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Melancholic Depression and Abdominal Fat Distribution: A Mini-Review

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Fat is stored around the abdomen in both subcutaneous and intra abdominal (visceral) sites. Visceral fat is associated in its own right with a set of metabolic abnormalities, including non insulin dependent diabetes, hypertension and dyslipidaemias. States of marked hypercortisolaemia, for example Cushing's syndrome, lead to the preferential accumulation of visceral fat. Since melancholic depression is known to be associated with elevated plasma cortisol levels, this review explores whether depressed patients are prone to excess visceral fat storage, with the subsequent risk of developing the associated metabolic disturbances. Though the literature is limited, there is evidence that intra abdominal fat is increased in major depression. There is also evidence that depression is associated with increased risk of death from cardiovascular disease. Is visceral fat and its association with metabolic abnormalities the link between depression and physical illness?

Keywords: Cortisol, depressive disorder, intra abdominal fat, physical illners

INTRODUCTION

Fat is stored around the abdomen in subcutaneous and visceral (intra abdominal) sites, though it is the subcutaneous fat (SCF) depot which makes subjects appear obese. Excess SCF and intra abdominal fat (IAF) may both be present in the same individual to the same extent, but this is not always the case as exampled by the Japanese Sumo Wrestlers, who despite having massive amounts of SCF have very small amounts of IAF (Karam, 1996). However, the reverse situation may also occur, in that subjects who are phenotypically slim, may in fact have excess deposits of IAF. This is important because visceral fat is independently associated with health risks similar to those of generalised obesity (Reaven, 1988), which include non insulin dependent diabetes and cardiovascular disease (Pi-Sunyer, 1993).

Inter individual differences in body fat content can be due to numerous variables. Comprehensive reviews of the regulation of regional fat distribution are provided by Bouchard *et al* (1993) and Bjorntorp (1996), revealing that there are important differences in the physiological control of adipose tissue between the subcutaneous and intra abdominal sites. Although a large number of factors are involved, the hypothalamic-pituitary-adrenal (HPA) axis influences fat deposition both subcutaneously and intra-abdominally.

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For example, adrenalectomy prevents all current single gene animal models of obesity from laying down excessive SCF (Bray, 1997). In contrast, states associated with hypercortisolaemia, such as Cushing's syndrome, are associated with central obesity, of which IAF is a major component (Yoshida *et al.*, 1991; Wajchenberg *et al.*, 1995).

This review will focus on the relationship between the dysregulated HPA axis observed in depression and its propensity to alter abdominal fat distribution.

PHYSIOLOGY OF LIPID METABOLISM

A brief consideration of the physiology of lipid metabolism is important in understanding adipose tissue accumulation (figure 1). Triglycerides (TG) and cholesterol (CHOL) within the plasma are derived from both exogenous and endogenous sources. They are both water insoluble, and are therefore transported in the plasma by lipoprotein particles, which contain the TG in the core and free CHOL in the outer layer. Lipoproteins are classified according to their density characteristics and include: Chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL).

Chylomicrons are responsible for transferring dietary TG and CHOL from the small intestine into the general circulation. In the plasma, chylomicrons are acted upon by lipoprotein lipase (LPL) which is an enzyme bound to the capillary endothelial cells adjacent to adipose, muscle and breast tissue. LPL hydrolyses the TG within the chylomicron releasing free fatty acids (FFAs) and glycerol. The remnant of the chylomicron is then transported to the liver for clearance of the CHOL. The FFAs may be taken up by local cells and re-esterified to be stored in adipose tissue as TG. The stored TG may be hydrolysed by another lipase enzyme, hormone sensitive lipase (HSL), which releases FFAs back in to the circulation. As such, LPL is responsible for laying down new fat, and HSL is the principal enzyme involved in adipose breakdown. The activity of these lipase enzymes is influenced by a number of factors including glucocorticoids and insulin. We shall examine this in more detail when considering the role of the HPA axis on fat distribution.

The liver, as well as excreting and synthesising CHOL, also synthesises VLDL, which transports TG and cholesterol from the liver to other tissues, via the circulation. LPL also acts on the triglyceride within VLDL, leaving a VLDL remnant which is converted to LDL by further action of LPL. LDL is the major carrier of CHOL in the circulation and its removal is mediated by the LDL receptor which is present on all cells within the body. High levels of plasma LDL CHOL (Grundy, 1997), and also of LDL TG (Austin, 1989), are associated with increased risk of ischaemic heart disease. In contrast to VLDL, HDL transports cholesterol from peripheral tissues to the liver for excretion or to cells that may require it. Low levels of HDL CHOL are associated with an increased risk of coronary artery disease (Assmann *et al.*, 1993). The levels of LDL and HDL mediate their effects on cardiovascular disease by influencing atherosclerosis. It has been shown that one of the important early factors in the development of an atherosclerotic plaque is the trapping, and subsequent oxidation, of LDL in the subendothelial space of an artery wall. HDL appears to exert at least a part of its protective effect on the cardiovascular system by inhibiting the oxidative process of LDL (Navab *et al.*, 1995).

