Regional Distribution of Body Fat, Plasma Lipoproteins, and Cardiovascular Disease

Jean-Pierre Després, Sital Moorjani, Paul J. Lupien, Angelo Tremblay, André Nadeau, and Claude Bouchard

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 lipid transport is a significant component of the relation between body fat distribution and CVD. (Arteriosclerosis 10:497-511, July/August 1990)

There is much scientific evidence to warrant that the regional distribution of body fat is an important consideration in the relationship between obesity, metabolism, and health. Although recent evidence from several prospective studies has demonstrated significant associations between regional body fat distribution and cardiovascular disease (CVD) and related mortality, the mechanisms responsible for this relationship have yet to be established. Numerous reports in the literature have confirmed the early clinical observations of Vague and have shown that the topography of adipose tissue (AT) was associated with metabolic complications that are considered to be risk factors for cardiovascular disease (insulin resistance, hyperinsulinemia and diabetes, hypertension, and changes in the concentration of plasma lipids and lipoproteins). Recently, three symposia have been entirely devoted to the clinical and metabolic aspects of body fat distribution, and the proceedings of these meetings have been published. In September 1989, the National Institutes of Health (U.S.A.) organized a workshop in Bethesda, Maryland, addressing the issue of body fat distribution and its clinical implications. These meetings undoubtedly reflect the increasing interest of the scientific community in the regional distribution of body fat as a significant biological phenomenon with important metabolic consequences and health implications. The aim of this review is to briefly summarize the current data on the metabolic correlates of body fat distribution and to review some potential mechanisms for the association between body fat distribution and metabolic complications, with an emphasis on lipoprotein metabolism.

Relation of Regional Body Fat Distribution to Metabolism

In the 1940s, Professor Jean Vague of the University of Marseille presented clinical observations suggesting that the topography of AT was an important variable in the relation of obesity to diseases. He suggested that lower-body obesity (gynoid) had rather minor effects on health, whereas upper-body obesity (android) was associated...
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{1-5} 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{19} 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{46} 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 had 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{76} 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 fat 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...
Table 1. Correlation Coefficients between Body Fat Mass, Waist-to-Hip Ratio, Abdominal Fat Areas, and Metabolic Variables

<table>
<thead>
<tr>
<th>Variable</th>
<th>Fat mass</th>
<th>Waist-to-hip ratio</th>
<th>Abdominal fat*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipoproteins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VLDL TG (log 10)</td>
<td>0.05</td>
<td>0.47‡</td>
<td>0.06</td>
</tr>
<tr>
<td>LDL CHOL</td>
<td>0.10</td>
<td>0.10</td>
<td>0.07</td>
</tr>
<tr>
<td>LDL apo B</td>
<td>0.10</td>
<td>0.27</td>
<td>0.11</td>
</tr>
<tr>
<td>HDL CHOL</td>
<td>-0.25</td>
<td>-0.47‡</td>
<td>-0.22</td>
</tr>
<tr>
<td>HDL₄ CHOL</td>
<td>-0.25</td>
<td>-0.43†</td>
<td>-0.22</td>
</tr>
<tr>
<td>HDL₅ CHOL</td>
<td>-0.20</td>
<td>-0.44†</td>
<td>-0.17</td>
</tr>
<tr>
<td>Lipoprotein ratios</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDL CHOL/LDL CHOL</td>
<td>-0.24</td>
<td>-0.34*</td>
<td>-0.19</td>
</tr>
<tr>
<td>LDL A-I/LDL B</td>
<td>-0.21</td>
<td>-0.33*</td>
<td>0.16</td>
</tr>
<tr>
<td>HDL₄ CHOL/HDL₃ CHOL</td>
<td>-0.19</td>
<td>-0.24</td>
<td>-0.17</td>
</tr>
<tr>
<td>LDL B/LDL CHOL</td>
<td>-0.04</td>
<td>0.35†</td>
<td>0.06</td>
</tr>
<tr>
<td>Glucose tolerance test</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glucose area</td>
<td>0.41†</td>
<td>0.44‡</td>
<td>0.16</td>
</tr>
<tr>
<td>Insulin area</td>
<td>0.47‡</td>
<td>0.25</td>
<td>0.44‡</td>
</tr>
<tr>
<td>C-peptide area</td>
<td>0.42†</td>
<td>0.34†</td>
<td>0.29*</td>
</tr>
</tbody>
</table>

