

Adipose tissue and the insulin resistance syndrome

Keith N. Frayn

Oxford Centre for Diabetes, Endocrinology and Metabolism, Radcliffe Infirmary, Oxford OX2 6HE, UK

Obesity is associated with insulin resistance. Insulin resistance underlies a constellation of adverse metabolic and physiological changes (the insulin resistance syndrome) which is a strong risk factor for development of type 2 diabetes and CHD. The present article discusses how accumulation of triacylglycerol in adipocytes can lead to deterioration of the responsiveness of glucose metabolism in other tissues. Lipodystrophy, lack of adipose tissue, is also associated with insulin resistance. Any plausible explanation for the link between excess adipose tissue and insulin resistance needs to be able to account for this observation. Adipose tissue in obesity becomes refractory to suppression of fat mobilization by insulin, and also to the normal acute stimulatory effect of insulin on activation of lipoprotein lipase (involved in fat storage). The net effect is as though adipocytes are 'full up' and resisting further fat storage. Thus, in the postprandial period especially, there is an excess flux of circulating lipid metabolites that would normally have been 'absorbed' by adipose tissue. This situation leads to fat deposition in other tissues. Accumulation of triacylglycerol in skeletal muscles and in liver is associated with insulin resistance. In lipodystrophy there is insufficient adipose tissue to absorb the postprandial influx of fatty acids, so these fatty acids will again be directed to other tissues. This view of the link between adipose tissue and insulin resistance emphasises the important role of adipose tissue in 'buffering' the daily influx of dietary fat entering the circulation and preventing excessive exposure of other tissues to this influx.

Adipose tissue: Insulin resistance syndrome: Triacylglycerols

Insulin resistance and adipose tissue

Accumulation of adipose tissue, as in obesity, is associated with insulin resistance. A deficiency of adipose tissue, as in the condition of lipodystrophy, is also associated with insulin resistance. Is there one unifying explanation for these two seemingly paradoxical observations? The aim of the present paper is to provide such an explanation.

A brief introduction to the concept of insulin resistance is necessary in order to understand these observations. HP Himsworth, working at University College Hospital, London, UK, in the 1930s, was the first clearly to differentiate between the concepts of insulin secretion and insulin sensitivity (Himsworth, 1936). He found that some individuals with diabetes (typically lean individuals with an early onset of the disease) responded rapidly to an injection of insulin with a fall in blood glucose concentration. Other individuals, typically more obese and with later-onset diabetes, were resistant to the blood glucose-lowering effect of insulin. In the 1960s this concept was applied to non-

diabetic but obese subjects whose metabolism was shown to be resistant to the effects of insulin (Rabinowitz & Zierler, 1961) and who were found to have high levels of circulating insulin in response to glucose infusion (Karam *et al.* 1963). Since that time it has been recognised that sensitivity to insulin is related to body fat content, even within relatively normal ranges of BMI (Insel *et al.* 1975; Bogardus *et al.* 1985). In studies of large numbers of healthy individuals, it has been claimed that 'at BMI >30 kg/m², nearly all subjects had a low insulin sensitivity index' (Clausen *et al.* 1996).

It is important to note that insulin resistance has been discussed so far only in terms of its effects on glucose metabolism. Most methods for assessing insulin resistance measure some combination of the ability of insulin to stimulate peripheral glucose disposal (mostly into muscle glycogen) and to suppress hepatic glucose production. Gerald Reaven (1988) proposed that insulin resistance could be seen as the centre of a constellation of changes that all adversely affect risk of cardiovascular disease (Table 1), a syndrome he suggested was common even amongst the

Abbreviations: NEFA, non-esterified fatty acids; TG, triacylglycerols; TNF, tumour necrosis factor.

Corresponding author: Professor Keith Frayn, fax +44 1865 224652, email keith.frayn@oxlip.ox.ac.uk

Table 1. Characteristics of the insulin resistance syndrome based on the original description by Reaven, 1988; but this description has been expanded since by many authors, for example, see Landin *et al.* 1990, Jeppesen *et al.* 1995, Tooke & Hannemann, 2000

Phenotype	Significance
Glucose intolerance Hyperinsulinaemia	Increase risk of type 2 diabetes mellitus
(Moderately) elevated fasting TG concentration Increased postprandial lipaemia Reduced HDL-cholesterol concentration Preponderance of small dense LDL particles Hypertension Impaired endothelial function Procoagulant state	

TG, triacylglycerol.

apparently healthy population, and which he termed syndrome X (now more usually termed the insulin resistance syndrome or the metabolic syndrome). Reaven (1988) did not discuss obesity *per se* as part of this constellation, although now the insulin resistance syndrome is usually considered to include obesity, particularly of the abdominal variety.

