES. Role of critical visceral adipose tissue threshold in metabolic syndrome: implications for controlling dietary carbohydrates: a review. *Nutr Metab* 2004; **1**: 12.
6. Bjorntrop P. Do stress reactions cause abdominal obesity and comorbidities. *Obes Rev* 2001; **2**: 73–86.
7. Wajchenberg BL. Subcutaneous and visceral adipose tissue: their relation to the metabolic syndrome. *Endocr Rev* 2000; **21**: 679–738.
8. Arner P. Obesity and the adipocyte. Regional adipocity in man. *J Endocrinol* 1997; **155**: 191–192.
9. Heinrich PC, Castell JV, Andus T. Interlukin-6 and the acute phase response. *Biochem J* 1990; **265**: 621–636.
10. Mårin P, Andersson B, Ottosson M, Olbe L, Chowdhury B, Kvist H, Holm G, Sjöström L, Björntorp P. The morphology and metabolism of intra-abdominal adipose tissue in men. *Metabolism* 1992; **41**: 1241–1248.
11. Hisra A, Vikram NK. Clinical and pathophysiological consequences of abdominal adiposity and abdominal adipose tissue depots. *Nutrition* 2003; **19**: 457–466.
12. Trayhurn P, Wood IS. Adipokines: inflammation and pleiotropic role of white adipose tissue. *Br J Nutr* 2004; **92**: 347–355.
13. Joyner JM, Hutley LJ, Cameron DP. Glucocorticoid receptors in human preadipocytes: regional and gender variations. *J Endocrinol* 2000; **166**: 145.
14. Rebuffe'-Scrive M, Lundholm K, Björntorp P. Glucocorticoid hormone binding to human adipose tissue. *Eur J Clin Invest* 1985; **15**: 267–271.
15. Bjorntorp P. Endocrine abnormalities in obesity. *Diabetes Rev* 1997; **5**: 52–68.
16. Mitzutani T, Nishikawa Y, Adachi H, Enomoto T, Ikegami H, Kurachi H, Nomura T, Miyake A. Identification of estrogen receptor in human adipose tissue and adipocytes. *J Clin Endocrinol Metab* 1994; **78**: 950–954.
17. Pedersen SB, Hansen 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* 1996; **26**: 259.
18. Hellmer J, Marcus C, Sonnefeld T, Arner P. Mechanisms for differences in lipolysis between human subcutaneous and omental fat cells. *J Clin Endocrinol Metab* 1992; **75**: 15–20.
19. Arner P, Hellstrom L, Wahrenberg H, Bronnegard M. β-adrenoceptor expression in human fat cells from different regions. *J Clin Invest* 1990; **86**: 1595–1600.
20. Imbeault P, Couillard C, Tremblay A, Després J-P, Mauriège P. Reduced alpha (2)-adrenergic sensitivity of subcutaneous abdominal adipocytes as a modulator of fasting and post-prandial triglyceride levels in men. *J Lipid Res* 2000; **41**: 1367.
21. Krief S, Lönnqvist F, Raimbault S, Baude B, Van Spronsen A, Arner P, Strosberg AD, Ricquier D, Emorine LJ. Tissue distribution of β3-adrenergic receptor MRNA in man. *J Clin Invest* 1993; **91**: 344–349.
22. Matsuzawa Y. Therapy insight: adipocytokines in metabolic syndrome and related cardiovascular disease. *Nat Clin Pract Cardiovasc Med* 2006; **3**: 35–42.
23. David CW, Dhillon B, Yan H, Szmitko PE, Verma S. Adipokines: molecular links between obesity and atherosclerosis. *Am J Physiol Heart Circ Physiol* 2005; **288**: H2031–H2041.
24. Tritos NA, Mantzoros CS. Leptin: its role in obesity and beyond. *Diabetologica* 1997; **40**: 1371–1379.
25. Maury E, Ehala-Aleksejev K, Guiot Y, Detry R, Vandenhooft A, Brichard SM. Adipokines oversecreted by omental adipose tissue in human obesity. *Am J Physiol Endocrinol Metab* 2007; **293**: E656–E665.

