Abstract

Obesity is a heterogeneous condition and not every obese patient is at increased risk of cardiovascular diseases (CVD). It is now well established that the regional distribution of body fat is a critical correlate of the metabolic complications of obesity. Studies that have assessed adipose tissue distribution by imaging techniques such as computed tomography have demonstrated the importance of the intra-abdominal (visceral) fat depot as a marker of a cluster of metabolic abnormalities which include glucose intolerance, insulin resistance, hyperinsulinemia, hypertriglyceridemia, elevated number of apo B-carrying lipoproteins as well as hypoalphalipoproteinemia. Although the association between visceral obesity and metabolic complications can hardly be questioned, it has been suggested that it may not necessarily represent a causal relationship. For instance, concomitant alterations in sex steroid levels have been found in both men and women with abdominal (visceral) obesity which have also been reported to be significantly correlated with the insulin resistant-dyslipidemic state found in abdominal obese subjects. In women, abdominal obesity is associated with increased free testosterone concentrations and reduced sex hormone binding globulin (SHBG) levels, whereas in men this condition is associated with reduced testosterone and adrenal C19 steroid (dehydroepiandrosterone, androstenedione, androstene-3β,17β-diol) levels as well as decreased SHBG concentrations. These altered steroid and SHBG levels have been reported to be independent correlates of the metabolic complications of visceral obesity although they cannot solely account for the increased CVD risk found in these patients. In this regard, intervention studies are clearly warranted to better quantify the respective contribution of excess visceral adipose tissue and of the concomitant alterations in sex steroid levels as modulators of metabolic disturbances increasing CVD risk in obesity.

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Introduction

Obesity has been associated with chronic diseases such as hypertension, diabetes and dyslipidemia and a higher prevalence of cardiovascular diseases is found among overweight subjects than in lean individuals (Sims & Berchtold 1982, Bray 1985, Garrison et al. 1987, Kissebah 1989). However, the clinician is confronted with the remarkable metabolic heterogeneity found among overweight individuals with the same excess of total body fat. In this regard, it has been shown that the regional distribution of adipose tissue is an important factor to consider when examining the association between obesity and chronic diseases (Kissebah et al. 1982, Björntorp 1984, 1985, Kissebah 1989). Indeed, prospective studies have demonstrated that a high accumulation of abdominal adipose tissue was associated with an increased risk of developing cardiovascular disease and related mortality and that this association was independent of the level of obesity (Lapidus et al. 1984, Larsson et al. 1984, Ducimetière et al. 1986, Donahue et al. 1987). In most of these studies (Kissebah et al. 1982, Björntorp 1984, 1985, Lapidus et al. 1984, Larsson et al. 1984, Ducimetière et al. 1986, Donahue et al. 1987, Kissebah 1989), the proportion of abdominal fat was estimated using a simple anthropometric measurement, i.e. the waist circumference divided by the largest hip circumference (the so-called waist-to-hip ratio, or WHR), the rationale being that the more abdominal fat one has the greater the waist circumference will be as opposed to the hip girth. Studies with the WHR have also shown that this variable is an independent predictor of the risk of developing diabetes mellitus (Ohlson et al. 1985, Haffner et al. 1990). In this regard, prospective studies published in the 1980s (Lapidus et al. 1984, Larsson et al. 1984, Ohlson et al. 1985, Ducimetière et al. 1986, Donahue et al. 1987, Haffner et al. 1990) have confirmed the early clinical observations made by Vague (1947) who was the first to suggest that upper body obesity was a health hazard and that peripheral obesity, frequently found in premenopausal women, was not associated with major
metabolic complications but, rather, was considered a cosmetic problem.

