PATHOPHYSIOLOGY OF HUMAN VISCERAL OBESITY: AN UPDATE

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Tchernof A, Després J-P. Pathophysiology of Human Visceral Obesity: An Update. Physiol Rev 93: 359–404, 2013; doi:10.1152/physrev.00033.2011.—Excess intra-abdominal adipose tissue accumulation, often termed visceral obesity, is part of a phenotype including dysfunctional subcutaneous adipose tissue expansion and ectopic triglyceride storage closely related to clustering cardiometabolic risk factors. Hypertriglyceridemia; increased free fatty acid availability; adipose tissue release of proinflammatory cytokines; liver insulin resistance and inflammation; increased liver VLDL synthesis and secretion; reduced clearance of triglyceride-rich lipoproteins; presence of small, dense LDL particles; and reduced HDL cholesterol levels are among the many metabolic alterations closely related to this condition. Age, gender, genetics, and ethnicity are broad etiological factors contributing to variation in visceral adipose tissue accumulation. Specific mechanisms responsible for proportionally increased visceral fat storage when facing positive energy balance and weight gain may involve sex hormones, local cortisol production in abdominal adipose tissues, endocannabinoids, growth hormone, and dietary fructose. Physiological characteristics of abdominal adipose tissues such as adipocyte size and number, lipolytic responsiveness, lipid storage capacity, and inflammatory cytokine production are significant correlates and even possible determinants of the increased cardiometabolic risk associated with visceral obesity. Thiazolidinediones, estrogen replacement in postmenopausal women, and testosterone replacement in androgen-deficient men have been shown to favorably modulate body fat distribution and cardiometabolic risk to various degrees. However, some of these therapies must now be considered in the context of their serious side effects. Lifestyle interventions leading to weight loss generally induce preferential mobilization of visceral fat. In clinical practice, measuring waist circumference in addition to the body mass index could be helpful for the identification and management of a subgroup of overweight or obese patients at high cardiometabolic risk.

I. INTRODUCTION

Numerous excellent scientific review papers and academic books have been published on the causes, health consequences, and pathophysiological aspects of obesity (67, 145, 211, 244, 266, 438, 579). A phenomenon that has received increasing attention is the fact that body shape, and more specifically the regional distribution of adipose tissue, is at least as important, if not more important, than the total amount of body fat in predicting disease-causing complications that have been traditionally associated with obesity. Literature on regional adipose tissue distribution and metabolism has flourished over the past 25 years, establishing beyond any doubt that the proportion of abdominal adipose tissue is a key correlate and perhaps driver of the health risk associated with overweight and obesity. Visceral obesity has now been established as being part of a complex phenotype including adipose tissue storage dysfunction and ectopic triglyceride accumulation in several sites including the liver (106). Such robust evidence has also been previously detailed in several review papers on body fat topography published over the last 20 years (48, 71, 72, 112, 113, 234, 263, 357, 360).

The objective of the present review paper is, therefore, not to replace these previous excellent review articles on the topic but rather to hopefully update them with a complementary angle and perspective. Our objective is to provide the reader with a comprehensive overview of the literature
relevant to regional adipose tissue morphology and physiology in terms of causes and health consequences.

II. EPIDEMIOLOGICAL AND METABOLIC ASPECTS OF REGIONAL BODY FAT DISTRIBUTION

A. Heterogeneity of Obesity: Importance of Body Fat Distribution

Every week a national newspaper somewhere around the globe publishes an article that has something to do with obesity, its prevalence, and the risk it carries for the health of our nations. As a consequence, the lay public is constantly exposed to the following messages: 1) obesity, or excess of body fat, is a major health issue and a risk factor for the development of numerous chronic diseases; and 2) the excess body fat that an increasing proportion of us carry is the consequence of our modern, comfortable lifestyle: we eat too much for the little energy that we expend. The energy balance equation is, at first glance, so simple that it may be difficult to understand why we have failed to solve this problem. After all, as we went to the moon 40 years ago, obesity should not be such a difficult public health issue. We should have begun to see favorable trends in its prevalence. Unfortunately, available data indicate that the epidemic is still growing, and the worldwide high prevalence of obesity denounced several years ago is not receding (151). This phenomenon is particularly worrisome for large emergent economies such as Asia, Southeast Asia, and Latin America (151). Obesity is no longer the concern of the occidental world, and the entire “global village” is now afflicted by this critical public health issue.

Obesity is defined by an excess of body fat. In clinical practice, it has been commonly assessed by expressing body weight as a function of height, the most frequently used index being the body mass index (BMI) calculated as weight in kilograms divided by height in meter squared (256). Numerous studies have shown that there is a J-shaped relationship between the BMI and morbidity/mortality risk (37, 343, 618, 637). Thus a very low BMI is associated with increased mortality, even after considering the fact that it may be a marker of underlying morbid conditions (for instance, cancers and other chronic conditions such as chronic obstructive pulmonary disease). On the other side of the spectrum, there is a progressive increase in the risk of comorbidities such as hypertension, dyslipidemia, type 2 diabetes, cardiovascular disease (CVD), gallstones, and cancers associated with an increase in BMI (76, 86, 620, 627). Population studies have clearly established the link between obesity defined by the BMI and comorbidities/mortality risk, and several organizations use categories of BMI to define underweight, normal weight, overweight, and various classes of obesity (TABLE 1) (2, 3).

Although the BMI is an adequate tool to report secular trends in the prevalence of obesity at the population level (256), its limitations have left health professionals at times puzzled by the fact that obesity is quite a heterogeneous condition. Overweight or obese subjects as a group are clearly at greater risk for comorbid conditions compared with normal-weight individuals, but physicians have been perplexed by the fact that while some obese patients clearly show complications associated with their excess of body fat, some other equally obese patients do not display expected metabolic abnormalities despite their significant excess of body fat (619). In other words, obesity does increase the likelihood of presenting complications, but not every individual obese will develop them. By using the BMI, one must rely on the assumption that adipose tissue is distributed evenly over the body (66), which does not take into account the heterogeneity of regional body fat deposition (114). As mentioned, this factor has been identified as an important correlate of metabolic disturbances leading to CVD (264). In this regard, several studies relating BMI to CVD outcomes in healthy individuals have reported inconsistent results. Some studies have found a linear relationship between BMI and cardiovascular risk, whereas others have failed to find a significant association (294, 298, 540, 608, 625). Most studies on this issue, however, have failed to consider regional body fat distribution.

A striking example of the limitations of the BMI relates to the metabolically obese, normal-weight (MONW) subject, a concept originally introduced by Ruderman et al. (482, 483). These MONW individuals, who have normal BMI values, nonetheless suffer from metabolic complications commonly found in obese people. The notion of MONW subjects has also been documented by St-Onge et al. (531). Conversely, metabolically healthy obese (MHO) individuals described by other research groups have a BMI above 30 kg/m² but are not characterized by insulin resistance or

<table>
<thead>
<tr>
<th>Classification</th>
<th>Body Mass Index Category, kg/m²</th>
<th>Risk of Developing Health Problems</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>Increased</td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5–24.9</td>
<td>Least</td>
</tr>
<tr>
<td>Overweight</td>
<td>25.0–29.9</td>
<td>Increased</td>
</tr>
<tr>
<td>Obese</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>30.0–34.9</td>
<td>High</td>
</tr>
<tr>
<td>Class II</td>
<td>35.0–39.9</td>
<td>Very high</td>
</tr>
<tr>
<td>Class III</td>
<td>≥40.0</td>
<td>Extremely high</td>
</tr>
</tbody>
</table>

For persons 65 yr and older, the “normal” range may begin slightly above body mass index 18.5 kg/m² and extend into the “overweight” range. Table can be used for adults aged 18 yr and older; not for use in pregnant and lactating women. Lower cut-offs for overweight (23.0 kg/m²) and obesity (27.5 kg/m²) have been proposed for the Asian population.

Table 1. Health risk classification according to body mass index
dyslipidemia (59, 148, 247). These observations suggest that high CVD risk may be observed even below the normal BMI cut-off of 25 kg/m². A key factor underpinning the difference in CVD risk between MONW and MHO individuals is the likely presence of excess visceral adipose tissue (116, 170, 524). Most MONW individuals with relatively low BMI likely have a significant excess visceral adipose tissue, and most MHO individuals with a high BMI likely have much less visceral adipose tissue (481). Similarly, Matsuzawa et al. (359) have demonstrated that very obese individuals with a small amount of visceral adiposity, active sumo wrestlers, for example, are quite insulin sensitive, whereas retired sedentary sumo wrestlers with greater amounts of visceral adipose tissue tend to be insulin resistant, dyslipidemic, and have a high prevalence of metabolic complications such as type 2 diabetes and CVD.

As reviewed here, clinical observations reported more than half a century ago combined with work reported in the early 1980s and later have shown that when the time comes to evaluate the risk associated with obesity in an individual patient, body shape must be evaluated as it is a key driver of the disease risk associated with any given amount of body fat. The following section will provide a brief historical perspective on the issue of body fat distribution.

### B. Historical Perspective

In 1947, Professor Jean Vague, a French physician from the University of Marseille, reported for the first time in a French medical journal clinical observations that patients with hypertension, CVD, gout, and diabetes were not necessarily more obese than patients without these complications (576). Despite not having access to sophisticated investigative tools, Vague identified two different body shapes representing both ends of a spectrum. He coined the term *android obesity* to refer to adipose tissue accumulated preferentially in the trunk/upper body area and suggested that this was a form of obesity closely associated with diabetes and heart disease (576). He also proposed the term *gynoid obesity* to refer to preferential adipose tissue accumulation in the hips and thighs, typically described as female obesity, a form much less associated with complications. Android and gynoid obesities have also commonly been referred to as “apple and pear shape” obesities, respectively, by the lay press. Vague later summarized his work in the English scientific literature in a paper which was initially received with skepticism by the medical community (575). Decades later, his seminal early contribution is now finally recognized, as hundreds of studies now support the notion that body fat topography is an important correlate of cardiometabolic health.

In the early 1980s, Per Björntorp, Marcin Krotkiewski, Lars Sjöström, and Ulf Smith from the University of Gothenburg reported in a landmark paper that adipose tissue morphol-ogy, body shape, and the regional accumulation of body fat were key factors related to metabolic complications (276). In 1984, the Gothenburg group also reported results of a prospective study conducted in middle-aged men and women in whom the ratio of abdominal waist over hip circumferences (WHR) was used as a simple index of body fat distribution (294, 298). They reported that an increased abdominal waistline relative to hip girth was predictive of a higher risk of coronary heart disease (CHD) (294, 298). One year later, they also reported in the same prospective study that men with a high proportion of abdominal fat were characterized by a markedly increased risk for the development of diabetes (403). By publishing these observations in the early 1980s, Björntorp and his colleagues sparked the interest of the scientific and medical community for body fat distribution as a clinically relevant phenotype. The mid 1980s should therefore be considered as a “renaissance” period during which regional adipose tissue distribution truly became the focus of interest of several obesity scientists.

For instance, during this period, Ahmed Kissébah and his team from the University of Wisconsin in Milwaukee published several papers (261, 262, 264, 265, 426) that were fully in line with the observations of the Gothenburg group in showing that the proportion of abdominal adipose tissue, crudely estimated by the WHR, was predictive of metabolic abnormalities increasing the risk of both type 2 diabetes and CVD. By 1985, these two groups were conceptually leading the field of obesity on the international scene by providing early evidence that body fat distribution assessed by anthropometry was a critical predictor of metabolic abnormalities. Such early evidence was received with considerable interest, and numerous studies were launched during that period to explore further the contribution of regional adiposity to metabolism and related risk.

The development of imaging technologies such as computed tomography (CT) and magnetic resonance imaging (MRI) has allowed remarkable advances in the field of body composition/adipose tissue distribution. With CT, on the basis of the specific range of attenuation values associated with adipose, muscle, and bone tissues, it became possible to scan the whole or specific parts of the body and to generate cross-sectional images where one could clearly distinguish the three tissues and calculate their respective cross-sectional areas (147, 516, 567). When they used CT for the first time for this specific purpose, investigators from the Department of Internal Medicine at the University of Osaka developed a method where the body was segmented into cylinders allowing accurate measurement of total and regional adipose tissue volumes (567). Furthermore, by scanning the abdomen, these investigators showed for the first time that it was possible to dissociate adipose tissue located in the abdominal cavity, the so-called intra-abdominal or visceral adipose tissue, from the abdominal adipose tissue...
located subcutaneously (567). Being able to measure selectively and precisely cross-sectional areas of abdominal visceral and subcutaneous adipose tissue was a remarkable advance that would revolutionize the field of body composition. For instance, CT would allow the exploration of the specific relationships between selective adipose tissue compartments and various health outcomes. Almost at the same time, Sjöström and his team (516) also documented that CT could indeed provide excellent measures of body composition and of regional adipose tissue distribution. Such early methodological work paved the way for the use of this imaging technology to precisely measure regional adipose tissue distribution and its relationship to various comorbidities.

