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Obesity and metabolic disease: is adipose tissue the culprit?

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Obesity is a risk factor for the development of type 2 diabetes and CVD. Is adipose tissue the culprit in the relationship between obesity and metabolic disease? It is certainly possible to argue that adipose tissue function is disturbed in obesity in such a way that adverse consequences may follow. For instance, lipolysis is down regulated, the sensitivity of lipolysis to insulin is reduced and there are disturbances in the regulation of adipose tissue blood flow. However, when examined critically these changes can be seen as adaptations to the increased adipose tissue mass, making the situation better rather than worse. In terms of the many peptide and other factors now known to be secreted from adipose tissue, it is easier to argue that adipose tissue is the culprit. However, for no single ‘adipokine’ is there as yet unequivocal evidence of a link between adipose tissue secretion and adverse metabolic events in other tissues. The best documented of these adipokines in relation to insulin resistance is adiponectin. Here, unusually, adiponectin confers insulin sensitivity, and its secretion is down regulated in obesity. It could be again that adipose tissue has down regulated its function in an attempt to compensate for its increased mass, although certainly that down-regulation is too extreme. On balance, it is clear that adipose tissue is a link in the chain of events leading to metabolic disease, but in many respects it is an innocent intermediary trying to deal with the consequences of positive energy balance, the real culprit.

Adipose tissue: Blood flow: Insulin resistance: Lipolysis

Obesity is a strong risk factor for the development of metabolic disease, especially type 2 diabetes and CVD. Obesity is a state brought about by positive energy balance over a prolonged period, but it is defined in terms of excess weight-for-height. In practice, that excess weight reflects excess fat accumulation, mainly in adipose tissue. It is, therefore, perfectly reasonable to ask whether the increased risk of metabolic disease is a consequence of the excess fat in adipose tissue. To put this question in different terms: when considering the relationship between obesity and metabolic disease, is adipose tissue the culprit?

The adverse metabolic changes associated with obesity are themselves mostly related to a reduction in sensitivity of the body’s tissues to insulin, the state known as insulin resistance. It is easy to support the argument that excess fat leads to insulin resistance. Insulin sensitivity varies widely

amongst apparently-healthy individuals, but even amongst non-obese individuals there is a fairly strong relationship between adiposity and insulin resistance (Insel *et al.* 1975; Bogardus *et al.* 1985). Amongst obese subjects (BMI >30 kg/m²) there is almost universally a low sensitivity to insulin (Clausen *et al.* 1996). (This relationship is sometimes disputed, and undoubtedly body fat distribution, ethnic origin and many other factors have important modulating effects, but in the present review those factors will not be taken into account.)

Adipose tissue might then be considered as the ‘culprit’ in mediating the increased risk of metabolic disease in obesity. This argument is not difficult to sustain and many researchers have done so, including the author, using various lines of attack against the defendant, adipose tissue. However, it is now time to give the case for the

Abbreviation: ATBF, adipose-tissue blood flow.

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defence. The argument will depend to some extent on semantics, but it will be shown that there have been many overly-simplistic facts written about adipose tissue and metabolic disease (with the author being as guilty as other researchers).

The case for the prosecution: metabolic and endocrine factors

Until 10 years ago, it was common to argue for an adverse role of adipose tissue in terms of its metabolic function, particularly the supply of NEFA into the circulation. In 1994 this view changed with the discovery of leptin, the first peptide hormone demonstrated to be secreted by adipose tissue (Zhang *et al.* 1994); this finding was followed 1 year later by the discovery of the protein now generally known as adiponectin (then termed Acrp30), now recognised as another peptide hormone produced almost exclusively by adipocytes (Scherer *et al.* 1995). Since that time it has been appreciated that adipose tissue is the site of expression of a large number of peptides that relate to metabolic regulation, including known cytokines such as TNF- α and IL-6 and known proteins with other functions such as angiotensinogen (potentially involved in raising blood pressure), plasminogen activator inhibitor-1 (potentially involved in generation of a prothrombotic state) and some of the acute-phase proteins that are markers of inflammation (Pittas *et al.* 2004; Ruan & Lodish, 2004). These proteins secreted by adipose tissue are now generally known as adipokines.