**Obesity and metabolic complications: importance of visceral adipose tissue**

With the recent development of imaging techniques such as magnetic resonance imaging or computerized tomography, it has been possible to measure body fat distribution with greater accuracy and, more particularly, to distinguish the subcutaneous adipose tissue from the amount of fat located in the abdominal cavity, which has been described as the intra-abdominal or visceral adipose tissue (Fujikawa et al. 1987, Sjöström 1988). By using computed tomography, we have measured subcutaneous and visceral adipose tissue accumulation in samples of men and women and reported independent associations between visceral adipose tissue accumulation and metabolic complications predictive of an increased risk of diabetes and cardiovascular diseases (Despres et al. 1990, 1991). As obesity per se is associated with significant metabolic alterations (Bray 1985, Kissebah 1989), we have used a very simple approach to quantify the independent contribution of obesity versus intra-abdominal adipose tissue accumulation (Pouliot et al. 1992). For that purpose we compared two groups of obese patients, matched for the level of total body fat but having a low/high accumulation of visceral adipose tissue measured by computed tomography, to a group of lean controls. As shown in Fig. 1, obese men with a low accumulation of visceral adipose tissue did not differ from the lean controls for plasma insulin levels measured either in the fasting state or following a 75 g glucose load. However, obese men with a high accumulation of visceral adipose tissue were characterized by hyperinsulinemia both in the fasting state and following the oral glucose challenge. Similar comparisons were performed for the plasma lipoprotein profile and essentially similar conclusions were reached regarding the importance of visceral adipose tissue in obesity. Indeed, obesity without a substantial accumulation of visceral adipose tissue was not associated with a significant increase in plasma triglyceride concentration, whereas visceral obese men were characterized by a dyslipidemic state which included hypertriglyceridemia and low high density lipoprotein (HDL)-cholesterol levels, leading to a significant reduction in HDL2/HDL3 cholesterol and HDL/total cholesterol ratios, suggesting an increased risk of coronary heart disease (Fig. 2).

It is important to emphasize the fact that plasma cholesterol levels are well within the normal range in visceral obesity (Pouliot et al. 1992). However, techniques which can estimate the number of low density lipoprotein (LDL) particles such as the measurement of apolipoprotein B concentration in the LDL fraction as well as methods used to separate LDL particles on the basis of their size and

![Figure 1](https://example.com/figure1.png)

**Figure 1** Comparison of fasting insulin levels, and plasma insulin and glucose responses to a 75 g oral glucose load. Obese men with either a low or a high visceral adipose tissue (AT) area were compared with lean controls. Adapted from Pouliot et al. (1992).
Figure 2 Comparison of plasma triglyceride and HDL cholesterol levels as well as HDL/HDL₄ cholesterol and HDL/total cholesterol ratios among two groups of obese men with either a low or a high visceral adipose tissue (AT) area as well as in a group of lean controls. Adapted from Pouliot et al. (1992).

density, have indicated that visceral obese individuals are characterized by a higher concentration (Després et al. 1990) and proportion (Tchernof et al. 1996) of small, dense LDL particles which have been reported to be more prevalent in coronary heart disease patients (Fisher 1983, Crouse et al. 1985, Austin et al. 1988, Griffin et al. 1990, Tornvall et al. 1991, Campos et al. 1992, Coresh et al. 1993, Jaakkola et al. 1993, Griffin et al. 1994). Therefore, clinicians should not be misled by normal cholesterol measurements that are commonly observed in visceral obese individuals. In the presence of abdominal obesity, high triglyceride and low HDL-cholesterol there is a very high likelihood that the patient may be characterized by a greater number of smaller LDL particles.

We have also been interested in the well known gender difference in visceral adipose tissue accumulation (Lemieux et al. 1993). As shown in Fig. 3, at any level of total body fat, premenopausal women appear to be relatively protected against visceral fat accumulation compared with men. We have previously reported that this well known gender difference in visceral adipose tissue accumulation was responsible for the much lower prevalence of metabolic alterations predictive of cardiovascular diseases in premenopausal women (Lemieux et al. 1993). This relative protection appears to be lost at menopause, where an acceleration of abdominal fat accumulation occurs (Enzi et al. 1986, Zamboni et al. 1992). Interestingly, this acceleration in visceral adipose tissue accumulation is concordant with the deterioration of the cardiovascular disease risk profile that is observed in women at this period (Heller & Jacobs 1978, Rosenberg et al. 1981, Bonithon-Kopp et al. 1989, Matthews et al. 1989, Jensen et al. 1990, Razay et al. 1992, Stevenson et al. 1993). Therefore, we believe that the gender difference in visceral adipose tissue accumulation is an important factor
involved in the well known sex dimorphism reported for cardiovascular disease risk.