HEALTH RISK FACTORS ASSOCIATED WITH EXCESSIVE INTRA ABDOMINAL FAT

Vague (1956) was the first to recognise that IAF was a risk factor for diabetes and cardiovascular disease, however, his findings were largely ignored up until the mid 1980s when a number of studies repeated and confirmed his original observations (Lapidus *et al.*, 1984; Ohlson *et al.*, 1985; Larsson, 1988; Lapidus and Bengtsson, 1988). Since then there has been considerable research into the possible aetiology and pathological effects of intra abdominal obesity. As already stated, IAF, even in the absence of generalised obesity, is associated with having similar medical complications to obesity. This set of complications is often referred to as syndrome X (Reaven, 1988), and

includes non insulin dependent diabetes (NIDDM), hypertension and dyslipidaemias. In addition IAF may also be associated with an increased risk of developing certain types of carcinoma (Schapira *et al.*, 1994). The underlying mechanisms responsible for these complications are of major interest and much of the research in this area has focused on the metabolic abnormalities associated with excess IAF.

Visceral obesity is associated with the development of non insulin dependent diabetes, which indicates an abnormality in glucose tolerance. Dietary derived glucose is directed towards storage by insulin which is secreted by the beta islet cells of the pancreas. It is well established that IAF is associated with hyperinsulinaemia, which is a consequence of insulin resistance (IR) (Reaven, 1988), which is defined as existing when "normal concentrations of insulin produce a less than normal biological response" (Kahn, 1978). Of interest is the fact that IR, and the development of NIDDM, are associated more strongly with the degree of central rather than generalised obesity (Peiris *et al.*, 1988). This is important as NIDDM is a known risk factor for cardiovascular disease (Pyorala *et al.*, 1987). The physiological mechanism responsible for the IR is not accurately established, though most of the attention has concentrated on the role of FFAs which are known to decrease glucose utilisation (Karam, 1996).

Hypertension and its consequent risks are also associated with an increase in IAF. In fact the ratio of IAF to SCF, as measured by Computerised Axial Tomography (CAT), has been shown to distinguish between hypertensive and normotensive obese subjects (Kanai *et al.*, 1990). In addition, the reduction in blood pressure brought about by weight loss induced by caloric restriction, has been shown to correlate more with a reduction in the ratio of IAF to SCF than the general change in body weight (Kanai *et al.*, 1996). The increase in blood pressure associated with visceral obesity may be the result of FFAs increasing sympathetic tone by means of a neural hepatic response, though this finding is based on a single study and requires replication (Grekin *et al.*, 1995).

The dyslipidaemic profile associated with excess IAF is known to be strongly associated with artherosclerosis and coronary heart disease, and consists of decreased HDL CHOL (Despres *et al.*, 1989) and increased VLDL TG (James *et al.*, 1997). There is no strong evidence for an elevated LDL cholesterol per se, but IR has been associated with the presence of small dense LDL particles, which are considered to have greater atherogenic properties than larger LDL particles (Reaven *et al.*, 1993). Insulin has profound effects on certain aspects of lipid metabolism, and the insulin resistance that accompanies IAF accumulation may be responsible for the abnormal lipoprotein state (Garg, 1996).

An excess of central body fat is also associated with changes in the level of plasminogen activator inhibitor (PAI 1). PAI 1 is a major rapid inhibitor of fibrinolysis and increased levels are associated with increased IAF (Cigolini *et al.*, 1996). PAI 1 production is stimulated both in vitro and in vivo by insulin and triglyceride rich lipoproteins (Byberg *et al.*, 1998), both of which are increased in states of visceral obesity. This relatively new finding extends the list of complications which come under the heading of "Syndrome X".

Other diseases besides those already mentioned are also associated with increased IAF. For example, in women with carcinoma of the breast, IAF as measured by CAT is significantly greater than in matched controls (Schapira *et al.*, 1994), and it has been postulated that the increased risk is particularly related to a history of weight gain in early adult life (Stoll, 1995). Other reports on associations between IAF and female carcinomas, for example of the endometrium (Austin *et al.*, 1991) have used indirect measurements and produced equivocal results. Overall, since visceral obesity is clearly related to medical diseases that result in increased morbidity and mortality, it is vital that factors such as hypercortisolaemia, which appear to promote the accumulation of IAF, are taken into account.

THE HPA AXIS AND REGIONAL FAT DISTRIBUTION

The HPA axis is known to exert a strong influence on the deposition of fat in both the subcutaneous and

intra abdominal compartments. In this section we shall focus on the preferential effect that hypercortisolaemia has on IAF accumulation. Firstly, however, we will briefly describe a simplified account of the normal physiology of the HPA axis with respect to glucocorticoid regulation (Reichlen, 1998).

