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Visceral fat and insulin resistance – causative or correlative?

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The association between abdominal fat accumulation and risk of chronic diseases, including type II diabetes and coronary heart disease, has long been recognized. Insulin resistance may be a key factor in this link. Many studies have pointed to an association between insulin resistance and intra-abdominal fat accumulation (visceral obesity). However there is no clear proof of a causal link between visceral fat accumulation and insulin resistance. In assessing the probability of a causal link, it is useful to consider potential mechanisms. One such potential causal link is the release of non-esterified fatty acids from visceral fat into the portal vein, so that they have direct effects on hepatic metabolism. Visceral fat has been shown in many studies to exhibit a high rate of lipolysis compared with subcutaneous fat depots. However, if the idea that visceral fat releases fatty acids into the portal vein at a high rate is examined critically, a number of difficulties appear. Not least of these is the fact that continued high rates of lipolysis should lead to the disappearance of the visceral fat depot, unless these high rates of fat mobilization are matched by high rates of fat deposition. There is far less evidence for high rates of fat deposition in visceral adipose tissue, and some contrary evidence. Evidence for high rates of visceral lipolysis *in vivo* from studies involving catheterization of the portal vein is not strong. If this potential link is discounted, then other reasons for the relationship between visceral fat and insulin resistance must be considered. One is that there is no direct causal link, but both co-correlate with some other variable. A possibility is that this other variable is subcutaneous abdominal fat, which usually outweighs intra-abdominal fat several-fold. Subcutaneous fat probably plays the major role in determining systemic plasma non-esterified fatty acid concentrations, which are relevant in determining insulin resistance. In conclusion, there is at present no proof of a causal link between visceral fat accumulation and insulin resistance, or the associated metabolic syndrome. The possibility of co-correlation with some other factor, such as subcutaneous abdominal fat accumulation, must not be forgotten.

Visceral fat: Insulin resistance: Non-esterified fatty acids: Subcutaneous abdominal fat

Introduction

Jean Vague drew attention more than 50 years ago to the existence of two relatively distinct patterns of fat distribution in adult humans, which he called android, or male-type, and gynoid, or female-type (Vague, 1947). He showed that android, or upper-body, fat deposition was associated with increased risk of a number of chronic diseases, including type 2 diabetes, atherosclerosis and gout (Vague, 1956). Since that time his prescient work has been reinforced by a large number of studies, both cross-sectional and, more recently, prospective. Prospective studies have confirmed a link between upper-body fat accumulation and subsequent mortality (Fontbonne *et al*. 1992; Folsom *et al*. 1993; Kalmijn *et al*. 1999).

The diseases that Jean Vague showed to be associated with upper-body obesity tend to cluster together. Reaven (1988) proposed that a common feature underlying this cluster of related conditions is insulin resistance, or a failure of insulin to act normally on target tissues. Insulin resistance, according to Reaven, is associated with a constellation of risk factors for coronary heart disease and type 2 diabetes (Table 1). It is now recognized that upper-body fat deposition and insulin resistance are closely associated, and many would argue that lower-body obesity is relatively harmless and is much less strongly associated with insulin resistance (Björntorp, 1988; Kissebah & Krakower, 1994). Many studies now show an association between upper-body obesity and insulin resistance, and also risk of developing type 2 diabetes (reviewed by Kissebah & Krakower, 1994).

Understanding of the metabolic basis of the adverse effects of upper-body fat distribution increased in the 1980s when Ashwell and others showed that upper-body obesity was associated with fat accumulation within the abdomen, visualized with computerized tomography (Ashwell *et al*. 1985). The technique of magnetic resonance

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Table 1. Metabolic and other factors that associate with insulin resistance

Factor	Comments	Reference
Hypertriacylglycerolaemia	Often mild	
Increased postprandial lipaemia		(Jeppesen *et al.* 1995)
Low HDL-cholesterol concentration		
Preponderance of small, dense LDL particles	LDL-cholesterol concentration is often normal or only mildly elevated	(Reaven *et al.* 1992)
Glucose intolerance		
Elevated PAI-1 concentrations	Associated with impaired fibrinolysis	(Landin *et al.* 1990)
Obesity, especially visceral obesity		
Hypertension		

The basis of this table is the original description of the 'insulin resistance syndrome' or Syndrome X by Reaven (1988), but it has been expanded since that time.

imaging has also been used more recently to visualize and measure these intra-abdominal depots (Ross *et al*. 1992). There are several abdominal fat depots, including anterior and posterior subcutaneous depots, and both intra- and retro-peritoneal intra-abdominal depots (Table 2). Of these the anterior subcutaneous depot is usually the largest and has the capacity to expand the most (Thomas *et al*. 1998). This 'paunch' depot has homologues in other primates, but is absent from rodents except when they are very obese (Pereira & Pond, 1995). Of the intra-abdominal depots, most attention has focused upon the omental and mesenteric depots (the visceral fat depots). One reason for this, which will be expanded upon below, is that venous drainage from these depots is directed mostly into the portal vein and therefore its metabolic products reach the liver directly (Björntorp, 1990).