The metabolic viewpoint

From the metabolic point of view, most attention has been focused on the liberation of NEFA from adipose tissue. It has been known for several decades that plasma NEFA concentrations are elevated in obesity (Opie & Walfish, 1963), not surprising in view of the increased adipose tissue mass (Flatt, 1972).

Inappropriately-elevated NEFA concentrations have many adverse metabolic and physiological effects. These effects include production of insulin resistance of glucose utilization by skeletal muscle (Randle *et al.* 1963; Boden *et al.* 1994) and inhibition of the normal suppression by insulin of hepatic glucose production (Ferrannini *et al.* 1983; Boden *et al.* 2002), which together could lead to glucose intolerance and insulin resistance of glucose metabolism. To these effects could be added a long-term effect of elevated NEFA concentrations to impair glucose-stimulated insulin secretion (Zhou & Grill, 1995; Carpentier *et al.* 1999). These effects together may well explain why elevated NEFA concentrations are a predictor of future development of type 2 diabetes (Paolisso *et al.* 1995; Charles *et al.* 1997; Pankow *et al.* 2004). The adverse effects of elevated NEFA concentrations also extend into other areas. NEFA are the substrate for hepatic triacylglycerol secretion in the VLDL, and hence potentially contribute to hypertriacylglycerolaemia, a consistent correlate of insulin resistance and a marker of increased risk of CVD (Hokanson & Austin, 1996). Elevated NEFA

concentrations impair endothelial function (Lind *et al.* 2000; Steinberg *et al.* 2000) and could therefore be seen to predispose to hypertension, another correlate of insulin resistance (Ferrannini *et al.* 1987; Haffner *et al.* 1996), and to CVD.

A somewhat more sophisticated (or at least integrated) viewpoint is that disturbances in adipose tissue metabolic function are the key feature linking increased adipose tissue mass with insulin resistance and its sequelae. It has been argued previously (Frayn, 2001, 2002) that adipose tissue metabolic function has to be viewed as a very dynamic system. Adipose tissue can be seen as a metabolic 'buffer', responding rapidly to intake of meals, sequestering fatty acids in the postprandial period and releasing them later when appropriate, in just the same way that the liver buffers the influx of glucose after meals. This buffering function of adipose tissue becomes disturbed as excess fat accumulates and this situation could lead to increased exposure of other tissues, such as skeletal muscle, liver and pancreatic islets, to excess fatty acid delivery. The consequence would be fat deposition in these extra-adipose tissues, now commonly known as 'ectopic fat deposition' and closely associated with insulin resistance (Ryysy *et al.* 2000; Kelley *et al.* 2002; Seppälä Lindroos *et al.* 2002). It has also been pointed out that adipose-tissue blood flow (ATBF), another dynamic aspect of adipose tissue function, is disturbed in obesity and that this disturbance of ATBF regulation is closely associated with insulin resistance (Summers *et al.* 1996; Jansson *et al.* 1998; Karpe *et al.* 2002; Virtanen *et al.* 2002). ATBF regulation in the postprandial period might well be an essential component of normal adipose tissue metabolic function; for instance, increased ATBF leads to increased clearance of triacylglycerol by the tissue (Samra *et al.* 1996). It might also be a further aspect of disturbed endothelial function in obesity.

The case for the defence: an alternative view of adipose tissue function in obesity

These arguments seem very persuasive, but the disturbances in adipose tissue metabolic function in obesity can be viewed in another way. Although an increased adipose tissue mass undoubtedly delivers more NEFA into the circulation, resulting in elevated NEFA concentrations when compared with lean subjects, the increase in NEFA concentrations is not always particularly marked. In some studies it is not even significant (Riemens *et al.* 2000). (This situation applies to obese subjects who do not have diabetes; in type 2 diabetes NEFA concentrations are much more clearly elevated (Riemens *et al.* 2000).) It is important to appreciate what this increase means in terms of adipose tissue function. Data on the body composition of obese women have been taken from Prentice *et al.* (1986). Their obese women (average BMI 33 kg/m²) had 39 kg body fat, compared with 16 kg in the lean control women (average BMI 22 kg/m²). If all this excess fat mass had been liberating NEFA at the same rate as in the lean women, the plasma NEFA concentration in the obese group would have been more than double that in the lean

Table 1. Potential for vastly increased plasma NEFA concentrations in obesity if lipolysis were not down-regulated*

	Lean	Obese
BMI (kg/m ²)	22.1	32.9
Fat mass (kg)	16.2	38.8
Plasma NEFA (μmol/l)	500	1010†

*Typical data for BMI and fat mass are taken from Prentice *et al.* (1986). A fasting NEFA concentration of 500 μmol/l is typical of lean subjects (Frayn *et al.* 1996).