The metabolic complications of visceral obesity increase the risk of ischemic heart disease

Visceral obesity is, therefore, associated with a cluster of metabolic abnormalities which may contribute to increase the risk of non-insulin dependent diabetes mellitus (NIDDM) and of cardiovascular diseases in men and post-menopausal women, although no prospective study has shown that visceral adipose tissue is an independent risk factor for cardiovascular diseases (Fig. 4). To date, although studies have shown that insulin resistance is a risk factor for development of NIDDM, no prospective study is available on the potential relationship of in vivo insulin resistance to the risk of cardiovascular disease. Prospective studies that have focused on the dyslipidemic state found in insulin resistance have indicated that the high triglyceride-low HDL dyslipidemia represents a risk factor for premature coronary heart disease (Manninen et al. 1992). Four prospective studies (Pyörälä 1979, Welborn & Ware 1979, Eschwege et al. 1985, Yarnell et al. 1994), that have used fasting insulin levels as a crude index of in vivo insulin sensitivity, have reported that individuals who developed coronary heart disease had higher fasting insulin levels at baseline, although the independent contribution of hyperinsulinemia as a risk factor has never been demonstrated. We had the opportunity to study a group of 2103 healthy men and to quantify the incidence of ischemic heart disease events over a 5-year follow-up. During this period, 114 men developed clinical signs of ischemic heart disease. We have recently reported that various dyslipidemic states were more prevalent among men who developed coronary heart disease (almost 70%) compared with subjects who remained healthy (50%) (Lamarche et al. 1995a). Furthermore, hyperapolipoprotein B, a well known correlate of visceral obesity, was the most prevalent dyslipidemia initially found among men who developed ischemic heart disease (Lamarche et al. 1995a). Fasting insulin concentrations were also measured at baseline in these subjects as well as in matched controls who remained free of ischemic heart disease during the follow-up period. Cases and controls were matched for age, body mass index (BMI), smoking and alcohol consumption. We found that cases were characterized by an 18% higher baseline fasting insulin concentration compared with controls (Lamarche et al. 1995b). Furthermore, fasting hyperinsulinemia (Lamarche et al. 1995b) and hyperapolipoprotein B (Lamarche et al. 1995a) were both associated with ischemic heart disease risk, independently of plasma lipid levels. Thus, the hyperinsulinemic-hyperapo B state, which characterizes visceral obesity, clearly represents an atherogenic combination.

Visceral obesity and metabolic complications: role of steroid hormones

Although visceral obesity is associated with a cluster of metabolic abnormalities which includes insulin resistance, hyperinsulinemia and a dyslipidemic state (Després et al. 1990), these results should not be considered as direct evidence that visceral obesity is causally related to these aberrations. For example, concomitant hormonal and metabolic alterations have also been reported in visceral obese individuals and it has been suggested that visceral obesity may be a marker of a maladaptive response to stress, leading to an activated hypothalamic–pituitary–adrenal axis and to reductions in sex steroid hormone levels (Björntorp 1995). In women, it has been shown that abdominal obesity is associated with low sex hormone binding globulin (SHBG) concentrations and with increased free testosterone levels (Evans et al. 1983). These alterations in SHBG and free testosterone levels were found to be independent predictors of the insulin resistant dyslipidemic state found in abdominal obese women (Shoupe & Lobo 1984, Peiris et al. 1987, Smith et al. 1987, Dunaif et al. 1989). Thus, the possibility that the concomitant hormonal and metabolic changes noted in visceral obesity are involved, at least to a significant extent, in the modulation of the insulin resistant-dyslipidemic state found in this condition cannot be excluded.

We have recently been interested in the study of steroid hormone levels and their relationships to body fat...
distribution in men. Alterations in sex steroid levels in obese men have already been studied and it has been reported that obese men are characterized by low testosterone levels as well as increased estrogen concentrations (Schneider et al. 1979, Seidell et al. 1990, Pasquali et al. 1991). We have studied a sample of 80 men who were recruited on purpose to cover a wide range of total body fat (from lean to obese). In this group, we observed that abdominal obesity was associated with reduced testosterone levels and SHBG concentrations (Fig. 5). Furthermore, adrenal C19 steroid levels, namely dehydroepiandrosterone (DHEA), androstenedione and androst-5-ene-3β,17β-diol (Δ5-DIOL), were also reduced in abdominal obese men compared with lean controls (Tchernof et al. 1995a). Thus, obesity and abdominal adipose tissue accumulation are not only associated with reductions in gonadal steroid levels but also with low levels of adrenal C19 steroids. We have also performed multiple regression analyses to identify the best steroid predictors of body composition and adipose tissue distribution. Results indicated that Δ5-DIOL was the best correlate of visceral adipose tissue accumulation as well as of total body fatness (Tchernof et al. 1995a).

