Several epidemiological studies have reported that the regional distribution of body fat is a significant and independent risk factor for cardiovascular disease (CVD) and related mortality. Although these associations are well established, the causal mechanisms are not fully understood. Numerous studies have, however, shown that specific topographic features of adipose tissue are associated with metabolic complications that are considered as risk factors for CVD such as insulin resistance, hyperinsulinemia, glucose intolerance and type II diabetes mellitus, hypertension, and changes in the concentration of plasma lipids and lipoproteins. The present article summarizes the evidence on the metabolic correlates of body fat distribution. Potential mechanisms for the association between body fat distribution, metabolic complications, and CVD are reviewed, with an emphasis on plasma lipoprotein levels and plasma lipid transport. From the evidence available, it seems likely that subjects with visceral obesity represent the subgroup of obese individuals with the highest risk for CVD. Although body fat distribution is now considered as a more significant risk factor for CVD and related death rate than obesity per se, further research is clearly needed to identify the determinants of body fat distribution and the causal mechanisms involved in the metabolic alterations. It appears certain, however, that an altered plasma lipoprotein transport is a significant component of the relation between body fat distribution and CVD. (Arteriosclerosis 10:497-511, July/August 1990)
with diabetes, gout, and atherosclerosis. More than 30 years later, Kissébah et al.\textsuperscript{11} provided the first scientific evidence of a relationship between body fat distribution and glucose tolerance when they reported that upper-body obese women showed a higher plasma glucose response during a glucose tolerance test than women with lower-body obesity. Kissébah et al. showed that insulin resistance and high plasma triglyceride (TG) levels were also correlates of upper-body obesity, and they were the first to propose a metabolic link between regional fat accumulation, regional variation in adipocyte morphology and lipolytic activity, and the metabolic profile. Since this report, the results from five epidemiological studies\textsuperscript{1-6} have shown that a high proportion of trunk or abdominal fat was associated with an increased probability of developing CVD and with an increased risk of mortality. These concordant results have also contributed to the marked interest of the scientific community in further characterizing the regional distribution of body fat and its association with metabolic events. In this section of the review, we will summarize the literature available on body fat distribution and metabolic complications. Since previous reviews have discussed in detail the associations between fat distribution and glucose-insulin metabolism and hypertension,\textsuperscript{7,8,12-17} these aspects will be only briefly discussed. In this review, greater emphasis will be given to the relation of body fat distribution to plasma lipoprotein levels and lipid metabolism.

**Body Fat Distribution, Insulin Resistance, Hyperinsulinemia, and Diabetes**

Four decades ago, Vague\textsuperscript{6} reported that women with a "male" pattern of fat distribution (he named it android obesity) were more metabolically affected than obese women with the typical female fat topography (gynoid obesity). Thirty-five years later, Kissébah et al.\textsuperscript{11} were the first to show significant associations between the regional distribution of AT and disturbances in glucose-insulin metabolism when they reported a greater incidence of diabetes and glucose intolerance in "upper-body obese" women compared to "lower-body obese" women. In a large survey of 15,532 obese women, it was shown that obese subjects with excessive upper-body fat had a relative risk of diabetes that was 10-fold higher than normal women with peripheral fat accumulation.\textsuperscript{18} Several investigators have reported that fat topography was associated with plasma insulin levels and with plasma glucose and insulin responses to a glucose tolerance test.\textsuperscript{19,20,21} Further analyses from the Gothenburg prospective study also demonstrated that the localization of body fat could predict the development of diabetes over a 13-year period.\textsuperscript{22} These results clearly demonstrated that body fat distribution is more important than obesity per se with regard to its effect on glucose and insulin metabolism. Thus, the link between fat distribution and diabetes could be considered as one of the mechanisms by which body fat topography is associated with CVD.

The studies described above have, however, measured the regional distribution of body fat by using anthropometric measurements such as skinfolds and the waist-to-hip circumference ratio. Computed tomography (CT) is an alternative approach that allows the precise measurement of AT surface areas at any site of the body,\textsuperscript{23-30} and particularly the delineation of the amounts of deep (or visceral) and subcutaneous fat. It is presently not possible to obtain such information from anthropometric measurements. Using CT, Sparrow et al.\textsuperscript{31} reported that the amount of intra-abdominal fat was significantly correlated with the concentration of plasma glucose at 2 hours after glucose ingestion. Accordingly, Fujioka et al.\textsuperscript{32} reported that glucose tolerance was negatively correlated with the proportion of intra-abdominal fat. In the latter study, the sample was, however, very heterogeneous for age, and it included both women and men as well as diabetic patients. To further investigate the associations between deep abdominal fat accumulation and glucose metabolism, we have studied a homogeneous sample of 52 obese nondiabetic premenopausal women.\textsuperscript{33} Our results not only showed a significant association between the level of deep abdominal fat and glucose tolerance, but also that this relationship was independent from the level of obesity in these obese women. It has also been shown that regional adiposity indices that included CT-measured levels of deep abdominal fat had independent and additive contributions to alterations in glucose insulin homeostasis.\textsuperscript{34} We have also reported that subcutaneous abdominal fat accumulation and abdominal fat cell hypertrophy were two conditions associated with a hypersecretion of insulin, whereas the level of deep abdominal fat was the best correlate of glucose tolerance. It therefore appears from these studies that various body fat distribution indicators display different levels of association with various indices of carbohydrate metabolism. Mechanisms responsible for the associations between regional body fat distribution, intra-abdominal fat accumulation, and glucose and insulin metabolism have been studied. Kinetic studies have shown that obesity was associated with an increased pancreatic insulin production, whereas a high proportion of abdominal fat was associated with a reduced metabolic clearance of insulin, due to a diminished hepatic insulin extraction.\textsuperscript{35,36} A high proportion of abdominal fat is also associated with a decreased insulin-stimulated glucose disposal.\textsuperscript{36,37} The mechanism for the association between body fat distribution and hepatic insulin extraction has not been fully elucidated, but it has been suggested that the concentration of plasma free fatty acids (FFA) could play an important role. It has been reported that abdominal-obese women have a greater basal FFA turnover than peripheral-obese women.\textsuperscript{38} Also, high FFA concentrations are associated with a reduction of glucose utilization through the glucose-fatty acid cycle,\textsuperscript{39,40} leading to glucose intolerance and to systemic hyperinsulinemia. Two recent studies\textsuperscript{41,42} have reported that a high concentration of FFA inhibits the binding and uptake of insulin in hepatocyte preparations. Thus, the high lipolytic activity of deep abdominal adipose cells,\textsuperscript{43} combined with their resistance to the antilipolytic action of insulin,\textsuperscript{44} could be conditions that would contribute to the exposure of the liver to high FFA concentrations through the portal circulation, leading to a reduction in hepatic insulin extraction. With increasing
levels of total body fat, men generally accumulate more abdominal and visceral fat than women.\textsuperscript{26,28} We had previously suggested that this sex dimorphism in body fat topography could be responsible for the fact that obesity is more readily associated with metabolic complications and CVD risk in men than in women.\textsuperscript{45,46,47} Because steroid hormones are important determinants of the sex dimorphism in body fat distribution, their associations with body fat distribution and metabolic complications will be reviewed separately in this paper.