The insulin resistance that accompanies obesity is also accompanied by these adverse changes in other systems. This factor is now accepted as the reason that obese individuals have a considerably increased risk of cardiovascular disease (Kaplan, 1989). Thus, we have to consider the mechanisms by which increasing fat storage in adipose tissue can lead to widespread changes in glucose and lipid metabolism, and other physiological systems including coagulation and blood pressure.

However, the situation is complicated by the fact that the disease of lipodystrophy, in which there is a deficiency of adipose tissue (either total or partial, usually involving loss of adipose tissue on the extremities), is also accompanied by insulin resistance and a high incidence of type 2 diabetes (Ganda, 2000). It would be satisfying to find an explanation that could unify these apparently contradictory observations.

Possible links between adiposity and insulin resistance

If increasing fat storage in adipose tissue is associated with increasing insulin resistance, the simplest explanation might be something like that shown in Fig. 1; adipose tissue releases some signal ('substance X' in Fig. 1) that affects muscle and liver glucose metabolism (since these are the metabolic variables measured as insulin resistance). That explanation does not seem unreasonable, but it is then difficult at first sight to see how we might reconcile this model with the observation of insulin resistance in lipodystrophy (Fig. 1(b)). I will return to this later (see p. 378).

Adipose tissue is now recognised as an important secretory organ (Spiegelman & Flier, 1996; Mohamed-Ali *et al.* 1998), releasing into the circulation many peptides that affect metabolism, including of course the hormone leptin. Thus, there are many possible candidates for 'substance X'. Much attention has focused on the possibility that substance X is the cytokine, tumour necrosis factor (TNF)- α (Hotamisligil & Spiegelman, 1994). However, there are

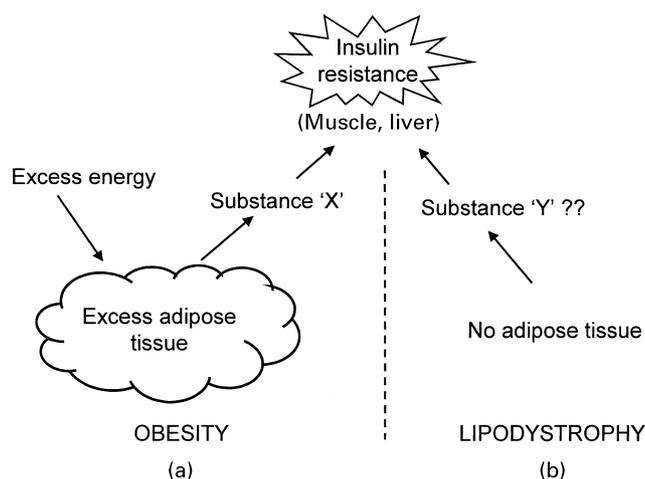


Fig. 1. (a) Schematic model for the association between obesity (excessive accumulation of triacylglycerol in adipose tissue) and insulin resistance of glucose metabolism, which is assessed in liver and skeletal muscle. The suggestion is that a substance 'X' signals from adipose tissue to these tissues. (b) Shows the apparent difficulty of extending this model to the link between deficiency of adipose tissue (lipodystrophy or lipoatrophy) and insulin resistance. It is not clear how absent adipose tissue can liberate a similar signal.

some difficulties with this concept (at least in human subjects). Studies of adipose tissue *in vivo* show that TNF- α , although expressed in adipose tissue at increased levels in obesity (Hofmann *et al.* 1994), is not released into the circulation (Mohamed-Ali *et al.* 1997). Systemic TNF- α concentrations are not consistently related to obesity or insulin resistance (Hauner *et al.* 1998), and adipose tissue TNF- α expression is not correlated with insulin resistance except in morbid obesity (Koistinen *et al.* 2000). Taken together with evidence that TNF- α expression is also up regulated in other tissues such as skeletal muscle in insulin resistance (Saghizadeh *et al.* 1996), these observations seem to point to TNF- α as a paracrine mediator of insulin resistance (Hauner *et al.* 1998), but not as a systemic signal between adipose tissue and glucose-metabolizing tissues.