In accordance with previous results, we found the expected relationship between visceral adipose tissue accumulation vs insulin and glycemic responses to an oral glucose load, as well as significant associations with steroid hormone levels. Indeed, men with higher testosterone and adrenal C19 steroid levels were characterized by lower fasting insulin levels and lower glycemic and insulimemic responses to oral glucose. However, correlation coefficients for the relationships between visceral adipose tissue vs indices of plasma glucose-insulin homeostasis remained essentially unaffected by control for concomitant variation in plasma testosterone and adrenal C19 steroids, indicating that the relationship of visceral adipose tissue accumulation to glucose tolerance and plasma insulin levels was largely independent of the concomitant alterations in sex steroid levels (Tchernof et al. 1995b).

We have also examined the relationship of testosterone, adrenal steroids and SHBG levels to plasma lipid and lipoprotein levels in this sample of men and we found...
that reduced testosterone and SHBG levels were associated with increased plasma triglyceride, total and LDL-cholesterol as well as apolipoprotein B levels. Therefore, the low HDL-hyperapo B-hypertriglyceridemic condition which characterizes visceral obesity is indeed associated with low testosterone, adrenal steroid and SHBG levels. Adjustment of correlations between lipid-lipoprotein levels and steroid concentrations for the concomitant variation in visceral adipose tissue accumulation largely eliminated these associations. These results indicate that the association of visceral adipose tissue to the concomitant dyslipidemic state is largely independent of the variations in adrenal or gonadal steroid levels. However, it appeared that SHBG concentrations remained significantly associated with plasma lipoprotein lipid concentrations after control for visceral adipose tissue accumulation and other metabolic variables, suggesting that there is an independent association between the lipoprotein profile and SHBG levels in men, high SHBG levels being associated with a more favorable plasma lipoprotein-lipid profile (Tchernof et al. 1994).

Therefore, visceral adipose tissue is an important covariate of an altered sex steroid profile predictive of an increased cardiovascular disease risk. This variable is more closely associated with indices of plasma glucose-insulin homeostasis and with plasma lipoprotein concentrations than with steroid hormones (Tchernof et al. 1994, 1995a,b). Mechanisms underlying this pattern of association remain unclear and further studies are needed to sort out which variables are causally related to the others. However, a few possibilities can be raised from the current literature available on this issue. As stated earlier, visceral obesity has been suggested to result from a maladaptive response to stress which would lead to an activation of the corticotropin-releasing factor–adrenocorticotropin—cortisol axis, increasing glucocorticoid levels (Björntorp 1991, Kissebah & Krakower 1994, Björntorp 1995). Activation of the axis would produce alterations in glucose transport, insulin sensitivity and adipose tissue metabolism and be associated with an inhibition of gonadotropin secretion, explaining the low androgen levels found in visceral obese men (Olefsky 1975, Amatruda et al. 1985, Crampes et al. 1988, Björntorp 1991, Kissebah & Krakower 1994). Intervention studies where abdominally obese men were treated with oral or transdermal testosterone restoring plasma testosterone levels within the normal range, resulted in a loss of visceral adipose tissue, presumably attributable to a direct effect of testosterone inhibiting lipoprotein lipase activity in abdominal adipocytes (Rebuffé-Schwire et al. 1991, Marin et al. 1992, 1993). The reduction of visceral adipose tissue mass in testosterone-treated men was also accompanied by improvements in risk factors for cardiovascular disease and diabetes (Marin et al. 1993), further emphasizing the importance of visceral adipose tissue in the associations between steroids and cardiovascular disease risk factors.

On the other hand, it has been suggested that adipose tissue acts as a steroid reservoir (Deslypère et al. 1985) and as a major site of peripheral steroid interconversion, as steroidogenic enzyme activities and mRNAs have been found in adipose tissue (Deslypère et al. 1985, Lueprantisakul et al. 1990, Labrie et al. 1991). Thus the enlarged adipose tissue mass found in obesity may contribute to the altered plasma steroid levels in this condition. Previous reports have suggested that the
increased estrogen levels found in obese men may result from an increased aromatisation of androgens in adipose tissue (Schneider et al. 1979, Tchernof et al. 1995a). Accordingly, studies on weight loss therapy have demonstrated significant changes in plasma steroid after weight loss (Stanick et al. 1981, Leenen et al. 1994). Although mechanisms underlying the associations between adipose tissue and steroid levels remain to be clearly established, the possibility of an equilibrium between steroid effects on adipose tissue and of adipose tissue itself altering steroid levels can be raised.