26. Mantzoros CS, Moschos S, Avramopoulos I, Kaklamani V, Liolios A, Doulgerakis DE, Griveas I, Katsilambros N, Flier JS. Leptin concentrations in relation to body mass index and the tumor necrosis factor-α system in humans. *J Clin Endocrinol Metab* 1997; **82**: 3408–3413.
27. Kirchgessner TG, Uysal T, Wiesbrock SM, Marino MW, Hotamisligil G. Tumour necrosis factor-alpha contributes to obesity related hypoleptinemia by regulating leptin release from adipocytes. *J Clin Invest* 1997; **100**: 2777–2782.
28. Morange P, Alessi MC, Ventura N, Casanova D, Magalon G, Juhan-Vague I. PAI-1 antigen production by human adipode tissue is correlated with that of TNF-α. Eighth international congress on obesity (Paris, France, August 29–September 3, 1998). *Int J Obes* 1998; **22**(Suppl. 3): P31–PS103.
29. Ouchi N, Kihara S, Arita Y, Maeda K, Kuriyama H, Okamoto Y, Hotta K, Nishida M, Takahashi M, Nakamura T, Yamashita S, Funahashi T, Matsuzawa Y. Novel modulator for endothelial adhesion molecules: adipocyte-derived plasma protein adiponectin. *Circulation* 1999; **100**: 2473–2476.
30. Brunn JM, Lihn AS, Verdich C, Pedersen SB, Toubro S, Astrup A, Richelsen B. Regulation of adiponectin by adipose tissue-derived cytokines: *in vivo* an *in vitro* investigations in human. *Am J Physiol Endocrinol Metab* 2003; **285**: E527–E533.
31. Motoshima H, Wu X, Sinha M, Hardy E, Rosato EL, Barbot DJ, Rosato FE, Goldstein BJ. Differential regulation of adiponectin secretion from cultured human omental and subcutaneous adipocytes: effects of insulin and rosiglitazone. *J Clin Endocrinol Metab* 2002; **87**: 5662–5667.
32. Lemieux I, Pascot A, Prud'homme D, Alméras N, Bogaty P, Nadeau A, Bergeron J, Després JP. Elevated C-reactive protein: another component of the atherothrombotic profile of abdominal obesity. *Arterioscler Thromb Vasc Biol* 2001; **21**: 961–967.
33. Pepys MB, Hirschfield C-M. C-reactive protein: a critical update. *J Clin Invest* 2003; **111**: 1805–1812.
34. Forouhi NG, Sattar N, McKeigue PM. Relation of C-reactive protein to body fat distribution and features of the metabolic syndrome in Europeans and South Asians. *Int J Obs Relat Metab Discord* 2001; **25**: 1327–1331.
35. Pou KM, Massaro JM, Hoffmann U, Vasan RS, Maurovich-Horvat P, Larson MG, Keaney JF, Meigs JB, Lipinska I, Kathiresan S, Murabito JM, O'Donnell CJ, Benjamin EJ, Fox CS, Adipose S. Visceral and subcutaneous adipose tissue volumes are cross-sectionally related to markers of inflammation and oxidative stress: the framingham heart study. *Circulation* 2007; **116**: 1234–1241.
36. Karlsson C, Lindell K, Ottoson M, Sjostrom L, Carlsson B, Carlson LMS. Human adipose tissue expresses angiotensinogen and enzymes required for its conversion to angiotensin II. *J Clin Endocrinol Metab* 1998; **83**: 3925–3929.
37. Dusserre E, Moulin P, Vidal H. Differences in mRNA expression of proteins secreted by adipocytes in human subcutaneous and visceral adipose tissue. *Biochim Biophy Acta* 2000; **1500**: 88.
38. Alessi MC, Peirretti 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* 1997; **46**: 860.
39. Abate N, Garg A, Peshock RM, Stray-Gundersen J, Grundy SM. Relationship of generalized and regional adiposity to insulin sensitivity in man. *J Clin Invest* 1995; **96**: 88–98.