†The value for obese subjects is calculated assuming the same rate of delivery of NEFA per kg fat mass as in the lean subjects, and assuming a constant value for metabolic clearance by lean body mass, taking data for body composition, again from Prentice *et al.* (1986). In reality, metabolic clearance would have to be down-regulated to protect target organs from excessive fatty acid uptake, so this value is an underestimate of the resultant plasma NEFA concentration in obesity if there were not down-regulation of lipolysis.

(Table 1). Such high NEFA concentrations would undoubtedly have grave metabolic consequences; but they are not observed. The only possible conclusion is that the rate of NEFA release per unit mass of adipose tissue has been considerably down-regulated. However, this conclusion is considered by many authors to be one of the characteristic 'metabolic aberrations' of obesity. Indeed, in one study molecular alterations in the expression of the key lipolytic hormone-sensitive lipase have been described, such that it is down-regulated in adipocytes from obese subjects (Large *et al.* 1999). It was noted that 'decreased lipolytic effect of catecholamines in adipose tissue has repeatedly been demonstrated in obesity and may be a cause of excess accumulation of body fat'. Surely, a perfectly reasonable alternative interpretation is that this effect is a physiologically-appropriate down-regulation of lipolysis per unit of fat mass so that the body is not swamped with excess NEFA.

Elegant tracer studies of NEFA turnover in lean and obese subjects have shed more light on this issue (Campbell *et al.* 1994). The rate of NEFA release per unit of fat mass (nmol/min per kg fat mass) is almost halved in obese subjects compared with lean in the basal state (obese 20 *v.* lean 37). This outcome is brought about in part because of fasting hyperinsulinaemia in the obese subjects. When insulin is infused to generate dose-response curves for NEFA production *v.* insulin, the curve in the obese subjects is shifted considerably to the right, indicative of insulin resistance of lipolysis in obese subjects. This insulin resistance of lipolysis has been a focus of many studies. It has been suggested that, because NEFA release is 'insulin resistant', there will be a failure of insulin to suppress lipolysis normally in the postprandial period. This resistance of lipolysis to insulin has been demonstrated in many insulin-resistant conditions, including obesity (Campbell *et al.* 1994; Riemens *et al.* 2000), familial risk of type 2 diabetes (Eriksson *et al.* 1999) and the lipid disorder, familial combined hyperlipidaemia (which is associated with insulin resistance; Aitman *et al.* 1997). These studies are usually conducted by infusion of insulin to raise the plasma insulin concentration to similar levels in control and test populations. However, it is easily overlooked that in daily life insulin infusions are not received; the pancreatic islets respond to plasma glucose

Table 2. Distribution of cardiac output to adipose tissue in the fasting state in lean and obese subjects

	Lean	Obese (actual)	Obese (if = lean)
ATBF (ml/min per 100g)*	3.0	1.5	3.0
Cardiac output (l/min)†	5.0	4.9	4.9
Percentage of cardiac output delivered to adipose tissue‡	10	12	24

ATBF, adipose tissue blood flow; obese (actual), typical observations of ATBF in obese subjects; obese (if = lean), potential situation if fasting ATBF were equal to that observed in lean subjects.

*Data are based on representative experiments from Summers *et al.* (1998; 1999).

†Values are from recent studies by Dr Monique Robinson (Oxford, UK) and used with her kind permission.

‡Based on the values for fat mass given in Table 1.

concentrations, and a characteristic (almost a definition) of insulin-resistant states is hypersecretion of insulin after meals. It is almost essential that the adipose tissue develops 'insulin resistance of lipolysis' in these conditions in order to allow any release of NEFA when required. Again, what appears to be a cellular 'defect' may be a perfectly reasonable biological adaptation to a metabolic alteration, i.e. prevailing hyperinsulinaemia.