The most consistent evidence in favour of a candidate for substance X relates to fatty acids. (The general term fatty acids, rather than non-esterified fatty acids (NEFA), has been used for reasons expanded later.) J-P Flatt (1972)

suggested such a link, reasoning that an increased mass of adipose tissue would deliver increased quantities of NEFA into the circulation. Increased plasma NEFA concentrations are a well-recognized feature of obesity (Opie & Walfish, 1963). There have been many studies of the rate of NEFA turnover (production and utilization) in obesity, but some confusion as to their interpretation. A brief summary, based on a comprehensive study of NEFA turnover and its regulation by insulin (Campbell *et al.* 1994), is as follows. NEFA release from adipose tissue is suppressed by insulin in both lean and obese individuals, but in obesity the process is 'insulin resistant' in that the dose–response curve is shifted to the right. NEFA release per unit fat mass is actually less in obese subjects than in lean subjects (effectively, it is down regulated by the fasting hyperinsulinaemia). However, because of the increased fat mass, total NEFA delivery to the circulation is increased in obesity. Furthermore, if 'lean body mass' (including skeletal muscle and liver) is used as the denominator for NEFA turnover, then NEFA delivery to the consuming tissues is clearly increased in obesity. The 'insulin resistance' of adipose tissue lipolysis may be particularly relevant in relation to the delivery of NEFA in the postprandial period. Despite high plasma insulin concentrations in response to a standard mixed meal, obese subjects fail to suppress NEFA release from adipose tissue at a time when it is completely suppressed in lean subjects (Coppack *et al.* 1992).

The adverse effects of increased fatty acid availability on insulin sensitivity are well known. Since the early work by Randle *et al.* (1963) showing that increased availability of fatty acids will decrease glucose utilization in muscle, it has also been recognized that NEFA are a potent stimulus to hepatic glucose production (Ferrannini *et al.* 1983; Boden *et al.* 1994). In addition, elevated NEFA concentrations will acutely potentiate glucose-stimulated insulin secretion (Carpentier *et al.* 1999), although there is a longer-term 'lipotoxic' effect of fatty acids on the pancreatic β -cell that may be part of the link between obesity, insulin resistance and development of type 2 diabetes (Unger, 1995; Grill & Qvigstad, 2000).

The increased flux of fatty acids from adipose tissue can be expanded beyond NEFA release. Since the enzyme lipoprotein lipase in adipose tissue is up regulated by insulin (Sadur & Eckel, 1982; Farese *et al.* 1991), adipose tissue is an important site for the disposal of dietary triacylglycerol (TG; in the form of chylomicron-TG) in the postprandial period (Coppack *et al.* 1990). The process of TG-fatty acid uptake by adipose tissue may also become insulin-resistant in obesity. This process comprises two steps (Sniderman *et al.* 1997). The first step is the action of lipoprotein lipase on the chylomicron-TG. There are many demonstrations that acute insulin activation of adipose tissue lipoprotein lipase becomes 'insulin resistant' in obesity (Eckel, 1987; Ong & Kern, 1989; Coppack *et al.* 1992). The second step involves the uptake of the fatty acids released by lipoprotein lipase into the adipocyte. The evidence here is less clear-cut, with some evidence for a reduction in this process in obesity (Coppack *et al.* 1992), but other evidence against such a reduction (Kalant *et al.* 2000). Nevertheless, on balance obesity is typically characterized by increased postprandial lipaemia (Coppack *et al.* 1992), reflecting at least in part

prolonged residence of dietary fatty acids in the circulation (Lewis *et al.* 1990). These fatty acids, in the form of TG in remnant particles, will be removed by a number of tissues, including skeletal muscle and liver. Hence, again, in obesity the insulin-sensitive glucose-consuming tissues are subjected to an increased influx of fatty acids, and this increase is particularly marked in the postprandial period when adipose tissue, through 'insulin resistance', fails to protect other tissues from the influx of dietary fatty acids.

