Obesity, non-insulin-dependent diabetes mellitus and the metabolic syndrome

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Obesity is characterised by alterations in metabolic function which result from a combination of increasing total body fatness and the regional distribution of adipose tissue. Abdominal visceral obesity is particularly associated with hyperinsulinaemia, increased portal vein free fatty acid concentration, hepatic gluconeogenesis, altered adrenocortical activity and androgen secretion and reduced plasma sex hormone binding globulin levels. These alterations, which are accompanied by changes in visceral adipocyte sensitivity to plasma catecholamine stimulation, enhance further visceral fat deposition and the perpetuation of the metabolic derangements. The characteristic dyslipidaemia associated with upper body obesity and the frequent development of NIDDM are predictable consequences. In contrast to the considerable knowledge about the biochemical background to these alterations, relatively little is understood about the mechanisms through which an individual’s ethnic background influences the changes. This chapter reviews these important issues.

Insulin secretion in obesity

Obesity is characterised by an elevated fasting plasma insulin and an exaggerated insulin response to an oral glucose load. Obesity and body fat distribution influence glucose metabolism through independent but additive mechanisms. Kissebah and colleagues have demonstrated that
increasing ‘upper body’ obesity is accompanied by a progressive increase in the glucose and insulin response to an oral glucose challenge. Individuals’ in vivo insulin sensitivity was assessed further by determining the steady state plasma glucose (SSPG) and insulin (SSPI) attained during a simultaneous intravenous infusion of somatostatin, insulin and dextrose. Since endogenous insulin production was suppressed by somatostatin and the SSPI was comparable in each situation, SSPG directly measured the subjects’ ability to dispose of an intravenous glucose load under the same insulin stimulus. SSPG can be taken as an index of insulin resistance. The results showed a positive correlation between increasing upper body obesity and SSPG. After adjustment for the effects of overall fatness (% ideal body weight), upper body obesity remained independently correlated with SSPG suggesting that the location of body fat is an independent factor influencing the degree of insulin sensitivity and, in turn, metabolic profile.

Measurement of portal plasma insulin levels (as an index of insulin secretion) show similar levels in upper body and lower body obesity but hepatic insulin extraction, both basally and during stimulation by intravenous or oral glucose, is reduced in upper body obesity. As a consequence, post hepatic insulin delivery is increased in upper body obesity leading to more marked peripheral insulin concentrations. Studies of insulin sensitivity and responsiveness of skeletal muscle and the relationship to overall glucose disposal in premenopausal women, with varying body fat distribution, have revealed a significant decline as upper body fatness increases. Insulin-stimulated activity of the glucose-6-phosphate independent form of glycogen synthase (GSI) was measured in quadricep muscle biopsies taken during a somatostatin-insulin-dextrose infusion. Despite comparable degrees of SSPI in all women, significant reductions in percentage GSI were seen as the degree of upper body fatness increased and this was accompanied by decreased efficiency in insulin-stimulated glucose disposal (reflected by increasing SSPG at similar SSPI levels). Furthermore, a significant trend was reported for a decreased number of cellular insulin receptors associated with increasing upper body fatness, which was associated in some subjects with reduced glucose disposal during supra-maximal insulin stimulation. Such findings suggest a defect at both the level of the insulin receptor and in post-receptor events.

The possibility that insulin resistance in obesity is either due to a decreased number of insulin-sensitive glucose transporters (GLUT) or an inability to stimulate recruitment of transporters from microsomes to the plasma membrane has been investigated in obese humans. Garvey and colleagues measured GLUT 4 expression in adipocytes — GLUT 4 is the transporter which mediates the bulk of insulin-stimulated transport activity. They found that obesity led to a depletion of intracellular GLUT
4 transporters with fewer carriers being available for insulin-mediated recruitment to the cell surface. The cellular content of GLUT 4 was determined by the GLUT 4 mRNA over a wide range of body weight. In non-insulin dependent diabetic patients (NIDDM), profound insulin resistance was caused by a more severe depletion of GLUT 4 mRNA compared to simple obesity and transporter loss involved both plasma membrane and intracellular compartments. In both obesity and NIDDM, pre-translational suppression of GLUT 4 transporters entirely accounted for impaired cellular insulin responsiveness in adipose tissue. In contrast, no significant differences were seen in skeletal muscle GLUT 4 content and GLUT 4 mRNA activity was similar to that seen control subjects. Other mechanisms which could potentially impair glucose transport activity in skeletal muscle include decreased functional activity of the transporters, or an impairment of insulin-stimulated translocation of intracellular GLUT 4 to the cell surface. It has been demonstrated that chronic exposure to high concentrations of glucose and insulin reduce the subsequent ability of insulin to maximally stimulate glucose transport by inhibiting transporter translocation. The in vivo efficacy of skeletal muscle glucose uptake has been shown to be inversely proportional to the glycosylated haemoglobin value in NIDDM subjects. Thus hyperglycaemia and/or hyperinsulinaemia could induce at least a component of insulin resistance in muscle via such mechanisms.

