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# Visceral Obesity and Diabetes

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## Abstract

Visceral obesity is a strong predictor of type 2 (non–insulin-dependent) diabetes and is associated with insulin resistance. In addition, research has indicated that the accumulation of visceral fat is regulated by endocrine mechanisms. Data suggest that progressive malfunction of the hypothalamic-pituitary-adrenal (HPA) axis, with elevation of levels of cortisol and reductions in levels of sex steroids and growth hormone, is associated with visceral accumulation of fat that contributes to circulating levels of free fatty acids, and that these factors are implicated in the development of insulin resistance. Furthermore, failure of central feedback control of the HPA axis by glucocorticoid receptors (GR) appears to be correlated with polymorphisms near the first exons of the GR gene. The HPA axis disturbances are similar to those seen after prolonged exposure to environmental stress. Psychosocial and socioeconomic factors, alcohol, depressive traits and anxiety are linked to HPA axis abnormalities.

Obesity is the most prevalent precursor of type 2 (non–insulin-dependent) diabetes; this is particularly the case when obesity is localised to central visceral fat depots.[1] Insulin resistance, which is more prominent in visceral obesity than in generalised obesity or that localised to peripheral gluteo-femoral depots, is considered to be related to this pattern of obesity.[2] The nature of the association between visceral obesity and insulin resistance may be discussed in terms of either of two alternatives: a direct cause-effect relationship or the presence of a third factor that causes both insulin resistance and accumulation of fat in intra-abdominal visceral depots (fig. 1).

## 1. Visceral Fat Causing Insulin Resistance

Free fatty acids (FFAs) have been implicated in the pathogenesis of insulin resistance in muscle through their interference with critical steps in glycolysis (the so-called glucose-fatty acid cycle).[3] Muscle tissue is the main regulator of systemic insulin sensitivity. It then remains to determine whether an enlarged visceral fat mass can contribute sufficient amounts of FFA to the systemic circulation to cause muscular insulin resistance.

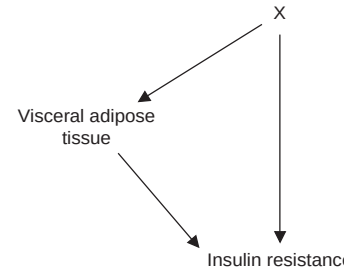


**Fig. 1.** The relationship between visceral adipose tissue and insulin resistance. Visceral fat might act directly on mechanisms causing insulin resistance. A third factor (X) might cause both visceral obesity and insulin resistance. A third possibility is a combination of these actions.

Visceral adipocytes have at least two characteristics that separate them from subcutaneous fat cells: their sensitivity to lipolytic stimuli is pronounced, and the antilipolytic effect of insulin is diminished. This means that the potential per unit mass of visceral adipose tissue to mobilise FFA is much larger than that of subcutaneous fat.

The next question refers to whether or not the mass of visceral fat is sufficient to contribute significantly to FFA levels in the systemic circulation, particularly since about half the FFAs released by visceral fat into the portal vein are captured by the liver beforehand. This is, unfortunately, difficult to measure directly in humans because of the topography of the portal vein. However, results of available data indicate that sufficient enlargement of the visceral fat mass may cause this depot to contribute significantly to systemic FFA levels (reviewed in detail by Björntorp[4]).

## 2. Visceral Fat and Insulin Resistance Caused by a Third Factor

Although the discussion above suggests a role of FFA from visceral fat in the pathogenesis of systemic insulin resistance, it does not explain why visceral fat mass is enlarged. The increased mass of visceral fat may be proportional to enlargement of other adipose tissue stores, but is often disproportionately greater. This suggests the operation of a mechanism that directs excess body fat preferentially to visceral depots.