**Fat Distribution and Blood Pressure**

Numerous studies have reported associations between body fat localization and hypertension.\textsuperscript{19,20,46-53} Indeed, Kalkhoff et al.\textsuperscript{20} reported a significant association between the waist-to-hip circumference ratio and blood pressure. It has also been reported that central adiposity has more detrimental effects on blood pressure than peripheral fat accumulation.\textsuperscript{48} Studies have also dealt with the respective contributions of body fat and fat distribution to variation in blood pressure, and an independent effect of fat localization on blood pressure has been reported.\textsuperscript{19,51,52} Similarly, when we controlled for the effects of biologic and lifestyle variables known to affect blood pressure, we observed a significant effect of trunk fat on diastolic blood pressure in men.\textsuperscript{53} Although all these studies showed an effect of fat distribution on blood pressure, the mechanisms by which these variables are linked remain unclear. There is increasing evidence that variations in plasma insulin levels, which have been shown to be associated with body fat topography, could play a role in the regulation of blood pressure.\textsuperscript{54-56} A model integrating obesity, body fat distribution, insulin levels, the activity of the sympathetic nervous system, and blood pressure has already been proposed.\textsuperscript{59} Although additional research is warranted to elucidate the mechanisms by which body fat distribution is associated with hypertension, there is enough evidence to show that high blood pressure undoubtedly contributes to the increased risk of CVD in subjects with truncal-abdominal obesity.

**Body Fat Distribution and Plasma Lipoprotein-Lipids**

Disturbances in glucose homeostasis and increased susceptibility to diabetes and hypertension are not the only factors contributing to the association between fat distribution and CVD. Early studies reported that excess trunk fat was associated with high plasma TG levels.\textsuperscript{60,61} More recently, others have also shown that abdominal obesity was related to high plasma TG levels.\textsuperscript{11,19,21} We have reported\textsuperscript{45} that the regional distribution of body fat, especially an excessive deposition of abdominal fat, was associated with low concentrations of serum high density lipoprotein (HDL) cholesterol. We also showed that, since men generally have more abdominal fat than women, the association between obesity and plasma HDL cholesterol level was stronger in men than in women.\textsuperscript{45} We further studied the associations between obesity, AT distribution, and serum HDL cholesterol levels in a sample of 429 men, and our results demonstrated that the effect of obesity on serum HDL cholesterol levels was no longer significant after controlling for abdominal fat deposition,\textsuperscript{62} thereby indicating that the association that had been reported in the past between obesity and serum HDL cholesterol levels was mainly explained by the amount of abdominal fat. These findings on the association between abdominal fat and serum HDL cholesterol levels have since been confirmed by others.\textsuperscript{13,63-75} However, all these studies have measured the distribution of body fat by anthropometric measurements such as skinfolds and circumferences. Since it had been suggested that intra-abdominal fat was important in the etiology of the metabolic complications of obesity,\textsuperscript{31,32} further work was required to document the associations between deep abdominal fat deposition and lipoprotein levels and metabolism.

Since CT accurately measures the amount of intra-abdominal fat, we have used this technique to study the associations between body fat localization and plasma lipoprotein levels in a sample of 52 premenopausal obese women. Our results\textsuperscript{76} clearly showed that a high proportion of intra-abdominal fat was associated with a reduction in the concentration of HDL cholesterol and with significant reductions in lipoprotein ratios (HDL cholesterol/low density lipoprotein [LDL] cholesterol, HDL apoprotein A-I/LDL apoprotein B, HDL\textsubscript{2} cholesterol/HDL\textsubscript{3} cholesterol) that are frequently used in the estimation of the CVD risk (Table 1).

Furthermore, these associations between intra-abdominal fat accumulation and plasma lipoprotein ratios were independent from the effect of obesity.\textsuperscript{77} Peiris et al.\textsuperscript{77} simultaneously reported similar findings suggesting that visceral fat deposition may represent a greater risk factor for CVD than obesity per se. Thus, in a sample of premenopausal women with varying levels of body fatness, it was reported that the amount of intra-abdominal fat measured by CT explained a higher proportion of the variance in the HDL cholesterol/cholesterol ratio than body mass per se.\textsuperscript{77} Since dyslipoproteinemic states have been associated with the development of CVD, the relation of fat distribution to plasma lipids and lipoproteins could be an additional factor linking abdominal fat to CVD.

Therefore, the measurement of the level of intra-abdominal fat becomes very important in the estimation of the CVD risk due to its independent association with alterations in glucose insulin homeostasis\textsuperscript{31-34} and plasma lipoprotein levels.\textsuperscript{76,77} As men generally possess a higher relative accumulation of visceral fat than women,\textsuperscript{26,28} the gender difference in this depot could be a major factor in the sex difference noted in the magnitude of the association between the level of fatness and metabolic complications. As for diabetes, the mechanisms relating fat distribution to plasma lipoprotein physiology are poorly understood, but studies conducted in different laboratories, including ours, have allowed the identification of some factors potentially involved in the regional fat distribution-lipoprotein association.