With the use of CT, Fujioka et al. (170) were the first in 1987 to provide evidence that a preferential accumulation of visceral adipose tissue could possibly explain the deterioration in glucose and lipid metabolism observed in obese patients. They reported that subjects with large amounts of visceral adipose tissue had higher fasting plasma triglyceride levels and higher plasma glucose responses following an oral glucose challenge than subjects who had the same BMI but a preferential accumulation of abdominal subcutaneous adipose tissue. However, as the sample was quite heterogeneous, these early findings had to be confirmed by additional studies. We (115, 116, 444) later quantified the respective contributions of subcutaneous and visceral abdominal adipose tissue. However, as the sample was quite heterogeneous, these early findings had to be confirmed by additional studies. We (115, 116, 444) later quantified the respective contributions of subcutaneous and visceral abdominal adipose tissue to dyslipidemia, glucose intolerance, and hyperinsulinemia in obese men and women. For that purpose, two groups of obese patients were carefully matched for the same amount of total body fat but with either low or high amounts of visceral adipose tissue. In both men and women, we found that obese individuals with low levels of visceral adipose tissue had normal glucose tolerance compared with lean controls (115, 444). However, obese subjects with high levels of visceral adipose tissue showed an increase in their glycemic and insulinemic responses to an oral glucose challenge, suggesting that they defined the subgroups truly at high risk of developing type 2 diabetes. Using the same analytical approach, Ross and co-workers (471, 474) further explored the relationships between abdominal subcutaneous and visceral adiposity measured by MRI and metabolic risk in men and women. When individuals who were carefully matched for similar abdominal subcutaneous adipose tissue but with different levels of visceral adipose tissue were compared, subjects with high levels of visceral adipose tissue were found to have higher glucose values following an oral glucose tolerance test and lower glucose disposal rates measured during a euglycemic–hyperinsulinemic clamp compared with subjects with low visceral adipose tissue (471, 474). These results provided additional support to the notion that obese individuals with excess visceral adipose tissue display alterations in indexes of plasma glucose-insulin homeostasis which increase their risk of developing type 2 diabetes. During the same period, Fujimoto and his group (36, 214) and Sparrow et al. (524) also provided evidence that visceral adiposity was independently associated with impaired plasma glucose homeostasis and with evidence of insulin resistance. Taken globally, such early work promoted the conduct of additional imaging body composition/metabolic studies (108, 159, 209, 229, 326, 357, 396) where not only the total quantity of body fat but also the amount of abdominal subcutaneous and visceral adipose tissue would be assessed along with the measurement of cardiometabolic risk variables.

In parallel to these studies, visceral adiposity was also found to be closely and independently related to an atherogenic dyslipidemia (115) and, later, with a proinflammatory, prothrombotic profile (80, 81, 231, 312). Visceral obesity was also found to be increased in patients with CHD compared with subjects asymptomatic for CHD (338, 391). Findings from these case/control and small longitudinal studies now suggest that excess visceral adiposity may, indeed, be predictive of increased CHD or CVD risk (338, 391). Prospective studies are underway to test this hypothesis.

C. Methodological Issues in the Measurement of Visceral Adiposity and Its Relationship With Metabolic Complications

Early work to develop CT as a tool to measure adiposity and body fat distribution had used a multiple scan approach and segmentation of parts of the body (516, 567). Because of the radiation involved, it became obvious that to use CT in large-scale cardiometabolic studies, the number of scans performed on study subjects should be limited. Most subsequent studies performed with CT have used single scan measures obtained either at L4-L5 or at the umbilicus (567), although some recent large studies have reported adipose tissue areas at two levels (68, 169). Because cross-sectional areas of visceral adipose tissue measured at various abdominal levels were found to be strongly correlated with each other (307, 411, 471, 474), it was concluded that the location of the abdominal scan does not have a major influence on the magnitude of the association found between visceral adiposity and comorbidities (471, 474). Yet, studies that have used multiple slices (which can be easily performed with MRI as there is no radiation involved) have shown that there was substantial variation in the absolute cross-sectional areas of visceral adipose tissue depending on the location of the scan (for example, from L1-L2 to L4-L5) (193, 307, 565). In this regard, one of the burning clinical questions is whether or not we could identify a cut-off value of desirable cross-sectional visceral adipose tissue area associated with optimal cardiometabolic health and another threshold value which would be predictive of increased health risk, similar to widely used cut-off BMI values. Studies have been conducted to suggest thresholds of visceral adipose tissue associated with low or pre-
sumably reduced cardiometabolic risk, but criteria for the identification of the low-risk reference group was highly variable across studies (111, 207, 228, 394, 622). Moreover, investigators have not acquired their abdominal images at the same level, not allowing proper validation across studies. To propose such cut-off risk values for visceral adiposity, it will be critical to standardize the location of the abdominal CT scan or at least to clearly identify the abdominal cross-sectional area (e.g., L2-L3 or L4-L5 or umbilicus) that was used. Although L4-L5 has been a popular location to perform the abdominal scan, it is important to point out that considerable variation exists in the literature, which does not always allow proper comparison of results across studies. For instance, in Japan, the umbilicus is often used as a reference landmark to position the abdominal scan (567), which is a different location than the L4-L5 positioning often used by other groups. Further standardization will clearly be needed to develop such normative data on visceral adiposity.

Some early studies had initially suggested that subcutaneous adiposity showed correlations with metabolic abnormalities of essentially the same magnitude as visceral adiposity (4, 190, 542). However, most studies reporting such correlations did not adjust for the concomitant variation in visceral adiposity. For instance, in a heterogeneous sample including lean and obese patients, even a simple variable such as body weight shows correlations with metabolic abnormalities which are almost as strong as for visceral fat (TABLE 2). One must keep in mind that in such a heterogeneous sample, all adiposity and weight indexes will be strongly interrelated. To sort out the specific contribution of visceral adiposity, one should rather compare individuals matched for subcutaneous adiposity and with high versus low levels of visceral adipose tissue. Conversely, individuals with similar levels of visceral adipose tissue but with high versus low levels of subcutaneous adipose tissue should also be compared. As discussed in the previous section, when such a simple analytical approach was used, a clear conclusion was reached: visceral adiposity is a better correlate of metabolic abnormalities than the amount of subcutaneous fat (112–114, 159, 471, 474).

As mentioned, measuring visceral adiposity by imaging is costly and, in the case of CT, involves radiation exposure. One important area of investigation has been the study of the relationship between anthropometry and body fat distribution. Initially, because of its early use, the WHR was a popular index, and cut-off values were even proposed to define excess abdominal adiposity in men and women (46, 443). However, it became obvious that the WHR could not reliably predict the absolute amount of visceral adipose tissue that is also related to total adiposity (114). As an example, two women with a WHR of 0.85 may have markedly different absolute amounts of visceral adipose tissue if one had a BMI of 22 kg/m² and the other of 35 kg/m². Furthermore, the change in WHR may underestimate the loss of visceral fat with weight loss if the patient lost both central and peripheral fat. Many years ago, we proposed the use of waist circumference alone as the best anthropometric correlate of the absolute amount of visceral adipose tissue (443). The advantage of waist circumference is that it allows a crude estimation of the absolute amount of visceral adipose tissue and that a reduction in waistline with weight loss is a clear sign that abdominal fat is lost. However, it also became obvious that variation in waist cannot distinguish subcutaneous from visceral adiposity (310, 314). Therefore, another marker was needed to predict visceral adiposity associated with visceral adipose tissue and that a reduction in waistline with weight loss is a clear sign that abdominal fat is lost. However, it also became obvious that variation in waist cannot distinguish subcutaneous from visceral adiposity (310, 314). Therefore, another marker was needed to predict visceral adiposity associated with a large waistline. Through a series of studies which began to be reported in 2000 (310), we first suggested that the combination of an elevated waistline along with the presence of a simple blood marker, elevated fasting triglyceride concentrations, was predictive of excess visceral adiposity. We defined this condition as “hypertriglyceridemic waist,” a simple clinical phenotype predictive of excess visceral adiposity (310, 314). For instance, whereas we found that men with both low waist and triglyceride values were at low risk of being viscerally obese (<20%), ~80% of individuals with hypertriglyceridemic waist were characterized by excess visceral adiposity and related metabolic abnormalities including elevated glucose and insulin concentrations as well as an altered blood lipid profile. To discriminate the two extreme forms (non-hypertriglyceridemic waist versus hypertriglyceridemic waist), we conducted sensitivity/specifity analyses in men and women separately and suggested cut-off values of 90 and 85 cm for

### Table 2. Relationship between adiposity indexes and metabolic variables in a sample of 270 asymptomatic middle-aged men heterogeneous for adiposity indexes (from lean to obese)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Body Weight</th>
<th>Body Mass Index</th>
<th>Waist Girth</th>
<th>Visceral Adipose Tissue</th>
<th>Subcutaneous Adipose Tissue</th>
</tr>
</thead>
<tbody>
<tr>
<td>Triglycerides</td>
<td>$r = 0.37^*$</td>
<td>$r = 0.45^*$</td>
<td>$r = 0.47^*$</td>
<td>$r = 0.44^*$</td>
<td>$r = 0.35^*$</td>
</tr>
<tr>
<td>HDL cholesterol</td>
<td>$r = -0.40^*$</td>
<td>$r = -0.45^*$</td>
<td>$r = -0.45^*$</td>
<td>$r = -0.39^*$</td>
<td>$r = -0.39^*$</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>$r = 0.52^*$</td>
<td>$r = 0.57^*$</td>
<td>$r = 0.53^*$</td>
<td>$r = 0.45^*$</td>
<td>$r = 0.50^*$</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>$r = 0.52^*$</td>
<td>$r = 0.55^*$</td>
<td>$r = 0.54^*$</td>
<td>$r = 0.46^*$</td>
<td>$r = 0.48^*$</td>
</tr>
</tbody>
</table>

HDL, high-density lipoprotein; HOMA-IR, homeostasis model assessment of insulin resistance. *$P < 0.0001$. (From Després et al., unpublished data.)
waist and of 2.0 and 1.5 mM for triglycerides for men and women, respectively (15, 51, 310, 314). It is important to point out that this algorithm has not been developed to replace a direct measurement of visceral adiposity but rather as an extremely simple tool to screen and identify at low cost individuals who may be at high risk of being visceral obese and who deserve to be further investigated.

For instance, in a recent analysis of the large EPIC-Norfolk study which involved 21,787 men and women followed for a mean period of 9.8 yr, we found that the presence of hypertriglyceridemic waist was not only associated with a markedly disturbed cardiometabolic risk profile but also with a hazard ratio for future coronary artery disease of 2.40 in men and of 3.84 in women compared with subjects without this clinical phenotype (15). A recent study conducted in type 2 diabetic patients also found that this clinical phenotype was a useful variable to discriminate for coronary artery disease in these patients (98). Again, hypertriglyceridemic waist is not meant to replace traditional risk assessment algorithms, but rather represents a simple screening approach to identify subjects likely to be characterized by excess visceral adipose tissue and related metabolic abnormalities. Along these lines, other approaches such as the lipid accumulation product (242, 243) and an equation to predict visceral adiposity based on BMI, waist, triglycerides, and HDL cholesterol (10) have also been proposed to identify high-risk, viscerally obese individuals. Further work in this area is warranted and could have major clinical and public health implications. These observations clearly indicate that use of BMI alone cannot properly identify individuals likely to have excess visceral adiposity and ectopic fat and that simple tools such as a waist circumference measurement and the assessment of fasting triglyceride levels could be helpful for the identification of a subgroup of overweight/obese patients at high cardiometabolic risk because of their pattern of body fat and ectopic fat accumulation.

III. METABOLIC ALTERATIONS AND DISEASES RELATED TO VISCERAL OBESITY

A. Insulin Resistance and Type 2 Diabetes

For more than two decades, abdominal obesity has been repeatedly associated with insulin resistance, and several seminal review papers have been published on this topic (45, 105, 263). Recently, the Insulin Resistance Atherosclerosis Study showed that waist circumference was a strong predictor of reduced peripheral insulin action in nondiabetic lean individuals (248). Wang et al. (607) also confirmed that waist circumference was a better predictor of type 2 diabetes than WHR or BMI. In a large international study involving 168,000 subjects, Balkau et al. (22) clearly showed that within any BMI category (“normal,” overweight, obese), there was a progressive increase in the prevalence of diabetes across quintiles of waist circumference. In addition, a prospective study by Boyko et al. (65) conducted among Japanese Americans followed for 6–10 yr examined the relationship between direct measurement of visceral adiposity by CT and incidence of type 2 diabetes. Excess visceral adiposity was found to precede the development of type 2 diabetes in Japanese Americans. In that study, visceral adipose tissue was predictive of type 2 diabetes independent of fasting insulin, insulin secretion, glycemia, total and regional adiposity, and family history of diabetes. This study suggested that excess visceral adiposity may be a key adiposity phenotype associated with the development of type 2 diabetes.

B. Atherogenic Dyslipidemia

The dyslipidemic state frequently observed in patients with visceral obesity is a key feature of the clustering abnormalities of the metabolic syndrome and has been extensively described in the literature (114, 115, 197, 263). It includes high levels of triglycerides, low levels of high-density lipoprotein (HDL) cholesterol, relatively normal total and low-density lipoprotein (LDL) cholesterol levels, but more LDL particles (as quantified by high apolipoprotein B levels) that are smaller and denser than normal (FIGURE 1). In abdominal obesity, HDL particles are also small in size because of the presence of hypertriglyceridemia (414). Total and LDL cholesterol levels are generally within the normal range unless unrelated abnormalities are present (107, 114, 556). In a typical clinical setting, hypertriglyceridemia and low HDL cholesterol will, therefore, be the two major detectable blood abnormalities associated with visceral obesity.

