Adipose tissue expandability: the metabolic problems of obesity may arise from the inability to become more obese

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Abstract

The prevalence of obesity is increasing and with it the prevalence of associated metabolic complications. Precisely how obesity results in metabolic disturbances remains unclear. In the face of persistent positive caloric balance, it has been postulated that the capacity of adipose tissue to safely store fat may be vital. This paper explores some of the evidence suggesting that the risk of developing metabolic disturbances is not related to how much fat an individual has, but how well their fat can expand to accommodate the caloric excess. If this is true, the metabolic consequences of obesity may arise from the inability to become more obese.

Introduction

Obesity is becoming increasingly prevalent worldwide and is projected to increase significantly over the next decade [1]. While it is accepted that obesity is the result of a positive imbalance between energy intake and output, the pathophysiology underlying the failure of energy homeostasis remains unclear. Whereas obesity relates to the expansion of the adipose tissue, it is unclear why it is associated with the development of metabolic complications: namely diabetes (T2DM (Type 2 diabetes mellitus)), insulin resistance and dyslipidaemia, resulting in the metabolic syndrome. The rise in the prevalence of obesity is mirrored by the rise in diabetes; for every kg of weight gain, the risk of diabetes increases between 4.5 and 9% [2]. Similarly, 60–90% of all patients with T2DM are or had been obese, and it is clear that interventions that reduce weight reverse these complications [3].

An adipocentric view of the metabolic syndrome encompasses two potential mechanisms to explain the development of metabolic complications resulting from obesity: namely (i) lipotoxicity, where excess lipids ‘spill over’ from an incompetent and dysfunctional adipose tissue [4]; and (ii) specific patterns of adipokines and pro-inflammatory cytokines released from dysfunctional adipose tissue [5,6] (Figure 1). While these mechanisms explain the contribution of various circulating factors in the development of insulin resistance, all require the presence of dysfunctional adipose depots. This raises a number of questions. (i) Why/how adipocytes become dysfunctional under conditions of caloric excess? (ii) Under what conditions do adipocytes change from a healthy storage tissue to one that seemingly promotes the metabolic syndrome?

These questions raise the idea of adipose tissue expandability [7], which postulates that the total adipose tissue in an individual may have a maximal fixed capacity for safely storing fat. This capacity may be determined by multiple factors including but not limited to the number of pre-existing pre-adipocytes, genetic programmes of adipogenesis, programmes of vasculogenesis or functionality of other cellular components within the adipose tissue (Figure 2). This hypothesis suggests that the capacity for adipose tissue expansion is not infinite and that an individual will remain metabolically healthy, provided the adipose depot can safely accommodate caloric excess. Once exceeded, the exhausted fat cells appear to promote insulin resistance. The purpose of the present review is to summarize the evidence supporting the idea of adipose tissue expandability and its implications in the management of obesity.

Testing the hypothesis

As a starting point, we can explore the metabolic changes that occur when fat mass is altered. It can be predicted that in the presence of metabolic complications, promotion of an increase in fat mass will improve the metabolic profile and vice versa. Furthermore, it would be expected that the amount of added capacity for fat-mass expansion will correlate with the degree of metabolic improvement. However, one caveat to consider is the dual role of adipose tissue as a storage organ and an endocrine organ. In this respect, alteration of fat mass will invariably lead to an alteration in adipokine profile, making it difficult to attribute metabolic improvements to fat storage exclusively.

Metabolic effects of manipulating fat mass

Models of fat-mass reduction

PPARγ (peroxisome proliferator-activated receptor γ) is a transcription factor crucial for the differentiation of precursor cells into mature adipocytes [8–10] and its manipulation affects the capacity of adipose tissue to expand. In fact,
An adipocentric view of obesity-related metabolic complications

In the presence of sustained caloric excess, adipocytes eventually fail as a storage organ. This results in the ‘spillover’ of lipids into organs not normally suited for fat storage. The adipocytes also release an unfavourable adipokine profile. This combination results in organ-tissue dysfunction and the metabolic syndrome.

Treatment with PPARγ agonists facilitates the expansion of fat mass [11], whereas inactivation of PPARγ limits fat-mass expansion. However, a certain amount of restraint must be exercised when attempting to correlate PPARγ-related metabolic changes with the effect of adipose tissue expansion. First, PPARγ is expressed in a variety of tissues, thus any observed metabolic change may not be exclusively attributed to its promotion of fat-mass expansion. In murine models of adipose tissue-specific PPARGKO (PPARG-knockout), PPARγ agonists still have demonstrable metabolic effects [12]. Secondly, the amount of PPARγ expressed may not always relate to its transcriptional activity. This is partly explained by its dependence on interactions with cofactors [13].