**Mechanisms Involved in the Association between Body Fat Distribution and Plasma Lipoproteins**

Changes in plasma lipoprotein concentration and composition and in plasma lipid transport have been associated...
with variations in the regional distribution of body fat. This section will summarize the literature on this issue. When possible, underlying mechanisms will be discussed, and possible avenues for further research will be suggested.

**Role of Lipoprotein Lipases**

TG lipases (lipoprotein lipase [LPL] and hepatic-TG lipase [H-TGL]) play important roles in lipoprotein metabolism. In numerous clinical and experimental conditions, a high plasma postheparin LPL activity has been associated with high plasma HDL levels, whereas a high plasma postheparin H-TGL activity has been associated with low plasma HDL concentrations. We have studied the relationships between body fat distribution, plasma postheparin LPL and H-TGL activities, and plasma lipoprotein levels in a sample of 16 premenopausal obese women (Table 2).

Plasma postheparin LPL activity was correlated neither with total adiposity nor with the level of intra-abdominal fat. Intra-abdominal fat deposition was, however, positively correlated with H-TGL activity (r=0.66, p<0.005). Furthermore, covariance analysis showed that the association between intra-abdominal and H-TGL activity was independent from total adiposity. Plasma postheparin LPL (Table 2) and abdominal AT-LPL (results not shown) activities showed no significant correlation with plasma lipoprotein levels. We found, however, a significant association between femoral AT-LPL activity and the HDL₂ cholesterol/HDL₃ cholesterol ratio (r=0.51, p<0.05; result not shown in Table 2). H-TGL activity was negatively correlated with HDL₂ cholesterol (r=-0.60, p<0.05), but not with HDL₃ cholesterol (r=-0.28, NS). Thus, these results suggested that the high H-TGL activity in obese women with excess deep abdominal fat could be responsible for the reduction in plasma HDL₂ cholesterol levels observed in these subjects. There is, however, no reason to believe that the accumulation of deep abdominal fat could be directly involved in the variation of H-TGL activity. As both visceral fat accumulation and H-TGL are, however, sensitive to sex steroids, it had been suggested that an increased exposure to androgens could produce simultaneous increases in the level of abdominal fat and in H-TGL activity. Our study confirms that, indeed, a
TG content of HDL, whereas the WHR was associated with a relative TG enrichment of HDL, as reflected by the HDL cholesterol/TG ratio.

Partial correlation analyses presented in Table 4 indicate that adjustment for fat mass or for the WHR failed to eliminate the associations between plasma VLDL-TG levels and lipoprotein lipid composition. These results emphasize the importance of plasma VLDL-TG level as a correlate of plasma LDL and HDL lipid composition in abdominal obesity. It therefore appears that obesity and abdominal fat accumulation (irrespective of the subcutaneous or visceral accumulation of fat) are associated with hypertriglyceridemia and that high plasma TG levels are associated with a TG enrichment of LDL and HDL.85 It is very likely that the high plasma TG levels observed in abdominal obesity represent an indirect risk for CVD, as they reflect disturbances in plasma lipid transport such as a reduced catabolism of TG-rich lipoproteins and a greater lipid exchange among lipoproteins leading to TG enrichment of LDL and HDL.85 This condition is associated with higher concentrations of dense, small LDL and with low HDL cholesterol levels in the plasma. It has been suggested that an altered composition of LDL, namely an increased ratio of LDL apo B to LDL cholesterol, was associated with an increased CVD risk.86 Indeed, many patients with coronary heart disease have high concentrations of smaller and denser LDL particles that contained less cholesterol than normal.87 Furthermore, as hypertriglyceridemic LDL contains less cholesterol, cellular cholesterol synthesis is inhibited to a lesser extent by dense LDL.88 In addition, because dense LDL particles have a reduced cholesterol content, less cholesterol is cleared from the plasma through the LDL receptor pathway, and a higher proportion of cholesterol is transported by VLDL in subjects with high TG levels, in comparison with individuals with normal plasma lipid transport.89 Such cholesterol transported by VLDL may be cleared from the plasma by potentially atherogenic routes such as macrophages and smooth muscle cells.89

The reduction in plasma HDL cholesterol observed in subjects with high plasma TG levels may first be the consequence of an increased exchange of lipids among lipoproteins through the action of lipid transfer proteins.90-92 The negative association between plasma TG and HDL cholesterol levels may also be attributed to a reduced catabolism of TG-rich lipoproteins, caused by a

Table 3. Full and Partial Correlations between Body Fat Mass, Proportion of Abdominal Fat, Plasma VLDL TG and HDL CHOL Levels, and Lipoprotein-Lipid Composition

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fat mass</th>
<th>Waist-to-hip ratio</th>
<th>Fat mass (adjusted for WHR)</th>
<th>Waist-to-hip ratio (adjusted for fat mass)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL TG</td>
<td>0.56‡</td>
<td>0.49‡</td>
<td>0.33†</td>
<td>0.34†</td>
</tr>
<tr>
<td>HDL CHOL</td>
<td>-0.47‡</td>
<td>-0.45‡</td>
<td>-0.27*</td>
<td>-0.30*</td>
</tr>
<tr>
<td>LDL CHOL/LDL TG</td>
<td>-0.42‡</td>
<td>-0.29*</td>
<td>-0.31*</td>
<td>-0.09</td>
</tr>
<tr>
<td>HDL CHOL/HDL TG</td>
<td>-0.27*</td>
<td>-0.46‡</td>
<td>-0.01</td>
<td>-0.41‡</td>
</tr>
</tbody>
</table>

A group of 76 premenopausal women was examined. This table was adapted from reference 85.

* p<0.05, † p<0.01, ‡ p<0.001.