Abdominal fat was measured by computed tomography in 52 obese premenopausal women. *p<0.05, †p<0.01, ‡p<0.001, §p<0.0001.

This table was adapted from references 33 and 76.

VLDL=very low density lipoprotein, TG=triglycerides, LDL=low density lipoprotein, apo=apolipoprotein, HDL=high density lipoprotein.

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 fat and H-TGL 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 HDL₄ cholesterol/HDL₅ cholesterol ratio (r=0.51, p<0.05; result not shown in Table 2). H-TGL activity was negatively correlated with HDL₄ cholesterol (r=-0.60, p<0.05), but not with HDL₅ 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 HDL₄ 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...
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. 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. Indeed, obese women had significantly higher plasma levels of very low density lipoprotein (VLDL)-TG, LDL cholesterol, LDL-TG, LDL apo lipoprotein (apo) B, and reduced HDL cholesterol levels compared to nonobese controls (p < 0.01). However, plasma concentrations of LDL apo A-I and HDL-TG were not different between obese and nonobese women. 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/LDL cholesterol ratio (r = 0.38, p < 0.01). 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.

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. 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. 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. Indeed, many patients with coronary heart disease have high concentrations of smaller and denser LDL particles that contained less cholesterol than normal. Furthermore, as hypertriglyceridemic LDL contains less cholesterol, cellular cholesterol synthesis is inhibited to a lesser extent by dense LDL. 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. Such cholesterol transported by VLDL may be cleared from the plasma by potentially atherogenic routes such as macrophages and smooth muscle cells.

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. 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
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. 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 glycemia could mediate the association between abdominal fat accumulation and TG levels, but that the relation of fat distribution to HDL and HDL2 cholesterol levels was independent from variations in plasma glucose and insulin concentrations.

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.

Table 4. Correlations between Plasma VLDL Triglyceride Concentration and Plasma Lipoprotein Levels and Lipid Composition without and with Adjustment for Fat Mass or for Waist-to-Hip Ratio

<table>
<thead>
<tr>
<th>Variable</th>
<th>Full correlations</th>
<th>Partial correlations (adjusted for fat mass)</th>
<th>Partial correlations (adjusted for WHR)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VLDL TG</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL CHOL</td>
<td>0.34t</td>
<td>0.11</td>
<td>0.16</td>
</tr>
<tr>
<td>LDL TG</td>
<td>0.68t</td>
<td>0.54t</td>
<td>0.59‡</td>
</tr>
<tr>
<td>LDL apo B</td>
<td>0.45t</td>
<td>0.32t</td>
<td>0.29†</td>
</tr>
<tr>
<td>LDL apo B/LDL CHOL</td>
<td>0.32t</td>
<td>0.49t</td>
<td>0.33†</td>
</tr>
<tr>
<td>LDL CHOL/LDL TG</td>
<td>-0.45t</td>
<td>-0.30*</td>
<td>-0.36†</td>
</tr>
<tr>
<td>HDL CHOL</td>
<td>-0.59t</td>
<td>-0.48t</td>
<td>-0.47‡</td>
</tr>
<tr>
<td>HDL TG</td>
<td>0.35†</td>
<td>0.46†</td>
<td>0.33†</td>
</tr>
<tr>
<td>HDL apo A-I</td>
<td>-0.15</td>
<td>-0.07</td>
<td>-0.03</td>
</tr>
<tr>
<td>HDL apo A-I/HDL CHOL</td>
<td>0.58t</td>
<td>0.51†</td>
<td>0.51‡</td>
</tr>
<tr>
<td>HDL CHOL/HDL TG</td>
<td>-0.59t</td>
<td>-0.56†</td>
<td>-0.47‡</td>
</tr>
</tbody>
</table>

A sample of 76 premenopausal women was studied.