The HPA axis is a closed loop system comprising of feedforward and feedback limbs. The hypothalamus secretes corticotropin releasing hormone (CRH) which regulates the production and secretion of adrenocorticotropin hormone (ACTH) from the anterior pituitary gland. It is also well established that arginine vasopressin (AVP), which is also secreted by the hypothalamus, acts in a synergistic fashion with CRH to stimulate the release of ACTH, which in turn stimulates the adrenal gland to synthesise and release cortisol. Cortisol then exerts a negative feedback effect at the level of the pituitary, hypothalamus and the limbic system, in order to restore homeostasis. Cortisol acts via two types of receptor at the pituitary and the brain. Type I receptors, prefer to bind mineralocorticoid-like substances, are primarily located within the septo-hippocampal complex, and play a very important role in determining the circadian activity of the HPA axis. Type II receptors, on the other hand, prefer to bind glucocorticoid-like substances, are located throughout the brain, and play a significant role in "switching off" the HPA axis.

Cortisol has a marked effect on regional fat distribution. For example, patients with Cushing's syndrome who have marked hypercortisolaemia, are consistently described as having increased amounts of visceral fat, when assessed by CAT scans (Yoshida *et al.*, 1991; Wajchenberg *et al.*, 1995). To date, no study has considered the degree of IAF in Addison's disease specifically, but one study comparing different imaging procedures of the adrenal gland noted that such patients had very small amounts of IAF (Adams *et al.*, 1983). Correction of the hypercortisolaemia leads to a reduction in IAF underscoring the importance of this adrenocorticoid (Lonn *et al.*, 1994). Of further interest is the fact that Cushing's syndrome is associated with all of the features of "Syndrome X", and reducing the cortisol levels to normal, as well as reducing the IAF mass, also ensures the restoration of normality in various metabolic processes (Zeiger *et al.*, 1993).

Glucocorticoids act on adipose tissue directly as revealed by the effects of dexamethasone on leptin secretion. Leptin is a protein secreted predominantly by fat and is the product of the obesity (ob) gene, which was recently isolated in experiments on transgenic mice (Zhang *et al.*, 1994) though is also present in humans. Leptin secretion correlates positively with total body adiposity, rather than the degree of IAF (Larsson and Ahren, 1996), and is thought to act as a satiety factor at the level of the hypothalamus. Dexamethasone in vitro leads to an increase in leptin secretion (Considine *et al.*, 1997), and has the same effect in vivo (Miell *et al.*, 1996). The hypothesis that cortisol may have the same effect in vivo is supported by the fact that patients with Cushing's syndrome have increased levels of plasma leptin, which are subsequently reduced by correction of the hypercortisolaemia (Masuzaki *et al.*, 1997).

The effects of glucocorticoids at the adipocyte have also been examined, with particular reference to known key components of lipid metabolism. Dexamethasone (Fried *et al.*,1993) and cortisol (Ottosson *et al.*, 1994) both increase the activity of lipoprotein lipase (LPL), which is the key enzyme responsible for laying down new fat. This effect is dependent on the presence of insulin (Fried *et al.*, 1993). Cortisol acts via glucocorticoid receptors to induce LPL activity as demonstrated by the concurrent administration of RU486, a synthetic potent glucocorticoid receptor antagonist, which inhibits the expected rise in LPL activity (Ottosson *et al.*, 1995). Of major significance is the fact that glucocorticoids increase LPL activity more in IAF than SCF (Fried *et al.*, 1993), suggesting that they have a preferential effect on increasing IAF stores. This increase in activity may be due to IAF fat stores having a glucocorticoid receptor density up to four times that of SCF (Pederson *et al.*,1994). In addition to promoting the formation of new adipose tissue, glucocorticoids also effect the lipolysis of previously formed fat stores, and cortisol has been shown to reduce the activity of hormone sensitive lipase (HSL) (Samra *et al.*, 1998), the enzyme responsible for fat breakdown.

Another important factor rendering IAF particularly susceptible to the effects of excessive plasma cortisol is the greater enzymatic conversion of inactive cortisone to active cortisol (Bujalska *et al.*, 1997). This is mediated by 11 beta hydroxy steroid dehydrogenase (11 beta- HSD), which possesses two isoforms, one of which, the 11 beta-HSD 1 enzyme is capable of converting cortisone to cortisol by an oxo-reductase mechanism. In comparison to SCF, visceral fat has a higher oxo-reductase activity, which could result in increased local concentrations of cortisol, developing a self perpetuating cycle which leads to further increases in IAF. To promote this effect further, the oxo-reductase activity of 1 beta-HSD 1 is increased when exposed to cortisol and insulin (Bujalska *et al.*, 1997). Therefore, glucocorticoids produced in excessive quantities can lead to an increase in IAF stores. Since major depressive disorder is associated with increased levels of circulating cortisol, it is important to delineate the relationship between depression and visceral obesity. However, let us first consider the evidence for a dysregulated HPA axis in major depression.