The significant associations that we have found in our sample of men (Tchernof et al. 1995b) between testosterone, adrenal C19 steroid levels and indices of plasma glucose-insulin homeostasis are in accordance with numerous previous reports (Phillips 1977, Seidell et al. 1990, Pasquali et al. 1991, Simon et al. 1992, Phillips 1993a). However, further studies are needed to sort out the issue of causality regarding these associations. Among the several possibilities, it has been suggested that insulin may act as a modulator of plasma DHEA levels (Nestler & Strauss 1991). Other studies have shown that DHEA secretion is reduced by insulin through inhibition of 17,20-lyase in the adrenals, and that DHEA treatment has no short-term effect on body weight, fat mass, BMI, WHR or insulin sensitivity in obese men, further supporting an effect of insulin on DHEA rather than the opposite (Nestler et al. 1989, 1992, Usiskin et al. 1990). Although we found that visceral adipose tissue is a critical covariate of the associations between insulin and DHEA levels, further studies examining the long term effect of DHEA treatment in visceral obese men are warranted. In addition, whether the inhibition of DHEA secretion by insulin is modified in the chronic hyperinsulinaemic-insulin-resistant state such as in visceral obesity needs to be studied.

There is no general consensus regarding the associations between endogenous plasma steroid levels and lipoprotein concentrations. For example, some studies have reported that endogenous testosterone levels were positively associated with HDL-cholesterol concentrations (Nordoy et al. 1979, Gutai et al. 1981, Lingholm et al. 1982, Heller et al. 1983, Dai et al. 1984, Hämäläinen et al. 1986, Mendoza et al. 1986, Lichtenstein et al. 1987) whereas others have reported no association (Mendoza et al. 1983, Semmens et al. 1983, Stefanick et al. 1987, Barrett-Connor & Khaw 1988, Kiel et al. 1989). Conflicting results have also been reported for the associations between testosterone levels and plasma triglyceride, total cholesterol, LDL-cholesterol and apolipoprotein B concentrations (Phillips 1977, Deutscher et al. 1986, Hämäläinen et al. 1986, Lichtenstein et al. 1987, Kiel et al. 1989, Phillips 1993a, Yarnell et al. 1993). As stated earlier, we have found that high DHEA or testosterone levels are associated with a favorable plasma lipid-lipoprotein profile but control for concomitant variation in visceral adipose tissue accumulation eliminates most of the associations found. These results indicate that, to a large extent, variations in steroid hormones cannot account for variations in plasma lipoprotein levels in visceral obese men. Instead, our results suggest that visceral obesity could have represented an important confounding factor in previous studies on steroids and lipoproteins, even in studies where overall obesity was controlled for.

Studies on the relationships of endogenous steroid hormone levels to coronary heart disease have also generated controversial data. No general consensus has been reached regarding the importance of testosterone and estrogen levels as risk factors for myocardial infarction (Kalin & Zumoff 1990, Phillips 1993b). Furthermore, studies on DHEA-sulphate (DHEA-S) levels have also yielded conflicting results as DHEA-S has been suggested to be associated with either an increased (Hautanen et al. 1994) or a decreased (Barrett-Connor et al. 1986) risk of coronary heart disease. Although we have not examined this issue in our studies, a metabolic profile predictive of an increased cardiovascular risk was found among men with low testosterone, DHEA and other adrenal C19 steroid hormone levels. However, visceral obesity appeared to be the critical correlate of the metabolic complications found in men with low testosterone and adrenal C19 steroid levels.

**Visceral adipose tissue, steroid hormones and metabolic complications: need for prospective studies**

Thus, we believe that visceral obesity represents a useful model for the study of the contribution of steroid hormones as modulators of metabolic complications found in this condition. However, most studies that have examined these interactions have been cross-sectional in design and secure conclusions can hardly be reached regarding the mechanisms underlying the associations found. For example, the effects of hormone replacement therapy on visceral adipose tissue metabolism need to be better documented. On the other hand, intervention studies leading to losses of visceral adipose tissue would provide interesting information helping us to sort out the importance of this fat depot in steroid metabolism. Therefore, there is a need for additional intervention studies with a more comprehensive set of physiological, metabolic and hormonal measurements in order to identify primary factors in the regulation of visceral adipose tissue accumulation and of metabolic variables predictive of cardiovascular disease risk.

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