**Normal adipose tissue function**

Fat tissue mass is dependent on the number and size of adipocytes. Adipocytes have the unique characteristic of being dominated by their contents of storage fats, triglycerides. The mass of triglycerides in an adipocyte is dependent on the balance between triglyceride influx and mobilisation; the latter in the form of free fatty acids (FFA) and glycerol is regulated by metabolic processes under hormonal and nervous system control. Formation of new adipocytes seems to occur when cells reach a certain size and is apparently dependent on various factors, such as age, gender and nutrition. The body fat's stores are almost entirely in the form of triacylglycerol (TAG) in adipocytes. The process of fat mobilisation consists of hydrolysis of the stored TAG to release non-esterified fatty acids (NEFA) into the circulation. The key enzyme is the intracellular TAG-lipase, hormone sensitive lipase (HSL). The major regulator of HSL is reversible phosphorylation by a cAMP-dependent protein kinase. Lipolysis is, therefore, stimulated by effectors which increase the activity of adenylate cyclase in adipocytes leading to the
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formation of cAMP from ATP. Adenylate cyclase is stimulated by hormones acting via the cell surface receptors and G-proteins, especially catecholamines acting via β-adrenoreceptors (β₁, β₂, β₃). Dephosphorylation of HSL occurs when cAMP concentrations fall. The main hormonal regulator of this is insulin, which lowers adipocyte cAMP concentrations. The suppression of fat mobilisation occurs in normal circumstances at very low insulin concentrations. Catecholamines acting on α₂-adrenoreceptors will also inhibit lipolysis. Thus catecholamines have dual effects on the lipolysis rates, both accelerating through β-adrenoreceptors and retarding through α₂-adrenoreceptors. HSL activity is suppressed after meals when the physiological drive is towards fat storage rather than mobilisation. In the postprandial state, the enzyme lipoprotein lipase (LPL) in adipose tissue is activated by insulin and possibly also by some gastrointestinal peptide hormones. This enzyme is synthesised within adipocytes but exported to the capillary endothelial cells, where it is attached to the luminal side of the capillary wall and acts on circulating TAG in the TAG-rich lipoproteins (chylomicrons and very low density lipoproteins, VLDL). LPL releases fatty acids which may be taken up into the tissue for esterification and storage as TAG. The fatty acids released by LPL action are not all taken up by adipose tissue for storage with approximately 50% entering the systemic circulation. This release of LPL-derived fatty acids is dependent upon the insulin response to the meal and the sensitivity of LPL activation to insulin and other hormones.

Regional distribution of body fat

There is considerable evidence for lipoprotein lipase (LPL) playing a controlling rate in the regional distribution of fat. There are significant gender and regional differences in LPL activity that largely parallel variations in fat size. Premenopausal women have higher LPL activities in gluteal and femoral regions than men but the differences disappear after the menopause. In addition, women have quantitatively more LPL in gluteal and femoral tissue, which contain larger fat cells than they do in abdominal adipose tissue. In contrast, men show minimal regional variations in LPL activity or fat cell size. These differences in fat distribution between men and women may explain the tendency for premenopausal women to deposit fat preferentially in lower body fat depots.