MAJOR DEPRESSION AND THE HPA AXIS

An alternative hypothesis to the Monoamine Theory of Depression is that major depression is a stress related disorder associated with hypercortisolaemia (Dinan, 1994). The exact mechanisms underlying excessive plasma levels of cortisol are as yet unknown though abnormalities in both the feedforward and feedback limbs of the HPA axis have been shown.

Elevated cortisol levels in patients with major depression have been consistently reported in a number of body fluids including plasma and urine. The excess cortisol may be the product of an increase in hypothalamic secretion of both CRH (Banki *et al.*, 1992) and AVP (van Londen, 1997), and an increase in the frequency of ACTH secretion (Rubin *et al.*, 1987). However, in depressed subjects, exogenously administered CRH produces a blunted ACTH response from the pituitary, though the adrenal cortisol response remains normal, indicating that the adrenal glands are hyperresponsive. This concept is supported by Magnetic Resonance Imaging (MRI) of the adrenal gland during depressive episodes which have found it to be enlarged, returning to normal size with successful treatment of the mood disorder (Rubin *et al.*, 1995). The HPA axis also appears to be resistant to the negative feedback effects of glucocorticoids, and nearly half of subjects with depression fail to suppress cortisol after taking dexamethasone (Ribiero *et al.*, 1993), which may be the result of abnormally functioning glucocorticoid receptors (Modell *et al.*, 1997).

For a more complete review of abnormalities of the HPA axis associated with major depression the interested reader should consult Dinan (1994) and Checkley (1996).

OTHER ENDOGENOUS DETERMINANTS OF FAT DISTRIBUTION

Although the HPA axis plays a primary role in the distribution of adipose stores, other physiological factors are also involved. It is worth considering the role of other major hormones and the sympathetic nervous system. It is beyond the scope of this review to consider them in great detail, but it is important that their influence on fat distribution, and any changes associated with major depressive episodes, is noted.

Sex Steroids

Males and females in general have different patterns of body fat distribution, with men having greater abdominal adipose tissue accumulation, often referred to as "android" obesity, and women having greater peripheral stores, often referred to as "gynoid" obesity (Vague, 1956). However, these phenotypic expressions are the result of an interaction between many factors and it is difficult to know how much of this difference in location of fat storage is attributable to the relative differences in sex steroid activity. This

point has been examined in more detail, and it is useful to consider the sexes separately.

In females there is evidence that sex hormones influence adipose tissue accumulation and distribution as demonstrated by the increase in intra-abdominal fat after the menopause, an effect which is prevented by hormone replacement therapy (Haarbo *et al.*, 1991). In premenopausal women, a number of studies have revealed that an increased amount of abdominal fat is associated with an increase in total testosterone (Mantzoros *et al.*, 1996), though there are some exceptions. In addition a decrease in sex-hormone binding globulin has also been shown in females with an android pattern of fat distribution (Haffner *et al.*,1991). The effect of progesterone on body composition has been less well studied but it does not appear to be as strong as that of oestrogen (Heymsfield *et al.*, 1994). Therefore it appears that in females a reduction in oestrogen or an increase in total testosterone promotes an increase in central fat storage. Expressed in a different way we can say that in women oestrogen exerts a protective effect, whereas testosterone increases the likelihood of central obesity. This seems to fit in well with oestrogen's physiological effects at the adipocyte which is to decrease lipoprotein lipase activity (Price *et al.*, 1998). However, in men, female sex hormones do not appear to correlate with total body or upper body fat, and levels of testosterone appear to be negatively correlated with upper body obesity (Marin, 1996). These are contradictory findings and indicate that the factors responsible for regulation of body fat may not have the same effects in males and females, and that no simple general principle is necessarily applicable. However, up until recently it was believed that the female sex hormones were not a specific regulator of fat distribution because there were no oestrogen or progesterone receptors in adipose tissue though this has now been challenged with the identification of both of these receptors in adipose tissue (Pederson *et al.*, 1996; O'Brien *et al.*, 1998). Furthermore, differences have been shown between the sexes, with females showing equal oestrogen binding capacity in both visceral and subcutaneous sites, whereas men's subcutaneous fat contains oestrogen receptors that have up to twice the binding capacity of those in their visceral site (Pederson *et al.*, 1996). This difference in receptor profile is reflected physiologically in that the effects of female sex steroids in men seem to have a greater affect on LPL reduction in peripheral rather then abdominal fat stores (Ramirez *et al.*,1997). This seems to adhere to the principle that oestrogen is protective against an android pattern of fat distribution in women, although in men this action is weaker possibly due to lower endogenous levels and a reduced binding capacity at the visceral site of fat storage.