40. Frayn KN. Visceral fat and insulin resistance: causative a correlative. *Br J Nutr* 2000; **83**(Suppl. 1): S71–S77.
41. Salans LB, Cushman SW, Weismann RE. Studies of human adipose tissue. Adipose all size and number in nonobese and obese patients. *J Clin Invest* 1973; **52**: 929–941.
42. Bjorntorp P. Metabolic difference between visceral fat and subcutaneous abdominal fat. *Diabetes Metab* 2000; **26**(Suppl. 3): 10–12.
43. Kadswaki T, Hara K, Yamauchi T, Terauchi Y, Tobe K, Nagai R. Molecular mechanisms of insulin resistance and obesity. *Exp Biol Med* 2003; **228**: 1111–1117.
44. Amer P. Differences in lipolysis between human subcutaneous and omental adipose tissues. *Ann Med* 1995; **27**: 435–438.
45. Lemieux S, Despres SP. Metabolic complications of visceral obesity: contribution to the etiology of life of type 2 diabetes and implications for prevention and treatment. *Diabetes Metab* 1994; **20**: 375–393.
46. Dobbelsteyn CJ, Joffres MR, MacLean DR, Flowerdew G. A comparative evaluation of waist circumference. Waist-to-hip ratio and body mass index as indicators of cardiovascular risk factors. The Canadian Heart Health Surveys. *Int J Obs Relat Metab Disord* 2001; **25**: 652.
47. Despres JP, Allard C, Tremblay A, Talbot J, Bouchard C. Evidence for a regional component of body fatness in association with serum in men and women. *Metabolism* 1985; **34**: 967–973.
48. Bergstrom RW, Newell-Morris LL, Leonetti DL, Shuman WP, Wahl PW, Fujimoto WY. Association of elevated fasting C-peptide level and increased intra-abdominal fat distribution with development of MID in Japanese-American men. *Diabetes* 1990; **39**: 104–111.
49. Rocchini A. Obesity hypertension. *Am J Hypertens* 2002; **15**: 505–525.
50. Sharma AM, Engeli S, Pischon T. New developments in mechansims of obesity-induced hypertension: role of adipose tissue. *Curr Hypertens Rep* 2001; **3**: 152–156.
51. Mc Farlane SI, Banerji M, Sowers JR. Insulin resistance and cardiovascular disease. *J Clin Endocrinol Metabol* 2001; **86**: 713–718.
52. Despres JP. The atherothrombotic and anti-inflammatory profile of visceral obesity. *Int Congr Ser* 2003; **23**: 27–34.
53. Tanko LB, Bagger YZ, Qin G, Alexandersen P, Larsen PJ, Christiansen C. Enlarged waist combined with elevated triglycerides is a strong predictor of accelerated atherogenesis and related cardiovascular mortality in postmenopausal women. *Circulation* 2005; **111**: 1883–1890.
54. Lemieux I, Pascot A, Couillard C, Lamarche B, Tchernof A, Alméras N, Bergeron J, Gaudet D, Tremblay G, Prud'homme D, Nadeau A, Després JP. Hypertriglyceridemic waist: A marker of the atherogenic metabolic triad (hyperinsulinemia, hyperapolipoprotein B, small dense LDL) in men. *Circulation* 2000; **102**: 179–184.
55. Harris MM, Stevens J, Thomas N, Schreiner P, Folsom AR. Association of fat distribution and obesity with hypertension in a bi-ethnic population: the ARIC study. Atherosclerosis Risk in Communities Study. *Obes Res* 2000; **8**: 516–524.
56. Planas A, Clará A, Pou J-M, Vidal-Barraquer F, Gasol A, de Moner A, Contreras C, Marrugat J. Relationship of obesity distribution to peripheral arterial occlusive disease in elderly men. *Int J Obes Relat Metab Disord* 2001; **25**: 1068–1070.
57. Mulyadi L, Stevens C, Munro S, Lingard J, Bermingham M. Body fat distribution and total fat as risk factors for microalbuminuria in the obese. *Ann Nutr Metab* 2000; **45**: 6–71.