As mentioned, the increased proportion of small, dense LDL and HDL particles is an important aspect of the dyslipidemic state frequently seen in visceral obese patients (FIGURE 1) (414, 556). This phenomenon is due to the remodeling of these lipoproteins in the circulation by enzymes such as cholesteryl ester transfer protein and hepatic triglyceride lipase (545, 546). Lipid exchanges by cholesteryl ester transfer protein have been shown to be largely driven by the concentration of triglyceride-donor lipoproteins (135). Thus in the presence of hypertriglyceridemia, increased concentration of large VLDL particles promotes the transfer of triglyceride molecules to LDL and HDL in exchange for cholesteryl ester molecules. As a consequence, both triglyceride-enriched LDL and HDL particles of viscerally obese patients become good substrates for hepatic triglyceride lipase, leading to the depletion of the lipid core of these lipoproteins, thereby forming small, dense LDL and HDL particles. Smaller HDL have reduced cholesteryl ester core content and become more sensitive to degradation and increased clearance from the blood. This phenomenon partly explains the low HDL cholesterol levels frequently found in individuals with visceral obesity (292).
Each component of the atherogenic dyslipidemia described could contribute, with many other factors, to the development of atherosclerosis. Hypertriglyceridemia per se has been proposed as an independent risk factor for atherosclerosis (i.e., risk unrelated to its impact on LDL and HDL remodeling), but this issue remains debated (16, 223, 635). Remnants of triglyceride-rich lipoproteins, which are elevated in hypertriglyceridemic states, are highly atherogenic, probably as much as small, dense LDL (545, 594).

Several factors could contribute to the atherogenicity of small, dense LDL particles (273, 290, 465, 545). First, small LDL particles bind less efficiently to LDL receptors, their normal route of clearance, which increases their residence time and number in the circulation, whereas insulin resistance worsens LDL clearance by reducing the ability of insulin to stimulate expression of the LDL receptor (290). This process favors the binding of small LDL particles to the arterial wall. Second, conformation changes in apolipoprotein B on the surface of small LDL particles may make them more likely to interact with the surface of endothelial cells lining the arteries. This retention and the smaller size of LDL particles facilitate their entry into the vascular wall. Third, small LDL particles are very sensitive to chemical modification (oxidation, etc.) once inside the artery wall. Fourth, the receptors of resident macrophages recognize and take up modified LDL, which gradually turns these macrophages into foam cells. Foam cell formation is an early step in the development of the atherosclerotic plaque (324).

In contrast, HDL could be antiatherogenic in a number of ways (27, 69). HDL particles promote cholesterol efflux from the arterial wall (as they do in all tissues) and favor its transport to the liver. HDLs also prevent chemical modification of LDls within the artery wall, thereby reducing their uptake by macrophages. In addition, HDLs hinder the processes that recruit macrophage precursors (monocytes) to the arterial wall, reducing the number of lipid-accumulating cells therein. It has also been shown that HDL parti-
The combination of high triglyceride, low HDL cholesterol levels and small, dense LDL particles has been termed the “atherogenic lipoprotein triad”; it has been recognized as a major CVD risk factor (17, 18, 196, 198). Another triad of metabolic abnormalities often found among individuals with visceral obesity, the atherogenic metabolic triad of hyperinsulinemia, elevated apolipoprotein B, and small LDL particles, has been shown to increase CHD risk by 20-fold in middle-aged men, such risk being largely independent from traditional risk factors and blood lipid variables (291).

To summarize cholesterol transport under the proatherogenic condition often observed in visceral obesity, chylomicron remnants, VLDL remnants, and small LDLs deliver cholesterol to the artery wall (proatherogenic), whereas HDLs may protect against atherosclerosis, but only partly because of their reverse cholesterol transport properties. Dyslipidemia linked to visceral obesity is a major CVD risk factor and represents one of the abnormalities upon which the definition of the metabolic syndrome is based.

C. Cardiovascular Disease

On the basis of the robust evidence linking abdominal obesity and excess visceral adiposity to an atherogenic dyslipidemic state, one should expect a link with clinical vascular outcomes. For instance, in the Heart Outcomes Prevention Evaluation prospective study conducted in men and women with stable CVD, Dagenais et al. (96) found that BMI was no longer an independent predictor of myocardial infarction after adjusting for abdominal obesity indexes such as WHR and waist circumference. Moreover, waist circumference and WHR were independent predictors of CVD death, myocardial infarction, and total mortality after adjusting for traditional risk factors and BMI (96). Other studies carried out in subjects without known CVD have also reported that WHR and waist circumference were better predictors of CHD than BMI (153, 294). For example, a 13-yr follow-up study of 792 men reported that a high WHR increased ischemic heart disease risk while indexes of total obesity had no predictive value (298). The authors concluded that although the association between WHR and CVD risk was not significant in multivariate analyses when cholesterol levels and blood pressure were taken into account, WHR was more closely related to CVD risk than other indexes of obesity such as skinfold thickness or BMI (298). An additional prospective study conducted in women also reported similar findings (294). This latter study examined whether the android phenotype also increased CVD risk in women. Over a 12-yr follow-up, the authors found that WHR was a better predictor of myocardial infarction in women than other indexes of total adiposity. Accordingly, the study concluded that women with a typically male pattern distribution of adipose tissue could represent a subgroup at high risk of CVD.

In an analysis of the Nurses’ Health Study conducted on a cohort of more than 44,000 women free of CHD at baseline, Rexrode et al. (458) examined the 8-yr incidence of CHD among tertiles of baseline BMI and waist circumference values. They found that both elevated WHR and waist circumference were independently associated with a two-fold increase in CHD risk, even after adjusting for hypertension, diabetes, and high cholesterol. They also reported that higher waist circumference values increased CHD risk, regardless of BMI tertile. In addition, they found that the CHD risk of overweight/obese women (BMI ≥25.2 kg/m²) who were not abdominally obese (waist circumference <73.7 cm) was similar to the CHD risk of nonobese women (BMI <22.2 kg/m²) with higher levels of abdominal fat (waist circumference ≥81.8 cm). These findings particularly highlight the need to go beyond body weight and BMI and take into account adipose tissue distribution in evaluating CHD risk.

A large myocardial infarction case/control study, INTERHEART, conducted in a sample of 27,098 participants from 52 countries, showed that WHR and waist circumference were closely tied to risk of myocardial infarction even after adjusting for other risk factors (637). The risk of myocardial infarction not only rose progressively with increasing WHR values, it also increased in each BMI category, suggesting that WHR is a good predictor of myocardial infarction in lean (BMI <25 kg/m²), overweight (BMI 1>25 kg/ m²), and obese individuals (BMI >30 kg/m²). The authors concluded that WHR was a stronger anthropometric correlate of myocardial infarction and could be significantly better than BMI in assessing the risk of myocardial infarction in the general population.

A prospective case-control study by Kuk et al. (278) examined 291 men (97 decedents and 194 controls) from the preventive medicine clinic in Dallas, Texas to establish whether abdominal fat was independently linked to mortality. The study revealed that visceral adiposity was a strong independent predictor of all-cause mortality in men. These findings could suggest that visceral fat should become a target of strategies to reduce obesity-related mortality and morbidity. Again, measuring waist circumference may facilitate the identification of patients with visceral obesity, insulin resistance, and metabolic complications increasing the risk of CVD and mortality (310). Recently, the Emerging Risk Factors Collaboration has published an important pooled analysis that examined the added value of assessing and interpreting the BMI, waist, and the WHR separately or in combination in CVD risk prediction (627). The authors reached the conclusion that these adiposity measures do not...
substantially improve CVD risk prediction in developed countries when information is available on traditional risk factors such as blood pressure, diabetes, and lipids. These findings derived from the analysis of 221,934 participants in 58 prospective studies provided robust evidence that simple anthropometric measures of adiposity cannot replace blood pressure, history of diabetes, and the important lipid variables in CVD risk assessment (627). However, the authors appropriately pointed out that both waist and the BMI were strongly associated with these intermediate risk factors. Therefore, as elevated adiposity is a key driving force behind the altered risk factor profile, it remains important to pay attention to these indexes of adiposity in clinical practice to target the likely underlying culprit cause of CVD: abdominal obesity.

The authors also questioned the relevance of measuring waist circumference since all three adiposity indexes appeared to equally predict CVD risk. Such conclusion brings the risk of abandoning the waist circumference measurement to go back to the use of BMI alone (627). The recommendations stemming from this finding are far from trivial and deserve some discussion. First, waist circumference is too often mistaken to be an index of visceral adiposity independent from total body fat adiposity. As shown in numerous previous studies, the correlation between the BMI and waist circumference is strong (in the area of $r = 0.85$) (106). Thus, when considered as a single anthropometric index, waist circumference most often barely outperforms the BMI as one of the risk factors (22, 627). However, we have previously shown that waist circumference is a useful discriminator of risk for a given BMI value (113). Thus waist circumference is useful as an index of abdominal adiposity only when the patient’s BMI value is available. For instance, as shown in FIGURE 2, despite the strong correlation between the BMI and waist circumference, there is a substantial individual variation in waist circumference at any given BMI unit. Therefore, for two overweight patients with the same BMI value (e.g., 27 kg/m²), the patient with a waistline of 98 cm will likely have more visceral adipose tissue and more diabetogenic and atherogenic metabolic abnormalities than the patient with a waist circumference of 83 cm. This information is completely lost if BMI or waist circumference are used as single adiposity indices. Thus, if only BMI is measured, we assume that the adiposity/fat topography and related risk of these two patients is the same, which is incorrect. However, as illustrated by the above cases, waist circumference complements BMI, but should not replace it as a single adiposity index.

In addition, both waist and BMI could be particularly helpful in clinical situations where they evolve in different directions. Many examples could be provided: 1) the sedentary postmenopausal woman increasing her waistline with out gaining weight as she is losing lean body mass and gaining abdominal fat; 2) the lipodystrophic HIV+ patient losing subcutaneous fat while gaining visceral fat; 3) the sedentary middle-aged man gaining abdominal fat while losing muscle mass; and 4) the patient with chronic obstructive pulmonary disease losing muscle mass and gaining abdominal fat because he is frail and inactive (317, 320, 485, 599). These represent just a few clinical examples where waist circumference could increase even in the absence of body weight change (BMI). In this regard, it is interesting to note that the Emerging Risk Factors Collaboration investigators also reported that patients with diabetes had a higher waistline at any BMI value, a finding fully concordant with the published evidence that patients with type 2 diabetes have more abdominal visceral fat and more ectopic fat than non-diabetic individuals matched for BMI (175, 270). Thus a high waistline for a given BMI is predictive of an increased risk, a finding confirmed by results of the Emerging Risk Factors Collaboration.

D. Hypertension

Hypertension is a powerful risk factor for an array of cardiovascular complications such as left ventricular hypertrophy, atrial and ventricular arrhythmias, diastolic heart failure, systolic heart failure, and ischemic heart disease with or without congestive heart failure (50). Hypertension also harms the central nervous system and kidneys. The presence of other risk factors (623), such as insulin resistance and the metabolic syndrome (112), potentiates the deleterious impact of hypertension on target organs and CVD risk.

The link between obesity and hypertension has long been recognized, with obese patients having higher rates of hypertension than normal-weight individuals (83, 536). Inter-
estingly, not every obese patient is hypertensive, indicating again the heterogeneity of obesity from the vascular standpoint (437). Waist circumference has been reported as the strongest independent predictor of systolic blood pressure and diastolic blood pressure in normoglycemic Chinese individuals (566). Furthermore, excess visceral fat has been found to be associated with hypertension in Japanese Americans (213). However, hypertension rates were rather high in both studies (56 and 25%, respectively) (213, 566). Since some antihypertensive medications may influence insulin sensitivity and the metabolic risk profile over time, it is important to study the relationship of abdominal obesity and blood pressure in population-based cohorts to avoid the influence of confounding factors (19).

In a population-based study, of which only 6.5% of subjects had hypertension, Poirier et al. (439) observed that waist circumference in men and women was most strongly linked to systolic blood pressure and diastolic blood pressure compared with other likely contributors such as insulin resistance and fasting insulin levels. The amount of visceral fat crudely estimated with waist circumference may, therefore, largely explain the association between obesity, fasting insulin, insulin sensitivity, and blood pressure at least in that study (439).

Which mechanisms underpin the elevated blood pressure found with visceral obesity independent of insulin resistance? One possible answer lies in the altered angiotensin II and aldosterone secretion in obesity (387, 644). Most components of the renin-angiotensin system have been identified in human adipose tissue (644). Obesity is also known to cause structural alterations in the kidneys that may eventually cause loss of nephron function and a further elevation in blood pressure (206). Accordingly, renal sinus fat deposition measured by CT was shown to be predictive of hypertension in the imaging substudy of the Framingham Heart Study, a finding which provides another possible explanation for the link between visceral adiposity, ectopic fat depots, and the control of blood pressure (157). Thus obesity, particularly abdominal obesity accompanied by ectopic fat deposition, seems to play an important role in the pathophysiology of hypertension and should not be neglected when determining therapeutic approaches to lowering blood pressure.

E. Cancers

Reviews of available epidemiological data reiterated the existence of a significant association between obesity (BMI) and increased risk for several cancers (28, 436). Seminal studies had provided significant evidence of increased risk for colon, postmenopausal breast, endometrial, kidney, esophageal, liver, and pancreatic cancer as well as non-Hodgkin’s lymphoma and myeloma in obese individuals (28, 76). More recent data have shown strong evidence for an increased risk of colorectal, esophageal, kidney, and pancreatic cancer in both sexes in addition to thyroid cancer in men and endometrial, gallbladder, and postmenopausal breast cancer in women (456). Weight loss intervention mostly in surgery-based studies seems to reverse this trend and lower the risk of cancer (28). Hence, a clear link between obesity and cancer risk has now been established.