However, despite these limitations, important information has been gathered from animal models in which PPARγ activity was progressively limited. These animals were shown to have a reduction in the capacity for adipose expansion. The global homozygous PPARGKO mice were embryonically lethal, and attempts at tetraploid rescue demonstrated severe lipodystrophy [14]. In contrast, the heterozygous PPARGKO animals [15,16] were viable, had the same degree of adiposity and had improved insulin-sensitivity compared with their controls. However, embryonic fibroblast harvests from these animals were less able to differentiate into mature adipocytes, and this supports the decrease in the capacity for expansion [16].

Other mouse models investigated the effects of dominant-negative mutations of PPARγ receptors, mutations first identified in humans with familial partial lipodystrophy. Heterozygous mice carrying the dominant-negative P465L PPARγ mutation [17,18] were phenotypically normal but had ex vivo evidence of diminished pre-adipocyte differentiation into mature adipocytes [17]. When these mice were calorically challenged with an HFD (high-fat diet), they were able to gain weight and fat mass to a degree comparable with controls and remained metabolically healthy, suggesting that the HFD may not have stretched the adipose depots to their limits. To address this issue, we went on to challenge our heterozygous PPARG dominant-negative mice (P465L/wt) with a greater caloric challenge by limiting leptin expression (P465L/ob) [17]. These mice were hyperphagic, had decreased energy expenditure and had increased fat mass well beyond that of the HFD-fed mice, supporting the idea that HFD was not an adequate caloric challenge in this model. Although obese, these mice had consistently 15% less fat compared with ob/ob controls despite similar food intake and energy expenditure, indicating a limitation in fat expansion. In agreement with the adipose tissue expandability hypothesis, these thinner mice had a more severe metabolic phenotype than the ob/ob mice.

Although not ideal, the manipulation of PPARγ to limit adipose tissue expansion has provided indirect evidence to support our hypothesis. It would appear that the adipose tissue depots may have a maximal physiological limit to safely store fuel, and the limitation of PPARγ has restricted this limit. Under conditions of caloric excess, this limit seems to determine the susceptibility to metabolic complications.

Lipodystrophy is a condition characterized by the selective loss of adipose tissue. Lipodystrophy could be an inherited or acquired disorder [19,20]. This loss is frequently associated with insulin resistance, diabetes, hypertriglyceridaemia, hepatosteatosis and low HDL (high-density lipoprotein)-cholesterol levels – a metabolic profile similar to that observed in obesity-related metabolic syndrome [19–21]. So consistent is this finding that even animal models of lipodystrophy (regardless of mechanism) reproduce this metabolic phenotype. Furthermore, the more severe the fat loss the more severe the metabolic disturbance. These observations support a central role of adipose tissue in the development of metabolic complications.

How does this fit with the idea of adipose tissue expandability? It would appear from the above observation that the
pathophysiological mechanism involved in lipodystrophy may also be relevant in the obese. The question is whether this is due to the loss of storage capacity or loss of adipokines [22]. The hypothesis postulates that an unlimited capacity for expansion of fat mass is predicted to improve insulin-sensitivity. In rodent models of lipodystrophy, fat transplant from wild-type donors improves the metabolic abnormalities in a fat-mass-dependent manner [23]. Similarly, restricting the caloric intake would be predicted to reduce the demand on fat storage, resulting in metabolic improvements. Indeed, this is consistent with the benefits observed with the anorectic effects of leptin replacement [24–26]. Although the lipodystrophy model cannot fully separate the effects of adipokines from adipose storage, the findings are still in keeping with the hypothesis, and it is likely that both factors are important in lipodystrophy.

In human studies, the procedure of liposuction has been in practice for over 20 years and predominantly used for cosmetic purposes. Previously, liposuction has been investigated as an intervention for treating obesity and its metabolic complications [27]. While the procedure is limited to the removal of subcutaneous fat, large volume of fat (4–5 litres) [28–30] can be removed, the degree of weight loss is comparable with that achieved by successful dietary/exercise intervention.

The hypothesis for the beneficial effect of liposuction is based on the observation that adipokines, such as TNFα (tumour necrosis factor α), resistin and IL-6 (interleukin-6), which promote insulin resistance, are elevated in adipose tissue of obese individuals. Hypertrophic subcutaneous fat cells in obese individuals have increased production of such adipokines, and their removal may conceivably lead to an improvement in metabolism.