The effect of testosterone as highlighted above appears to have different effects depending on the sex of the subject. In women an increase in testosterone is associated with an increase in visceral fat whereas in men the opposite situation applies. In fact, in obese men with testosterone values in the lower range of normal the replacement of testosterone has been shown to reduce abdominal obesity, and in particular to reduce the visceral fat mass specifically (Marin, 1995). This action in men is in keeping with the physiological effect at the adipocyte in which testosterone has been shown to reduce lipoprotein lipase activity (Marin *et al.*,1995).

The literature regarding depressive illness and female sex hormones mainly relates to the menopause and child birth, with low levels of oestrogen implicated in the genesis of depressive episodes in both of these physiological states (Fink *et al.*, 1996). This fact is supported by reports stating that oestrogen therapy can be useful in the treatment and prophylaxis of these conditions (Sherwin, 1988; Sichel *et al.*, 1995). As such it can be clearly stated that oestrogen exerts profound effects upon mood, which it does so by influencing both monoamine and neuropeptide transmitter systems in the brain (Fink *et al.*, 1996). In keeping with the above, low levels of oestradiol have also been demonstrated in premenopausal women suffering with depression, with the levels showing a significant negative correlation with the Hamilton depression scores (Baischer *et al.*, 1995). However, in men suffering with depression the levels of oestradiol have been found to be normal (Rubin *et al.*, 1989). The report of a lowered oestradiol in women is inter-

esting as this may be a factor that would predispose to visceral fat accumulation.

The male sex hormone testosterone has also been examined in relation to depression. In men with major depression testosterone levels have not revealed any consistent abnormalities (Rubin *et al.*, 1989; Levitt and Joffe, 1988). However, testosterone levels have been found to be increased in premenopausal women with depression (Baischer *et al.*, 1995). This is of importance as increased levels of testosterone would have a protective effect on visceral fat accumulation in men, but an opposite effect in women. Implicating reduced testosterone levels as a possible aetiological factor in depressive illness is the fact that hypogonadal men with low levels of testosterone and depressive illnesses non-responsive to specific serotonin reuptake inhibitor treatment have been found to respond to testosterone replacement therapy (Siedman and Rabkin, 1998). However, the HPA axis is known to influence the hypothalamic-pituitary-gonadal axis, and it has been shown that in depressed males with an abnormal dexamethasone suppression test in the acute stage of their illness, that testosterone levels may subsequently be reduced (Unden *et al.*, 1988). This is of particular importance for male patients as low levels of testosterone would predispose the individual to central adipose tissue storage. Overall however, despite some reports of a dysregulation of the pituitary-gonadal system in depression the findings are inconsistent and it therefore seems likely that this is not the major factor contributing to an accumulation of visceral fat. However, the interaction between a hyperactive HPA axis and lowered testosterone in men is of significance as they might interact synergistically to promote abdominal fat accumulation.

Growth Hormone

It has been shown that in men with a specific growth hormone (GH) deficiency there is excessive deposition of fat around the abdomen and trunk, and this is also accompanied by an increased visceral fat mass (de Boer *et al.*, 1996). This also applies to patients who have a more generalised multiple pituitary hormone deficiency. Importantly, replacement of growth hormone has been shown to significantly reduce this effect in both of these groups (De Boer *et al.*, 1996). Therefore growth hormone seems to offer a protective effect against visceral obesity by virtue of its marked lipolytic effects (Richelsen, 1997)

There is evidence of altered growth hormone regulation in depression as demonstrated by the altered release response of GH to a number of pharmacological stimuli. For example, in major depression the GH response to growth hormone releasing hormone (GHRH), clonidine (an alpha-2 adrenoceptor agonist), and dexamethasone is blunted in comparison to normal subjects, whereas the response to pyridostigmine (an anti cholinesterase) is enhanced. Again there is an interaction between the HPA axis and GH, with DST non-suppressors showing a lower GH response to clonidine than suppressors (Mokrani, 1997). In females with a major depressive illness there may be a decrease in the total GH secretion, which appears to result from a reduction of GH secretion during the nocturnal period (Fiasche *et al.*, 1995). This same pattern also applies to men (Voderholzer *et al.*, 1993). However, the finding is by no means universal and contradictory reports of normal baseline GH have been documented (Galard *et al.*, 1988). Therefore in some individuals a low GH could be important as it would promote the development of weight gain and an increase in visceral fat. However, from the available evidence it does not appear that abnormalities of GH in depression are of the magnitude or consistency to be responsible for increased intra abdominal fat in depression.