A number of studies have been aimed at identifying which of these various abdominal depots is most closely associated with insulin resistance. This is problematic since the subcutaneous and intra-abdominal depots are themselves correlated, with correlation coefficients from 0·72 (Abate *et al*. 1995) to 0·92 (Thomas *et al*. 1998; raw data kindly supplied by Dr E. Louise Thomas). One approach used specifically to examine the contribution of the intra-abdominal depots has been to select subjects with large or small amounts of intra-abdominal fat, but to match them for total body fat and for subcutaneous abdominal fat. One study using this approach seemed to show that intra-abdominal fat accumulation is associated with insulin resistance (Després *et al*. 1989). However the correlation between depots makes this difficult, and in this particular study the groups did also differ in subcutaneous abdominal fat (by 11 % on average). Furthermore, the complementary experiment, matching for intra-abdominal fat and comparing people with high and low amounts of subcutaneous abdominal fat, has not been done. Another approach is to study a large number of people and use correlation analysis. Studies using this technique show that the closest correlation with insulin resistance is seen with the subcutaneous abdominal depots (Abate *et al*. 1995, 1996; Misra *et al*. 1997). Interestingly, these studies seem to show that the posterior subcutaneous depot is more closely associated with insulin resistance than is the anterior depot (paunch) (Misra *et al*. 1997). The perirenal depot in these studies is clearly not associated with insulin resistance (Abate *et al*. 1995, 1996).

Table 2. Major abdominal fat depots in humans

Depot	Approximate size (kg)	Comments
Subcutaneous (anterior + posterior)	1–20	The most variable of the abdominal depots
Intra-abdominal		
Omental	0·5–3	'Visceral' depots; drain mostly to portal vein
Mesenteric	0·5–2	
Perirenal	0·5–2	Retro-peritoneal

Data from Abate *et al.* (1995, 1997); Thomas *et al.* (1998) and also collated with help from Dr Caroline Pond, Open University, UK.

There is, then, a clear association between abdominal obesity and insulin resistance. Some studies suggest that the intra-abdominal or visceral depots show the closest link with insulin resistance, although others do not, and more evidence on this point is needed. However the observation of a link between abdominal obesity and insulin resistance does not mean that the former causes the latter. It could mean that insulin resistance causes abdominal obesity, or that both abdominal obesity and insulin resistance co-correlate with some other factor. This dilemma was encapsulated by Seidell and Bouchard when they asked: ''Visceral fat in relation to health: is it a major culprit or simply an innocent bystander?'' (Seidell & Bouchard, 1997).

How can causality be proved? One clear proof would be to show that specific removal of abdominal fat relieves insulin resistance. Although complete omentectomy is a standard surgical procedure, its effects on insulin resistance or lipid metabolism have not been reported. In one study in rats, elderly (and therefore obese) rats were subjected to surgery to remove two intra-abdominal fat depots, the epididymal and the perirenal. This resulted in marked improvement of the insulin resistance characteristic of elderly, obese rats (Barzilai *et al*. 1999). However, it should be noted that these two particular depots are not the typical visceral depots, and as noted above the perirenal depot has not been found to relate to insulin resistance in humans. Therefore whilst such a study seems to prove causality, in this case its relevance to human abdominal obesity is not clear.

Table 3. Potential mechanisms linking visceral obesity with insulin resistance

Mechanism	Comments
Mechanical	No evidence for this although volume of intra-abdominal fat may be considerable (see text)
Secretion of proteins or other factors	Differential secretion or expression of a few factors has been shown (in visceral versus subcutaneous fat) and is discussed in the text
Liberation of non-esterified fatty acids (NEFA)	Visceral depots drain mostly into the portal vein, so NEFA released from them would have direct effects on hepatic metabolism. Discussed further in the text

I thank Dr Peter Arner for suggesting these hypotheses.

Mechanisms linking abdominal obesity with insulin resistance

In the absence of definitive proof in humans of a causal link between visceral obesity and insulin resistance, it is helpful to ask if a plausible mechanism (or mechanisms) exists that could explain such a link. There are perhaps three major hypotheses (Table 3).