Tissue triacylglycerol accumulation as a unifying feature

Although the pioneering work of Randle *et al.* (1963) on the link between fatty acids and insulin sensitivity is often cited as pertaining to circulating NEFA, in fact their seminal paper clearly states that excess fatty acid availability may arise also from the local breakdown of tissue TG: 'We suggest that there is a distinct biochemical syndrome . . . due to breakdown of glycerides in adipose tissue and muscle, the symptoms of which are a high concentration of plasma NEFA, impaired sensitivity to insulin . . .'. A unifying theory of insulin resistance in obesity that again focuses on the accumulation of tissue TG is now emerging from a large number of observations. Insulin resistance is associated with high levels of TG in skeletal muscle fibres (Phillips *et al.* 1996; Forouhi *et al.* 1999), liver (Banerji *et al.* 1995; Björntorp, 1995; Goto *et al.* 1995), and pancreatic islets (Koyama *et al.* 1997; Shimabukuro *et al.* 1997). Whilst there has been some debate about whether the accumulation of muscle TG is a cause or effect of insulin resistance, manipulation of tissue TG content in rodent models is associated with marked alterations in insulin sensitivity (Koyama *et al.* 1997; Shimabukuro *et al.* 1997). Accumulation of muscle TG may be accentuated by the defect in skeletal muscle fat oxidation observed in obese subjects (Blaak *et al.* 1994; Colberg *et al.* 1995).

A summary, then, is that in obesity the fat cells, perhaps because they are already 'overloaded' with TG, fail in their normal role of protecting other tissues from the daily influx of dietary fatty acids. The increased flux of fatty acids (both as NEFA and TG) in the circulation has acute adverse effects on insulin sensitivity, but also leads in the longer term to accumulation of TG in glucose-metabolizing tissues such as skeletal muscle, liver and the pancreatic β -cell. Accumulation of TG in these tissues, by some unknown mechanism, but probably involving local TG hydrolysis and availability of fatty acids or fatty acyl-CoA (Ellis *et al.* 2000), leads to an impairment of the normal sensitivity of glucose metabolism to insulin (or, in the case of the β -cell, to an impairment of insulin secretion in response to glucose). This view is, I believe, consistent with a large number of disparate observations in human subjects and experimental animals. It confirms the view that adipose tissue is a highly-active closely-regulated metabolic tissue that performs the vital role of buffering fluxes of fatty acids in the circulation in the face of variable input of dietary fatty acids from hour to hour. When eventually its buffering capacity is overwhelmed by consistent intake of fat above the rate of oxidation, the dietary fat has to go elsewhere, and its deposition in other tissues leads to insulin resistance.

It might be noted that insulin resistance in general leads to fat oxidation at the expense of glucose. Insulin resistance is associated with diminished glucose utilization at a given insulin concentration (by definition) and failure to suppress NEFA release from adipose tissue. It is also associated with impaired activation of adipose tissue lipoprotein lipase by insulin (discussed earlier) and therefore generally with a partitioning of fatty acids towards oxidative tissues such as muscle. This situation leads to the idea that insulin resistance may even be seen as a metabolic adaptation to increasing obesity (Flatt, 1988; Frayn *et al.* 1991; Eckel, 1992). However, as will be discussed later, insulin resistance is clearly maladaptive in terms of the risk it confers of other chronic diseases.

We are left then with the question of why insulin resistance is also a feature of the lack of adipose tissue in lipodystrophy. Human lipodystrophy is relatively rare, and detailed metabolic studies are infrequent, although there has been success recently in identifying the genetic mutations involved in some forms of lipodystrophy (Cao & Hegele, 2000; Shackleton *et al.* 2000). (The genes identified the code for nuclear envelope proteins, so this finding is not informative in terms of understanding insulin resistance.) This condition has been thoroughly investigated, however, in rodent models. Several mouse models have been created that lack adipose tissue wholly or partially. In one of the most severe models, the A-ZIP/F-1 mouse, the mice lacking adipose tissue are diabetic and severely insulin resistant, and have a twofold elevation of TG content in liver and skeletal muscle (Kim *et al.* 2000). Surgical transplantation of normal adipose tissue under the skin of these animals produces adipose tissue depots that become normally vascularized. Transplantation of adipose tissue reduces the TG content in liver and skeletal muscle, and reverses the insulin resistance and diabetes, in a dose-dependent manner; transplantation of normal physiological amounts is required to completely normalise the insulin responsiveness (Gavrilova *et al.* 2000; Kim *et al.* 2000). The effect of lipodystrophy has been described as 'alteration in the partitioning of fat between the adipocyte and muscle/liver leading to accumulation of TG in the latter tissues with subsequent impairment of insulin signalling and action' (Kim *et al.* 2000).