Whether visceral adiposity is specifically associated with the risk of cancer has also been examined. The most abundant data relate to colorectal cancer. A number of studies including a meta-analysis support the notion that abdominal and/or visceral obesity specifically increases the risk for colorectal cancer independent of total adiposity (245, 299, 573, 630). Increased visceral adipose tissue accumulation also seems to predict poorer response to chemotherapy treatment and increased complication rates as a result of surgery (200, 400). Whether rates of adenomatous polyps, the precursor of colorectal cancer, are related to abdominal obesity is uncertain (259, 489). Abdominal obesity also possibly seems to be related to both pre- and postmenopausal breast cancer risk (468, 493, 605), prostate cancer risk (604), and esophageal cancer (486). It could also lead to a poorer outcome of surgical treatment for pancreatic cancer (20).

A large number of mechanisms are currently being investigated to explain the potential link between cancer and obesity/visceral obesity (28). Detailing these mechanisms is beyond the scope of this review as they have been described in many review articles and books. Insulin, insulin-like growth factors (IGF), sex hormones, inflammation, cytokines, or hypoxia and oxidative stress are among the mechanisms that have received scientific attention in recent years (28). More studies are needed to clarify the etiology of obesity- and visceral obesity-related cancer. Obviously, the complex etiology of these two conditions, combined with the confounding effects of physical activity as well as the sheer variety of compounds included in the diet, poses significant challenges to these studies (460).

F. Sleep Apnea

The link between obstructive sleep apnea (OSA) and obesity has been recognized for a long time (168, 427, 457). For reasons such as upper airway pressure or reduced chest compliance related to upper trunk fat accumulation, upper body adiposity (389, 495, 503) and, more specifically, excess visceral adiposity has also been associated with OSA (340). Such relationship could be bidirectional: on one hand, visceral adiposity may be a feature of ectopic fat deposition including excess neck fat which may increase risk of OSA through metabolic and mechanic phenomena (389, 495, 503); on the other hand, OSA is also associated with reduced physical activity level, reduced quality of sleep, and increased appetite, and these factors may further
increase susceptibility to visceral fat deposition (526). Therefore, the viscerally obese patient with OSA may enter a vicious cycle leading to marked exacerbation of their clinical condition and cardiometabolic risk profile.

G. Metabolic Syndrome

The constellation of abnormalities associated with obesity or abdominal obesity has been termed “metabolic syndrome,” and a number of clinical criteria have been put forward by various organizations to help identify high-risk individuals (112). Although waist circumference was initially identified as one of the five clinical criteria to diagnose the metabolic syndrome by the National Cholesterol Education Program—Adult Treatment Panel III (1), there has been a debate as to whether this feature should be a mandatory clinical criterion as initially proposed by the International Diabetes Federation guidelines (7, 8). The rationale for not imposing waist as an obligatory criterion was that some individuals could be characterized by the metabolic syndrome despite being lean. To examine this possibility, we have used a population-based sample to assess waist circumference values among all possible combinations of three of the five clinical criteria (FIGURE 3) (117). Results presented in FIGURE 3 clearly show that all combinations of criteria selected individuals with an elevated waist circumference, perhaps not always reaching the arbitrary cut-off of 102 cm but nevertheless being quite elevated (117). These results do not exclude the possibility that some rare forms of insulin resistance/metabolic syndrome will be identified as one of the five clinical criteria to diagnose the metabolic syndrome by the National Cholesterol Education Program—Adult Treatment Panel III (117, 232, 509).

Although visceral adiposity and features of the metabolic syndrome are associated with an increased relative risk of CVD (173, 177, 382, 624), one cannot use a clinical diagnosis of the metabolic syndrome or a direct measurement of visceral adipose tissue (not convenient clinically) to estimate CVD risk (112). We have previously made the point that to assess CVD risk, one should first assess risk on the basis of classical risk factors (age, sex, smoking, blood pressure, LDL cholesterol, HDL cholesterol, family history of premature CHD, and others) (112, 113). Whether abdominal obesity and related metabolic syndrome features add to global CVD risk predicted by classical risk factors remains uncertain. For the time being, although meta-analyses have shown that metabolic syndrome increases relative risk of type 2 diabetes and CVD (154, 173, 177, 382), it cannot be used as a CVD risk estimate but rather as a tool to emphasize the need to target excess abdominal adiposity by proper lifestyle habits (healthy eating and physical activity/exercise).

The inability of the metabolic syndrome to be used as a CVD risk calculator has led to the introduction of the concept of cardiometabolic risk, which is simply the global risk of CVD resulting from the presence of traditional risk factors combined with the possible added contribution of emerging factors such as visceral obesity/ectopic fat and features of the metabolic syndrome (112). A full discussion of cardiometabolic risk is beyond the scope of the present paper and can be found in several previous reviews (109, 112, 113, 117, 232, 509).

IV. ETIOLOGY OF VISCERAL OBESITY

As mentioned, the propensity to preferentially accumulate visceral fat in conditions of excess energy intake is highly variable from one individual to the other. The mechanisms that could explain associations between visceral adiposity and cardiometabolic risk also likely involve many possible phenomena and pathways. The following sections will review the main etiological factors contributing to visceral fat accumulation.

A. Age

Several studies have documented age-related changes in adipose tissue distribution as reflected by an increase in the WHR (293, 569). In a sample of 52,953 women, the body weight increase observed with age was more likely to accumulate in the abdominal area than in the gluteofemoral area (293). In the 1,179 participants of the Baltimore Longitudinal Study of Aging, a WHR increase was reported across various age groups (from 17 to 96 yr of age) in both men and women (510). In another sample of Dutch volunteers (men and women), age was found to be a strong correlate of selective abdominal adipose tissue accumulation as estimated by an increased waist circumference (208). In young individuals (men and women) and middle-aged women, excess energy is preferentially stored in subcutaneous fat depots, although visceral adipose stores may also increase

![FIGURE 3. Waist circumference among men (n = 907) of the Québec Health Survey according to the different combinations of the National Cholesterol Education Program-Adult Treatment Panel III clinical criteria for the identification of the metabolic syndrome. None of the patients was characterized by combinations 7 and 9. [Adapted from Després et al. (117), by permission of Oxford University Press.]](image-url)
selectively (140) in some genetically susceptible individuals (293). In this regard, the ratio of abdominal subcutaneous to visceral adipose tissue has been shown to be markedly higher in women than in men and to decrease with age in both genders. In another study, age was again positively correlated to visceral adiposity and negatively correlated with the amount of abdominal subcutaneous adipose tissue (638). DeNino et al. (103) estimated that in nonobese women, visceral adipose tissue area assessed by CT increases with age at a rate of 2.36 cm²/yr.

Increased visceral adipose tissue deposition with age is particularly significant among men and postmenopausal women who, on average, have up to twice the amount of visceral adipose tissue than premenopausal women (268). However, even in middle-aged premenopausal women, visceral adipose tissue deposition was higher compared with young women, suggesting that age was associated with an increase in abdominal adiposity in women even before the onset of menopause (415). FIGURE 4 shows the significant positive associations between visceral adiposity relative to subcutaneous adiposity and age in men and women based on a survey of existing publications using CT.

In young premenopausal women, age-related changes in visceral adipose tissue relative to total body fat have been reported to be greater than the increase in total body fat over a 4-yr follow-up period, and this phenomenon was found to be independent of race (296). The latter study also reported that the age-related increase in total adiposity was greater in African-American women than in Caucasian women. However, visceral adiposity was greater in Caucasian women at baseline; it increased with age and remained higher in Caucasian than in African-American women.

In a 7-yr follow-up study of premenopausal women, a 30% increase in visceral adiposity was reported although total adiposity indexes did not change (318). Over the same period, waist circumference and WHR were also significantly increased. In addition, the increase in waist circumference over the 7-yr follow-up predicted the increase in visceral adiposity. The latter finding suggests that monitoring changes in waist circumference over time could be useful in clinical practice to detect changes in visceral adiposity. This study provides further evidence that clinicians should look beyond body weight measurements and the BMI to properly assess whether patients are accumulating abdominal, visceral fat over time.

The prevalence of CVD increases with age and the greater number of CVD risk factors in older than in younger individuals partly explains this phenomenon (102, 199). For instance, the age-related increase in visceral adiposity has been shown to be an important correlate of alterations in lipoprotein-lipid metabolism and in plasma glucose homeostasis in middle-aged premenopausal women compared with young women (415). In the same cross-sectional study, when young and middle-aged women with similar levels of visceral adipose tissue and body fat mass were compared, some of the well-known age-related differences in the metabolic profile (apolipoprotein B, fasting glucose and glucose area following a 75 g oral glucose challenge) were eliminated (415). Results from our 7-yr follow-up study in premenopausal women also showed that the deterioration in plasma glucose and insulin homeostasis indexes more closely reflected the age-related increase in visceral adipose tissue than that in total adiposity (318).

Middle-aged men generally have a more atherogenic plasma lipoprotein-lipid profile than young men (317). However, when middle-aged men with similar total body fat mass and visceral adiposity were compared with young adult men, many age-related differences in the plasma lipoprotein-lipid profile were eliminated, suggesting that the age-related increase in total and visceral adiposity explained many (but not all) age-associated changes in lipoprotein-lipid levels. Lemieux et al. (313) have reported that age is associated with an increased LDL particle concentration. Such an age-related increase of small, dense LDL particles observed in some individuals appears to be largely related to an increase in triglyceride levels in both sexes (313, 363). As hypertriacylglyceridemia is another consequence of abdominal obesity and especially visceral obesity, these results highlight the importance of maintaining low levels of visceral fat over time. Clinicians should be aware of the fact that the increase...
in visceral adiposity with age predicts a deterioration of their patient’s risk factor profile.

### B. Gender

Human males and females differ greatly in terms of body fat distribution. In fact, such substantial anatomical differences attributable to regional adipose tissue partitioning are practically unique to this species (441). Men are more likely to accumulate adipose tissue in the upper body (trunk, abdomen), whereas women usually accumulate adipose tissue in the lower body (hips, thighs) (276, 281, 576). Thirty-five years after the seminal observations of Vague referring to android (male) and gynoid (female) obesities, Krotkiewski et al. (276) suggested that sex hormones might be involved in regulating the typical gender differences in regional body fat distribution. Their seminal work suggested that these differences were mainly due to the number of local fat cells: men had more fat cells in the abdominal region while women had more fat cells in the gluteal/femoral adipose depots (276). They also observed that this regional adipose tissue distribution was unrelated to the presence or absence of obesity.

According to CT measurements, the amount of visceral adipose tissue is up to twofold higher in men than in premenopausal women (281). In men, visceral adipose tissue accumulation generally increases with the amount of total body fat, whereas in women, the volume of visceral adipose tissue is less affected by the amount of total body fat compared with men (281). In another study (316), even after correcting for total body fat mass, women had a lower ratio of visceral adipose tissue to total body fat mass compared with men. Estimated total visceral adipose tissue volume was 5.23 ± 2.39 liters in men and 3.61 ± 1.91 liters in women. Women had less visceral adipose tissue even though they had higher BMI, total body fat, and abdominal subcutaneous adipose tissue values. Premenopausal women will, therefore, accumulate a substantial amount of total body fat before a substantial amount of visceral adipose tissue is observed. Through CT and MRI studies, several groups (443, 478, 500) have tested the usefulness of the waist circumference measurement as an index of abdominal adipose tissue deposition in both men and women. For a given waist circumference, women generally have higher body fat mass and abdominal subcutaneous adipose tissue than men (279, 443). Moreover, Kuk et al. (279) demonstrated that for the same waist circumference, men had more visceral adipose tissue than women. They also found that for a given increase in waist girth, men had a greater accumulation of visceral adipose tissue than did women.

Kotani et al. (268) also noted a clear sex dimorphism when comparing regional adipose tissue distribution, abdominal adipose tissue accumulation in particular, across age groups. For instance, visceral adipose tissue deposition was found to increase with age mostly in men and in menopausal and postmenopausal women. Data extracted from a survey of available studies using CT show a similar trend (FIGURE 4).

The gender difference in CVD risk observed between men and women could very well be explained, at least in part, by the gender difference in body fat distribution (163, 297, 498). Lemieux et al. (315) have studied gender differences in visceral adiposity and CVD risk profile using CT. They found that although premenopausal women had more total body fat than men, they also had lower visceral adipose tissue accumulation and a better metabolic risk profile. After controlling for both total body fat and visceral adipose tissue as potential confounders of the sex difference in the metabolic risk profile, gender differences in plasma triglyceride and apolipoprotein B levels and the HDL2/ HDL3 cholesterol ratio were eliminated. However, plasma HDL cholesterol levels remained significantly lower and fasting plasma glucose concentrations significantly higher in men than in women. These results suggest that visceral adipose tissue accumulation is an important correlate of the gender difference observed in some, but not all, variables predictive of type 2 diabetes and CVD risk.

Many studies (274, 504, 532) have shown that high levels of small, dense LDL particles are associated with an increased CHD risk. The sex dimorphism in LDL particle size, women have larger LDL particles than men, is also well established (78, 323, 364, 397). However, Lemieux et al. (311) reported that sex differences in visceral adiposity and circulating triglyceride levels (18, 364, 556) could not entirely explain the LDL particle size dimorphism. Carr et al. (78) suggested that higher hepatic lipase activity in men, which affects LDL and HDL heterogeneity and responds to testosterone stimulation, may also explain the gender difference in the cardiovascular risk profile.

In addition to LDL size, HDL particle size is another marker of the gender difference in the circulating lipid profile. Women have larger HDL particles than men, a phenotype generally associated with an overall low-risk lipoprotein-lipid profile (413). In both sexes, HDL particle size has been associated with CHD risk factors such as triglyceride, HDL cholesterol, and apolipoprotein B levels as well as with the cholesterol-to-HDL cholesterol ratio. When men and women with similar HDL particle size were compared, the dimorphism in lipoprotein-lipid profile was virtually eliminated, despite the fact that women still had higher levels of total body fat and lower visceral adiposity than men.