The idea that accumulation of intra-abdominal adipose tissue causes mechanical interference, for instance with hepatic function, has no supporting evidence and will not be considered in detail. This is not to say that it is not plausible. In gross obesity (BMI $>40\,kg/m^2$) the intra-abdominal fat depots may exceed 6 litres in volume (Thomas *et al*. 1998). Professor Peter Jones (Loughborough University), using data from Snyder (1975), has estimated the normal intra-abdominal volume at 8·8 litres (P. Jones, unpublished results). Therefore the accumulation of intra-abdominal fat in massive obesity is almost certain to cause compression of the viscera and, by displacement of the diaphragm, of the lungs. Whether this will have metabolic effects is not clear.

The recent recognition of adipose tissue as a major secretory organ (Siiteri, 1987; Mohamed-Ali *et al*. 1998) has led to the suggestion that visceral fat might release some factor that leads to systemic disturbances in metabolism. In a number of studies, differential display or similar techniques have been used to investigate genes that might be over-expressed in visceral fat compared with subcutaneous fat. Some differences have been found: for instance, the cellular inhibitor of apoptosis protein-2 is expressed more highly in visceral than subcutaneous adipose tissue (Montague *et al*. 1998). Amongst secreted peptides there are two major differences between the depots: leptin is both more highly expressed in, and secreted from, subcutaneous than visceral adipose tissue (Montague *et al*. 1998; Van Harmelen *et al*. 1998), whereas plasminogen activator inhibitor-1 (PAI-1) is more highly secreted from visceral fat (Alessi *et al*. 1997). Both provide possible links with some aspects of insulin resistance. If fat is deposited more in visceral than subcutaneous depots, it could be argued that the lower leptin secretion from the visceral fat will lead to less effective responses to obesity, and thus fat accumulation and associated insulin resistance is more likely to increase. But that does not really address the specific relationship between visceral fat and insulin resistance. Elevated circulating concentrations of PAI-1 are associated with insulin resistance (Landin *et al*. 1990) and may have a role in the impaired fibrinolysis associated with that condition. Therefore visceral fat accumulation could lead directly to some of the consequences of insulin resistance, although no-one has proposed that PAI-1 itself can lead to all aspects of insulin resistance.

There has been considerable interest in the finding that adipocytes express a number of cytokines including interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α) (Mohamed-Ali *et al*. 1998). Of these, IL-6 is more highly secreted from visceral than subcutaneous adipose tissue (Fried *et al*. 1998), whereas there is no difference (at least in expression) for TNF-α (Montague *et al*. 1998). It is also relevant, as discussed earlier, that the venous drainage from visceral fat enters the portal vein and so cytokines secreted from visceral adipose tissue could have particularly marked effects on hepatic metabolism. The relevance to insulin resistance is not clear, however. Insulin resistance (as usually measured with the euglycaemic–hyperinsulinaemic clamp technique) involves a reduction in peripheral sensitivity to insulin, and it seems more likely that local expression of TNF-α is involved: its expression is up-regulated in skeletal muscle (Saghizadeh *et al*. 1996) as well as in adipose tissue (Hotamisligil *et al*. 1995) in insulin-resistant states. This view is reinforced by the recent demonstration that no secretion into the circulation of TNF-α is detectable from human adipose tissue *in vivo*, although IL-6 is released (Mohamed-Ali *et al*. 1997).

The third plausible mechanism linking visceral adiposity with insulin resistance is the liberation of non-esterified fatty acids (NEFA) from visceral depots. This hypothesis is attractive for several reasons. Many of the conditions associated with insulin resistance might reflect increased delivery of fatty acids to the liver: for instance, stimulation of hepatic glucose production (Ferrannini *et al*. 1983) would lead to glucose intolerance; stimulation of hepatic VLDL-triacylglycerol (TG) secretion would lead to hypertriacylglycerolaemia, and potentially to impaired postprandial lipid metabolism (via competition with chylomicron-TG for peripheral clearance); and fatty acids have been shown to interfere with hepatic insulin removal (Svedberg *et al*. 1990; Wiesenthal *et al*. 1999), thus leading to hyperinsulinaemia. NEFA released from visceral adipose tissue, and delivered into the portal vein, might therefore have a particularly important role in bringing about many of the features of insulin resistance. In addition, in studies of adipose tissue explants or isolated adipocytes from different depots, it has consistently been shown that omental and mesenteric adipocytes have higher rates of lipolysis than subcutaneous, and that their lipolysis is more readily stimulated by catecholamines and less readily suppressed by insulin (Östman *et al*. 1979; Engfeldt & Arner, 1988). The mechanisms that bring about this high lipolytic capacity in visceral adipocytes include greater sensitivity to the stimulatory β-adrenoceptors and lower sensitivity to the anti-lipolytic α-adrenoceptors, as well as to the receptors for other inhibitory agents such as adenosine and insulin (Mauriège *et al*. 1987; Van Harmelen *et al*. 1997; Arner,