The potential differences in FFA metabolism between lean and obese subjects may reflect the anti-lipolytic effectiveness of insulin in obesity, the relationship of FFA release to the amount of body fat and the
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lipolytic responsiveness of obese individuals to catecholamines. It is relevant that adipocytes from various body regions differ from one another in many respects; fat cell size and basal lipolysis varying in adipocytes from omental, abdominal subcutaneous and gluteal-thigh depots. The basal release of FFA from adipose tissue to meet lean body mass energy needs is greater in upper body obese women than obese women with lower body fat distribution and non-obese women. Differences in the ability of insulin to suppress lipolysis and of catecholamines to stimulate lipolysis also varies according to fat distribution. In both men and women, the lipolytic response to noradrenaline, which acts via \( \alpha_2 \) - and \( \beta \)-adrenoceptors, is more marked in abdominal than gluteal or femoral tissues. A detailed analysis has suggested that the usual pattern of male fat distribution (greater abdominal fat accumulation) results from a greater \( \alpha_2 \) activity in the abdominal tissue of men. The findings from studies looking at radioligand binding of \( \beta \)-adrenergic antagonists have uniformly shown twice as many \( \beta \)-adrenergic binding sites in abdominal adipocytes as in femoral adipocytes. Lonnqvist and colleagues have recently elucidated the pathogenic role of visceral \( \beta_3 \)-adrenoceptors in obesity. These authors studied the responsiveness of isolated omental fat cells from obese and non-obese subjects to adrenergic-subtype receptor antagonists by measuring the rate of FFA and glycerol response. They found that the visceral fat cells from the obese subjects were highly responsive to noradrenaline stimulation. This appeared mainly due to an enhanced lipolytic response and not to FFA re-utilisation. The main finding was the markedly augmented \( \beta_3 \)-adrenoceptor sensitivity and coupling efficiency; the authors suggested that this enhanced \( \beta_3 \)-adrenoceptor activity was due to an increased receptor number in obese subjects. In contrast, the net lipolytic response to adrenaline is reduced in upper obese women compared to lower obese and non-obese women. In order for lower obese women to maintain appropriate FFA availability despite increasing fatness, there must be downregulation of lipolysis to prevent FFA release. Martin and colleagues measured FFA release from the leg, non-leg and splanchnic adipose tissue in obese women of differing body fat distribution. The most significant observation was the contrasting differences in lipolytic activity of splanchnic fat between those obese women with predominantly upper body fat and those lower body obese women. This difference was emphasised by the finding of similar FFA release from leg fat in the two groups. The important metabolic interpretation of these data is the apparently elevated rate of lipolysis in visceral fat cells due largely to increased \( \beta_3 \)-activity and, partly to \( \alpha_2 \)-adrenoceptor activity. As a consequence, more FFA is released into the portal system.
Hormonal influences

The hormonal mechanisms regulating adipose tissue LPL activity are not completely understood. Insulin is permissive for LPL synthesis and glucocorticoids enhance the activity of LPL when added with insulin \textit{in vitro}\textsuperscript{23}. Sex steroids have been implicated in the regional distribution of body fat and gender differences are seen in LPL activity most particularly during pregnancy and lactation\textsuperscript{24}. Regional variation in receptors for glucocorticoids or sex steroids could play a role in determining regional differences in adipose tissue. The reverse situation may also be true—adipose tissue having an effect on the production of sex hormones. Abdominal visceral adipose tissue is more sensitive to lipolytic stimuli than subcutaneous fat while it is less sensitive to the inhibitory action of insulin; this appears to be associated with a low density of insulin receptors. Hyperinsulinaemia of obesity mainly inhibits lipolysis of insulin sensitive subcutaneous adipocytes and thus may accentuate the fraction of systemic FFA originating from visceral fat\textsuperscript{25,26}. In addition, elevated portal concentrations of FFA, produced by active visceral adipocytes, results in the liver being exposed to excessive FFA concentrations. The excessive visceral fat lipolysis may create a vicious chain of events with insulin resistance in liver and skeletal muscle resulting in additional systemic insulin resistance.