Thyroid Hormones

Thyroid hormones are known to have an effect on energy balance and in particular on thermogenesis (Silva, 1995). In humans they have a direct effect on the basal metabolic rate and also influence energy expenditure in the form of exercise (Danforth and Burger, 1984). States of hypothyroidism may therefore result in weight gain and obesity. Surprisingly, there is no literature regarding the direct relationship between thyroid disease and visceral fat in either

humans or animals. Furthermore, reviews on the regulation of adipose distribution do not address its role. This is of some significance as hypothyroid states may alter lipid profiles and predispose to cardiovascular disease (Heimberg, 1985).

Thyroid axis abnormalities have been investigated in patients with depression and there is evidence that the thyroid stimulating hormone response to thyroid releasing hormone is blunted. In addition, the circulating levels of TSH have been shown to be significantly lower than in normal controls, though still within the normal reference range (Rao *et al.*, 1996). Furthermore, the differences in plasma thyroxine (T4) have been shown to distinguish between patients with major depression and controls, particularly in males (Sullivan *et al.*, 1997). Though it remains controversial, there is some evidence that subclinical hypothyroid states may predispose to the development of major depressive disorders (Woeber, 1997), and that thyroid hormones may be of therapeutic use in the treatment of some depressive episodes (Joffe *et al.*, 1995). Therefore it can be shown that the thyroid axis may be abnormal in states of depression, but what the effects of this on visceral fat might be is unknown and there is a need for more research to be conducted in to the effects of thyroid dysregulation on adipose tissue distribution.

Sympathetic Nervous System

Adrenergic receptors play an important role in lipid metabolism. Lipolysis is encouraged by stimulation of the beta-adrenoceptors (beta-1, beta-2 and beta-3), though stimulation of the alpha-2 adrenoceptor inhibits lipolysis. Of interest is that in obese subjects visceral fat seems to have a greater catecholamine induced lipolysis compared to subcutaneous fat because of an increase in the function of beta-3 adrenoceptors and a reduction in the function of alpha-2 adrenoceptors (Van Harmelen *et al.*, 1997). As a result it has been postulated that this increased lipolysis of visceral adipose tissue might lead to a greater delivery of free fatty acids directly to the liver, and be responsible for the development of some aspects of the metabolic syndrome (Hoffstedt *et al.*, 1996). This difference in lipolysis related to the sympathetic nervous system also applies to non obese subjects, with men showing increased lipolysis in the intra abdominal fat depot, mainly as a result of beta-adrenergic differences, which may be related to differences in sex steroid hormones (Rebuffe-Scrive *et al.*, 1989).

There is evidence that the sympathetic nervous system is overactive in depression (Veith *et al.*, 1994) and it is possible that this is mediated by the HPA axis, as CRH is known to increase sympathetic drive (Leonard, 1997). Abnormalities of adrenoceptors have also been reported though are not always easy to interpret. Post mortem studies on medication free depressives who completed suicide have revealed an increase in the number of alpha-2 adrenoceptors in the frontal cortex (De Paermentier *et al.*, 1997). However post mortem results are in general extremely difficult to generalise from and no comparison can be made with regard to the function of these receptors in adipose tissue. Abnormalities of adrenoceptors have also been demonstrated in living depressed subjects (on lymphocytes or platelets) where reduced numbers of beta and increased sensitivity of alpha adrenoceptors have been reported respectively (Jeanningros *et al.*, 1991; Garcia-Sevilla *et al.*, 1986). However, this does not mean that the adipose tissue in depressed subjects has similar abnormalities, though if it did this would favour the inhibition of lipolysis and therefore lead to increased fat storage. This appears to be another area where research is needed, though it seems at present that the importance of the SNS is that its overactivity in states of depression results in a greater turnover of lipid metabolism and thus increased production of free fatty acids, which are implicated in the aetiology of certain aspects of the metabolic syndrome.

Therefore, it can be seen that changes in any of these physiological components could theoretically lead to either an increase or decrease in the likelihood of storing fat in the intra abdominal compartment.

However, these systems do not operate independently and have an influence upon one another, and it may be that the net result of the interactions in an

individual with depression influence whether or not they accumulate excessive visceral fat.

MELANCHOLIC DEPRESSION AND INTRA ABDOMINAL FAT DEPOSITION

In comparison to eating disorders such as generalised obesity and anorexia nervosa, in which there are clear psychological and health risk implications associated with changes in body weight and shape, the literature relating to psychiatric illness and intra abdominal fat is limited. The melancholic subtype of major depression is clearly associated with a dysregulated HPA axis, and evidence for overactivity of the feedforward limb, and abnormalities of negative feedback have been well documented (Dinan, 1994; Thakore, 1998). As such, circulating cortisol levels in major depression are elevated, which may lead to the excessive accumulation of visceral fat. A number of studies have addressed this important question, though nearly all of these have used indirect techniques, such as the waist hip ratio (WHR), to assess the degree of IAF. In addition the diagnosis of depression has often not been confirmed clinically and as such it is difficult to draw definite conclusions from these studies, though some interesting inferences can be made.