## 3. Hormonal Regulation of Visceral Fat Mass

Clinical observations offer suggestions for the nature of the factor responsible for directing excess fat to visceral depots. Cushing's syndrome and exposure to adrenal corticosteroids for therapeutic purposes are dramatic examples of conditions in which fat is centralised in visceral depots. These observations strongly suggest that glucocorticoid hormones are involved. In addition, aging in both men and women is associated with increased central adipose tissue mass. Levels of both sex steroids and growth hormone decrease with aging, whereas cortisol secretion is unaffected. This observation indicates involvement of steroid and growth hormone deficiency in the accumulation of visceral fat. Indeed, both decreased estrogen production and centralisation of body fat occur abruptly and in parallel in women.

Research has now shown that accumulation of visceral fat is indeed strongly regulated by endocrine mechanisms. Although hormones have effects on adipose tissue throughout the body, the effects are more pronounced in visceral fat for several reasons. Firstly, blood flow and innervation are more abundant in visceral than in other depots. This means that the adipocyte microenvironment in visceral fat is such that any systemic alteration in availability of lipid substrate or change in hormonal secretion has more pronounced consequences in visceral fat than in other depots. Secondly (and probably more importantly), the density of specific hormone receptors is higher in visceral fat than in other depots. This applies whether the data are expressed as per unit of adipose tissue mass or per adipocyte (reviewed by Björntorp[5]).

### 3.1 Effects of Cortisol, Sex Steroids and Growth Hormone on Adipocyte Metabolism

Cortisol exerts its effects on adipocyte metabolism by powerful stimulation of the rate-limiting enzyme for lipid uptake, lipoprotein lipase. However, lipid mobilisation cannot satisfy this increased influx of fat; indeed, lipid mobilisation is inhibited in the presence of elevated insulin levels (as is the case in visceral obesity), and insulin also amplifies the effects of cortisol on lipid uptake. The net result of these processes will clearly be fat accumulation.

Sex steroids and growth hormone have opposing effects to cortisol. Testosterone in men exerts powerful effects on lipid mobilisation, which is stimulated at several levels, while the action of enzymes involved in lipid accumulation is inhibited. The same effects are characteristic of estrogen action (although this is less certain). Growth hormone seems to act by amplifying the effects of sex steroids.[5]

Thus, the net effect on accumulation and mobilisation of lipids stored in adipocytes depends on the balance between cortisol and insulin, which facilitate lipid accumulation, and sex steroids and growth hormone, which prevent lipid accumulation and facilitate lipid mobilisation. This is more pronounced in visceral than other fat depots because of an increased density of specific hormonal receptors and an adipocyte microenvironment that facilitates alterations in adipose tissue metabolism. These observations explain the high turnover of visceral fat relative to that of other adipose tissues. They also probably explain the enlargement of visceral adipose tissue mass when the balance between cortisol/insulin and sex steroid/growth hormone shifts in favour of the former pair. This is seen in Cushing's syndrome and after exogenous administration of glucocorticoid for therapeutic purposes when cortisol is already present in excess, and insulin levels are elevated as a consequence of concomitant insulin resistance. With aging, or decreases in secretion of sex steroids and/or growth hormone for other reasons, normal cortisol antagonism is disturbed in favour of visceral fat accumulation, because the inhibition of lipid storage and stimulation of lipolysis are not sufficiently powerful to counteract the effect of cortisol.

These hypotheses have been tested in intervention trials in humans in which visceral fat mass has been nearly or fully normalised after treatment of Cushing's syndrome or after correction of sex steroid hormone deficiency (reviewed by Björntorp[5]).

## 4. Endocrine Factors and Insulin Resistance

Interestingly, the same hormones that are involved in the accumulation of visceral fat also seem to be involved in insulin resistance. Cortisol clearly causes insulin resistance; the same seems to apply with low levels of sex steroids (reviewed by Björntorp[6]). The conventional view is that growth hormone causes insulin resistance. However, patients with total growth hormone deficiency are insulin resistant, a situation that is improved by administration of exogenous growth hormone.[7]

Elevated cortisol levels and low sex steroid and growth hormone levels would therefore be expected to cause insulin resistance in parallel with visceral fat accumulation. The effect of cortisol on insulin resistance is clearly established. Again, hormonal effects on insulin resistance have been verified in intervention trials in humans. When men with low testosterone levels and insulin resistance are given testosterone in dosages appropriate for their ages, their insulin resistance is largely corrected.[8] The same is seen in patients with correction of growth hormone deficiency.[7,9]

It is therefore likely that the endocrine disturbances that cause visceral fat accumulation are also responsible for insulin resistance, a phenomenon strongly associated with visceral obesity. As stated earlier, it is also possible that, with sufficient enlargement of visceral depots, FFAs originating from these depots will amplify muscular insulin resistance.