In summary, the tendency of men to accumulate visceral adipose tissue appears to be a key factor in predicting why obesity is much more hazardous in men than in women. Yet differences in male and female visceral adipose tissue accumulation cannot entirely explain the gender difference in

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the metabolic risk profile. Sex hormones may play a significant role in further modulating metabolic risk parameters beyond their effects on visceral fat accumulation.

C. Sex Hormones

The marked sex dimorphism in body fat patterning in humans indirectly suggests that sex hormones play a key role in regional fat accumulation (551). Further confirmation of this notion is provided by the example of transsexuals who have been treated with sex hormones. Female-to-male transsexuals treated with intramuscular testosterone injections show a progressive shift in body fat distribution from the gynoid to android pattern over a few months to 3 yr (136–138). Conversely, estrogen treatment of male-to-female transsexuals significantly increases fat deposition in all subcutaneous fat depots, while having little effect on the visceral fat compartment (136–138). These results suggest that the prevailing hormonal milieu is a critical determinant of regional body fat distribution in both women and men. The impact of androgens and estrogens on human body fat patterning will be briefly reviewed in this section.

In men, low circulating levels of total testosterone are generally associated with abdominal and/or visceral obesity (178, 431, 497, 507). Whether free testosterone levels are related to body fat distribution patterns remains uncertain due to methodological limitations in the measurement of free testosterone (470, 595). Some investigators have reported low free testosterone in viscerally obese men (507). Many studies also demonstrated that plasma concentrations of sex hormone-binding globulin (SHBG), a determinant of testosterone bioavailability, are negatively associated with abdominal obesity in both men and women (90, 178, 180, 257, 497, 431, 552, 572). Interestingly, men with low plasma SHBG or testosterone levels are also generally characterized by an altered metabolic profile and a greater number of metabolic syndrome features (53, 205, 285, 431). The concomitant presence of elevated visceral adipose tissue accumulation appeared as a critical determinant of the metabolic alterations found in these individuals (53, 553, 555, 557). Circulating levels of dehydroepiandrosterone (DHEA) or its sulfated form (DHEA-S) have been found to be low in viscerally obese men (90, 204, 552). However, these data are far from unanimous, as reviewed in Reference 554.

With respect to exogenous androgens, supraphysiological testosterone treatment of female-to-male transsexuals leads to increased visceral adipose tissue accumulation and concomitant alterations in the metabolic profile (137, 138). In a similar manner, anabolic androgen use by athletes also leads to pronounced and lasting alterations of the metabolic profile and cardiovascular risk (187). However, restoration of testosterone levels within the physiological range in men with initially low endogenous levels generally leads to a decrease in visceral adiposity (64, 347). Androgen supplementation also leads to increased insulin sensitivity (64, 348, 626), while having rather neutral effects on the lipid profile (195). Hence, within the physiological range, higher testosterone concentrations are associated with a favorable metabolic profile, either when considering endogenous levels or following physiological replacement in men with low baseline testosterone concentrations (52, 53, 205, 285, 431). On the other hand, studies on DHEA replacement continue to be notoriously discordant with respect to their impact on body fat distribution and variables of the metabolic profile (390, 554, 597). The most recent studies convincingly demonstrated that this hormone precursor had relatively small effects that could not be sustained in long-term therapies (31, 42, 390, 530).

In women, based on the common observation of abdominal obesity in patients with the polycystic ovary syndrome (PCOS), investigators have often concluded that hyperandrogenism in women leads to abdominal obesity and hyperinsulinemia (133). Recent advances in our understanding of PCOS reveal that the link between hyperandrogenism and abdominal obesity may be more complex than initially thought. For example, a recent study showed that once differences in BMI are taken into account, there is no difference in fat distribution patterns between PCOS cases and control women, putting into question a notion that had been considered as common knowledge in PCOS (25). Moreover, findings that insulin sensitizing treatments improve the ovarian and androgenic component of PCOS also led to reconsider the basic causal relationship implying high androgens as the direct cause of visceral obesity in these patients (133). In vitro experiments show that androgen treatment of abdominal adipocytes or adipose tissue explants does not lead to increased adipogenesis or higher uptake of lipids as assessed by lipoprotein lipase (LPL) activity (55). In fact, androgens had the opposite effect as they inhibited these indirect measures of fat storage, even at very high doses (55). Elevated circulating androgens in PCOS women may also need to be considered in light of the body of evidence suggesting that prenatal androgenization of the fetus may be an important etiologic factor for this condition (reviewed in Ref. 628).

Association studies on circulating androgens and body fat distribution in women are also equivocal. In some studies including non-PCOS women, high total or free plasma testosterone levels are positively associated with visceral fat accumulation (142, 420, 499). However, others have reported negative associations (12, 99, 574), and some failed to observe any correlation (254, 280). Again limitations in the measurement of androgen levels in women may possibly explain these discrepancies (470). Similar to men, circulating androgen levels are negatively related to abdominal adiposity measures at least in some studies (53, 205, 431), while associations between body fat distribution and
DHEA or DHEA-S remain equivocal (554). The metabolic impact of androgen supplementation in women has not been formally characterized, but one study reported an antiadiposity effect of dihydrotestosterone (DHT) treatment (194).

Estrogens are produced mainly by the ovaries in premenopausal women (32). However, in both women and men, estrogens are also generated through peripheral aromatization of androgens in several tissues, especially fat (34, 361). Peripheral estrogen sources are especially important in men and postmenopausal women (288). The parallel sex dimorphisms in estrogen levels and body fat distribution as well as transsexual studies have highlighted the possibility that this hormone is critically involved in human body fat patterning. Moreover, as mentioned, reduced estrogen levels after menopause have been associated with increased adiposity and visceral fat accumulation (176, 202, 203, 255, 331, 487).

In rodent models, estrogens exert a tonic inhibitory effect on food intake throughout the ovarian cycle, while ovariectomy leads to hyperphagia and exaggerated weight gain (70, 463). Elegant studies by the group of Clegg and collaborators (70, 506) have demonstrated that estradiol signaling in the brain closely interacts with neurological pathways regulating energy balance. In addition to these central effects, other studies have reported direct estrogen action on peripheral metabolism in the muscle and adipose tissue independent of energy balance (95). In humans, exogenous estradiol administration decreases LPL activity in lower body adipose tissue of premenopausal women (445), but the opposite effect is apparently observed in postmenopausal women (453). Estrogenic effects on adipose tissue lipolysis are inconsistent (235, 453, 554). Moreover, high concentrations of estradiol decrease LPL and increase hormone-sensitive lipase expression in subcutaneous mature adipocytes while the opposite is observed at low estrogen doses, suggesting that estrogens may have a biphasic action on adipose tissue lipogenic and lipolytic capacity (408). Studies have also reported that estrogens stimulate preadipocyte proliferation and that this effect is depot-specific and more pronounced in preadipocytes from women compared with preadipocytes from men (11, 125). Direct action of estrogens in adipose tissue is supported by the presence of both receptor isoforms α and β (94, 124). Sex- and depot-related differences in estrogen receptor levels have been reported, but the data remain unclear (54, 124, 421, 609). Interestingly, deletion of the estrogen receptor α in male and female mice is associated with increased adiposity independent of food intake (216). Polymorphisms in the estrogen receptor α and β genes are also associated with slightly higher body fat mass and visceral fat accumulation compared with women with the more frequent genotype (191, 398, 404).

In summary, estrogens have a significant influence on adipose tissue function and metabolism and may actually be closely involved in determining the sex dimorphism in both body composition and body fat distribution. While we have a growing understanding of how each sex hormone may influence fat tissue function, more studies are needed to better integrate how they interact in each specific fat depot, especially in humans.

D. Genetics

The genetic determinants of obesity have been intensely studied in the past decades. Family studies have shown that heritability rates of total body fat mass are ~50% (218, 252, 462). A Human Obesity Gene Map has been generated and updated during several years (429). In the last updates of this authoritative review, as many as 135 candidate genes had been identified as being linked and/or associated with obesity-related phenotypes, in addition to 233 quantitative trait loci (429). A recent study on obesity-related genetic variants was performed in close to 250,000 individuals in whom ~2.8 million single-nucleotide polymorphisms were genotyped (525). In addition to known variants, this study identified 18 new loci that were related to BMI. However, the combined effect of these genetic variants on obesity was modest, accounting for ~6–11% of the genetic variation in BMI. Hence, factors other than DNA sequence variants alone are likely to explain the high heritability rates of obesity. These possibly include gene-gene interactions, gene-environment interactions, as well as epigenetics.

With regard to body fat distribution, rather high heritability rates have been reported. Indeed, familial transmission reaches ~50% of the age-, sex- and total body fat-adjusted variance (60, 224). Segregation analyses even pointed toward a major gene effect accounting for 51% of the variance in visceral adipose tissue accumulation (61). This notion is further supported by seminal twin studies in which weight gain was induced by overfeeding (62). These studies showed that the variance in visceral adipose tissue gain between pairs of twins was approximately six times higher than within twin pairs (62), again supporting a major genetic effect on visceral fat distribution. Family studies have shown a clear clustering of visceral adiposity (428, 462). Genome-wide scans for measures of body fat distribution including waist circumference, or CT-measured visceral adipose tissue area, have led to the identification of several loci and candidate genes that could be of potential interest (158, 401, 430, 461). Similarly, several recent studies have identified genetic variants that may be related to preferential accumulation of visceral adipose tissue accumulation in various populations (38, 63, 249, 385, 419, 424, 425). Several studies have also identified genetic variants that are associated with an increased susceptibility to the metabolic complications of visceral obesity (93, 442, 533, 534, 601–603). Most of these genetic variants need to be further val-
E. Ethnicity

The pronounced differences in regional adipose tissue distribution among various populations worldwide are well known. For a given amount of weight gain, some populations may be prone to accumulate adipose tissue in the subcutaneous adipose depots, whereas other populations may be more likely to accumulate adipose tissue in the visceral cavity. Ethnicity, therefore, critically needs to be considered in the identification of high-risk cases of obesity, especially in the definition of cut-off values of anthropometric measurements (250, 300, 303).

A national United States study of 9,179 individuals with over sampling of minority ethnic groups showed significant ethnic differences in body weight, with African-American and Hispanic populations at highest risk of obesity compared with Caucasian populations (367). Obesity onset occurred 2.1 and 1.5 times earlier for African-American and Hispanic women, respectively, compared with Caucasian women. In men, Hispanics had the earliest obesity onset (367). A meta-analysis of 32 studies revealed significant BMI differences among Ethiopians, Chinese, Indonesians, Thais, Caucasians, African Americans, and Polynesians for the same age, sex, and body fatness (120). In Asian populations, a higher body fat content was reported at lower BMI values compared with Caucasians (119). The significant ethnic differences in mean BMI may possibly be explained by intrinsic differences in body composition (304). Since the general World Health Organization obesity cutoff value of 30 kg/m² can no longer be applied worldwide without taking into account ethnicity, revised threshold values were suggested for South Asians, Chinese, and Aboriginals (449). Interestingly, cut-off BMI values related to high blood glucose, dyslipidemia, and hypertension were found to be lower in these populations than in individuals of European origin (449).

Differences have also been reported regarding susceptibility to abdominal visceral obesity. For a similar level of total adiposity, Caucasian subjects have been shown to have more visceral adipose tissue than African Americans (9, 77, 87, 110, 251, 332). On the other hand, Asians and Indian Asians seem to be especially prone to visceral fat accumulation despite lower total adiposity values compared with individuals from other ethnic backgrounds (241, 301, 374). Several hypotheses have been put forward regarding the physiological explanation of ethnicity-related differences in body fat distribution, the most plausible being related to genetic and epigenetic programming of the propensity of each fat compartment to store lipids (374, 521). A large number of studies have assessed visceral adiposity in various ethnic groups such as Caucasian, Asian, Indian, and Aboriginal populations (9, 110, 174, 302, 304, 332). Ethnicity-related differences in the propensity to accumulate visceral fat for a given adiposity are illustrated by our examination of published average values of CT-measured visceral and subcutaneous areas according to sex and ethnicity in available publications (FIGURE 5). Overall, the greater propensity of some populations to accumulate visceral adipose tissue could contribute to their higher rates of type 2 diabetes and CVD. Further research is needed to establish a clear definition of high-risk abdominal obesity in various populations worldwide. Large epidemiological studies that use CT and metabolic profiling to measure visceral fat will address these important questions.

F. The Endocannabinoid System

In the past years, discoveries on the regulation of body weight and food intake by endogenous agonists of the en-
docannabinoid receptor type 1 (CB$_1$) have brought a major breakthrough in our understanding of the pathophysiology of obesity (121, 432). The most studied endocannabinoids are anandamide and 2-arachidonoylglycerol. Together with the receptors and the enzymes that synthesize them, they form the endocannabinoid system (121). Evidence showing that the endocannabinoid system is chronically activated in obese individuals and interacts with several major players in the multiple cascades of metabolic regulation has been reviewed elsewhere (121, 494). The use of CB$_1$ receptor antagonists has been shown to decrease food intake, to induce significant weight loss, and successfully address several metabolic alterations associated with obesity; however, side effects of the first generation compounds still remain an issue (44, 494). For instance, one compound that had initially been approved by regulatory agencies in Europe had to be withdrawn due to adverse effects related to psychiatric disorders including anxiety and depression (44). Development of alternate compounds may eventually lead to further advances in this area.