To aid understanding of the following studies a brief account of how visceral fat is measured is needed. Visceral fat can be measured indirectly, by the WHR, or directly by imaging techniques. In the indirect method the waist and hip measurements reflect central and peripheral fat storage respectively, with the ratio of these measurements reflecting the degree of abdominal obesity. The WHR provides a better indication of the amount of IAF than the body mass index (BMI), which is more useful in the assessment and classification of generalised obesity (Seidell *et al.,* 1989). The BMI is calculated by dividing weight in kilograms by height in metres squared. The average values of the WHR for men and women are 0.93 and 0.83 respectively (Garrow, 1996), with higher values reflecting greater IAF storage. Increasing health risk is associated with WHR values of 1.0 and 0.9, in men and women respectively (Bray, 1987). Direct methods of measuring IAF are more accurate and the current gold standard and most widely used technique is Computerised Axial Tomography (CAT) In humans a single slice scan 2mm thick at the level of L4, which in most patients corresponds to the level of the umbilicus, is normally used. Let us now consider the studies.

Rosmond *et al* (1996) studied 1040 middle aged Swedish men selected from the Revenue Office Register. By means of a self report questionnaire they gathered data about the use of some forms of psychiatric medication, and the degree of life satisfaction and melancholy. They also obtained information concerning behavioural factors such as smoking and alcohol intake, both of which are associated with an increase in the abdominal distribution of fat (Barrett-Connor and Khaw, 1989; Cigolini *et al.,* 1996) . Subjects took their own measurements of weight and height (to estimate BMI), and waist and hip circumferences (to estimate WHR). The WHR, but not the BMI, was associated with the use of psychiatric medications including antidepressants, anxiolytics and hypnotics. The WHR was also associated with the degree of melancholy (not a diagnosis of melancholic depression), and reduced feelings of life satisfaction, both of which were measured on a simple seven point scale. These associations remained significant when alcohol and smoking patterns were accounted for. The authors have argued that the above results were not due to the effects of medication influencing the WHR, for even though some antidepressants are known to induce weight gain, this should have led to an increase in the BMI rather then WHR. In addition, the variables indicating depressive traits were not independently associated with the BMI, but were with the WHR.

Wing *et al* (1991) studied the WHR in 487 middle aged women who were participating in a Healthy Women Study in Pennsylvania. They collected data including WHR, BMI, and scores from the Beck Depression Inventory. They also performed lipid profiles, fasting glucose and insulin levels (including an oral glucose tolerance test). The subject's blood pressures and information on their smoking, exercise, and calorie intake were also collected. The women were

aged between 42 and 50 and so a proportion of the women may have been menopausal, an endocrine state which is known to result in increased IAF deposition and thus effect the WHR (Haarbo *et al.*, 1991). However, the WHR was found to be associated with depressive symptomatology, even when the analyses were restricted to premenopausal women only. As expected from previous studies, the WHR, again in the premenopausal group, was associated with factors relating to increased risk of coronary heart disease. A number of women (108) in the study had data regarding anthropometric measurements, blood lipids and activity level collected at 2 points in time, from baseline and three years later. This revealed that there had been a non significant increase in the WHR, though both waist and hip circumferences had increased significantly when considered separately. The increases in waist and hip size were significantly correlated with reduced HDL cholesterol, and lower amounts of physical activity. Unfortunately, from our perspective, there is no data available to examine a possible link between changes in depressive symptomatology and changes in WHR.

This point has been addressed by Lloyd *et al* (1996) in a study on 592 patients with established insulin dependent diabetes. Data was collected on both WHR and depressive symptomatology, at baseline and after 2 years. Patients also had a full clinical examination. In both sexes, higher WHRs were associated with depressive symptoms. Of greater interest is the fact that increasing depressive symptomatology was significantly and independently associated with increasing WHRs, providing some longitudinal evidence that depression directly influences the WHR, with the inference that IAF is increased as well.

Animal models of chronic stress appear to lend support to the hypothesis that cortisol effects body fat distribution. Cynomolgus monkeys, like humans, display individual variability in the amount and distribution of fat. It has also been shown that in female Cynomolgus monkeys, like humans, increased truncal deposition of fat is associated with coronary artery atherosclerosis (Shively *et al.*, 1987). Jayo *et* al (1993) has examined the effects of chronic stress, brought about by repeatedly rearranging the social hierarchy, on 79 adult male monkeys. The monkeys were placed in four groups, sedentary with stress (n=20), sedentary without stress (n=19), exercise with stress (n=20), and exercise without stress (n=20). Various anthropometric measurements, including BMI and WHR, were taken throughout the study, and at the end of the study period ten monkeys from each group had CAT scans of the abdomen to directly quantify the amount of fat in different compartments. The anticipated effects of different degrees of exercise on fat accumulation between the groups were less than expected as the sedentary group exercised more than was controlled for. The effects of stress on adipose tissue deposition however was striking, with chronically stressed monkeys showing a significant increase in IAF. Furthermore, the ratio of IAF to SCF increased, revealing that there was a preferential deposition of IAF, as seen in humans with hypercortisolaemia. However, as stated in their paper, no hormonal or metabolic data were collected and therefore no robust pathophysiological mechanisms can be proposed.

