

The impact of insulin resistance, gender, genes, glucocorticoids and ethnicity on body fat distribution

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Abstract

The metabolic consequences of obesity are highly dependent on body fat distribution and total body fat mass. Visceral adipose tissue in particular has been found to play an important aetiological role in obesity-related disorders. The contrasting fat distribution between genders, with gynoid and android obesity being characterised by increased subcutaneous and visceral fat deposition respectively, may be directly responsible for differences in obesity-related co-morbidities between the sexes. These differences in adiposity are likely to be directly due to the influence of the sex steroids. Glucocorticoids may further modify body fat distribution, as observed in Cushing's syndrome in which hypercortisolaemia leads to increased visceral fat mass. Hereditary factors have also been found to be important, with studies demonstrating that up to 55% of the variance in visceral fat mass is genetically determined. Recently, it has been proposed that insulin sensitivity is a major factor that plays a role in determining fat distribution. Although it is accepted that excess adiposity results in insulin resistance, it has been suggested that insulin sensitivity at the level of the adipocyte may modulate the size of the subcutaneous and visceral fat depots. This occurs because insulin resistance retards triglyceride deposition in adipocytes and is therefore associated with reduced adipose tissue growth. It is thought that the subcutaneous depot is the prime site for triglyceride accumulation and, once this depot is lipid replete, triglycerides are diverted to the visceral tissue. The principal determinant of subcutaneous lipid storage capacity is the prevailing level of insulin resistance. This review will discuss all the factors that are thought to influence body fat distribution and will describe the possible role of insulin resistance in this process.

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Introduction

The incidence of obesity and, consequently, obesity-related co-morbidities is rapidly increasing in both the developed and developing worlds. Recently, the importance of total body adiposity has been eclipsed by the finding that visceral fat associated with central obesity contributes more to pathogenicity than subcutaneous fat.¹ This may be due to the greater ability of visceral than subcutaneous adiposity to increase insulin resistance¹ which, in turn, is thought to be an important aetiological factor in the development of type 2 diabetes, dyslipidaemia and cardiovascular disease.² Body fat distribution is therefore highly important and may be seen as a possible future predictor of obesity-related disease. Understanding the factors that regulate body fat distribution should not only give insight into the aetiology of obesity-related co-morbidities but also potentially allow

for different therapeutic interventions depending on body phenotype. Whereas increased lipid accumulation in the visceral adipose depot may contribute more to whole-body insulin resistance than a comparable expansion in subcutaneous fat,¹ it is possible that insulin resistance may regulate lipid accumulation differentially in subcutaneous and visceral adipose depots. This review will discuss how insulin resistance, gender, hereditary factors and glucocorticoids may sculpture body fat and change the pathogenicity of obesity.

Insulin resistance and body fat distribution

The physiological purpose of insulin resistance may be to limit triglyceride deposition within adipocytes and thus reduce the accumulation of additional body fat mass in

obese subjects.³ This is likely to be a remnant of an archaic response that would have limited weight gain in our distant ancestors, maintaining mobility and allowing them to avoid predation. Accordingly, it has been found that subjects with the highest level of insulin resistance gain less weight over time.^{4,5} Thus, a study of 192 Pima Indians demonstrated that those with insulin resistance gained less weight than insulin-sensitive subjects (3.1 versus 7.6 kg; $p < 0.0001$) over a period of 3.5 years.⁴ In addition, an investigation examining 95 children with an age range of 9.7–14.5 years showed that, after three years of follow-up, weight gain was lowest in those in the highest tertile of insulin resistance for both boys and girls.⁵

The accumulation of triglyceride in the subcutaneous and visceral adipose tissue depots does not occur at the same rate. The greater insulin sensitivity of subcutaneous compared to visceral adipose tissue^{6,7} allows the former depot to expand at a quicker rate in response to lipid loading in non-obese subjects. With increasing body mass index (BMI), the subcutaneous depot will expand and insulin resistance will increase, and this will lead to a reduction in the rate of both adipocyte hyperplasia and hypertrophy at this site. Triglycerides not taken up by the subcutaneous adipose tissue will then accumulate in the visceral depot, a process driven by hyperinsulinaemia. Triglycerides will also be deposited at ectopic sites such as the liver, skeletal muscle and islet β -cells.⁸ This process of lipid 'overflow' from the subcutaneous to the visceral depot has been postulated by a number of investigators,^{9,10} and a recent publication has suggested that the factor that limits triglyceride deposition within the subcutaneous depot is insulin resistance.¹¹ The net result of increased visceral adiposity and ectopic fat deposition will be much higher levels of insulin resistance, but with a small change in total body fat. This may have been an important evolutionary adaptation that occurred in our ancestors to limit fat deposition during periods of higher nutrient intake. However, in modern times cheap, calorie-dense foods are plentiful in all developed and most developing countries, and this metabolic process for limiting weight gain may now have been overwhelmed by excessive caloric intake. The consequence of this is a high population level of visceral adiposity, leading to an increased prevalence of the metabolic disorders associated with obesity.^{8,12,13}