Dysregulation of the endocannabinoid system in humans seems to be preferentially associated with visceral obesity rather than with overall adiposity (56, 88). Adipose tissue expresses CB$_1$ receptors, and endocannabinoids have been detected in both subcutaneous and visceral adipose tissue in humans (358). Their impact is a proadipogenic and prolipogenic activity (121). The endocannabinoid system is currently hypothesized to play a role by activating adipose tissue adipogenesis and lipogenesis in a depot-specific manner, thereby contributing to visceral obesity and the concomitant metabolic alterations (121). Such an hypothesis of a peripheral overactivation of the system is consistent with the metabolic benefits of endocannabinoid antagonist treatments, which were found to go beyond the effects of dietary restriction and weight loss alone (123).

**G. Growth Hormone**

Human studies have shown that growth hormone (GH) levels or secretion are altered in visceral obese individuals with a high cardiometabolic risk (85, 239, 339, 373, 375, 434, 577, 589, 590, 613). Many reports suggested that the association between visceral and/or abdominal obesity is independent of total adiposity (85, 339, 373, 434, 613). In fact, adiposity and fat distribution along with aging and the sex steroid milieu interact in a highly complex manner to modulate GH secretion (589–592). However, weight loss has also been shown to lower IGF-I and increase insulin-like growth factor binding protein-3 (IGFBP-3) concentrations, thereby altering the association between visceral adipose tissue accumulation and these serum markers (100). Thus, whether the blunted GH secretion profile observed among abdominally obese patients is a cause or a consequence is not fully understood. The effects of GH supplementation therapy will be discussed in a subsequent section of this article.

**H. Hypothalamo-Pituitary-Adrenal Axis, Stress, and Glucocorticoids**

Excessive circulating glucocorticoid concentrations, as observed in Cushing’s syndrome, create a pathological phenotype of abdominal obesity, dyslipidemia, insulin resistance, and hypertension (423). In most cases, cortisol hypersecretion originates from the pituitary gland (Cushing’s disease) and results from excessive adrenocorticotropic hormone secretion (32). While individuals with idiopathic abdominal obesity share several of the morphological and metabolic alterations observed in Cushing’s syndrome, alterations in the sensitivity and drive of the hypothalamo-pituitary-adrenal (HPA) axis have been shown to be much more subtle (131, 345, 416). Early studies by the group of Björntorp and collaborators (48, 346) had demonstrated that the cortisol response to stress induced by cognitive tests or cold exposure was positively related to abdominal sagittal diameter in premenopausal women. More recently, primate studies have suggested that social stress in primate colonies may be related to increased visceral obesity and coronary artery disease (512, 513). A number of studies and review articles seem to point toward such an effect in humans (97, 101, 126, 128, 282, 284, 383, 455, 600, 612). These studies suggest that chronic stress or poor coping in stressful situations is associated with mild hypercortisolism and prolonged sympathetic nervous system activation, which in turn could favor accumulation of visceral fat (283). Increased local cortisol synthesis in adipose tissue, without marked central HPA axis alterations, is now clearly recognized as an important etiologic factor for non-Cushing abdominal obesity (269, 355, 356, 496). Conversion of inactive cortisone to active cortisol (11β-oxoreductase activity) is catalyzed by type 1 11β-hydroxysteroid dehydrogenase (11β-HSD-1). In vitro, inactivation of cortisol to cortisone (11β-dehydrogenase activity) may be catalyzed either by the type 1 or type 2 11β-HSD isoforms. However, 11β-oxoreductase activity is predominant for 11β-HSD-1 in adipose tissue, and the enzyme is primarily a glucocorticoid-activating enzyme (75, 139, 306). Local production of glucocorticoids by adipose tissue 11β-HSD-1 has been clearly linked to the development of abdominal obesity in animal models. 11β-HSD-1 knockout mice show attenuated hyperglycemia compared with wild-type mice in conditions of stress and diet-induced obesity (269). Conversely, moderate overexpression of the 11β-HSD-1 gene in adipose tissue is sufficient to induce specific fat accumulation in the visceral fat compartments. These experiments show that increased adipose tissue 11β-HSD-1 expression alone is sufficient to induce specific visceral adipose tissue accumulation and concomitant metabolic alterations such as dyslipidemia and insulin resistance, especially when mice are fed with a high-fat diet (355). This phenotype is also accompanied by increased adipocyte size especially in the visceral fat compartment, as well as increased nonesterified fatty acid release (355). Authors of this elegant study concluded that exces-
sive local cortisol production by 11β-HSD-1 is a common molecular etiology for visceral obesity and the metabolic syndrome.

Only a few studies directly examined peripheral cortisol homeostasis and 11β-HSD-1 expression in the context of human abdominal obesity. One study reported low rates of glucocorticoid uptake and release by adipose tissue, suggesting that adipose tissues are isolated from rapid circadian changes in circulating glucocorticoids (227). Expression levels and in vitro activity of 11β-HSD-1 are generally higher in visceral compared with subcutaneous adipose tissue (74, 371, 587, 588), although this is not unanimous (104, 417, 568). 11β-HSD-1 expression measures in human adipose tissue have been mainly performed in women, but higher 11β-HSD-1 expression levels in both omental and subcutaneous adipose tissue were observed in men compared with women (417). Activity and mRNA abundance of the enzyme in whole adipose tissue samples are increased in obese compared with lean women and men (104, 246, 306, 325, 371, 417, 587, 588). The existence of positive correlations between 11β-HSD-1 expression in subcutaneous adipose tissue and adiposity measures is clearly established (104, 246, 306, 325, 417, 446, 587, 588). A few studies that had access to human visceral adipose tissue show that 11β-HSD-1 expression in visceral adipose tissue is positively associated with overall adiposity (104, 306, 371, 417, 587, 588). However, visceral obesity is more closely related to 11β-HSD-1 expression and o xo reductase activity in visceral than in subcutaneous adipose tissue (371, 587, 588). We have shown that relatively elevated 11β-HSD1 o xo reductase activity in visceral compared with subcutaneous adipose tissue is associated with increased visceral fat accumulation as well as with concomitant metabolic alterations, independent of obesity levels (587, 588).

Other genes may also be involved in the regulation of local adipose tissue cortisol levels in obese individuals, including 11β-HSD-2, the glucocorticoid-inactivating enzyme, hexose-6-phosphate dehydrogenase which colocalizes and interacts with 11β-HSD-1 by generating the NADPH cofactor needed for cortisone-oxoreductase activity (640), and glucocorticoid receptor α. Insufficient data limit our ability to reach firm conclusions on the direct impact of these molecules in obesity and body fat distribution patterns. At the same time, the lack of a clearly demonstrated effect reinforces the hypothesis that visceral 11β-HSD-1 expression may be the main determinant of local active glucocorticoid levels and a major etiological factor for human visceral obesity.

I. Nutritional Factors

Only a few studies identified nutritional factors that could predispose to specific accumulation of visceral fat. Rat studies have shown that saturated fat intake might predispose to preferential accumulation of visceral fat compared with other fatty acids (508). Saturated fat feeding in dogs leads to significant gains in both the visceral and subcutaneous fat compartments (258). In monkeys, trans fatty acid intake had a specific effect on visceral fat accumulation that was associated with the development of insulin resistance (253), a finding that was also observed in rats (127). In general, studies on animal fat distribution are difficult to extrapolate to humans, in whom the sexual dimorphism in fat distribution is much more pronounced. Moreover, demonstrating that a given nutrient modulates the accumulation of visceral fat does not necessarily imply a specific impact of this nutrient on body fat distribution. Indeed, one must also demonstrate that a qualitatively distinct regime including a similar amount of calories does not have the same effect.

One such study has shown that including monounsaturated fat to the diet (Mediterranean diet) prevented visceral fat gain within an isocaloric design including other types of dietary fats (410). Consistent with this study, a large epidemiological survey has shown that adherence to the Mediterranean diet was associated with lower waist circumference values independent of BMI in both sexes (466). In vitro, oleic acid and palmitic acid had a distinct effect on lipid accumulation in cells isolated from various fat depots in children (488). A number of cross-sectional studies have shown associations between dietary fatty acid composition and visceral fat accumulation (179, 181, 219, 260). Overall, fatty acid composition of the diet may have an impact on body fat distribution patterns above and beyond its impact on overall adiposity levels. However, more studies are needed to further substantiate this hypothesis.

Soft drink consumption and the concomitant intake of fructose have become a public health issue in recent years (584). Some meta-analyses on the topic of sugar-sweetened beverages, obesity, and cardiometabolic risk have shown that increased consumption of such beverages is likely to be associated with obesity, metabolic alterations, and the development of type 2 diabetes (156, 341, 405, 584). The impact of high-fructose consumption in animal models as well as humans has been nicely reviewed elsewhere (537, 543, 544). Overall, available studies demonstrate that fructose consumption increases fasting triglyceride and glucose levels, stimulates deposition of triglycerides in nonadipose tissues (ectopic fat), deteriorates glucose and insulin responses to an oral sucrose challenge, and leads to hepatic insulin resistance (538, 543, 564). Fructose has a stimulatory impact on hepatic de novo lipogenesis which possibly explains its impact on triglyceride responses (539). Quite interestingly, fructose appears as one of the only nutrients to have a potential effect on body fat distribution independent of its impact on overall adipose tissue accretion. Indeed, elegant studies in which men and women were given either glucose- or fructose-sweetened beverages providing
25% of energy requirements for 10 wk showed a specific increase in visceral fat in the fructose treatment arm (539). The mechanisms explaining this effect are still unclear but may involve depot-specific modulation of lipogenic enzymes. Further studies are required to establish whether body fat distribution patterns can be influenced by specific nutrients independent of their impact on total adiposity.

### J. Sedentary Lifestyle/Physical Inactivity

A sedentary lifestyle could obviously make an individual more susceptible to be in positive energy imbalance when facing a contemporary diet rich in energy-dense, processed foods and sugar-containing beverages. Whether lack of physical activity increases susceptibility to selective abdominal fat deposition is not firmly established. However, Ross and Janiszewski (475) have reviewed all studies reporting nonsignificant changes in body weight from randomized and nonrandomized exercise trials. The authors found that regular physical activity was associated with a marked reduction in waist circumference even in studies which reported no statistically significant change in body weight. Significant reduction in waist circumference in the absence of weight loss was accompanied in most studies by improvements in cardiometabolic risk variables. These results provide some evidence that regular physical activity/exercise could selectively or at least preferentially reduce abdominal adiposity.

When they selectively examined studies that had measured the amount of visceral adipose tissue by imaging techniques, Ross and Janiszewski (475) also found that regular physical activity/exercise could induce a substantial reduction in visceral adiposity even in the absence of weight loss. Studies that have compensated for the energy expenditure of exercise sessions by a corresponding increase in energy intake have nevertheless shown a loss of visceral adipose tissue (between −10 and −19%) associated with exercise training programs (308, 473, 477).

How could someone lose visceral adipose tissue with exercise training without losing weight? Such finding is likely explained by the fact that under these circumstances, regular exercise can increase fat free mass. This will be the key difference between an energy deficit produced by caloric restriction or by regular exercise. For instance, a negative energy balance resulting from caloric restriction and inducing weight loss should mobilize the visceral fat depot probably to the same extent as regular exercise. However, the potential to increase lean mass associated with regular exercise may explain the discordance between changes in body weight and visceral adiposity when regular exercise and not a hypocaloric diet is used as the modality to create an energy deficit. From a biological standpoint, the peculiar β-adrenergic responsiveness of visceral adipose tissue (166, 549, 581) could explain the selective and greater mobilization of lipids from this depot compared with subcutaneous fat which is driven by the sympathetic drive associated with vigorous exercise. Definite evidence supportive of this possible mechanism is lacking. Nevertheless, it appears from cross-sectional studies and exercise intervention trials that physically active/exercise-trained individuals have a lower proportion of visceral adipose tissue than sedentary/unfit individuals after control for their amount of total body fat.

### V. BIOLOGY OF ABDOMINAL ADIPOSE TISSUES

The biological and physiological nature of adipose tissues located in and around the abdominal cavity can help deciphering the cellular determinants of human body fat distribution patterns as well as the pathophysiologic association of visceral obesity and cardiometabolic risk. This section summarizes basic concepts on the biology of abdominal adipose tissues.

#### A. Anatomical Localization and Morphology and Cell Composition of Abdominal Adipose Tissues

A detailed article was published by Shen et al. (505) proposing a systematic classification of the anatomical localization of human adipose tissues. Whole body adipose tissue has generally been subdivided in two main components: subcutaneous and internal adipose tissue. Subcutaneous adipose tissue is usually defined as the layer found between the skin and the aponeuroses and fasciae of the muscles; it generally includes mammary adipose tissue (505). Closer examination of the subcutaneous adipose tissue depot has led to the identification of two distinct compartments, at least in the trunk region: a superficial layer of adipose tissue evenly distributed under the abdominal skin layer and a deeper subcutaneous adipose tissue compartment, located under the superficial adipose tissue layer (350) (FIGURE 6).

These anatomically distinct abdominal subcutaneous fat compartments are separated by a fascial plane (term superficial or subcutaneous fascia), which is circumferential and fuses with the underlying muscle wall in radiating strands at particular anatomic locations (238, 350).