Steroid hormones

Obese subjects have a normal circulating plasma cortisol concentration with a normal circadian rhythm and normal urinary free cortisol but an accelerated degradation of cortisol which is compensated by an increased cortisol production rate\textsuperscript{27,28}. It is likely that the increase in metabolic clearance of cortisol is secondary to a decrease in cortisol-binding globulin plasma concentrations. Slavnov and colleagues\textsuperscript{29} have reported a moderate elevation in plasma corticotrophin (ACTH) levels in obesity to explain the increased cortisol production. The increased peripheral clearance rate of cortisol is probably mediated by binding to the glucocorticoid receptor present in glucocorticoid responding tissue\textsuperscript{30}. An increased peripheral density of this receptor will be followed by an increased metabolic clearance rate. Cortisol has effects on both lipid accumulation and mobilisation. Cortisol inhibits the anti-lipolytic effect of insulin in human adipocytes and this may be particularly pronounced in visceral abdominal fat\textsuperscript{23}. It also has a permissive effect on lipid mobilisation stimulated by catecholamine. Enlarged visceral adipocytes, as found in abdominal obesity, could be the site where this occurs.
because such tissue appears to have a higher density of glucocorticoid receptors compared to adipose tissue\textsuperscript{31,32}. Abdominal subcutaneous adipose tissue demonstrates a higher expression of cortisol-induced LPL as well as a higher density of glucocorticoid receptors than femoral subcutaneous adipose tissue. Furthermore, there is a higher LPL activity in visceral compared to subcutaneous adipose tissue in both men and women\textsuperscript{33}. This could be an explanation for the functional hypercortisolism associated with abdominal obesity in subjects who are only moderately overweight. There is a close analogy between upper body obesity and Cushing's syndrome because both conditions are characterised by hypercortisolism and excessive visceral fat accumulation\textsuperscript{34}. Moreover, both have similar consequences—increasing plasma cortisol leading to insulin insensitivity and glucose intolerance, an increase in hepatic gluconeogenesis, reduced hepatic insulin uptake and insulin resistance in skeletal muscle.

The increased peripheral clearance and the obesity-associated acceleration in overall adrenocortical function leads also to an increase in adrenal androgen production. Urinary 17-ketosteroids (17-KS), which measure various androgen metabolites including etiocholanolone, androsterone, dehydroepiandrosterone (DHEA), and its sulphate conjugate (DHEAS), are elevated in obese subjects\textsuperscript{35}. The changes in adrenal androgen production may simply occur in compensation for an increasing metabolic clearance, but there is additional evidence to suggest alterations in adrenocortical dynamics. Kurtz and colleagues\textsuperscript{36} noted an increased turnover of DHEA in obese women. These authors demonstrated a significant correlation between upper body obesity and the metabolic clearance of DHEA and androstenedione, which suggests that the androgenic effects of DHEA may have a role in fat distribution. In premenopausal women, serum DHEA concentration correlates positively with trunk fat and negatively with leg fat accumulation, whereas no such effect is seen in men\textsuperscript{37,38}. A shift in fat accumulation in women towards abdominal obesity may be an androgenic effect of DHEA. In healthy postmenopausal women, androgen levels are inversely related to fasting plasma glucose levels and are predictive of central obesity 10–15 years later\textsuperscript{39}. Brody et al.\textsuperscript{40} have reported a positive correlation between body weight and changes in DHEA and the DHEA/17-hydroxy progesterone ratio after exogenous administration of ACTH. This is suggestive of hyper-responsiveness of adrenal androgens in obesity. Weaver and colleagues\textsuperscript{41} have also provided evidence for increased ACTH release in obesity by reporting an association between the ACTH response to insulin-induced hypoglycaemia and increasing body weight. Moreover, alterations in adrenocortical production of adrenal androgens probably reflects the influence of other factors, including adrenal androgens themselves. In vitro studies have suggested
a lesser degree of inhibition of human 17-hydroxylase activity by DHEA as compared to the inhibition of human 17,20-desmolase activity. The increased adipose tissue breakdown and the higher urinary excretion of DHEA in such circumstances could lead to decreased intra-adrenal concentrations of the steroid. As a consequence, the inhibition of 17,20-desmolase will be further diminished and a selective increase in the production of DHEA and its metabolites occur.