WHR=waist-to-hip ratio. See the legend to Table 1 for other abbreviations.

high intra-abdominal fat deposition is associated with a high H-TGL activity and with low HDL cholesterol levels. In our sample of obese women, we reported that plasma postheparin LPL activity was not related to body fat distribution. To further investigate the potential associations between body fatness, fat distribution, and plasma postheparin LPL activity, we have studied a sample of 29 premenopausal women with body fatness levels ranging from lean to massively obese.84 In this sample, LPL activity was negatively correlated (r= -0.45, p<0.05) with the level of total body fat. In addition, a low LPL activity was associated with high plasma TG levels and with low HDL cholesterol levels. These results suggest that obesity per se is associated with a reduction in plasma postheparin LPL activity, whereas obesity combined with a high level of visceral fat is associated with a high H-TGL activity leading to reduced HDL cholesterol levels. These results may explain the reported independent and additive effects of obesity and of fat distribution on the concentration of plasma TG and HDL cholesterol.

Role of Plasma Triglyceride Levels

Our observation that plasma TG levels were not associated with intra-abdominal fat deposition per se in a sample composed of obese subjects alone led to further investigations to measure the independent effects of obesity and of the proportion of abdominal fat on plasma lipoprotein concentration and lipid composition in a sample of women with wide variations in their levels of total body fat.85 Indeed, obese women had significantly higher plasma levels of very low density lipoprotein (VLDL)-TG, LDL cholesterol, LDL-TG, LDL apolipoprotein (apo) B, and reduced HDL cholesterol levels compared to nonobese controls (p<0.01). However, plasma concentrations of HDL apo A-I and HDL-TG were not different between obese and nonobese women.86 Partial correlation analyses revealed that both fat mass and abdominal fat accumulation significantly contributed to VLDL-TG and HDL cholesterol variances (Table 3).

After control for body fat mass, the waist-to-hip circumference ratio (WHR) remained significantly correlated with the LDL apo B/HDLC cholesterol ratio (r=0.38, p<0.01).86 Body fat mass was, however, associated with TG enrichment of LDL (p<0.01). After control for WHR, body fat mass showed no significant association with the relative TG content of HDL, whereas the WHR was associated with a relative TG enrichment of HDL, as reflected by the HDL cholesterol/TG ratio.
Role of Carbohydrate Metabolism

Because insulin resistance and glucose intolerance are associated with abdominal obesity, we have investigated the potential role of alterations in carbohydrate metabolism in mediating the effects of fat distribution on lipoprotein levels. Numerous studies have indicated that plasma lipid transport and lipoprotein levels are altered in diabetes, and the evidence for associations between glucose tolerance, insulin resistance, plasma insulin levels, and plasma lipoproteins is abundant (for reviews, see references 14, 17, 93). It is thus relevant to verify to what extent the alterations in plasma lipid transport observed in abdominal obesity are related to changes in glucose-insulin homeostasis. In a previous study in men, we found that, during an oral glucose tolerance test (OGTT), the proportion of trunk fat was positively correlated with the plasma insulin response, as well as with plasma LDL cholesterol and LDL apo B levels, suggesting that these variables are all interrelated.84 In women, we reported that the hyperinsulinemia associated with a high proportion of abdominal fat was a significant correlate of plasma TG and VLDL levels, but that other mechanisms explained the negative association between abdominal obesity, visceral obesity, and plasma HDL cholesterol levels (Ferland et al., unpublished observations). In the San Antonio Study, it was found that insulinemia and glucose intolerance were associated with reduced cholesterol content of both HDL and HDL2 cholesterol levels (adjusted for fat mass or for WHR). Our results suggest that the high VLDL-TG levels observed in abdominal obesity are associated with a reduced cholesterol content of both HDL and HDL2 cholesterol levels (due to a TG enrichment) and also with a reduced conversion of HDL2 to HDL3 during the intravascular lipolytic process. These metabolic alterations indicate disturbances in plasma lipid transport that are associated with an increased risk of cardiovascular complications.

Effect of Obesity Per Se on Plasma Lipoproteins

Most observations that have been reported so far on body fat distribution and metabolism have been derived from samples of obese individuals or samples including obese individuals. Landin et al.95 have recently studied the associations between the proportion of abdominal fat estimated by the WHR and metabolism in lean and obese postmenopausal women. Whereas they reported significant associations between the WHR and alterations in metabolism in obese women, no relationship of fat distribution to metabolic complications was observed in lean women. These results suggested that obesity is a necessary condition for the documented associations between fat distribution and metabolic alterations. To further dissociate the effects of obesity from those related to fat distribution, we have studied the potential associations between fat distribution, regional variation in fat cell size, and plasma lipoprotein levels in a sample of 22 lean women with a mean body mass index (BMI) of 21 kg/m²96 (Table 5). In this sample, very few significant associations were observed between the WHR, intra-abdominal fat accumulation, and plasma lipoprotein levels. However, we observed in these nonobese women that a high trunk-abdominal fat accumulation measured by CT was associated with increased LDL cholesterol (r=0.56, p<0.01) and LDL apo B levels (r=0.70, p<0.01). Furthermore, abdomi-
ional fat cell weight was positively correlated with the LDL apo B/LDL cholesterol ratio \( (r=0.58, \ p<0.01) \) and negatively correlated with plasma HDL apo A-I \( (r=-0.51, \ p<0.05) \). On the other hand, femoral fat accumulation and femoral fat cell weight showed no association with plasma lipoprotein levels.\(^{96}\) These results show that in nonobese premenopausal women, subcutaneous trunk-abdominal fat accumulation and abdominal fat cell hypertrophy are related to changes in plasma lipoprotein levels, whereas the WHR and the level of deep abdominal fat show little association with the metabolic profile of lean women.