Internal adipose tissue includes intrathoracic and intra-abdomino pelvic adipose tissue; the former includes pericardial adipose tissue while the latter includes intraperitoneal and extraperitoneal adipose tissue. Intraperitoneal adipose tissue is composed of two major compartments: the greater omentum and mesentery (FIGURE 6); retroperitoneal adipose tissue includes preperitoneal and retroperitoneal adipose tissues (505). Studies using imaging methods of the abdomen have generally focused on the abdominopelvic region, and the usual anatomical boundaries have been the abdominal muscle wall. Thus the compartment corre-
sponding to the widely used “visceral adipose tissue” designation generally has indistinctly included omental, mesenteric as well as extraperitoneal adipose tissue. Only intraperitoneal adipose tissues (mainly mesenteric and omental tissues) are drained by the portal vein, a feature which has been at the center of some hypotheses linking visceral adipose tissue accumulation and metabolic disease (35, 45). Moreover, notable morphological differences have been observed between these adipose tissue compartments. Specifically, fat lobules of the superficial subcutaneous adipose tissue layer are organized in a regular fashion, whereas those of the deep subcutaneous layer and internal compartments, especially the greater omentum, are large, irregular, and less organized (350). Vascularization, blood flow, and innervation may also be quite different among the various compartments, as suggested in other publications (47, 229, 275).

Obviously, significant methodological limitations arise from these anatomical and morphological considerations. The study of abdominal adipose tissue accumulation requires the use of imaging techniques such as CT or MRI, which cannot precisely distinguish each anatomical compartment. Considering all intraperitoneal depots as a single compartment with imaging techniques may have led to an underestimation of the theoretical association between the amount of fat in each subcompartment and metabolic alterations. From the physiological standpoint, visceral adipose tissue samples are relatively difficult to obtain in humans. To gain access to the abdominal cavity, a surgical procedure under general anesthesia is required. The vast majority of available surgery-based studies have focused on omental adipose tissue. Moreover, most studies did not distinguish superficial from deep subcutaneous adipose tissue in the sampling procedure. Hence, while experiments on the biological nature of abdominal adipose tissues certainly are relevant and useful, they must always be considered with caution, due to the sampling method involved (surgical condition often accompanied by either severe obesity or other conditions requiring surgery) and the fact that adipose tissue samples are considered in an isolated manner, without the potential impact of local innervation or blood flow.

B. Adipocyte Size

The size of each fat compartment results from the integration of the size and number of lipid-laden adipocytes, which represent the main cellular component of adipose tissue. Wide interindividual variations are observed in these parameters. The following section will summarize data on abdominal adipose tissue cellularity.

In general, mean adipocyte sizes from all anatomical locations and in both sexes increase along with adiposity level,
but reach a plateau in massively obese individuals (13, 57, 221, 384, 549, 560, 615) (FIGURE 7). This plateau indirectly suggests that the presence of large adipocytes may trigger the generation of new adipocytes to store excess dietary fat (351). Accordingly, adipocyte number is positively associated with adiposity level, and adipose tissue cell populations appear to regenerate constantly during adulthood (522). On the other hand, studies using 14C dating of adipocytes in adults showed that low generation rates of new adipocytes were associated with adipose tissue hypertrophy, whereas high generation rates were associated with adipose tissue hyperplasia (13). Hence, failure to increase adipogenesis during weight gain in adulthood could favor the development of hypertrophic adipose cells.

As mentioned, adipose tissue cellularity is strongly influenced by sex and anatomical localization (57, 165, 549). The association between number or size of adipocytes and obesity level is modulated as a function of anatomical localization and sex of the tissue donor. Lower body fat compartments of obese women contain more adipocytes than those of lean women, whereas obesity is not related to cell number in lower-body compartments of men (560). Consistent with these findings, a longitudinal study performed in men and women showed that adipocyte progenitor cells of the lower body fat compartments can develop rapidly into mature adipocytes in response to overfeeding and that this response depends partially on sex of the participant and baseline adipocyte size (563). These results indirectly suggest that during weight gain, lower-body adipose tissues tend to expand through hyperplasia in women, but through hypertrophy in men (560, 563). Accordingly, lower-body subcutaneous adipocytes of women tend to be larger than those of men for any given adiposity level, while sex differences in abdominal subcutaneous adipocyte size are less apparent (165, 384, 560, 561).

With regard to visceral adipocyte size and number, lean to moderately obese men tend to have larger omental adipocytes than women (165). Conversely, omental fat cells of massively obese women reach a higher maximal cell diameter value (~130 µm) compared with massively obese men (~120 µm) (522). In lean to moderately obese individuals of both sexes, a strong correlation is observed between abdominal subcutaneous adipocyte size and total body fat mass, suggesting that the contribution of adipocyte hypertrophy to abdominal adipose tissue expansion may be similar in men and women (560). As a logical consequence, the higher subcutaneous fat mass values observed in women compared with men may be partly attributable to higher adipocyte number (560). In adult women, expression of genes involved in preadipocyte differentiation is relatively higher in subcutaneous than in visceral adipose tissue (130). Moreover, only subcutaneous expression of these genes tracks with adiposity values. This finding suggests that in women, expansion of the subcutaneous adipose tissue depot relies more heavily on adipocyte hyperplasia than the visceral adipose tissue compartment, which may be predominantly hypertrophic (130).

In women, omental adipocytes are 20–30% smaller than abdominal subcutaneous adipocytes over much of the spectrum of adiposity values (57, 165, 406, 451, 459, 549) (FIGURE 7). In fact, omental and abdominal subcutaneous adipocytes only tend to reach similar sizes at very high BMI values (>60 kg/m²) (57, 406, 451, 459, 549). Women also tend to have larger adipocytes in the lower-body subcutaneous regions compared with abdominal subcutaneous sites (165, 561). Interestingly, as women reach menopause, depot differences in adipocyte size tend to be attenuated since the size of omental cells seems to be specifically increased (554). The presence of larger omental adipocytes along with increased visceral fat accumulation in postmenopausal women suggests that ovarian hormone defi-
ciency may affect adipocyte hypertrophy in this depot (331, 554). In men, adipocytes of the visceral and abdominal subcutaneous fat compartments have similar sizes across the range of adiposity values (57, 134, 165, 167, 348, 451). This suggests that visceral adipocytes become as large as or even larger than abdominal subcutaneous adipocytes in men. Taken together, regional differences in fat cell size and number reflect the propensity of premenopausal women to store more lipids in lower-body and abdominal, subcutaneous compartments through adipocyte hyperplasia, while visceral adipose tissue depots of men (and postmenopausal women) are more prone to manage incoming lipids through adipocyte hypertrophy.

C. Metabolic Activity

Adipocyte size is a critical determinant of adipose tissue function, independent of obesity levels (13, 49, 221, 305, 336, 615). The association between adipose tissuecellularity and obesity-related metabolic alterations is also well established (13, 49, 305, 336, 615). Subcutaneous adipocyte size is related to measures of insulin resistance in both women and men (13, 221, 305, 336, 615). The latter cross-sectional studies are supported by two prospective studies showing that subcutaneous adipocyte hypertrophy is an independent risk factor for developing type 2 diabetes independent of adiposity and body fat distribution (330, 615). Detailed characterization of subcutaneous adipocyte morphology shows that adipose tissue hypertrophy is associated with higher fasting insulin levels and homeostasis model assessment of insulin resistance (HOMA-IR) index independent of body fat mass (13). We have suggested that visceral fat accumulation may have represented an important confounding factor in the relation between subcutaneous adipocyte morphology and measures of insulin resistance (586). Accordingly, Ledoux et al. (305) reported that omental adipocyte size was more closely related to glucose and insulin alterations in obese individuals than subcutaneous adipocyte size. With regard to blood lipid alterations, visceral adipocyte hypertrophy was a better predictor of plasma and very-low-density lipoprotein (VLDL) triglyceride levels and a higher total cholesterol-to-HDL cholesterol ratio than subcutaneous adipocyte hypertrophy (221). Moreover, we found that only visceral adipose tissue hypertrophy predicted fasting hypertriglyceridemia when controlling for body composition and fat distribution in women (586). Adipocyte sizes in both visceral and abdominal subcutaneous adipose tissue compartments have been related to hypertension (305). Such associations of fat cell size with cardiometabolic risk factors likely emerge from adverse changes in the metabolic function of enlarged adipocytes in each compartment.

Hydrolysis of triglyceride-rich lipoproteins catalyzed by LPL and triglyceride synthesis are major determinants of the fatty acid flux and triglyceride storage in a given fat compartment. As mentioned, these processes are tightly related to adipocyte size (134, 146, 606). Most studies which included more men than women showed a higher LPL activity in visceral adipose tissue compared with subcutaneous fat (165, 362, 451, 484, 549, 550). Conversely, most of the studies that included more women than men found higher LPL activity in the subcutaneous fat compartment compared with visceral fat (57, 345, 409, 422). Hence, a large part of the regional differences in LPL activity is explained by the sex of the participants examined. This does not, however, preclude some differences to appear independent of simple sex- and adiposity-related variations in fat cell size. For example, in men, adipose tissue LPL activity is higher in visceral than in subcutaneous adipose tissue (57, 345, 452), despite the fact that similar adipocyte sizes are generally seen in these fat compartments (57, 134, 165, 167, 345, 451). In general, however, LPL activity reflects fat cell size and varies with the propensity of each fat compartment to accumulate lipids in men and women.

Other studies have focused on regional variations in lipid accumulation in vivo. In women, meal-derived fatty acid storage increases in proportion to lower body subcutaneous fat mass, while no association is found between relative lipid uptake in abdominal subcutaneous fat and adiposity measures (272). A preservation of the relative capacity to store fatty acids in adipose tissue from the thigh and femoral regions with increasing adiposity may promote the development of the gynoid fat partitioning phenotype in women. In men, the capacity of abdominal subcutaneous fat to assimilate fatty acids is higher compared with that of the femoral depot (502). Moreover, a significant proportion of fatty acid uptake occurs in visceral adipose tissues of men during the postprandial period (349, 393, 467). Indirect assessment of visceral adipose tissue lipid uptake suggests that this compartment contributes more significantly to remove fatty acids from the circulation in men than in women (393, 467). These observations are corroborated by direct in vivo measurement of fatty acid uptake in each abdominal adipose tissue compartment showing that fatty acid uptake is 30% higher in visceral compared with subcutaneous fat of young healthy males (210). However, when the mass of each fat compartment is taken into account, the net contribution of subcutaneous fat to systemic lipid extraction was 1.5 times higher than that of visceral adipose tissue (210).

Adipose tissue blood flow in the postprandial state may also represent an important determinant of regional differences in lipid accumulation (467). Increased blood flow is observed in lower body adipose tissue following meal ingestion in women, but not in men (467). Consistent with these observations, triglyceride synthesis from glucose is lower in omental compared with abdominal subcutaneous adipose tissue in women (134, 354), but is similar in both fat depots in men (134). These findings suggest that slightly divergent mechanisms may be at work in the regulation of lipid accu-
mulation in each fat compartment (606). Also consistent with this hypothesis, femoral fat has a lower fatty acid flux than abdominal subcutaneous fat (286, 366) and in proportion seems to rely more heavily on plasma nonesterified fatty acids and VLDL triglyceride-derived fatty acids compared with abdominal fat which relies more heavily on chylomicrons (366).

The expandability of adipose tissue has now emerged as a major determinant of dyslipidemia and insulin resistance in obesity, and also as a major target for therapeutic intervention. Insulin resistance and dyslipidemia can be observed in rare genetic forms of lipodystrophies in humans or in a number of murine models of fat storage deficiency (192). These models show that lack of adequate lipid storage, much like excess lipid storage, is associated with metabolic disturbances. For example, selective disruption of the key adipose tissue adipogenic transcription factor peroxisome-proliferator activator receptor-γ2 (PPAR-γ2) in mice leads to phenotypes of insulin resistance, with or without lipodystrophy (368, 639). Conversely, through stimulation of fat cell hyperplasia with compounds such as PPAR-δ dystrophy (368, 639). Conversely, through stimulation of fat cell hyperplasia with compounds such as PPAR-γ agonists (thiazolidinediones; TZDs), small, insulin-sensitive adipocytes are generated in subcutaneous compartments and lead to improvements of the metabolic profile, especially in prediabetic subjects (171, 186). Such findings demonstrate that metabolic alterations may arise from reduced adipose tissue expandability when facing caloric excess and spillover of lipids to other tissues such as the liver and muscle (162, 192, 386, 454) [FIGURE 8]. According to this concept, adipose tissue stores, especially the peripheral subcutaneous compartments, are viewed as lipid-buffering tissues that help maintain the homeostasis of daily lipid fluxes (162). In recent in vivo studies, fatty acid storage from the pool of plasma triglycerides was reduced in subjects with abdominal obesity (365). Specifically, abdominal obesity was associated with a relative inability to induce fat storage after meals, and failure to extract fatty acids derived from chylomicron triglycerides (365). Consistently, elegant single-cell experiments in simian adipose tissues have also shown that insulin sensitivity and lipid uptake decreases in proportion to fat cell size, and that adipocytes larger than 80–100 μm have a reduced capacity to accommodate more lipids (583). The latter mechanisms likely describe a major contributor to the metabolic alterations related to visceral obesity in humans (365, 583).

Lipid accumulation in a given fat compartment reflects the balance between triglyceride synthesis and lipolytic rates. Again, fat cell size is a critical determinant of lipolytic responsiveness. Analyses of adipocyte populations separated according to cell size show that larger adipocytes have higher basal and stimulated rates of lipolysis (146). A large number of studies have now reported higher basal lipolysis in subcutaneous compared with omental abdominal subcutaneous adipose cells (24, 58, 134, 166, 217, 222, 362, 406, 448, 452, 459, 464, 549, 581, 641), with little exceptions (57, 334), regardless of the participant’s sex and degree of adiposity.