DHEA may, therefore, contribute to a spiral of events — the greater androgenic action of DHEA contributing to abdominal fat cell accumulation with resulting hyperglycaemia and hyperinsulinaemia. Androgens have a clear effect on adipose tissue metabolism; this includes enhancement of lipolytic sensitivity by expression of lipolytic β-adrenergic receptors via an androgenic receptor, which is positively autoregulated by testosterone.

The density of androgen receptors, which are specific for androgens, varies in different adipose tissue regions with a higher density in intra-abdominal than subcutaneous depots in rats. Indirect evidence suggests a higher density in central visceral fat in man compared to peripheral adipose tissue. Testosterone, in the presence of growth hormone (GH), exerts a dramatic effect on the regulation of lipolysis by increasing the number of β-adrenoceptors through an action at the level of adenylate cyclase and protein kinase A and/or HSL.

Sex steroid secretion

There appear to be contrasting situations between men and women in relation to the influence of sex steroids on adipose tissue function. Men, with excessive abdominal fat, often have relatively low serum testosterone concentrations despite reduced levels of sex hormone binding globulin (SHBG). Marin and colleagues have demonstrated a significant decrease in visceral fat mass and abdominal:sagittal diameter in middle aged abdominally obese men treated with 8 months of oral testosterone supplements. This reduction occurred without a detectable change in subcutaneous fat. In addition, there was an improvement in plasma glucose disposal and increased insulin sensitivity. The authors concluded that such men have relative hypogonadism and associated metabolic abnormalities, which are partly corrected by testosterone supplementation. Calculations of lipid uptake and LPL activity, using isotope labelling techniques, suggested diminished activity in abdominal adipose tissue but no change in femoral fat. The effects of testosterone were much more marked in visceral fat compared to subcutaneous abdominal fat because the uptake of lipid was inhibited by
approximately 50% in the intra-abdominal tissues. This has been confirmed by studies of lipid turnover in visceral adipose tissue from rats. Thus, testosterone supplementation in obese men decreases uptake of lipid particularly in visceral fat and increases the rate of fat mobilisation.

Obese women are also characterised by distinct alterations in circulating sex hormone levels. Obese women demonstrate lower circulating SHBG levels and, thereby, an increased fraction of circulating oestradiol. In postmenopausal obese women, serum levels of oestrone and oestradiol are correlated with the degree of obesity and fat mass. The plasma ratio of oestrone to oestradiol is also increased in obesity. Interestingly, a similar pattern of changes of sex steroid concentrations and binding are found in women with the polycystic ovary syndrome.

Longcope and colleagues have reported significant associations between body weight and conversion of testosterone to oestradiol. The interconversion of oestrone to oestradiol has been observed in vivo and in vitro in adipose tissue with a greater conversion being found in omental fat than subcutaneous fat. Adipose tissue 17-β-hydroxysteroid dehydrogenase activity, measured by the conversion of oestrone to oestradiol, is higher in premenopausal than in postmenopausal women and all women have a higher activity compared to men.

Evans and colleague have shown that body weight and increasing upper body obesity in women are inversely correlated with SHBG levels and directly correlated to free testosterone concentrations. Others have described a higher production rate from the adrenal cortex and ovaries and increased metabolic clearance of testosterone and dihydrotestosterone (DHT). The clearance of testosterone increases as SHBG decreases, the consequence of an increased fraction of unbound testosterone available for hepatic extraction and clearance. Such a mechanism may protect some obese women from the development of frank hirsutism. Fat tissue is able to sequester various steroids, including androgens, probably as a result of their lipid solubility. Most sex steroids appear to be preferentially concentrated within adipocytes rather than in the plasma. As a result, the overall steroid pool in severely obese subjects is far greater than that of normal weight individuals—the volume of fat in obese subjects is much larger than the intravascular space and tissue steroid concentration is 2–13 times higher than in plasma. Fat may serve not only as a reservoir but also as a site for steroid metabolism. Androgens can be irreversibly aromatised to oestrogens or reversibly converted to other androgens. Peripheral aromatisation increases with age and is 2–4 times higher in postmenopausal women. Androstenedione is the major substrate for peripheral oestrogen formation. In contrast, only a small amount of testosterone is converted to oestradiol, although this may be of greater clinical significance.
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The androgen receptor in adipose tissue from women seems to have the same specificity and affinity as in men suggesting the receptor is identical. 17-β oestradiol appears to decrease androgen receptor density because oophorectomy is necessary for testosterone to result in an increase in visceral fat mass in a woman. It seems possible that oestrogen protects from the androgen effects by down-regulation of androgen receptors. The centralisation of body fat after the menopause, leading to a male type of adipose tissue, could be due to the loss of this protective effect of oestrogen from androgens by allowing the expression of more androgen receptors. It is of interest that hyperandrogenic women have body fat distribution which resembles males. Oestrogen replacement in postmenopausal women leads to a marked elevation of LPL activity specifically in the gluteo-femoral region, which results in a similar metabolic pattern of activity of adipose tissue from this region compared to that seen in pre-menopausal women. No specific hormonal receptors have been identified for oestrogen and progesterone and these effects may be mediated through competition with glucocorticoid receptors thereby protecting against the effects of cortisol, possibly by downregulation of the receptor.