To date there has only been one study on humans using radiological methods to determine the direct measurement of IAF in established cases of psychiatric illness. Thakore *et al* (1997) used CAT to assess the amount of IAF in depressed patients of melancholic subtype. Seven female subjects with a DSM-III-R (American Psychiatric Association, 1987) diagnosis of major depressive disorder were recruited for the study and the severity of the depression was measured using the 17-item Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960). Seven healthy females, with no personal or family psychiatric history, participated as controls. The mean HAM-D score of the melancholic subjects was 26.1. The WHR values of depressives and controls were 0.79 and 0.77, respectively. The BMI (kg/m2) of depressives and controls were 23.6 and 24.4, respectively. Therefore there was no difference between the groups regarding WHR and BMI. The mean age of melancholic subjects and controls were 36.6 and 32.7 respectively, and none of the women were taking any form of anovulant contraception. The CAT scans were all taken during the follicular phase of their menstrual

cycle. Of the melancholic patients, three were completely drug naive, and four were medication free for at least six weeks before testing. CAT scans at the level of L4 revealed that depressives had just over twice the amount of IAF compared to controls. In addition to this radiological finding, depressed subjects were also found to have elevated base line cortisol levels, in keeping with evidence of a hyperactive HPA axis. Despite the small sample size this study provides important evidence for an association between depression and IAF accumulation. However, metabolic indices, such as lipid profiles and glucose tolerance, were not examined and so the possible link between IAF accumulation and subsequent complications in this patient group were not examined. Neither were patients retested after treatment and thus no longitudinal data is available, which is of significance because as yet no single study, of humans or animals, has examined in detail the longitudinal relationship between depression, HPA axis function, degree of IAF and health implications.

With this in mind it is important to establish whether or not there is any evidence associating depression directly with adverse physical health outcomes. It must be noted that there is a wealth of literature regarding medical illness and depressive states, and it is beyond the scope of this review to try and summarise it. However, a recent review by Harris and Barraclough (1997) states that all mental disorders are associated with an increased risk of premature death, and though suicide is of prime importance, there is also some evidence that physical illnesses play a part in this reduced life expectancy. For example, bipolar affective disorder is associated with a greater risk of death from circulatory disorders and neoplasms, and major depression, when considered separately, is associated with an increased risk of death from nervous and respiratory system disorders. Therefore, the expected link between major depression and cardiovascular disease, as mediated by the features of Syndrome "X", are not highlighted in this review. However, the literature search for the review (Harris and Barraclough, 1997) was conducted between 1966 and 1995, and there are reports, some of which were published after 1995, that are of particular interest when considering major depression and physical illness alone. For example, depressive symptoms have been shown to be associated with an increased prevalence of diabetes (Moldin *et al.,* 1993), a low HDL cholesterol (Horsten *et al.,* 1997) and hypertension (Jonas, 1997), all of which are features of "Syndrome X". Depression is also known to be associated with an increased mortality in patients with coronary artery disease (Barefoot *et al.,* 1996). However, the most striking evidence relating depression to cardiovascular disease comes from a recent epidemiological study completed in California by Everson *et al* (1998), which followed up a community sample of 6676 subjects for 29 years. Depressive symptoms recorded at baseline were clearly associated with an increased risk of death from stroke. This association remained significant even when alcohol use, smoking, BMI, hypertension and diabetes were adjusted for. It is possible that these complications may all be mediated by the increased amounts of intra abdominal fat which appears to develop in patients with depression.

CONCLUSION

If it is clearly established that patients with depression are prone to developing excess IAF this raises a number of important issues. Firstly, depressed patients will need to be screened more carefully for undetected physical complications, which should then be treated appropriately if required, and reviewed as their psychiatric condition improves. Secondly, patients with established medical diseases such as diabetes and ischaemic heart disease, should be screened for psychiatric illness, and in particular depression, which if identified should be treated aggressively. Lastly, the association between psychiatric illness and IAF would alter the management of such patients, requiring a more holistic approach including active advice about diet and exercise, as well as smoking and drinking habits. Of course, providing advice to change certain aspects of behaviour is not always successful (Hodge, 1996) and pharmacological advances in the treatment of IAF are awaited.

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