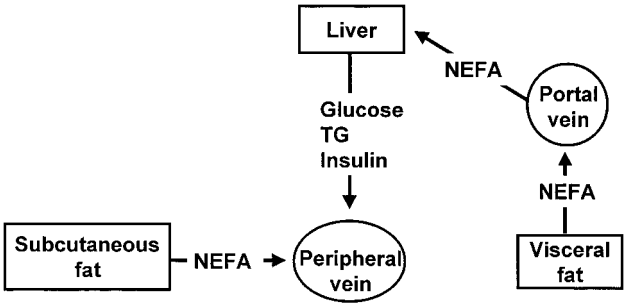

Fig. 1. Scheme for the effects of NEFA from different depots on metabolism in obesity. Redrawn from Arner (1999) with permission.

1999). In rats (Tavernier *et al*. 1995) but not in humans (Lefebvre *et al*. 1998) there is greater expression of hormone-sensitive lipase in intra-abdominal than subcutaneous adipocytes.

The idea that insulin resistance, or at least many of its deleterious features, could arise through high rates of NEFA liberation from visceral adipose tissue has attracted much attention, and has been called the Portal Theory (Arner, 1997; Fig. 1). However, it is at present no more than a theory, and needs critical evaluation.

A critical look at the Portal Theory

There are some difficulties with the simple statement of the Portal Theory given above. The first and most obvious is that any adipose depot that releases fatty acids at a high rate should ultimately disappear, and presumably along with it, insulin resistance. In most people the opposite is true: visceral fat is rather obstinate and tends to accumulate rather than disappear. Therefore we must postulate that the depot is characterized by a high rate of lipid turnover, with high rates of lipolysis at certain times matched by high rates of lipid deposition at other times. Presumably TG will be accumulated after meals, and lipolysis will be most marked in the fasting state or in stressful conditions.

Much less attention has been paid to the necessary high rates of lipid deposition in visceral fat than to the regulation of lipolysis. In one study *in vivo*, subjects were given isotopically labelled fatty acids, and biopsies of different depots were taken at abdominal surgery 24 h later (Mårin *et al*. 1992); accumulation of label was most marked (per g TG) in the omental and retroperitoneal depots. This is in agreement with a high rate of lipid turnover. Studies of the pathway of TG deposition have been less convincing. There have been many studies of the expression or activity of lipoprotein lipase (EC 3·1·1·34) in omental versus subcutaneous adipose tissue, but with conflicting results (e.g. Mårin *et al*. 1992; Pedersen *et al*. 1994; Mauriège *et al*. 1995; Lefebvre *et al*. 1998). Studies of fatty acid incorporation into TG in isolated adipocytes show a lower rate of TG synthesis in omental than subcutaneous tissue (Maslowska *et al*. 1993), which is difficult to reconcile with the Portal Theory.

Furthermore, a high rate of lipid deposition in visceral adipose tissue in the postprandial period could be seen in another light. It can be argued that increased delivery of fatty acids to the liver is most likely to lead to the adverse

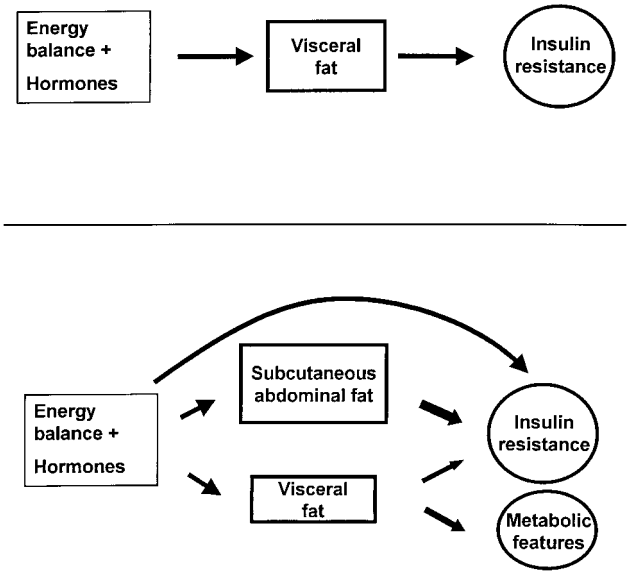

Fig. 2. Possible schemes for the relationship between visceral obesity and insulin resistance. Both envisage visceral obesity to result from positive energy balance, perhaps reinforced by specific hormonal effects. Top panel, 'causative' model, whereby visceral fat accumulation causes insulin resistance. There is little evidence for such a model. Lower panel, one possible 'correlative' model, whereby visceral fat co-correlates with other factors that may be more directly responsible for insulin resistance. Possible co-correlates envisaged here are subcutaneous abdominal fat, and the hormonal imbalance that is responsible for visceral fat accumulation. However, the possibility is allowed that visceral fat might have a causal role in some of the metabolic abnormalities that accompany insulin resistance.