The lower level of insulin resistance in subcutaneous, compared to visceral, adipocytes would mean that, in subjects with a low/normal BMI, fat deposition will occur primarily in the subcutaneous depot whilst, in subjects with a higher BMI, subcutaneous lipid accumulation will be slower but triglyceride deposition in the visceral depot will

be enhanced. This sequential expansion of adipose depots in response to rising levels of insulin resistance has been observed in epidemiological studies,^{14,15} in which a rapid increase in waist circumference occurs only at high levels of insulin resistance. Also, a study has shown that, in lean subjects, free fatty acid uptake in subcutaneous adipose tissue is much higher than that observed in obese, insulin-resistant subjects.¹⁶

Insulin resistance is not the only agent that controls body fat distribution, with gender, genes and glucocorticoids all having important roles. However, it is possible that the influence of these factors on body fat depot size occurs via the modulation of insulin sensitivity.

Gender-related differences in body fat distribution

Gender differences are observed in body fat distribution, with women tending to have less visceral but more subcutaneous fat than men.^{17,18} These differences are thought to be due to the effects of the sex steroids,¹⁹ although the mechanisms by which they influence body fat distribution are not fully understood. Given the possible role of insulin sensitivity in modifying adipose tissue depot size, it is tempting to speculate that the sex steroids may influence the responsiveness of adipocytes to insulin, and there is some evidence to support this.

Oestrogen may increase subcutaneous fat deposition in women by increasing insulin sensitivity. Studies in the ob/ob mouse have shown that administration of oestrogen leads to improved insulin sensitivity,²⁰ and adipocytes isolated from rats treated with oestrogen have higher insulin receptor numbers²¹ and increased insulin binding.²² Oestrogen may also have effects downstream of the insulin receptor, as treatment of the murine 3T3-L1 adipocyte cell line was found to increase insulin-stimulated glucose uptake, mediated by increased tyrosine phosphorylation of insulin receptor substrate 1.²³ Furthermore, the effect of oestrogen on insulin signalling has been recapitulated in humans, with naturally occurring mutations of oestrogen receptor- α resulting in insulin resistance.²⁴

Testosterone in men is associated with lower levels of both visceral²⁵ and subcutaneous²⁶ adiposity and reduced triglyceride uptake into subcutaneous adipocytes.²⁷ These effects may be mediated by the ability of testosterone to reduce insulin sensitivity by affecting signalling downstream of the insulin receptor. An in vitro study of human subcutaneous adipocytes showed that administration of testosterone led to reduced insulin-stimulated glucose uptake, which was mediated by a reduced level of protein

kinase C ζ phosphorylation.²⁸ Testosterone may also indirectly reduce insulin sensitivity, since it has been shown that testosterone treatment of men leads to lower serum levels of adiponectin.²⁹

The ability of sex steroids to modulate body fat distribution may not only be due to their effects on insulin sensitivity. A number of in vitro experiments and animal studies have shown that both testosterone and oestrogen can directly alter adipocyte metabolism via interactions with androgen and oestrogen receptors.³⁰ Furthermore, it is also known that adipocytes express enzymes that metabolise sex steroids. Thus, aldo-ketoreductase 1C enzymes (AKR1C) metabolise androgens, whilst aromatase converts androgens to oestrogens. The former enzymes may be important in regulating body fat distribution, as studies have shown that increased visceral adiposity is related to higher levels of AKR1C expression.^{31,32} It is therefore possible that android and gynoid body fat distribution are partly the result of the level of secreted sex hormones, as well as adipose depot-specific differences in the level of expression of the enzymes that metabolise testosterone and oestrogen and of the respective sex hormone receptors.