From reference 65, reproduced with the permission of Clinical and Investigative Medicine.

*p<0.05, †p<0.01; ‡p<0.001.
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\(^\text{13,21,97,98}\) 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.\(^\text{97}\) Although a high androgenic activity was associated with both an increased deposition of abdominal fat and a decreased insulin sensitivity, 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.\(^\text{21}\) 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.\(^\text{21}\) Recent results have indicated that the systemic hyperinsulinemia associated with abdominal obesity was partly attributed to a reduced hepatic extraction of insulin.\(^\text{98}\) 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.\(^\text{98}\) 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.
through a mechanism partly independent from variations in sex hormone levels.\(^{26}\)

Numerous studies have also shown that sex steroids have significant effects on lipoprotein metabolism.\(^{42}\) In a sample of 73 healthy men, Stefanick et al.\(^{26}\) 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 HDL\(_2\) 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, HDL\(_2\) 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 after lipoprotein metabolism through additional mechanisms. As indicated in a recent review,\(^{82}\) sex steroids produce changes in plasma HDL\(_2\) cholesterol concentration by up- or down-regulating the H-TGL activity, as steroids with androgenic activity increase H-TGL activity and reduce plasma HDL\(_2\) cholesterol levels. Administration of an androgenic steroid, stanozolol, was associated with an increase in H-TGL activity that preceded the decrease in plasma HDL\(_2\) cholesterol levels, suggesting a cause-and-effect relationship between the enzyme and plasma HDL\(_2\) cholesterol levels.\(^{100}\) 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 HDL 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 OGTT has also been reported.\(^{102}\) The effects of glucocorticoids on lipid metabolism have been recently reviewed.\(^{104}\) Glucocorticoids stimulate hepatic VLDL secretion\(^{104-107}\) and decrease the binding and degradation of LDL by rat hepatocytes.\(^{108,109}\) The high cortisol levels frequently observed in abdominal obesity could