**Sex hormone binding globulin in obesity**

SHBG is a circulating globulin produced by the liver which binds in high affinity, but low capacity, to many of the circulating sex hormones. Alterations in SHBG levels have a profound impact on the metabolism and action of bound steroids. A decrease of SHBG concentration is associated with an increase in metabolic clearance and free fraction of testosterone and oestradiol. The hypothesis that insulin may regulate the hepatic production of SHBG is supported by the finding of a direct inhibitory action of insulin on SHBG secretion by cultured human hepatoma cells. Peiris and colleagues have shown upper body obesity in women to be associated with increased pancreatic insulin production and decreased hepatic insulin clearance. Thus, increasing splanchnic insulin concentrations may account for decreased hepatic SHBG production in this type of obesity. These authors also showed the severity of the peripheral insulin resistance to be positively correlated with the magnitude of free testosterone—the greater the free testosterone level, the greater the degree of insulin resistance. The changes in circulating androgens do not appear to influence plasma insulin levels but, conversely, increasing plasma insulin may increase androgen secretion by a number of mechanisms which include direct stimulation of androgen production by the ovary. There is recent
evidence to suggest that both insulin and insulin-like growth factor 1 (IGF-1) may be important regulators of ovarian thecal and stromal androgen production with an interaction at the receptor level on the ovarian stroma of these two hormones.

**Dyslipidaemia and upper body obesity**

Hyperinsulinaemia and insulin resistance are both significant correlates of a dyslipoproteinaemic state which is characteristic of upper body obesity. The lipolysis of insulin resistant visceral adipocytes results in predictable and characteristic changes. These are reflected by an elevated fasting plasma triglyceride concentration, reduced HDL-cholesterol, marginal elevations of cholesterol and LDL-cholesterol concentrations and increased number of apo-B carrying lipoproteins. Measurement of the volume of visceral fat, using computerised tomography (CT) scanning, confirms a close relationship between the volume of visceral adipose tissue, elevation of plasma triglyceride and decreased concentration of HDL and HDL₂-cholesterol in both men and women. Moreover, these levels are comparable in men and women when matched for similar degrees of visceral adiposity.

The elevated plasma NEFA concentrations have a number of deleterious actions: plasma NEFAs are the major substrate for hepatic TAG synthesis and there is a close correlation between NEFA and VLDL-TAG concentrations or turnover rates. This increased turnover appears to alter the balance between intracellular degradation of newly synthesised hepatic lipoprotein-B (apo-B) and its secretion as VLDL. The increased availability of NEFA not only increases VLDL-TAG secretion but also the number of VLDL particles secreted. This may be particularly important in the postprandial period.