In summary, a combination of elevated cortisol, low sex steroid and growth hormone levels results in visceral accumulation of excess fat that then contributes to circulating levels of FFA. These factors are likely to be causally associated with insulin resistance (reviewed by Björntorp[5,6]).

## 5. Endocrine Status of Visceral Obesity

As stated above, visceral obesity is a condition characterised by elevated cortisol and low sex steroid and growth hormone levels. Cortisol secretion in obesity is a much-discussed problem. Observations indicate increased production and peripheral uptake resulting in normal or even decreased circulating levels.[10] These studies have, however, been performed without consideration of the distribution of adipose tissue, which is of fundamental importance in determining the endocrine characteristics of obesity. It is clear that abdominal visceral obesity is associated with disturbance of the regulation of cortisol secretion, as summarised below.

Cortisol secretion is dependent on the regulation of the hypothalamic-pituitary-adrenal (HPA) axis. Afferent signals from the central nervous system are coordinated in the hypothalamus with corticotropin (ACTH) from the pituitary gland. The activity of this chain of events is regulated by an inhibitory feedback mechanism controlling the HPA axis via centrally localised glucocorticoid receptors (GRs) which, when occupied by cortisol, control secretion to prevent accumulation of excessive and harmful levels of cortisol in the periphery.

This complex regulatory system is difficult to study in humans because it is easily disturbed by environmental changes. Data suggest that urinary cortisol secretion is elevated in visceral obesity (although these findings remain to be confirmed).[11] Furthermore, stimulation by maximal concentrations of ACTH and corticotropin-releasing hormone result in elevated cortisol and ACTH levels in individuals with visceral obesity.[11,12]

These results suggest disturbances in the HPA axis regulatory system in persons with visceral obesity, but they do not yield much information on the long term 'everyday' status of the HPA axis. However, new methods based on salivary cortisol measurements have made investigation of this possible. These studies show that individuals with visceral fat accumulation are clearly characterised by disturbance of the regulation of cortisol secretion by the HPA axis. In particular, daily stress-related cortisol secretion is elevated; under chronic conditions, this appears to be followed by derangement of diurnal cortisol secretion that results in a flat, rigid daytime curve with abnormally low morning cortisol levels. At this stage there is also evidence for a derangement of inhibitory feedback control, and sex steroid and growth hormone secretions are inhibited.[13,14]

These new data show clearly the disturbance of HPA regulation associated with elevated cortisol secretion, and in more advanced stages low secretion of sex steroid and growth hormone and deficient feedback control of the HPA axis, in persons with visceral obesity. Insulin resistance accompanies these changes, together with dyslipidaemia and hypertension, both of which are known to be associated with insulin resistance.

## 6. Pathogenetic Factors

What causes these abnormalities in hormonal regulation? The decrease in levels of sex steroids and growth hormone is most likely to be caused by activation of the HPA axis, a well established phenomenon,[15] and stress seems to be involved in the activation of the HPA axis itself. These disturbances are seen most clearly after cortisol measurements in persons who report concomitant perceived stress; previous studies of cortisol reactions to laboratory stress tests have indicated similar stress sensitivity.[11,16]

Stress, the best known stimulator of the HPA axis,[17] may be defined as any factor that threatens to disrupt homeostasis and includes mental and physical factors. Among the former are psychosocial and socioeconomic handicaps and life events, whereas the latter include pain, fever, cold, exhausting physical work and toxins. Some authors include psychiatric equivalents of depression and anxiety in this category.[18] We have seen clear associations between HPA axis disturbance and visceral obesity and several such stress factors in previous and recent work (reviewed by Björntorp et al.[19]). Such factors include psychosocial and socioeconomic handicaps, alcohol and smoking, in addition to depression and anxiety.