### 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></td>
<td>Low (n=10)</td>
</tr>
<tr>
<td>% Body fat</td>
<td>28.0±5.6</td>
<td>47.0±6.4*</td>
</tr>
<tr>
<td>Deep abdominal fat area (cm(^2))</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>LDL 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/180 min]×10(^{-7}))</td>
<td>1.07±0.19</td>
<td>1.14±0.22</td>
</tr>
<tr>
<td>Insulin area ([pmol/l/180 min]×10(^{-7}))</td>
<td>46.6±19.4</td>
<td>82.1±46.3*</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=apolipoprotein. 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, especially intra-abdominal fat cells, could stimulate hepatic TG synthesis by exposing the liver to high FFA concentrations. In addition, it has been reported that the retroperitoneal fat depot has metabolic characteristics similar to those of subcutaneous abdominal fat, whereas the adipose depots drained by the portal vein show differences in metabolic activity in comparison with the nonportal adipose depots. Additional in vitro studies are, therefore, needed to further address the issue of the role of variation in the metabolic activities of the various deep abdominal adipose depots in the etiology of the metabolic complications of visceral obesity. Direct experimental evidence for this highly plausible model is, however, lacking. In vivo studies that we have conducted have shown that fasting plasma FFA levels measured in the morning were significant correlates of glucose tolerance and of VLDL-TG content. An obvious limitation of these studies is that systemic, rather than portal, plasma FFA levels were measured. We have also observed that the lipolytic response of subcutaneous abdominal fat cells to β-adrenergic stimulation was positively correlated with plasma insulin and TG levels, suggesting that abdominal adipose cell lipolysis may be etiologically involved in the metabolic complications of abdominal obesity. No data are, however, available on the potential associations between omental fat cell lipolysis and in vivo carbohydrate and lipid metabolism. In addition, human fat cells specifically bind HDL, and regional variation in HDL binding to human adipose cells has been reported. Furthermore, the HDL binding to isolated human abdominal adipose cells is proportionate to fat cell size, and it is increased in obesity. It has also been reported that the binding of HDL to the fat cell plasma membrane leads to a disproportionate uptake of HDL cholesterol ester by the hypertrophied adipose cell. Such a high uptake of cholesterol ester by large abdominal fat cells may contribute to the reduction in plasma HDL cholesterol levels observed in abdominal obesity. No information is, however, available on the cellular HDL metabolism of femoral adipose cells, and further studies are needed to address the role of the regional variation in adipose cell HDL metabolism in the reduction in plasma HDL cholesterol levels observed in abdominal obesity. Weight loss has, however, reportedly decreased HDL binding to abdominal 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 HDL₄ cholesterol/HDL₃ 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 individuals, and 2) abdominal-obese individuals. However, it has been recently suggested that abdominal-obese individuals may be further divided into two subgroups displaying different metabolic profiles that may be suggestive of variable risks of CVD.\(^{10,127}\) Gluteal-femoral obesity is characterized by mild insulin resistance, hyperinsulinemia, 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 truncal-abdominal fat (trunk-abdominal obesity). Evidence for a role of upper-trunk fat per se in the metabolic complications associated with body fat distribution is primarily derived from studies that have shown a significant relationship 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.\(^{128}\) Whether these compositional changes are preferentially associated with deep or subcutaneous abdominal fat is presently not clear. On the other hand, subcutaneous truncal fat accumulation was shown to be negatively correlated with the large LDL mass, and this association was independent of the WHR.\(^{74}\) These results suggest that subcutaneous abdominal-truncal fat accumulation may be associated with LDL compositional changes. Although the data suggest an independent association between truncal 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 associated with further insulin resistance probably of hepatic 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 different from that in non obese subjects, whereas CVD risk increases in truncal-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 obesity 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 components 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 metabolic complications will become diabetic. These observations suggest that the genetic susceptibility to NIDDM is an important component of the fat distribution–NIDDM association.\(^{15,16,17}\) Unsuppressed hepatic glucose production 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 lipoprotein levels, variation in "candidate genes" relevant to lipoprotein metabolism (e.g., genes coding for LPL, H-TGL, lipoprotein receptors, and apoproteins\(^{120}\) 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. 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. 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.

Table 7. Correlations between Body Fat Mass, Deep Abdominal Fat Deposition, and Plasma VLDL Cholesterol and LDL Cholesterol in Women with the Apo E2 or the Apo E4 Isoprotein

<table>
<thead>
<tr>
<th>Variable</th>
<th>Apo E2 (n=22)</th>
<th>Apo E4 (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Deep abdominal fat mass</td>
<td>Deep abdominal fat mass</td>
</tr>
<tr>
<td>VLDL cholesterol</td>
<td>0.571</td>
<td>0.10</td>
</tr>
<tr>
<td>LDL cholesterol</td>
<td>0.09</td>
<td>0.16</td>
</tr>
</tbody>
</table>

*p<0.05, t p<0.01.

This table was adapted from reference 131.

VLDL=very low density lipoprotein, LDL=low density lipoprotein, apo=apolipoprotein.

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

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REGIONAL BODY FAT DISTRIBUTION AND LIPOPROTEINS  

Index Terms: obesity • body fat distribution • deep abdominal fat • lipoprotein metabolism • lipoprotein lipase • hepatic lipase • sex steroids • glucocorticoids • adipose tissue metabolism
Regional distribution of body fat, plasma lipoproteins, and cardiovascular disease.
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