We have also compared obese women with similar levels of total body fat who markedly differ in their level of intra-abdominal fat to nonobese women (Despres et al., unpublished observations). This approach with three distinct groups (25 nonobese women, 10 obese women with low levels of intra-abdominal fat, and 10 obese women with high levels of intra-abdominal fat) has allowed us to dissociate the independent effects of obesity and of intra-abdominal fat accumulation on risk factors for CVD (Table 6). Although obese women with low levels of intra-abdominal fat had much higher adiposity than nonobese controls, increased plasma TG and insulin levels were the only two metabolic alterations observed in these obese women. In contrast, obese women with high levels of intra-abdominal fat displayed numerous metabolic complications compared to nonobese women, including increased plasma TG, cholesterol, LDL cholesterol, LDL apo B, glucose and insulin areas under the curve measured during an OGTT, reduced HDL cholesterol levels, and reduced ratios of HDL cholesterol/LDL cholesterol and HDL apo A-I/LDL apo B. Therefore, despite comparable levels of obesity in the two obese groups, obese women with low levels of intra-abdominal fat had fewer metabolic alterations than obese women with visceral obesity (Despres et al., unpublished observations).

Results from these studies emphasize two notions. First, since no significant correlation was observed between deep abdominal fat deposition and plasma HDL cholesterol levels in nonobese women, these results indicate that, at least in premenopausal women, obesity has to be present for there to be significant associations between intra-abdominal fat accumulation and plasma lipoprotein concentrations. However, among obese subjects, the level of intra-abdominal fat is a more important correlate of a potentially atherogenic profile than obesity per se. It should be emphasized, however, that these notions have not been verified in men, as the association between fatness and visceral fat deposition is greater in men than in women. It is possible that obesity is not a prerequisite for the metabolic complications of visceral fat accumulation in men.

**Effects of Sex Steroids and Glucocorticoids**

Several studies performed by Kissebah and colleagues\(^{13,21,97,98}\) have suggested that the association between abdominal obesity and metabolic complications might not represent a cause-and-effect relationship but could rather reflect the influence of sex steroids on both body fat distribution and metabolism. The association between androgenic activity, abdominal fat accumulation, and metabolism was investigated in a sample of 80 premenopausal women with adiposity levels ranging from lean to massively obese.\(^{97}\) Although a high androgenic activity was associated with both an increased deposition of abdominal fat and a decreased insulin sensitivity,\(^{97}\) it has been found that, although of lower magnitude, the correlations between body fat distribution and alterations in glucose metabolism remained significant after controlling for steroid hormone levels.\(^{21}\) After adjustment for the effect of abdominal fat accumulation as estimated by the WHR, no significant correlation remained between androgenic activity and metabolic indices, suggesting that the relationship was largely mediated by the regional accumulation of body fat.\(^{21}\) Recent results have indicated that the systemic hyperinsulinemia associated with abdominal obesity was partly attributed to a reduced hepatic extraction of insulin.\(^{38}\) Sex hormone binding globulin (SHBG) level was positively correlated with the hepatic insulin extraction, whereas the percentage of free testosterone was negatively correlated with the hepatic insulin extraction.\(^{98}\) After correction for the effects of percent free testosterone and of SHBG, correlations between the proportion of abdominal fat (as estimated by the WHR) and the hepatic extraction of insulin remained significant, suggesting that body fat distribution could, per se, affect insulin metabolism.

### Table 5. Correlations between Fat Mass, Waist-to-Hip Ratio, Deep Abdominal Fat, and Plasma Lipoproteins in Lean Women

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fat mass</th>
<th>Waist-to-hip ratio</th>
<th>CT-measured deep abdominal fat</th>
</tr>
</thead>
<tbody>
<tr>
<td>VLDL TG</td>
<td>-0.29</td>
<td>-0.20</td>
<td>-0.11</td>
</tr>
<tr>
<td>LDL CHOL</td>
<td>0.46*</td>
<td>0.21</td>
<td>0.38</td>
</tr>
<tr>
<td>LDL apo B</td>
<td>0.51*</td>
<td>0.36</td>
<td>0.52†</td>
</tr>
<tr>
<td>HDL CHOL</td>
<td>-0.24</td>
<td>0.03</td>
<td>-0.18</td>
</tr>
<tr>
<td>HDL apo CHOL</td>
<td>-0.26</td>
<td>0.05</td>
<td>-0.27</td>
</tr>
<tr>
<td>HDL apo CHOL</td>
<td>-0.10</td>
<td>0.16</td>
<td>0.03</td>
</tr>
</tbody>
</table>

A sample of 22 lean menopausal women was studied.

This table was adapted from reference 96.

\(^*p<0.05, \ †p<0.01.\)

See the legend to Table 1 for an explanation of the abbreviations.
through a mechanism partly independent from variations in sex hormone levels.89,90
Numerous studies have also shown that sex steroids have significant effects on lipoprotein metabolism.89 In a sample of 73 healthy men, Stefanick et al.89 have shown that plasma estradiol levels were correlated negatively with total cholesterol as well as with LDL cholesterol, whereas testosterone levels were positively correlated with apo B levels. SHBG correlated positively with HDL2 mass determined by analytical centrifugation and with plasma apo A-I levels. However, after adjustment for the amount of abdominal fat, as estimated by the WHR, no significant correlations remained between SHBG and TG, HDL2 mass, and apo A-I. These results suggest that some of the effects of sex steroids on plasma lipoprotein levels are mediated by variations in regional body fat distribution. Soler et al.75 also studied the associations between abdominal adiposity (estimated by the WHR), fasting insulin and sex hormone levels, and plasma lipoprotein levels in a sample of 75 postmenopausal women. They reported that, after adjustment for insulin, SHBG, and estrone level, abdominal obesity was still significantly associated with plasma TG, HDL cholesterol, and apo A-I and B levels.75 These results also support the notion that mechanisms other than sex hormone levels are involved in the fat distribution-lipoprotein association.