The impairment of ATBF regulation that is very distinctive in obesity has already been mentioned and it has been suggested that it might have adverse metabolic consequences. However, it is again instructive to analyse this factor in relation to whole-body fat mass. (ATBF is usually measured per unit weight of tissue.) Table 2 shows that it is, again, almost a biological necessity that ATBF be down-regulated per unit mass of tissue in obesity, and particularly that the responsiveness to meals be damped; otherwise, a massive proportion of cardiac output would be diverted to adipose tissue in the postprandial period, with undoubted adverse consequences for blood pressure and for the perfusion of other essential organs such as the brain. Again, therefore, what appears at first sight to be an adverse alteration in obesity may also be seen as a necessary adaptation to the excess accumulation of adipose tissue.

Adipokines and metabolic disease

The discovery of adipose tissue's endocrine function has opened up many new possibilities for pointing an incriminating finger at that tissue. This field has been reviewed recently by several expert researchers (for example, see Mohamed-Ali *et al.* 1998; Frühbeck *et al.* 2001; Pittas *et al.* 2004; Ruan & Lodish, 2004). In general, this view of adipose tissue fits in with an emerging concept of chronic low-grade inflammation in relation to insulin resistance, obesity and CVD. Indeed, the recent demonstration that adipose tissue in obesity is infiltrated with macrophages (Weisberg *et al.* 2003; Xu *et al.* 2003) emphasises both fundamental similarities between the adipocyte and the macrophage (Lehrke & Lazar, 2004), and the fact that not all adipose tissue function should be ascribed to the adipocytes.

Could it be that enlarged and 'inflamed' adipose tissue is producing signals that induce insulin resistance and metabolic disturbances in other tissues? It is certainly plausible, although it can be argued that the picture is far from complete at present. A few of the candidate signals will be discussed.

Leptin is a superficially obvious candidate; its expression increases as fat cells enlarge, and plasma leptin concentrations are increased in most obese subjects (Considine *et al.* 1996). Although there are some suggestions for adverse roles of leptin, e.g. leptin impairs insulin signalling in rat adipocytes (Perez *et al.* 2004) and leptin may inhibit insulin secretion (Pallett *et al.* 1997), in general, leptin seems to be essential for the maintenance of insulin sensitivity and metabolic health. Leptin stimulates glucose metabolism *in vivo* (Kamohara *et al.* 1997; Frühbeck & Salvador, 2000; Yaspelkis *et al.* 2004) and leptin administration to patients with lipodystrophy (who are severely insulin resistant and have low levels of leptin) produces a dramatic improvement in their metabolic condition (Oral *et al.* 2002; Petersen *et al.* 2002). Thus, it does not seem likely that adipose tissue secretion of leptin can be blamed for the adverse metabolic consequences of obesity.

There has been consistent interest in the secretion of true 'pro-inflammatory' cytokines from adipose tissue, including TNF- α and IL-6. There is no doubt that TNF- α can have a number of adverse metabolic effects, aimed, at least in part, at the insulin-signalling pathway. However, it has been very difficult to prove conclusively in human subjects that adipose tissue-derived TNF- α is a source of circulating TNF- α and, hence, of adverse metabolic consequences in other tissues. Adipose tissue TNF- α expression does not correlate well with insulin resistance (Koistinen *et al.* 2000), it is not possible to demonstrate TNF- α secretion from human adipose tissue *in vivo* (Mohamed-Ali *et al.* 1997) and, perhaps more importantly, TNF- α expression is independently up regulated in target tissues, such as skeletal muscle, in insulin resistance (Saghizadeh *et al.* 1996). All these factors seem to argue that whilst TNF- α may be a key local mediator of insulin resistance, it is not a signal from an enlarged adipose tissue mass to other tissues in the body. The case for IL-6 is much less clear. In some studies circulating IL-6 concentrations correlate strongly with insulin resistance, but insulin resistance does not seem to be related to adipose tissue IL-6 secretion (Kern *et al.* 2001), implying that other tissues may be a more important source. Infusion of low-dose IL-6 into human volunteers does not produce insulin resistance of glucose metabolism (Steensberg *et al.* 2003), perhaps arguing that correlations between plasma IL-6 and insulin resistance may reflect some other aspect of an inflammatory state. In fact, the IL-6 secretion observed during exercise (in which state skeletal muscle is the major source) has anti-inflammatory properties (Starkie *et al.* 2003).