A cohort study by Klein et al. [29] compared the metabolic status of obese female subjects with insulin resistance, before and after large-volume liposuction. Despite a significant decrease in BMI (body mass index) and fat mass, there was no change in insulin-sensitivity. In contrast, D’Andrea et al. [30] performed a similar study in obese females with normal glucose tolerance and found that an averaged weight lost of 3.6 kg by liposuction was associated with significant improvements in insulin-sensitivity. These conflicting results were reproduced in other studies; some of the studies demonstrated an improvement [28,31,32], whereas others did not [33,34]. However, data from these studies were confounded by multiple factors.

How does this fit into the idea of adipose tissue expandability? The expandability hypothesis postulates that any loss of capacity for storing fat will worsen insulin resistance, provided that adipose tissue storage has already reached its maximal capacity. If this limit has not been reached, then removal of fat from one depot could potentially stimulate the expansion of another [35]. Indeed, studies that were performed on individuals with normal BMI, where adipose tissue capacity is unlikely to be stretched, documented no change in metabolism [33,36].

How then could we explain the lack of changes observed in studies where individuals have documented insulin resistance? One possibility is that subcutaneous fat is relatively more benign compared with visceral fat and its loss is unlikely to have any impact on metabolism [37]. We would postulate that, in a patient whose adipose mass has achieved its limit and has developed evidence of lipotoxicity, the metabolic disturbances should worsen regardless of the site or amount removed. However, this detrimental effect is likely to compete with the potential benefit gained in adipokine profile [30]. It is conceivable that if caloric excess persists, the remaining fat cells would be under further demands to store fat and metabolism would worsen over time.

**Models of fat-mass expansion**

The expandability hypothesis postulates that an increase in adipose storage capacity would improve metabolic complications.

In human trials, the PPARγ agonists TZDs (thiazolidenediones) have been shown to improve lipid profile, insulin-sensitivity, diabetes and hepatosteatosis [38,39]. In vivo studies have shown that TZD increases fat mass and increases adipogenesis [40,41]. However, these improvements could be brought about by a direct influence on adipokine production [42] and by effects outside of the adipose tissue [43,44]. The observed metabolic improvements may not be solely related to the expansion of adipose tissue storage capacity. Indeed, recent concerns regarding the use of TZD are likely to be related to their effects on non-adipose tissues [45,46]. However, no one disputes that the greatest effect of TZDs is on adipogenesis and lipid metabolism [47]. The glucose-lowering effects of TZD appear to be dose-dependent and so is TZD’s effect on weight gain, further supporting the idea that stimulating adipose expansion and improving adipose tissue capacity are associated with improvements in all aspects of metabolic disturbances.

In the presence of sustained positive caloric balance, an improvement in metabolism is associated with adipose tissue expansion. In animal models, a number of interventions would appear to improve insulin-sensitivity without an increase in fat mass. These studies are invariably explained by an increase in oxidation and/or a decrease in intake, making it difficult to quantify the contribution of adipose tissue expansion. However, in mouse models, a net positive energy balance can be consistently achieved in the leptin knockout mouse (ob/ob). Kim et al. [48] demonstrated that the overexpression of adiponectin in the ob/ob mouse did not result in an increase in energy expenditure or reduction in intake. Instead, these mice expanded their fat mass, which resulted in an improvement in insulin-sensitivity.

The expandability hypothesis predicts that, provided an individual can continue to safely store fat, they will remain metabolically healthy even if they become obese. MHO (metabolically healthy but obese) individuals do exist [49–52]. Karelis et al. [49] demonstrated that 12.5% of obese non-diabetic post-menopausal women had no metabolic complications and remain insulin-sensitive. A similar estimate of 11% was recorded by Brochu et al. [50,53] among 413 unselected obese subjects. Detailed analysis of
such metabolically healthy but obese individuals reveals that they had less visceral fat (∼50% less) compared with the metabolically affected obese individuals [50,53]. However, visceral adiposity accounted for only 22% of the observed variation in insulin resistance.

What is surprising is that MHO individuals have a greater fat mass relative to their lean mass compared with metabolically less healthy obese controls, suggesting a greater capacity for fat expansion [50]. Quantitatively, these individuals were significantly obese, had large visceral fat depots and yet they had similar glucose disposal rates per kilogram of lean mass compared with healthy lean women half their age [50]. Individuals who can expand their adipose tissue capacity further appear to be more resistant to the metabolic effects of caloric excess.

**Saturation of fat storage precedes adipokine derangements**

As discussed above, it is difficult to separate the role of adipokine derangements from failure of fat storage in the development of the metabolic syndrome. However, several lines of evidence suggest that as adipocytes achieve their maximal storage capacity, they begin to alter their secretion profile towards one that drives insulin resistance, suggesting that limitation in storage capacity precedes the development of pathology.