consequences of insulin resistance in the postprandial, rather than the postabsorptive, state. In the postprandial state the liver receives a substantial proportion of its fatty acid supply in the form of chylomicron remnant-TG fatty acids. A high rate of TG deposition in omental adipose tissue could therefore be seen to protect the liver from an influx of fatty acids in the postprandial period, which should be beneficial rather than deleterious.

Confirmation of the Portal Theory *in vivo* really requires assessment of NEFA concentrations in the portal vein, just as arteriovenous difference measurements across a subcutaneous adipose depot have clarified the regulation of NEFA delivery from this site (Frayn *et al*. 1993). Sampling from the portal vein is not easy in humans, but it has been performed in a small number of metabolic studies. In these studies, concentrations of NEFA or glycerol (another product of lipolysis) in the portal vein have been found to be close to those in arterial plasma (Hagenfeldt *et al*. 1972; Björkman *et al*. 1990; Blackard *et al*. 1993). One example is the study of Blackard *et al*. (1993): during laparotomy in obese women the portal vein was catheterized and samples taken. On the arguments above, surgical stress is one time when the high rates of lipolysis postulated for omental adipose tissue might be most evident, and yet there was no consistent difference in NEFA concentrations between arterial and hepatic portal plasma.

An alternative to catheterization of the portal vein is the assessment of splanchnic fatty acid release using tracer methods. If an isotopically labelled fatty acid is infused

intravenously, its specific radioactivity or isotopic enrichment as measured in arterial plasma will be diluted in the splanchnic bed as unlabelled fatty acids are added from the visceral depots. Assuming that the liver does not release fatty acids (it will take them up), then the specific radioactivity or enrichment will not change further during passage through the liver. Therefore the specific radioactivity or enrichment measured in the hepatic vein (which can be catheterized relatively easily) will be lower than in arterial plasma, to an extent that reflects splanchnic NEFA release. (An assumption has to be made about the relative contributions of portal vein and hepatic artery blood flow to the liver.) Several such studies have been performed. In an early study in non-obese, normolipidaemic subjects, Havel *et al*. (1970) found that fatty acids released within the splanchnic bed (presumably from visceral adipose tissue) contributed about 10 % of the total NEFA delivery to the liver. More recently Jensen and colleagues have used this technique, in combination with selective catheterization, to estimate the delivery of fatty acids from different regions of the body. Their studies have shown clearly increased release of fatty acids in women with upper-body obesity compared with non-obese women; women with lower-body obesity were more similar to the non-obese (Martin & Jensen, 1991). However, the source of the additional fatty acids, according to these studies, is not splanchnic (visceral) adipose tissue, but upper-body non-splanchnic (subcutaneous) tissue (Martin & Jensen, 1991). The same group have now been able to demonstrate increased delivery of fatty acids to the liver in upper-body obesity, and again have shown that the source of these additional fatty acids is not splanchnic but upper-body non-splanchnic adipose tissue (Guo *et al*. 1999). These observations are interesting, and fit well with the greater mass of subcutaneous adipose tissue, as well as with the correlation studies described earlier showing that insulin resistance is more highly related to subcutaneous than to intra-abdominal fat (Abate *et al*. 1995, 1996). However, they cast further doubt upon the Portal Theory.

Other interpretations of the link between visceral fat and insulin resistance

Given that the putative mechanistic link between visceral fat accumulation and the development of insulin resistance is not so solid as is sometimes suggested, it is important to look for other possible interpretations of the link between visceral fat and insulin resistance (Fig. 2).

There seem to be two other major possibilities. One is that insulin resistance causes visceral fat accumulation. This is not implausible. Insulin resistance affects the ability of adipose tissue to take up fatty acids. If subcutaneous adipose tissue were to become ‘insulin resistant’ then fat might tend to be deposited in visceral fat stores. However the mechanisms behind such a process are not clear, and there is no real evidence that this is so.