Insulin has an acute suppressive action on both NEFA supply to the liver and hepatic VLDL secretion in the postprandial period. In cultured hepatocytes, insulin inhibits VLDL secretion. This action reduces the competition for clearance and reduces the postprandial rise in TAG concentration. A failure to normally suppress the NEFA supply, seen in subjects with increased intra-abdominal fat tissue, will lead to a sustained production of VLDL and an impaired clearance of TAG-rich lipoproteins in the postprandial period. Plasma NEFA arise in the postprandial period both from intracellular lipolysis and from the action of LPL in capillaries. A failure of the entrapment of fatty acids in adipose tissue during the action of LPL on chylomicron-TAG may be an important mechanism leading to increased VLDL secretion. A further consequence is an increase of LDL particles — VLDL is a precursor of
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VISCERAL OBESITY
- Altered sex steroids
- Glucocorticoids
- Insulin resistance
- Hyperinsulinemia

SKELETAL MUSCLE
- Potential for FFA oxidation
- Insulin sensitivity

Fig. 1  A schematic outline of the alterations observed in plasma lipid transport and lipoprotein metabolism associated with abdominal visceral obesity. Alterations in adrenocortical function (including sex steroids) and plasma insulin concentrations create a chain of events illustrated in the diagram. Enlargement of visceral adipocytes is accompanied by increased free fatty acid (FFA) in the portal and systemic circulation which results in increased triglyceride synthesis and VLDL secretion. This, in turn, may contribute to the prevailing hyperinsulinaemia. The slower catabolism of triglyceride-rich lipoproteins due to reduced lipoprotein lipase (LPL) activity in skeletal muscle and adipose tissue, may explain the reduced HDL-cholesterol levels in visceral obesity. Hepatic-triglyceride lipase (H-TGL) activity is increased which also leads to reduced HDL-cholesterol levels. Elevated triglyceride levels favour the transfer of lipids among lipoproteins resulting in triglyceride enrichment of HDL and LDL while VLDL are enriched in cholesterol esters (CE). The small triglyceride-rich LDL and HDL particles are good substrates for H-TGL and this leads to the formation of dense LDL particles. Elevated plasma concentrations of dense LDL particles are associated with the development of coronary heart disease. Reproduced from Despres71 with kind permission of the author and the editors of Bailliere's Clinical Endocrinology and Metabolism.

LDL — but not necessarily an increase in LDL-cholesterol concentration since, in the presence of high VLDL-TAG concentrations, LDL particles are lipid depleted and thus more dense. An elevation of total plasma apo-B concentration is a frequent association with upper body obesity which, by itself, heightens the risk of coronary heart disease.8

Other factors which contribute to the dyslipoproteinaemia in upper body obesity include increased sex steroid and glucocorticoid: gluco-
corticoids stimulate VLDL and apo-B production, decrease the activity of the LDL receptor and contribute to the insulin resistant state. Figure 1 summarises the alterations in plasma lipid transport and lipoprotein metabolism seen in viscerally obese subjects.

From obesity to NIDDM

The deleterious metabolic effects of altered regulation of adipocyte function, observed particularly in visceral obesity, frequently leads to the development of impaired glucose tolerance and NIDDM.

In obesity, the rate of non-esterified fatty acid (NEFA) turnover/unit lean body mass is increased. The ability of insulin to suppress NEFA release in vivo is diminished in obese subjects as a result of alterations in insulin sensitivity of both lipolytic processes and fatty acid re-esterification. It is, therefore, unsurprising that plasma NEFA increases when insulin action is deficient (as in NIDDM). A cycle of events is thereby entered with increasing insulin resistance resulting in increasing NEFA plasma concentration which, in turn, contributes to diminishing insulin sensitivity. The defect in insulin sensitivity observed in skeletal muscle may accentuate the defects in the regulation of lipolysis.

A number of mechanisms link NEFA supply and impairment of glucose utilisation with the supply of NEFA to the liver being an important determinant of the rate of hepatic glucose production. The elevation in plasma NEFA concentration, particularly postprandially when they are usually suppressed, will lead to an inappropriate maintenance of glucose production and an impairment of glucose utilisation (impaired glucose tolerance). These mechanisms may be critical links leading from obesity to the development of NIDDM. The progression to NIDDM may be enhanced by the suppressive effects of high NEFA concentrations on insulin secretion or even by potentially ‘toxic’ effects of NEFA on pancreatic β cells. A further mechanism linking increased plasma NEFA concentrations to insulin resistance is the reduced hepatic clearance of insulin—increasing delivery of NEFA to the liver reduces insulin binding to the hepatocytes. In normal circumstances, the liver removes 40% of insulin secreted from the pancreas; an impairment of this process will have a significant effect on peripheral (systemic) insulin concentrations, which contributes to hyperinsulinaemia, and leads to further down-regulation of insulin receptors and increasing insulin resistance.