## 7. Feedback Control

What is the mechanism underlying the breakdown of feedback control of the HPA axis? It is known that deterioration and eventual total destruction of the system may occur after excessive and prolonged activation of the HPA axis by a variety of stress factors.[18] It is therefore possible that stress factors of the type we have found (as mentioned above) are involved in the down-regulation of GR control.

Data from several studies show disturbed GR functions in persons with visceral obesity. Sensitivity to the suppressive effect of dexamethasone is diminished,[20] and GRs in adipose tissue fail to

function normally, which results in decreased responsiveness and sensitivity when exposed to cortisol (Ottosson et al., unpublished observations). Taken together, these observations strongly suggest disturbance of GRs and their controlling effect on cortisol secretion in visceral obesity.

As visceral accumulation of body fat and HPA axis regulation are profoundly influenced by genetic factors,[21,22] studies of the GR gene are now under way. This gene consists of 9 exons, of which the final exon has an α and β form. Sequencing of the exons responsible for steroid binding (exon 9) and DNA binding of the receptor-hormone complex (exon 2) has shown no abnormalities (unpublished observations). However, restriction fraction length polymorphism examinations (carried out in collaboration with the Bouchard group in Canada) have revealed a polymorphism after cleavage with the enzyme Bcl I. This polymorphism is associated with visceral obesity, insulin resistance and hypertension[23-26] and, more interestingly, with feedback inhibition by GRs of HPA axis activity.[26] Homozygotes with this polymorphism are found in no less than 13.7% of Swedish males.

Polymorphism of the GR gene is localised to the first intron,[27] and its functional importance may therefore be questionable. However, any contribution it may make cannot yet be excluded. Polymorphisms in early introns of a gene may interfere with transcription, particularly if the splicing of the primary mRNA is hampered. The polymorphism may also indicate an adjacent abnormality in the promoter region, and it is this that is now being sequenced.

These findings are potentially very important. A molecular genetic fault in the expression of GR function might explain many of the pathological features of visceral obesity, mediated via the central disturbance of HPA axis regulation. This would include both visceral accumulation of body fat and insulin resistance as reviewed in preceding sections.

## 8. Conclusions

The results of our studies suggest the following: environmental stresses of different kinds, possibly with a preponderance of psychosocial and socioeconomic factors, activate the HPA axis. In susceptible individuals, prolonged, repeated periods of HPA axis arousal may follow. In those who are genetically predisposed, this may be followed by a breakdown of counter-regulatory mechanisms that results in increased cortisol secretion and inhibition of sex steroid and growth hormone secretion. These endocrine disturbances together direct excess fat to visceral depots and cause insulin resistance. This interpretation of events encompasses all phenomena included in the syndrome of visceral obesity and accounts for the importance of insulin resistance. It probably also explains why visceral obesity is a notable risk factor for, and the most common precursor to, type 2 diabetes.

However, this explanation does not take into account the frequent presence of obesity, defined as an increase in total fat mass. Obesity is clearly attributable to a positive energy balance, either through increased energy intake, decreased energy output or (most commonly) a combination of the two. It might be considered that when HPA axis involvement as described here is combined with obesity, visceral obesity, defined as an increased total and visceral fraction of body fat mass, will result. It is also possible that the HPA axis disturbances described here are directly coupled to the regulatory leptin system,[28,29] which might explain the phenomenon of 'stress eating'. This requires further study.

Thus, there are several putative primary pathogenetic factors underlying visceral obesity. These include overeating, physical inactivity, stress, alcohol and smoking, all of which are undesirable lifestyle features of our urbanised society. We have therefore suggested previously that this syndrome might be referred to as a 'civilisation syndrome'.[6]

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