Another possible explanation is that both visceral fat accumulation and insulin resistance are related to some other biological process (Fig. 2). For instance, Björntorp has pointed out the relationships between stress and visceral obesity (Björntorp, 1997*a*, *b*). Activation of the hypothalamic–pituitary axis might lead to both conditions (Björntorp, 1996, 1997*a*).

A further potential common correlate is upper-body subcutaneous fat (Fig. 2). As stated earlier, abdominal subcutaneous and intra-abdominal fat are strongly correlated. The subcutaneous depot is generally considerably larger than the intra-abdominal and so has a greater potential to contribute to insulin resistance through release of NEFA into the systemic circulation. In fact, insulin resistance is usually measured by the euglycaemic–hyperinsulinaemic clamp procedure, and reflects mainly impaired peripheral glucose uptake. If this is a result of competition from fatty acids, those fatty acids presumably reflect subcutaneous adipose tissue (see Fig. 1). Such an interpretation also fits the tracer studies described earlier (Martin & Jensen, 1991; Guo *et al*. 1999).

Conclusions

There is a clear link between visceral adiposity and insulin resistance. The nature of this link is, unfortunately, not so clear. The Portal Theory, which holds that increased release of NEFA from visceral adipose depots leads to insulin resistance through effects on the liver, lacks supporting evidence *in vivo*. Of several alternative explanations for the link between visceral adiposity and insulin resistance, I prefer the idea that both are common correlates of subcutaneous abdominal adipose tissue accumulation.

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References

Abate N, Garg A, Peshock RM, Stray Gundersen J & Grundy SM (1995) Relationships of generalized and regional adiposity to insulin sensitivity in men. *Journal of Clinical Investigation* **96**, 88–98.

Abate N, Garg A, Peshock RM, Stray-Gundersen J, Adams-Huet B & Grundy SM (1996) Relationship of generalized and regional adiposity to insulin sensitivity in men with NIDDM. *Diabetes* **45**, 1684–1693.

Abate N, Garg A, Coleman R, Grundy SM & Peshock RM (1997) Prediction of total subcutaneous abdominal, intraperitoneal, and retroperitoneal adipose tissue masses in men by a single axial magnetic resonance imaging slice. *American Journal of Clinical Nutrition* **65**, 403–408.