There is, however, experimental evidence indicating that sex hormones alter lipoprotein metabolism through additional mechanisms. As indicated in a recent review,82 sex steroids produce changes in plasma HDL2 cholesterol concentration by up- or down-regulating the H-TGL activity, as steroids with androgenic activity increase H-TGL activity and reduce plasma HDL2 cholesterol levels. Administration of an androgenic steroid, stanozolol, was associated with an increase in H-TGL activity that preceded the decrease in plasma HDL2 cholesterol levels, suggesting a cause-and-effect relationship between the enzyme and plasma HDL2 cholesterol levels.83 In summary, it appears that sex steroid levels, through regulation of H-TGL activity, play an important role in the regulation of plasma HDL cholesterol levels in abdominal obesity, particularly in situations of visceral fat accumulation. We believe that variations in sex steroid levels may contribute to the association that we have recently reported between intra-abdominal fat deposition, H-TGL activity, and plasma HDL2 cholesterol levels.83 Mechanisms responsible for these associations clearly require further investigation.

In addition to sex steroid hormones, glucocorticoids have also been proposed as a factor involved in the body fat distribution-metabolism association. It is well known that Cushing’s disease is associated with a preferential accumulation of abdominal fat and with body fat distribution-related metabolic complications such as insulin resistance, hypertension, and hyperlipidemia.101 These results suggest a significant role for cortisol in the control of regional fat accumulation and carbohydrate and lipid metabolism. A higher cortisol production rate was reported in subjects with abdominal obesity compared to individuals with peripheral fat accumulation.102,103 A significant positive correlation between the cortisol production rate and the plasma insulin response during an OGT1 has also been reported.102 The effects of glucocorticoids on lipid metabolism have been recently reviewed.104 Glucocorticoids stimulate hepatic VLDL secretion101,106,107 and decrease the binding and degradation of LDL by rat hepatocytes.106,107 The high cortisol levels frequently observed in abdominal obesity could

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Table 6. Metabolic Characteristics of Nonobese Women, and of Obese Women with Low or High Levels of Deep Abdominal Fat

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonobese (n=25)</th>
<th>Obese: level of deep abdominal fat</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=10)</td>
<td>Low (n=10)</td>
</tr>
<tr>
<td>% Body fat</td>
<td>28.0±5.6</td>
<td>47.0±4.6*</td>
</tr>
<tr>
<td>Deep abdominal fat area (cm²)</td>
<td>50.3±16.8</td>
<td>107.0±33.4*</td>
</tr>
<tr>
<td>TG (mmol/l)</td>
<td>0.79±0.35</td>
<td>1.47±0.79*</td>
</tr>
<tr>
<td>CHOL (mmol/l)</td>
<td>4.59±0.88</td>
<td>5.18±0.93</td>
</tr>
<tr>
<td>LDL CHOL (mmol/l)</td>
<td>3.00±0.87</td>
<td>3.56±0.92</td>
</tr>
<tr>
<td>LDL apo B (mg/dl)</td>
<td>68.4±23.2</td>
<td>77.8±21.8</td>
</tr>
<tr>
<td>HDL CHOL (mmol/l)</td>
<td>1.36±0.24</td>
<td>1.25±0.18</td>
</tr>
<tr>
<td>HDL apo A-I (mg/dl)</td>
<td>116.8±13.5</td>
<td>126.5±24.1*</td>
</tr>
<tr>
<td>HDL CHOL/LDL CHOL</td>
<td>0.50±0.23</td>
<td>0.37±0.09</td>
</tr>
<tr>
<td>HDL apo A-I/LDL apo B</td>
<td>1.90±0.74</td>
<td>1.71±0.47</td>
</tr>
<tr>
<td>Fasting insulin (pmol/l)</td>
<td>39.0±12.4</td>
<td>91.5±59.9*</td>
</tr>
<tr>
<td>Glucose area ([mmol/l/day]×10⁻³)</td>
<td>1.07±0.19</td>
<td>1.14±0.22</td>
</tr>
<tr>
<td>Insulin area ([pmol/l/day]×10⁻³)</td>
<td>46.6±19.4</td>
<td>82.1±46.8*</td>
</tr>
</tbody>
</table>

The values represent means ± SD. The number of subjects is shown in parentheses. Triglyceride data were log 10 transformed for statistical analysis.

*Significantly different from nonobese women, †significantly different from obese women with low levels of deep abdominal fat, p<0.05.

TG=triglycerides, CHOL=cholesterol, LDL=low density lipoprotein, HDL=high density lipoprotein, apo=apoprotein. Glucose and insulin areas represent integrated plasma concentrations for 3 hours after oral glucose (75 g) ingestion.

From Depris et al., unpublished observations.
lead to an increased VLDL production and to a decreased clearance of LDL through the apo B,E receptor. Clearly, more research is warranted on the interaction between body fat distribution, glucocorticoids, and metabolism in humans. It is, however, very likely that glucocorticoids play a significant role in the metabolic complications associated with abdominal obesity.

Role of Regional Variation in Adipose Tissue Metabolism

There are well-established regional differences in AT metabolism. It has been suggested that the high lipolytic activity of abdominal adipose tissue leads to a disproportionate uptake of HDL cholesterol ester by the hyperplasia and increased plasma HDL cholesterol levels observed in abdominal obesity. Weight loss has, however, reportedly decreased HDL binding to adipose cell plasma membranes and increased plasma HDL cholesterol levels. Whether these reciprocal changes represent cause-and-effect relationships or simultaneous variations will require further experimentation.

Finally, the response of AT-LPL to insulin is reportedly blunted in obesity. Preliminary results suggest that there is no regional variation in the AT-LPL response to insulin. We have recently reported that, whereas abdominal AT-LPL activity was not associated with plasma HDL levels, the LPL activity measured in the femoral adipose tissue was positively correlated with the plasma HDLc, cholesterol/HDLa, cholesterol ratio, suggesting that a high femoral fat accumulation and LPL activity could contribute to a generation of more HDL particles in individuals with peripheral obesity. Further studies are needed to document the potential associations between fat distribution, regional variation in AT-LPL activity, and plasma lipoprotein levels.