These results are, of course, completely in accord with the view put forward earlier, that the normal role of adipose tissue is to 'buffer' the daily influx of dietary fat entering the circulation (Fig. 2). If adipose tissue is overloaded, as in obesity, this buffering capacity is lost and other tissues are exposed to an excessive influx of fatty acids. If there is a deficiency of adipose tissue, as in lipodystrophy, then again this normal buffering action of adipose tissue is deficient (or absent) and other tissues are again exposed to an excessive flux of fatty acids. The result is accumulation of fatty acids in the form of TG in other tissues and interference with insulin-mediated glucose disposal (or glucose-stimulated insulin secretion, in the case of the β -cell).

One caveat to this unifying view needs to be expressed. There is powerful experimental evidence for another view of the insulin resistance of lipodystrophy, that it reflects leptin deficiency. Re-establishment of leptin expression in mouse

models lacking adipose tissue can also normalize many metabolic variables including insulin resistance and tissue TG content (Koyama *et al.* 1997; Shimabukuro *et al.* 1997). However, the existence of leptin without adipose tissue is not a physiological situation and, furthermore, this model does not help explain the link between human obesity (a condition in which leptin concentrations are almost universally elevated; Considine *et al.* 1996) and insulin resistance. Nevertheless, this observation does add to our understanding of the normal vital role of adipose tissue in maintaining energy homeostasis through multiple mechanisms.

Other adipose tissue components of the insulin resistance syndrome

The point was made earlier that insulin resistance means more than just insensitivity of glucose metabolism to insulin. It affects lipid metabolism and is also associated with hypertension, endothelial dysfunction and adverse effects on other physiological systems. It is not my intention to discuss these other effects of insulin resistance here, since their pathogenesis has been covered in many reviews (Frayn, 1993; Björntorp, 1994; Brunzell & Hokanson, 1999). However, it is interesting to note that again adipose tissue can be seen to play an important role, especially in the dyslipidaemia associated with insulin resistance, which may stem largely from impaired postprandial coordination of lipid metabolism (Patsch *et al.* 1984; Miesenböck & Patsch, 1992; Frayn, 1993). Recent evidence that elevated NEFA concentrations can impair endothelial function (Steinberg *et al.* 1997, 2000; Lind *et al.* 2000) provides yet another link between adipose tissue function and components of the insulin resistance syndrome.

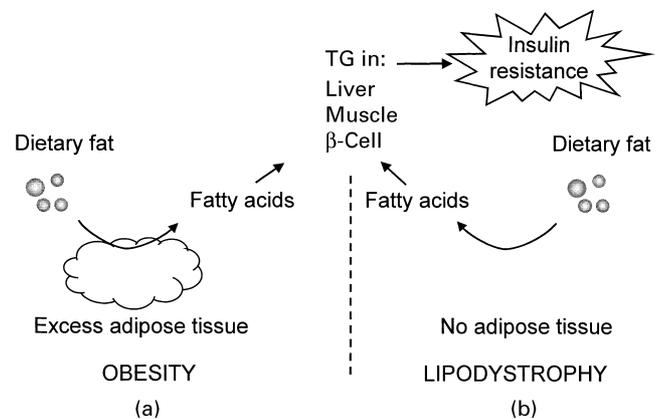


Fig. 2. A model that explains both a and b of Fig. 1. Loss of the normal 'buffering' effect of adipose tissue against the daily influx of dietary fat into the circulation in both obesity (when the fat cells are effectively overloaded) and lipodystrophy (when the adipose tissue necessary to perform such a function is lacking) leads to an excessive flux of fatty acids (both non-esterified fatty acids and triacylglycerol (TG)) into the circulation. This excess is deposited as TG in other tissues where it interferes with insulin responsiveness (liver and skeletal muscle) or with glucose-stimulated insulin secretion (pancreatic β -cell).

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