Data therefore demonstrate that oestrogen has insulin-sensitising^{20,23} and testosterone has insulin-desensitising effects on adipocytes,²⁸ which may lead to increased lipid storage in women compared to men. The direct effects of the sex steroids on adipocyte metabolism³⁰ would augment these gender differences. Therefore, with increasing BMI, women would accumulate more fat in the subcutaneous depot than men, whilst men would begin to accumulate fat in the visceral depot at a lower BMI than do women. Such patterns have been observed in cross-sectional studies.^{17,33} However, longitudinal investigations of body fat deposition across genders, as well as studies to analyse the effects of the sex steroids on insulin sensitivity in both subcutaneous and visceral adipocytes, are required to confirm these data.

Genetic input into body fat distribution

Adipose tissue depot size has important consequences, both metabolically and physically, and therefore the mechanisms that modulate body fat distribution must have a number of control points that allow efficient and appropriate regulation. The most basic of these regulatory inputs is from the genome. Evidence for a strong genetic input into body fat distribution comes from heritability studies that show that 50–55% of the variance in visceral fat mass is derived from genetic factors.³⁴ Nevertheless, a recent investigation has shown that gene polymorphisms that affect appetite regulation and that have been repeatedly

linked to BMI in genome-wide association (GWA) studies do not associate with MRI-assessed levels of visceral and subcutaneous fat.³⁵ These findings were confirmed in two GWA studies in which visceral and subcutaneous adipose tissue depot size³⁶ and waist-to-hip ratio³⁷ were linked with novel gene polymorphisms that had not previously been uncovered in GWA studies that used BMI as the principal phenotype. These polymorphisms were near genes that may be functionally linked to body fat distribution, namely regulator of G-protein signalling 6 (*RSG6*)³⁶ and lysophospholipase-like protein 1 (*LYPLAL1*).³⁷ The gene *RSG6* encodes a protein that has been linked to opioid-associated signalling,³⁸ which would in turn modulate cortisol secretion. *LYPLAL1* is a triglyceride lipase that is involved in the control of triglyceride breakdown within adipocytes.³⁷ A third gene, insulin-induced gene 2 (*INSIG2*), has also been linked to visceral and subcutaneous adipose depot mass³⁹ and to BMI in some, but not all, association studies.^{40,41} These inconsistent results have been attributed to *INSIG2* being more strongly associated with body fat distribution than with total adiposity.³⁹ *INSIG2* has been proposed to function in the feedback inhibition of fatty acid and cholesterol synthesis.⁴²

Polymorphisms in the fat mass and obesity-associated (*FTO*) gene show the strongest and most frequently replicated associations with obesity.⁴³ However, only one study has looked at the input of genetic variation at this site on visceral and subcutaneous adipose depot size.⁴⁴ This investigation reported that a single polymorphism in the *FTO* gene was related to BMI, body weight and total body fat mass, as well as both visceral and subcutaneous adiposity. This demonstrates that sequence variation in the *FTO* gene modulates body fat depot size, but this is largely due to its effect on total body fat mass.

These data demonstrate that the genetic aetiology of total body adiposity may be different from that of body fat distribution. It is also possible that eligible candidate genes for regulating body fat distribution may control adipose tissue insulin sensitivity, and it is noteworthy that polymorphisms close to the insulin receptor substrate (IRS) 1 gene have been associated with increased visceral fat levels in a genome-wide linkage scan.⁴⁵ However, this result needs to be replicated in a larger patient cohort. The association of *INSIG1* polymorphisms with body fat distribution also implicates adipocyte insulin responsiveness as a possible factor in the control of visceral and subcutaneous adipose depot mass.

The role of glucocorticoids in the control of body fat distribution

Body fat distribution is influenced by hormones other than insulin, particularly the glucocorticoids, which directly modify adipocyte gene transcription and promote adipocyte insulin resistance.^{46,47} Thus, increased visceral fat mass observed in Cushing's syndrome is a consequence of the inherent hypercortisolaemia of the disease.⁴⁸ As well as the effects on insulin sensitivity, cortisol is able to initiate adipogenesis in combination with insulin⁴⁹ and also increases lipid deposition in mature adipocytes by up-regulating adipocyte lipoprotein lipase⁵⁰ and inhibiting lipolysis.⁵¹ Cortisol is produced in adipocytes from inactive cortisone by the action of the enzyme 11 β -hydroxysteroid dehydrogenase (11 β HSD), the expression of which is increased in both visceral and subcutaneous adipocytes with increasing body fat mass.^{52,53} The cellular effects of cortisol are transduced via interaction with the glucocorticoid receptor, which has been shown to be expressed at higher levels in visceral than subcutaneous adipocytes.⁵⁴ Thus, with increasing BMI, adipocyte production of cortisol will increase, leading to high local concentrations of the hormone. This will have greater effects in the visceral adipose depot due to higher glucocorticoid receptor expression at the intra-abdominal site.⁵⁴ The greater exposure or sensitivity of visceral, compared to subcutaneous, adipose tissue to cortisol has been suggested by other investigators as the reason for the visceral adipocentric effects of cortisol.^{53,55} Thus, glucocorticoids may augment lipid accumulation in the visceral adipose tissue of obese subjects, allowing increased clearance of the triglycerides not taken up by the adipocytes within the subcutaneous fat depot.