Classification of Obesities and Cardiovascular Risk

The genetic, morphological, and clinical evidences support the notion that obesity is a heterogeneous phenotype. There is some confusion in the fat distribution literature regarding measurements and indices used to assess regional fat distribution. Subcutaneous skinfolds, skinfold ratios, circumferences, or circumference ratios (including WHR) have been used and, more recently, CT has been used to distinguish between measurements of subcutaneous and deep fat accumulation at any site of the body. With regard to the commonly used WHR, we do not know exactly what it represents, and this measurement cannot be clearly interpreted, because two variables are involved. The WHR is generally correlated with age, with the level of total body fat, and with the level of visceral fat. It is, therefore, not surprising that the WHR has emerged as a significant correlate of the metabolic complications of obesity. Important limitations of the WHR are that a high ratio may be obtained in an individual with a small hip circumference or a low ratio in an individual with a large hip circumference, for the same abdominal girth. These two individuals may not necessarily differ with regard to their absolute amount of abdominal fat and in their risk profile, but it may be falsely concluded that they do on the basis of different WHR values. In addition, the WHR is not necessarily responsive to weight loss or weight gain, whereas the waist circumference is obviously so. The significant correlations between total body fat, visceral fat, and the WHR is also a phenomenon that should be carefully considered. The relationship is too low to allow the use of WHR as a surrogate for the other two fatness variables. However, the interrelationships should always be controlled when the associations between total body fat, body fat distribution assessed by the WHR, and metabolism are studied. We believe that the practice of using the WHR as an independent indicator of regional fat distribution should be abandoned in favor of more direct and absolute measurements of truncal-abdominal fat, such as those provided by truncal and abdominal skinfolds or by the waist circumference. CT or nuclear magnetic resonance
clearly remain the best techniques available to measure
the amount of visceral fat.

From the evidence available, obese individuals can be
classified into two main groups: 1) gluteal-femoral-obese
indivduals, and 2) abdominal-obese individuals. How-
ever, it has been recently suggested that abdominal-
obese individuals may be further divided into two sub-
groups displaying different metabolic profiles that may be
suggestive of variable risks of CVD.10,127 Gluteal-femoral
obesity is characterized by mild insulin resistance, hyper-
insulinemia, and increased plasma TG levels, due to a
reduced plasma postheparin LPL activity and/or to an
increased VLDL production. The first subgroup of
abdominal-obese individuals would be composed of
obese subjects with high levels of subcutaneous trunk-
abdominal fat (trunk-abdominal obesity). Evidence for a
role of upper-trunk fat per se in the metabolic complica-
tions associated with body fat distribution is primarily
derived from studies that have shown a significant rela-
tionship between the level of trunk fat and metabolic
variables after control for the level of total body fat and the
WHR.65,74 Metabolic complications observed in this
group have been associated with a high proportion of
upper-trunk or abdominal fat (as estimated by skinfolds
or by circumferences) but not preferentially associated
with an accumulation of visceral fat. These complications
would include further insulin resistance, leading to a
decrease in plasma postheparin LPL activity and to a
further increase in plasma TG levels. HDL is enriched with
TG, leading to a reduction in the cholesterol content of
HDL. Increased levels of small (dense) LDL are also
observed. The proportion of abdominal fat estimated by
the WHR ratio has been positively correlated with the
concentration of denser small LDL mass determined by
analytic ultracentrifugation.74 Using subfractionation by
equilibrium density ultracentrifugation, others have also
reported that a high WHR ratio was associated with heavy
and dense LDL, as compared to subjects with low
WHR.127 Whether these compositional changes are pref-
erentially associated with deep or subcutaneous abdom-
inal fat is presently not clear. On the other hand, subcu-
taneous trunk fat accumulation was shown to be
negatively correlated with the large LDL mass, and this
association was independent from the level of obesity
and from the WHR.74 These results suggest that subcu-
taneous abdominal-trunk fat accumulation may be asso-
ciated with LDL compositional changes. Although the
data suggest an independent association between trunk
fat and LDL metabolism, further research is warranted.

The other subgroup of abdominal-obese individuals
would include obese subjects with high levels of deep
abdominal fat (visceral obesity). This condition is asso-
ciated with further insulin resistance probably of he-
patic origin, leading to glucose intolerance, and with the
proper genetic susceptibility, to noninsulin-dependent
diabetes mellitus (NIDDM). H-TGL activity is also
increased, leading to further reduction in plasma HDL
cholesterol levels.

Obese subjects with gluteal-femoral or peripheral fat
accumulation do not show substantial changes in their
CVD risk profile and in their death rate. These individuals
are, however, prone to varicose veins and exhibit the
orthopedic problems commonly associated with excess
body weight. It is proposed that the risk of CVD in
gluteal-femoral-obese individuals is only moderately dif-
f erent from that in nonobese subjects, whereas CVD risk
increases in trunk-abdominal-obese individuals and
would be the highest in the subgroup of abdominal-
obese subjects with high levels of deep abdominal fat.
From the literature available, there is little doubt that
subjects with visceral obesity represent the subgroup of
obese individuals with the highest risk for CVD. Obese
subjects with both high levels of trunk-abdominal fat and
high levels of deep abdominal fat will also be found.
These obese subjects should presumably be at greater
risk for CVD than obese subjects with visceral obesity
only.

In our opinion, this working classification of obesities is
supported by a reasonable body of data. The metabolic
correlates of each obesity subtype reviewed in this article,
especially for plasma lipoprotein metabolism and plasma
lipid transport, clearly warrant additional clinical and
experimental research. This field has, however, the
potential to provide better answers to an old and difficult
problem, namely the role of obesity in the etiology of
dyslipoproteinemias. Further progress in this area will
require the use of proper body fatness and fat distribution
variables for the assessment of the various obesity com-
ponents and for the proper classification of the metabolic
correlates of obesity.