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

Arner P (1997) Impact of visceral fat. *International Journal of Obesity* **21** (Suppl. 2), S20.
Arner P (1999) Catecholamine-induced lipolysis in obesity. *International Journal of Obesity* **23** (Suppl. 1), 10–13.
Ashwell M, Cole TJ & Dixon AK (1985) Obesity: new insight into the anthropometric classification of fat distribution shown by computed tomography. *British Medical Journal* **290**, 1692–1694.
Barzilai N, She L, Liu BQ, Vuguin P, Cohen P, Wang J & Rossetti L (1999) Surgical removal of visceral fat reverses hepatic insulin resistance. *Diabetes* **48**, 94–98.
Björkman O, Eriksson LS, Nyberg B & Wahren J (1990) Gut exchange of glucose and lactate in basal state and after oral glucose ingestion in postoperative patients. *Diabetes* **39**, 747–751.
Björntorp P (1988) Abdominal obesity and the development of noninsulin-dependent diabetes mellitus. *Diabetes/Metabolism Reviews* **4**, 615–622.
Björntorp P (1990) 'Portal' adipose tissue as a generator of risk factors for cardiovascular disease and diabetes. *Arteriosclerosis* **10**, 493–496.
Björntorp P (1996) The regulation of adipose tissue distribution in humans. *International Journal of Obesity* **20**, 291–302.
Björntorp P (1997*a*) Neuroendocrine factors in obesity. *Journal of Endocrinology* **155**, 193–195.
Björntorp P (1997*b*) Stress and cardiovascular disease. *Acta Physiologica Scandinavica Supplement* **640**, 144–148.
Blackard WG, Clore JN, Glickman PS, Nestler JE & Kellum JM (1993) Insulin sensitivity of splanchnic and peripheral adipose tissue *in vivo* in morbidly obese man. *Metabolism* **42**, 1195–1200.
Després JP, Nadeau A, Tremblay A, Ferland M, Moorjani S, Lupien PJ, Thériault G, Pinault S & Bouchard C (1989) Role of deep abdominal fat in the association between regional adipose tissue distribution and glucose tolerance in obese women. *Diabetes* **38**, 304–309.
Engfeldt P & Arner P (1988) Lipolysis in human adipocytes, effects of cell size, age and of regional differences. *Hormone and Metabolic Research Supplement* **19**, 26–29.
Ferrannini E, Barrett EJ, Bevilacqua S & DeFronzo RA (1983) Effect of fatty acids on glucose production and utilization in man. *Journal of Clinical Investigation* **72**, 1737–1747.
Folsom AR, Kaye SA, Sellers TA, Hong C-P, Cerhan JR, Potter JD & Prineas RJ (1993) Body fat distribution and 5-year risk of death in older women. *Journal of the American Medical Association* **269**, 483–487.
Fontbonne A, Thibult N, Eschwège E & Ducimetière P (1992) Body fat distribution and coronary heart disease mortality in subjects with impaired glucose tolerance or diabetes mellitus: the Paris Prospective Study, 15-year follow up. *Diabetologia* **35**, 464–468.
Frayn KN, Coppack SW & Humphreys SM (1993) Subcutaneous adipose tissue metabolism studied by local catheterization. *International Journal of Obesity* **17** (Suppl. 3), S18–S21.
Fried SK, Bunkin DA & Greenberg AS (1998) Omental and subcutaneous adipose tissues of obese subjects release interleukin-6: depot difference and regulation by glucocorticoid. *Journal of Clinical Endocrinology and Metabolism* **83**, 847–50.
Guo Z, Hensrud DD, Johnson CM & Jensen MD (1999) Regional postprandial fatty acid metabolism in different obesity phenotypes. *Diabetes* **48**, 1586–1592.
Hagenfeldt L, Wahren J, Pernow B & Raf L (1972) Uptake of individual free fatty acids by skeletal muscle and liver in man. *Journal of Clinical Investigation* **51**, 2324–2330.
Havel RJ, Kane JP, Balasse EO, Segel N & Basso LV (1970) Splanchnic metabolism of free fatty acids and production of triglycerides of very low density lipoproteins in normotriglyceridemic and hypertriglyceridemic humans. *Journal of Clinical Investigation* **49**, 2017–2035.
Hotamisligil GS, Arner P, Caro JF, Atkinson RL & Spiegelman BM (1995) Increased adipose tissue expression of tumor necrosis factor-α in human obesity and insulin resistance. *Journal of Clinical Investigation* **95**, 2409–2415.
Jeppesen J, Hollenbeck CB, Zhou M-Y, Coulston AM, Jones C, Chen Y-DI & Reaven GM (1995) Relation between insulin resistance, hyperinsulinemia, postheparin plasma lipoprotein lipase activity, and postprandial lipemia. *Arteriosclerosis, Thrombosis, and Vascular Biology* **15**, 320–324.
Kalmijn S, Curb JD, Rodriguez BL, Yano K & Abbott RD (1999) The association of body weight and anthropometry with mortality in elderly men: The Honolulu Heart Program. *International Journal of Obesity* **23**, 395–402.
Kissebah AH & Krakower GR (1994) Regional adiposity and morbidity. *Physiological Reviews* **74**, 761–811.
Landin K, Stigendal L, Eriksson E, Krotkiewski M, Risberg B, Tengborn L & Smith U (1990) Abdominal obesity is associated with an impaired fibrinolytic activity and elevated plasminogen activator inhibitor-1. *Metabolism* **39**, 1044–1048.
Lefebvre A-M, Laville M, Vega N, Riou JP, van Gaal L, Auwerx J & Vidal H (1998) Depot-specific differences in adipose tissue gene expression in lean and obese subjects. *Diabetes* **47**, 98–103.
Mårin P, Andersson B, Ottosson M, Olbe L, Chowdhury B, Kvist H, Holm G, Sjöström L & Björntorp P (1992) The morphology and metabolism of intra-abdominal adipose tissue in men. *Metabolism* **41**, 1242–1248.
Martin ML & Jensen MD (1991) Effects of body fat distribution on regional lipolysis in obesity. *Journal of Clinical Investigation* **88**, 609–613.
Maslowska MH, Sniderman AD, MacLean LD & Cianflone K (1993) Regional differences in triacylglycerol synthesis in adipose tissue and in cultured preadipocytes. *Journal of Lipid Research* **34**, 219–228.
Mauriège P, Galitzky J, Berlan M & Lafontan M (1987) Heterogeneous distribution of beta and alpha-2 adrenoceptor binding sites in human fat cells from various fat deposits: functional consequences. *European Journal of Clinical Investigation* **17**, 156–165.
Mauriège P, Marette A, Atgie C, Bouchard C, Theriault G, Bukowiecki LK, Marceau P, Biron S, Nadeau A & Després JP (1995) Regional variation in adipose tissue metabolism of severely obese premenopausal women. *Journal of Lipid Research* **36**, 672–684.
Misra A, Garg A, Abate N, Peshock RM & Stray-Gundersen J (1997) Relationship of anterior and posterior subcutaneous abdominal fat to insulin sensitivity in nondiabetic men. *Obesity Research* **5**, 93–99.
Mohamed-Ali V, Goodrick S, Rawesh A, Katz DR, Miles JM, Yudkin JS, Klein S & Coppack SW (1997) Subcutaneous adipose tissue secretes interleukin-6 but not tumor necrosis-factor-α *in vivo*. *Journal of Clinical Endocrinology and Metabolism* **82**, 4196–4200.
Mohamed-Ali V, Pinkney JH & Coppack SW (1998) Adipose tissue as an endocrine and paracrine organ. *International Journal of Obesity* **22**, 1145–1158.
Montague CT, Prins JB, Sanders L, Zhang J, Sewter CP, Digby J, Byrne CD & O'Rahilly S (1998) Depot-related gene expression in human subcutaneous and omental adipocytes. *Diabetes* **47**, 1384–1391.
Östman J, Arner P, Engfeldt P & Kager L (1979) Regional differences in the control of lipolysis in human adipose tissue. *Metabolism* **28**, 1198–1205.
Pedersen SB, Jønler M & Richelsen B (1994) Characterization of regional and gender differences in glucocorticoid receptors and