58. Fontbonne A, Charles MA, Thibult N, Richard JL, Claude JR, Warnet JM, Rosselin GE, Eschwège E. Hyperinsulinemia as a predictor of coronary heart disease mortality in a healthy population: the Paris Prospective Study, 15-year follow-up. *Diabetologica* 1991; **34**: 356–361.
59. Kissebah AH. Central obesity: measurement and metabolic effects. *Diabet Rev* 1997; **5**: 8–20.

60. Lemieax S, Després JP, Moorjani S, Nadeau A, Thériault G, Prud'homme D, Tremblay A, Bouchard C, Lupien PJ. Are gender differences of cardiovascular disease risk factors explained by the level of visceral adipose tissue. *Diabetologica* 1994; **37**: 757–764.
61. Tanko LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C. Central and peripheral fat mass have contrasting effect on the progression of aortic calcification in post menopausal women. *Eur Heart J* 2003; **24**: 1531–1537.
62. Tanko LB, Bagger YZ, Alexandersen P, Larsen PJ, Christiansen C. Peripheral adiposity exhibits an independent dominant antiatherogeneic effect in elderly women. *Circulation* 2003; **107**: 1626–1631.
63. Lassner L, Bjokelund C, Heitmann BL, Seidell JC, Bengtssan C. Larger hip circumference independently predicts health and longitivity in a Swedish female cohort. *Obes Res* 2001; **9**: 644–646.
64. Dagenais GR, Yi Q, Mann JF, Bosch J, Pogue J, Yusuf S. Prognostic impact of body weight and abdominal obesity in women and men with cardiovascular disease. *Am Heart J* 2005; **149**: 54–60.
65. Allison DB, Fontaine KR, Manson JE, Stevens J, VanItallie TB. Annual death attributable to obesity in the United States. *JAMA* 1999; **282**: 1530–1538.
66. Lee IM, Blair SN, Allison DB, Folsom AR, Harris TB, Manson JE, Wing RR. Epidemiologic data on the relationships of calori intake, energy balance, and weight gain over the lifespan and longevity and morbidity. *J Gerontol A Biol Sci Med Sci* 2001; **56**: 7–19.
67. Zhang X, Shu XO, Yang G, Li H, Cai H, Gao UT, Zheng W. Abdominal obesity and mortality in Chinese women. *Arch Intern Med* 2007; **167**: 886–892.
68. Kuk JL, Katzmarzyk PT, Nichaman MZ, Church TS, Blair SN, Ross R. Visceral fat is an independent predictor of all-cause mortality in men. *Obesity* 2006; **14**: 336–341.
69. Bjorntorp P. Regional obesity. In: Bjorntorp P, Brodoff BN (eds). *Obesity*. JB Lippincott Co.: Philadelphica, PA, 1992, pp. S79–S86.
70. Armellini F, Zamboni M, Rigo L, Bergamo-Andries IA, Robbi R, De Marchi M, Bosello O. Sonography detection of small intra abdominal fat variation. *Int J Obes* 1991; **15**: 847–852.
71. Hall KD, Hallgreen CE. Increasing weigh loss attenuates the preferential loss of visceral vs. subcutaneous fat: a predicted result of an allometric model. *Int J Obes* 2008; **32**: 722.
72. Selvin E, Paynter NP, Erlinger TP. The effect of weight loss on C-reactive protein: a systematic review. *Arch Intern Med* 2007; **167**: 31–39.
73. Corpeleijn E, Feskens EJM, Jansen EH, Mensink M, Saris WHM, Blaak EE. Lifestyle intervention and adipokine levels in subjects at high risk for type 2 diabetes: the study on lifestyle intervention and impaired glucose tolerance Maastricht (SLIM). *Diabetes Care* 2007; **30**: 3125–3127.
74. WHO Eastern Mediterranean Region: Annual Report of the Regional Director. The work of WHO in the Eastern Mediterranean Region (2006): Annual Report of the Regional Director. [WWW document]. URL http://www.emro.who.int/rd/annualreports/2006/chapter1_6.htm (accessed 22 March 2009).
75. Martorell R, Khan LK, Hughes ML, Grummer-Strawn LM. Obesity in women from developing countries. *Eur J Clin Nutr* 2000; **54**: 247–252.