First, in human subjects and rodent models, obesity is associated with an elevation in IL-6 and TNFα and a decline in adiponectin, a profile that favours insulin resistance and reduces adipogenesis [54,55]. Our hypothesis postulates that the derangement in adipokine secretion occurs after the adipose tissue has reached its maximal capacity. Prior to this, the coping adipocytes would produce a profile in favour of adipogenesis and insulin-sensitivity. In rodent models of diet-induced obesity, the initial response to a positive caloric balance is a rise in both leptin and adiponectin; only after a certain level of obesity is achieved would the derangement in adipokine profile be observed [56,57]. In our own laboratory, a 4-week-old leptin-deficient mouse produces more adiponectin compared with a 16-week-old mouse [57]. These observations support the idea that saturation of adipose tissue precedes the alteration in adipokine secretion.

Secondly, adipose cell size is closely linked to its adipokine-secretory profile and insulin-sensitivity. Large adipocytes that are engorged with lipids are more insulin-resistant and have altered adipokine-secretory profile [58]. Furthermore, PPARγ agonist or adiponectin overexpression, both of which improve insulin-sensitivity, is consistently associated with an increase in the proportion of smaller adipocytes [40,48]. It would appear that, at the cellular level, adipocytes with large lipid stores have achieved their maximal capacity and become dysfunctional. Similarly, at the tissue level, the lack of smaller adipocytes reflects a failure of pre-adipocyte recruitment. Both observations support the idea that, when pushed to the limit of storage capacity, adipose tissue has a fixed capacity for expanding and this signals the onset of metabolic disturbances.

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**Figure 3** | The effects of enhancing adipose tissue storage capacity

(A) In the metabolic syndrome, the required fat storage capacity (broken line) exceeds that of the natural storage capacity (continuous line) of an individual. (B) The adipokine secretory profile is initially pro-adipogenic, but as storage capacity is reached, it alters to become anti-adipogenic and pro-inflammatory. Solid line: if natural storage capacity can be enhanced to meet the required storage demand, lipid ‘spillover’ could be prevented and the adipokine profile remains favourable.

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**Conclusions**

Based on these observations, our model suggests that in the presence of caloric excess, the development of metabolic complications is preceded by a period of normal metabolism when the adipose depot is able to expand and adipocytokine production and circulating lipids remain favourable. If caloric excess persists, the fat depots reach their maximal storage capacity, which appears to trigger a cascade of events that result in the metabolic syndrome. At what point the adipose tissue begins to fail is likely to be determined by genetic and epigenetic factors. Individuals with a higher capacity for storing fat will probably remain metabolically normal for a longer period despite an obesogenic environment. This capacity would probably deteriorate with time, as aging affects adipose tissue expandability and susceptibility to insulin resistance [56,59,60].

If this hypothesis is correct, it will affect our approach to the therapy of obesity-related metabolic complications. First, weight reduction therapy would be tailored to the individual: targeted weight loss, which aims to reduce weight until it falls within a subject’s maximal fuel storage capacity. The amount
of weight loss may be above or below the recommended 10% weight reduction and is likely to be independent of the starting weight. Secondly, therapies that increase adipose storage capacity can ameliorate the prevailing metabolic disturbances. While counterintuitive, the increase in fat mass can temporarily improve metabolic disturbances, reduce complications and, most importantly, allow additional time for caloric restriction to take effect (Figure 3).

A number of questions remain unanswered. (i) How does an adipocyte sense that it is approaching its storage limit? (ii) What are the molecular mechanisms that control and determine adipose tissue expandability? (iii) When adipose tissue fails, why does it respond in the manner that we observe?

In an attempt to answer these questions, we postulate that adipocytes should have a nutrient-sensing mechanism. This could either be direct, by detecting the amount of fuel already in storage, or indirect, by sensing peripheral signals that inform it of a pending caloric load and the biophysical properties of the surrounding overstretched adipocytes. It is interesting that molecular targets involved in metabolism such as PPAR, FABP4 (fatty-acid-binding protein 4), HNF4A (hepatocyte nuclear factor 4α) and lipocalins require fatty acids as ligands. To this end, detailed analysis of the lipid content within adipocytes may document adipocytes’ sensing. We hope to identify nutritional signals that promote adipose expansion and signals that trigger an unhealthy metabolic response. Lipidomic technology coupled with a system biology approach has yielded useful information in our mouse models [57,61]. The answers to these questions will ultimately improve our understanding of the metabolic syndrome and result in an improvement of patient care.

This work has been supported by grants from FP6 (Framework Programme 6) Hepadip and the Medical Research Council.

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Received 28 April 2008
doi:10.1042/BST0360935