lipoprotein lipase activity in human adipose tissue. *Journal of Clinical Endocrinology and Metabolism* **78**, 1354–1359.
Pereira ME & Pond CM (1995) Organization of white adipose tissue in Lemuridae. *American Journal of Primatology* **35**, 1–13.
Reaven GM (1988) Role of insulin resistance in human disease. *Diabetes* **37**, 1595–1607.
Reaven GM, Chen Y-DI & Krauss RM (1992) Resistance to insulin-mediated glucose uptake and hyperinsulinaemia in subjects with small, dense LDL. *Circulation* **86** (Suppl.), I-73.
Ross R, Leger L, Morris D, de Guise J & Guardo R (1992) Quantification of adipose tissue by MRI: relationship with anthropometric variables. *Journal of Applied Physiology* **72**, 787–795.
Saghizadeh M, Ong JM, Garvey WT, Henry RR & Kern PA (1996) The expression of TNF-α by human muscle. Relationship to insulin resistance. *Journal of Clinical Investigation* **97**, 1111–1116.
Seidell JC & Bouchard C (1997) Visceral fat in relation to health: is it a major culprit or simply an innocent bystander? *International Journal of Obesity* **21**, 626–631.
Siiteri PK (1987) Adipose tissue as a source of hormones. *American Journal of Clinical Nutrition* **45**, 277–282.
Snyder WS (1975). *Report of the Task Force on Reference Man*, International Commission on Radiological Protection. Oxford: Pergamon Press.
Svedberg J, Björntorp P, Smith U & Lönnroth P (1990) Free-fatty acid inhibition of insulin binding, degradation, and action in isolated rat hepatocytes. *Diabetes* **39**, 570–574.
Tavernier G, Galitzky J, Valet P, Remaury A, Bouloumie A, Lafontan M & Langin D (1995) Molecular mechanisms underlying regional variations of catecholamine-induced lipolysis in rat adipocytes. *American Journal of Physiology* **268**, E1135–E1142.
Thomas EL, Saeed N, Hajnal JV, Brynes A, Goldstone AP, Frost G & Bell JD (1998) Magnetic resonance imaging of total body fat. *Journal of Applied Physiology* **85**, 1778–1785.
Vague J (1947) La différenciation sexuelle, facteur déterminant des formes de l'obésité. *La Presse Médicale* **30**, 339–340.
Vague J (1956) The degree of masculine differentiation of obesities: a factor determining predisposition to diabetes, atherosclerosis, gout and uric calculous disease. *American Journal of Clinical Nutrition* **4**, 20–34.
Van Harmelen V, Lönnqvist F, Thörne A, Wennlund A, Large V, Reynisdottir S & Arner P (1997) Noradrenaline-induced lipolysis in isolated mesenteric, omental and subcutaneous adipocytes from obese subjects. *International Journal of Obesity* **21**, 972–979.
Van Harmelen V, Reynisdottir S, Eriksson P, Thörne A, Hoffstedt J, Lönnqvist F & Arner P (1998) Leptin secretion from subcutaneous and visceral adipose tissue in women. *Diabetes* **47**, 913–917.
Wiesenthal SR, Sandhu H, McCall RH, Tchipashvili V, Yoshii H, Polonsky K, Shi ZQ, Lewis GF, Mari A & Giacca A (1999) Free fatty acids impair hepatic insulin extraction *in vivo*. *Diabetes* **48**, 766–774.