Novel adipokines have been proposed to account for the link between adipose tissue and insulin resistance. One of these substances, resistin (Steppan *et al.* 2001), is an interesting candidate, not least because it was discovered as a gene product down regulated by thiazolidinedione

treatment (thiazolidinediones are insulin-sensitising drugs that may have adipose tissue as their key target tissue). However, the literature on resistin in relation to insulin resistance in man has been very conflicting. Human resistin appears to be a product more of macrophages than of adipocytes, and its biology is probably different from that in the mouse, the species in which it was discovered (Hotamisligil, 2003).

The best-substantiated candidate adipokine for the link between adipose tissue and insulin resistance at present seems to be adiponectin (Acrap30). The pertinent facts may be summarised as follows. Adiponectin secretion from adipose tissue is down regulated in obesity, so much so that plasma concentrations of adiponectin are actually lower in obese than in lean subjects (Arita *et al.* 1999). This situation is also found in patients with type 2 diabetes compared with subjects without diabetes (Hotta *et al.* 2000), and the low adiponectin concentrations in these conditions correlate strongly with insulin resistance (Weyer *et al.* 2001). Thus, adiponectin induces insulin sensitivity, unlike the other adipokines for which the reverse is true. This effect has been demonstrated directly by administration of recombinant adiponectin to insulin-resistant rodents (Yamauchi *et al.* 2001) and by the presence of insulin resistance in mouse models of adiponectin deficiency (Kubota *et al.* 2002; Maeda *et al.* 2002; although Ma *et al.* (2002) have found that insulin resistance is not present in all adiponectin-deficient models). The correlation between adiponectin levels and insulin sensitivity has also been demonstrated clearly in rhesus monkeys (Hotta *et al.* 2001). It seems fairly clear, therefore, that reduced adiponectin secretion in obesity is associated with insulin resistance. Why should adipose tissue so down regulate adiponectin expression and secretion that circulating levels fall? It could perhaps be argued that adiponectin is such a potent molecule that it would be dangerous to have high levels; the association with insulin sensitivity, for instance, is so strong that an obese subject in whom adiponectin secretion had not been down regulated could actually suffer from persistent hypoglycaemia. However, there is no doubt that adipose tissue has 'over-compensated' in the down-regulation of adiponectin secretion in obesity; so perhaps in this way it could be regarded as the culprit.

Conclusions

The relationships between adipose tissue function and insulin resistance are complex and it is all too easy to take an over-simplistic view. It has been argued here that some of the metabolic disturbances of adipose tissue function that may well predispose to metabolic disease in fact represent an 'attempt' by adipose tissue to compensate for its increased size, and that if such compensation did not take place the consequences would be far more severe. Thus, perhaps adipose tissue should be regarded not as the culprit but as an innocent intermediary doing its best to help out, and ending up being in the line of fire and getting blamed. The real culprit, from this viewpoint, is the positive energy balance that led to the increase in adipose tissue mass.

However, there is no doubt that excess adipose tissue is intimately associated with a chronic inflammatory state, mediated in part by adipokines secreted from the enlarged adipose tissue mass. It is as yet difficult to know how far this relates to whole-body insulin sensitivity. The strongest evidence to suggest that an adipokine links adipose tissue and insulin resistance relates to adiponectin, which is curious because, unlike other adipokines that have been implicated in this relationship, adiponectin secretion is powerfully down-regulated in obesity. Again, it is as though adipose tissue is 'trying' to compensate for its increased mass, but in this case goes too far. In such a circumstance it is difficult to know whether adipose tissue should be regarded as the culprit.

Despite this attempt to shift some blame from adipose tissue, it is not implied that adipose tissue function could not be a target for manipulation. It could certainly still be argued that there are aspects of adipose tissue function in obesity that might be altered beneficially. However, it is safe to conclude that any such intervention should be carefully thought through; it would be all too easy to make the situation worse rather than better.

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