Ethnic differences in body fat distribution

It is known that in subjects from the Indian subcontinent, type 2 diabetes, hypertension, ischaemic heart disease and the metabolic syndrome are all more common than in other population groups⁵⁶ and that, at any given level of BMI or waist circumference, the level of cardiovascular disease risk factors is higher in Indian than in European subjects.⁵⁷ It has been demonstrated that the level of visceral fat is higher in Indian than in European individuals when matched for BMI or waist circumference,^{56,58} and this may partially explain the higher prevalence of cardiovascular disease in the former population. We might explain the higher level of visceral adiposity in Indian subjects by suggesting that, in this population, the subcutaneous fat depot has a lower capacity for triglyceride accumulation, and hence increased lipid accumulation in the visceral depot would occur at lower BMIs, as also hypothesised by Sniderman et al.¹⁰

A possible explanation for this is that the subcutaneous adipocytes in Indian subjects are more insulin resistant compared to adipocytes in other ethnic groups, as has already been demonstrated,⁵⁹ and this would lead to lower lipid storage in this fat depot. Also, serum levels of free fatty acids (FFAs) are higher⁶⁰ and adiponectin lower⁶¹ in the Indian population. Both these molecules are products of adipocytes, with high levels of FFAs and low levels of adiponectin being associated with insulin resistance. However, given the multitude of recently discovered but yet to be fully characterised adipokines, it remains a point of conjecture whether ethnic differences in the production of one or more of these molecules by subcutaneous adipocytes might lead to higher levels of insulin resistance within the subcutaneous adipose depot of Indian subjects.

It is known that Indian neonates, although they have lower birth weights than those of other population groups, have proportionally higher levels of body fat, a phenotype that is preserved into adulthood.⁶² This suggests that the body fat pattern observed in Indian populations may be genetically determined. However, the genes involved have not yet been identified.

African women are known to have lower visceral^{63,64} but higher subcutaneous⁶⁴ fat mass than BMI-matched European women. This suggests that, in African women, the lipid storage capacity of the subcutaneous depot is greater than in European subjects, thus reducing lipid overflow into the visceral depot. The greater triglyceride storage capacity of the subcutaneous fat depot in African than European subjects may be related to the greater adipogenic rate observed in preadipocytes isolated from the former population group.⁶⁵ Higher adipogenesis may reflect increased sensitivity to the adipogenic properties of insulin in subcutaneous preadipocytes of African subjects. However, one study has shown that mature adipocytes taken from the abdominal and femoral subcutaneous fat depots of African women are less sensitive to the anti-lipolytic action of insulin than those taken from European women.⁶⁶ These data were obtained using adipocytes isolated from obese subjects, and the study would have had greater relevance if the insulin sensitivity of adipocytes taken from lean individuals had also been examined. Therefore, more data are required to fully explain the differences in body fat distribution observed between European and African populations, although current observations suggest that the greater adipogenic capacity of subcutaneous preadipocytes in African women may play some role in producing ethnic differences in adipose depot mass.

Conclusion

The control of body fat distribution must be viewed as an integration of different control systems, of which adipocyte insulin sensitivity is but one component. Other systems, particularly the endocrine axis, act directly on adipocytes but may also modulate adipocyte insulin functionality, which subsequently affects body fat distribution. The complex nature of the interactions that exist between these control mechanisms leads to difficulties in investigating and understanding the nature of the regulation of body fat distribution. It is for this reason that the use of high-throughput molecular screening techniques may allow a clearer understanding of the subcellular mechanisms that are involved in the control of lipid deposition in the different adipose tissue depots. Already, GWA studies have revealed interesting new data with regard to the genetic input into body fat distribution, and the use of proteomic and gene expression profiling technology will undoubtedly add to our limited knowledge of how body fat depot size and function are controlled. A fuller understanding of these pathways will lead to increased knowledge on the aetiology of obesity-related metabolic disorders and will hopefully progress to new interventions for these diseases.

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