In the initial phases of this process, the pancreas can respond by maintaining a state of compensatory hyperinsulinaemia with gross decompensation of glucose tolerance being prevented. With ever
increasing plasma concentrations of NEFA, the insulin resistant individual cannot continue to maintain this state of compensatory hyperinsulinaemia, and hyperglycaemia prevails in time. Thus, increasing NEFA concentrations, associated with a small decline in insulin secretion, will further decrease glucose uptake by muscle, increase hepatic NEFA oxidation and stimulate gluconeogenesis. This has an additive effect on plasma elevations of NEFA and glucose which, in turn, further compromises β cell function.

The effect of weight reduction

The beneficial action of weight reduction suggests that many, if not all, of the deleterious events associated with upper body obesity are a consequence, rather than a cause, of excessive visceral adipose tissue.

Weight reduction in women with upper body obesity has a marked effect on the regulation of lipolysis. There is approximately a 5-fold increase in the sensitivity to noradrenaline with a specific effect on adrenoreceptor subtype — there is increased sensitivity to β2-receptors but no change in β1 or α2. However, no change occurs in the numbers of β2 receptor binding sites which suggests possible facilitation of G proteins. More recently, a similar pattern of increased sensitivity has been reported for β3-adrenoreceptors. Weight loss is accompanied by a decrease in circulating insulin levels and a fall in plasma noradrenaline. The beneficial effects of these changes are a decrease in basal lipolysis (with decreased HSL function) and an increase in sensitivity to catecholamine stimulation of lipolysis. Thus weight reduction appears to restore a more efficient regulation of lipolysis with less FFA being released at rest and lower catecholamine levels required for lipolysis activation.

The possible influence of ethnicity on adipocyte distribution and function

Epidemiological studies have identified ethnic difference in both total adiposity and adipocyte distribution. Differences can be demonstrated between nationalities and also within differing ethnic populations in one country. Kertzman and colleagues have identified higher levels of upper body obesity in Israelis from European backgrounds compared to those of other ethnic backgrounds. This difference is maintained despite correction for sporting activity, cigarette smoking and education. Differences have also been shown in body composition between
Polynesians and Caucasians: Polynesians are significantly leaner than Caucasians for any given body size. Such differences in overall body size and fat distribution have implications for health. Some populations appear more at risk than others from visceral adiposity and the concomitant metabolic derangement. South Indians living in the UK have a higher mortality from heart disease than Europeans. Studies have demonstrated higher mean waist hip ratios and trunk skinfold thickness in South Asians compared to Europeans of similar body weight. The South Asian group are also characterised by higher blood pressures, higher fasting and post oral glucose insulin levels, higher triglyceride and lower HDL cholesterol. These results suggest that South Asians are particularly prone to the development of upper body obesity and the associated derangements of metabolic function. In contrast, subjects of Afro-Caribbean origin have a low mortality rate from coronary heart disease in spite of a high prevalence of diabetes. Glucose intolerance in Afro-Caribbean subjects is twice as common compared to Europeans, while the prevalence of probable heart disease in Afro-Caribbean men is approximately half that seen in European males. Interestingly, Afro-Caribbean men generally have less abdominal adiposity compared to Europeans and this seems to confer an advantageous lipid profile. It is speculated that the favourable lipoprotein profile, which persists despite glucose intolerance, is related to body fat distribution in Afro-Caribbeans and explains the lower levels of cardiac mortality.

There is little published work addressing possible differences in adipocyte function between subjects from different ethnic backgrounds. An investigation of the ability of insulin to stimulate glucose transport and suppress lipolysis, suggests that ethnicity is important. In this study, abdominal and gluteal adipocytes from white women with upper body obesity were less sensitive, in vitro, to insulin stimulated glucose transport and lipolytic suppression compared to adipocytes from black women of similar body weight and fat distribution. The findings support the epidemiological evidence that black women, with upper body obesity, fare better in terms of insulin resistance and dyslipidaemia than their white counterparts and confirm the need for additional studies examining men and women from other ethnic groups.

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