Adipose Tissue Distribution and
Dyslipoproteinemia. Relevance of Genetic
Variation to Metabolic Heterogeneity of
Abdominal Obesity

Although significant associations have consistently
been found between the regional distribution of AT and
changes in plasma lipid transport, the various metabolic
profiles measured in abdominal-obese subjects suggest
the presence of a metabolic heterogeneity among these
individuals. A good example of this situation is provided
by NIDDM; this issue has been extensively reviewed by
Kasebah and co-workers.15,16,17 Indeed, although these
investigators have shown that a high proportion of
abdominal fat is associated with disturbances in glucose
homeostasis, insulin resistance, and hyperinsulinemia,
not every abdominal-obese person showing these meta-
bolic complications will become diabetic. These observa-
tions suggest that the genetic susceptibility to NIDDM is
an important component of the fat distribution–NIDDM
association.15,16,17 Unsuppressed hepatic glucose pro-
duction and decreased pancreatic insulin secretory
capacity have been proposed as two important sites in
the genetic control of the susceptibility to NIDDM in
subjects with abdominal obesity.

Regarding plasma lipid transport and plasma lipopro-
tein levels, variation in "candidate genes" relevant
to lipoprotein metabolism (e.g., genes coding for LPL,
H-TGL, lipoprotein receptors, and apoproteins129) could
potentially alter the relation of AT distribution to plasma
lipoproteins. Since apoprotein E polymorphism is known
to affect plasma lipoprotein metabolism (for a review, see reference 130), we have used this approach to study the associations between obesity, AT distribution, and plasma lipoprotein levels in three groups of women defined on the basis of their apo E phenotypes.131 Our results indicated that the associations typically observed between total body fat, AT distribution, and plasma lipoproteins were altered in the subgroups of women carrying either the apo E2 or the apo E4 isoprotein (Table 7). In women with the apo E2 isoprotein, which has been shown to have a lower affinity for the apo E and B,E receptors than the apo E4 isoprotein, body fatness variables were significantly correlated with plasma VLDL cholesterol levels, whereas in contrast, no relationship was found between total body fat, the level of deep abdominal fat, and LDL cholesterol levels (Table 7).

In the apo E4 group, obesity was not significantly correlated with the level of plasma VLDL cholesterol, whereas a high level of deep abdominal fat was positively correlated with plasma LDL cholesterol levels. The mechanisms by which lipoprotein metabolism is related to the apo E polymorphism have been previously discussed in this journal, and the reader is referred to the comprehensive review of Davignon et al.130 Figure 1 illustrates the effects of the increased hepatic VLDL synthesis observed in abdominal obese subjects on plasma VLDL and LDL metabolism in relation to apo E2 and apo E4 phenotypes.

Thus, in abdominal-obese women, subjects carrying the apo E2 isoprotein showed no increase in plasma cholesterol or LDL cholesterol levels, but higher plasma VLDL cholesterol concentrations. Abdominal-obese women in the E4 group had higher levels of plasma cholesterol and LDL cholesterol, but showed no increase in plasma VLDL levels.

This study provides the first indication that a variation in genes relevant to lipoprotein metabolism may substantially alter the association between obesity, regional AT distribution, and plasma lipoprotein levels. We therefore propose that obesity and abdominal-visceral fat accumulation are conditions that may exacerbate the disturbances in lipoprotein metabolism and plasma lipid transport. We believe that the analogy with the genetic susceptibility to NIDDM in abdominal obesity is relevant to the issue of the susceptibility to dyslipoproteinemia and CVD in abdominal obesity. This topic is challenging and promising, and additional studies are clearly warranted for a further understanding of the interactions between fat distribution, genes relevant to lipoprotein metabolism, and plasma lipid transport.

Conclusions

From this review, it is likely that the strong independent effect of body fat distribution on CVD can be explained by the hormonal and metabolic disturbances observed in abdominal obesity. In addition to the independent effects of insulin resistance and diabetes, of the altered plasma lipoprotein-lipid profile, and of hypertension on CVD, it should be emphasized that several of these metabolic complications will often be simultaneously observed in subjects with abdominal obesity. Therefore, the interac-
tion of these risk factors could markedly increase the probability of a cardiovascular accident in these individuals. Results from CT indicate that intra-abdominal fat accumulation is a critical variable in the study of the relation of body fat distribution to metabolic complications. As there are marked gender differences in regional body fat distribution, sex steroids are likely candidates for an important role in the determination of individual differences in body fat distribution and related metabolism.

Issues that will require further investigation include 1) the role of regional variation in AT metabolism, 2) the mechanisms involved in the lipoprotein compositional changes associated with high plasma TG levels in abdominal obesity, 3) lipoprotein turnover studies in relation to body fat distribution, 4) the role of sex steroids and glucocorticoids in the regulation of fat distribution and lipoprotein metabolism, and in lipoprotein metabolism per se. Additional research on the genetic and nongenetic determinants of body fat distribution and on the proper measurement of fat topography is also warranted.

Finally, the study of genetic variation in apolipoprotein, enzymes and receptor genes involved in lipoprotein metabolism could contribute to a better understanding of the metabolic heterogeneity of abdominal obesity. Studies should be undertaken to clarify the potential relationship between DNA variation for these genes and the lipoprotein phenotypes with proper controls over obesity and regional fat distribution. It is likely that DNA polymorphism will contribute to individual differences in the sensitivity of lipoprotein metabolism and other processes involved in the development of atherosclerosis in the presence of an excessive accumulation of abdominal fat. This area of research represents an important challenge to those of us involved in the body fat distribution—CVD issue.

Acknowledgments

Thanks are expressed to the subjects and to the dedicated staff of the Physical Activity Sciences Laboratory for their excellent cooperation. The authors express their gratitude to Judith Leblanc for their help at various stages of the studies. We also acknowledge the assistance of the Physical Activity Sciences Laboratory for their excellent assistance in data collection. The excellent assistance of the Lipid Research Center and the Diabetes Research Unit staff is also acknowledged.

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Index Terms: obesity • body fat distribution • deep abdominal fat • lipoprotein metabolism • lipoprotein lipase • hepatic lipase • sex steroids • glucocorticoids • high density lipoproteins • adipose tissue metabolism

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Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease.

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doi: 10.1161/01.ATV.10.4.497

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