Yet, subcutaneous and visceral adipose tissues seem to display depot-specific responsiveness to lipolytic regulators. Lipolysis was shown to be more responsive to β-adrenergic agonist stimulation in omental adipocytes compared with subcutaneous cells (134, 459, 464, 549). Omental cells are also clearly less sensitive to insulin-mediated suppression of lipolysis in both sexes (58, 362, 369, 641). In lower body fat stores, lipolysis is almost completely blunted at high doses of insulin while visceral adipose tissue lipolysis is only suppressed by half in these conditions (369). Regional differences have also been documented in basal and insulin-stimulated glucose uptake, with higher rates in omental than in subcutaneous adipocytes (335, 344, 541, 614). However, while visceral adipocytes are resistant to the antilipolytic effect of insulin compared with subcutaneous adipocytes (362, 641), no obvious difference in the sensitivity of glucose uptake to insulin has been observed (335, 344, 541, 614). Studies on adipose tissue expression of genes coding for molecules of the insulin signaling cascade are also concordant with an apparent dissociation of lipolysis and glucose uptake in response to insulin (29, 182, 335, 337, 585, 641). These results indirectly suggest that lipolysis and glucose uptake could be regulated in a divergent manner by insulin in each fat compartment.

Abundant in vivo studies by the Jensen group (30, 201, 233, 353, 395) have now shown that whole body subcutaneous adipose tissue is the major source of circulating nonesterified fatty acids, contributing more than 85% of systemic nonesterified fatty acid release in various clinical conditions. In lean individuals, as little as 5–10% of nonesterified fatty acid released in the portal vein are predicted to originate from visceral adipose tissue lipolysis. However, with increasing visceral fat mass, visceral adipose tissue is predicted to contribute to nearly 50% of portal vein nonesterified fatty acid release (395). Elegant studies in dogs are also consistent with a potential role of excess lipolysis in the development of obesity-related metabolic alterations. High-fat feeding leading to increases in visceral and subcutaneous fat generates a highly significant stimulation of nocturnal nonesterified fatty acid release which could contribute to excess nonesterified fatty acids under conditions of high-fat feeding (258).

Overall, available studies on adipose tissue metabolism suggest that adipocyte size is a crucial determinant of regional differences in lipid metabolism (13, 49, 221, 305, 336, 615). A relatively more efficient accumulation of lipids in the visceral fat compartments is observed in men compared with women (165). The inability to efficiently store postprandial lipids likely contributes to excess nonesterified
fatty acids and subsequent development of metabolic alterations (162, 192, 365, 386, 454, 583). On the other hand, the proportion of fatty acids released from visceral adipose tissues increases with visceral obesity, possibly through the combination of visceral adipocyte hypertrophy as well as increased relative lipolytic responsiveness to positive lipolytic stimuli and blunted inhibition by insulin specifically in visceral adipose tissue (134, 362, 459, 464, 549, 641). Accordingly, in vivo experiments demonstrated that while visceral adipose tissue lipolysis accounts for a small proportion of whole body nonesterified fatty acid release, the contribution of this depot may be particularly apparent in the nocturnal phase (258) and increases up to ~50% along with visceral fat accumulation (395).
D. Adipose Tissue Cytokine Release

Adipose tissue secretes a number of cytokines, also termed adipokines, as well as many other factors involved in the regulation of several biological processes (6, 378, 571). Adipokines are mainly secreted by adipocytes or preadipocytes, but also, especially in obesity, by macrophages invading the tissue (149, 392, 571). Chronic, low-grade inflammation caused by altered adipokine secretion may alter glucose and lipid metabolism and contribute to cardiometabolic risk of individuals with visceral obesity (149, 571). Again, adipocyte size and adipose tissue distribution are key determinants of inflammatory cytokine secretion (129, 189, 215, 226, 517). A detailed review of the literature on every adipose tissue-derived adipokine is beyond the scope of this article, and the reader is referred to excellent review papers on this specific topic (21, 407, 447). This section will briefly highlight how adiponectin, leptin, and inflammatory cytokine secretion relates to visceral obesity.

Circulating concentrations of adiponectin, an adipocyte-derived adipokine with insulin-sensitizing and anti-inflammatory properties, are inversely associated with visceral obesity (617). Adiponectin secretion by omental adipocytes is markedly reduced in viscerally obese women, suggesting that reduced visceral adipocyte adiponectin secretion is a significant contributor to hyperadiponectinemia in abdominally obese women (129, 381). Although adiponectin has numerous effects on the arterial wall, on the liver, as well as on insulin actions, its independent contribution to the etiology of CVD remains controversial as a systematic review and meta-analysis failed to identify this adipokine as an independent risk factor for cardiovascular outcomes (491). It appears clear, however, that low adiponectinemia predicts an increased risk of type 2 diabetes (322, 529). Therefore, it remains premature to identify adiponectin as a target for CVD prevention.

Leptin, an adipokine mostly derived from the adipocyte, plays a key role in the regulation of energy intake and energy expenditure and circulates in concentrations that are proportional to body fat mass (515). Leptin expression and secretion are higher in subcutaneous than in visceral adipocytes (580). Moreover, subcutaneous adipocyte size is positively correlated with plasma leptin levels independent of adiposity, suggesting that hyperleptinemia in obese subjects is likely due to a combination of increased subcutaneous fat accumulation through hypertrophy and higher secretion rates (336, 580). As for adiponectin, the contribution of leptin as a CVD risk factor remains quite debated as there is currently little evidence that it is an independent CVD risk factor (91, 433, 490). Leptin rather appears to be related to total adiposity rather than to visceral adiposity/ectopic fat (92, 582).

Adipose tissues also secrete other factors potentially involved in the regulation of metabolic pathways. Abdomi-
lowest in omental preadipocytes. Consistent differences were also observed regarding other markers of preadipocyte differentiation such as glycerol-3-phosphate dehydrogenase activity, aP2 protein abundance, PPAR-γ and CCAAT/enhancer binding protein-α expression (558).

A few other studies have focused on additional characteristics of mesenteric adipose tissue in humans. For example, both subcutaneous and mesenteric preadipocytes seem to have a higher replicative potential compared with omental cells and a reduced apoptosis rate in response to TNF-α (559). Although the number of cells from the stroma-vascular cell fraction that are committed to the adipocyte lineage appears to be quite similar among abdominal fat compartments, the number of macrophages expressing aP2 was found to be higher in omental than in subcutaneous fat cells, while being intermediate in the mesenteric fat depot (562). In diabetic subjects, CD36 and 11β-HSD-1 expression were increased in mesenteric fat compared with subcutaneous and omental fat, suggesting that this depot may, indeed, play a role in the development of metabolic alterations (632). The activity of AMP kinase was found to be lower in both mesenteric and omental fat tissue compared with the subcutaneous depot of obese individuals, which was associated with increased expression of genes related to inflammation (185). Finally, a number of studies have shown that mesenteric fat may be involved to some extent in the pathophysiology of Crohn’s disease (26, 34, 39, 492).

More research is needed to characterize the biological nature of mesenteric adipose tissue and its role in the pathophysiology of the metabolic diseases related to visceral obesity. Studies on the measurement of mesenteric fat thickness (327, 328) may also eventually help decipher the relative contribution of this fat depot to cardiometabolic risk.

VI. INTEGRATIVE VIEW OF VISCERAL ADIPOSE TISSUE/ECTOPIC FAT AND ITS RELATION TO METABOLIC COMPLICATIONS

Robust evidence shows that visceral obesity is associated with an insulin-resistant state that increases the risk of developing type 2 diabetes. However, whether there is a causal relationship between excess visceral adiposity and insulin resistance remains uncertain. We have previously proposed three scenarios (112, 113) to explain how excess visceral adiposity could be linked to metabolic complications [FIGURE 8]. 1) The first model would focus on the peculiar metabolic profile of visceral versus subcutaneous adipocytes, the former being hyperlipolytic and resistant to the antilipolytic effect of insulin, leading to overexposure of nonesterified fatty acids to the liver, to impairment in liver metabolism leading to overproduction of apolipoprotein B-containing lipoproteins, increased hepatic glucose production, and reduced hepatic degradation of insulin, exacerbating systemic hyperinsulinemia. 2) The second possibility is the inflammatory profile of visceral adipose tissue, which is infiltrated by inflammatory macrophages when hypertrophied, contributing to the generation of a global proinflammatory profile, further exacerbating insulin resistance. 3) Finally, we have also proposed (as discussed in previous sections) that excess visceral adiposity may be a consequence of the relative inability of the subcutaneous adipose tissue to act as an expanding metabolic buffer, protecting other organs against ectopic fat deposition, not only in the liver, the heart, and the skeletal muscle but also in other potentially important organs such as the kidney and the pancreas.

Hypertriglyceridemia is a central correlate of visceral obesity. It is caused by a combination of increased liver VLDL triglyceride production and impaired clearance from the circulation (547). Fatty acid availability within the hepatocyte and insulin are two major modulators of VLDL assembly and secretion. Because of the hyperlipolytic state of the expanded visceral adipose tissue, the liver of viscerally obese patients is exposed to an increased flux of fatty acids which contribute to an increased synthesis of triglycerides, which are incorporated into VLDL particles and secreted into the circulation mainly as large VLDL₁ particles. Therefore, liver steatosis due in part to increased adipose-derived fatty acids is a major contributor to the hypertriglyceridemic state of visceral obesity (545, 546, 634). Impaired insulin action in the liver is another feature contributing to hypertriglyceridemia. In viscerally obese patients, hyperinsulinemia promotes lipogenesis via the activation of sterol-regulatory binding protein 1c, a transcription factor controlling the expression of enzymes involved in hepatic fatty acid synthesis (150, 511, 629). Normally, insulin would reduce VLDL secretion by the liver (84, 319, 342, 523). However, insulin has a blunted ability to inhibit VLDL secretion in visceral obesity, leading to increased VLDL secretion and hypertriglyceridemia (545, 546, 634). The insulin resistance of visceral obesity is also associated with reduced availability of the triglyceride-hydrolyzing enzyme LPL (237, 440). Such phenomenon combined with subtle changes in VLDL composition is associated with a reduced clearance of VLDL remnants along with an increase in their residence time (237).

As mentioned, visceral obesity is also associated with a low-grade inflammatory state (79, 89, 164, 295, 312, 636). Both the inflammatory cells (macrophages) and the adipocytes themselves secrete many molecules, including proinflammatory cytokines that can impact tissues locally and systemically (152). A key factor regulating lipid oxidation in the liver is adipose tissue-derived cytokine adiponectin, and plasma concentrations of this cytokine are reduced in visceral obesity and type 2 diabetes (89, 225, 295, 616). Altered cytokine levels may reach the liver through portal circulation and act with locally produced cytokines to alter
hepatic lipid metabolism, exacerbating steatosis and VLDL triglyceride output into the bloodstream (377).

In addition to VLDL secretion by the liver, insulin resistance may also be associated with overproduction of triglyceride-rich lipoproteins by the intestine from endogenous fatty acids. Such phenomenon may contribute to fasting hypertriglyceridemia (132), although its relative importance remains to be quantified. This topic represents a very fertile area of investigation for future studies. Overall, there is solid evidence that liver fat content, being so proximal to the plasma cardiometabolic risk profile, is closely related to overproduction of triglyceride-rich lipoproteins and glucose, contributing to the impaired glucose homeostasis/dyslipidemic state found in viscerally obese patients (5, 267, 634). Some studies even suggested that the relationship between visceral obesity and metabolic complications may be largely explained by concomitant variation in liver fat content (143, 271).

VII. CAN WE FAVORABLY ALTER BODY FAT DISTRIBUTION?

A. Pharmacotherapy

1. Weight loss drugs

The development of obesity pharmacotherapy has been a very difficult quest as the safety record of some of the agents that were developed and introduced in clinical practice has led to their withdrawal due to undesirable side effects (230, 321, 548, 621). For example, three drugs that had been previously approved by regulatory authorities for weight loss (dexfenfluramine, sibutramine, and rimonabant) and with different mechanisms of action were found to induce variable losses of visceral adipose tissue but were removed from clinical use because of various side effects (230, 321, 548, 621). Currently, the only remaining drug still indicated in clinical practice for the long-term management of obesity is orlistat. It inhibits the activity of gastric and pancreatic lipases and decreases dietary lipid digestion and absorption by ~30% (212). Although many clinical trials have reported that it can induce a slightly greater weight loss than the use of a placebo combined with a lifestyle modification program, there is no evidence that this pharmacological approach can selectively mobilize visceral adipose tissue/ectopic fat depots beyond what is to be expected by overall weight loss.

During the preparation of this review article, two new weight loss drugs have been approved by the Food and Drug Administration for chronic management of obesity. The first, lorcaserin, is a selective serotonin 2C receptor agonist that has been shown to reduce body weight in obese patients as well as in obese patients with type 2 diabetes (352, 402, 518, 519). The other drug approved is actually a combination of phentermine, a central norepinephrine-releasing agent, with topiramate which has been used for the treatment of epilepsy and migraine (172, 183). Although both lorcaserin and phentermine/topiramate have been considered by the Food and Drug Administration to have a favorable benefit-to-risk ratio and to induce greater weight loss than a placebo combined with a lifestyle modification program, both drugs have been largely tested in lower risk obese women rather than in higher risk men. Therefore, these drugs have not been selectively tested in high-risk viscerally obese patients, and we do not know whether these compounds could have a selective effect on visceral adiposity/ectopic fat beyond the mobilization of “harmful” fat depots to be expected from weight loss per se. There is, therefore, a paucity of data on the ability of these newly approved drugs to possibly induce a mobilization of visceral adipose tissue and of related ectopic fat depots. Considering the fact that excess visceral adiposity/ectopic fat is an important modulator of cardiometabolic risk in overweight/obese patients, we have previously proposed that a new paradigm was needed in the evaluation of “weight loss” drugs and that other end points such as loss of visceral adipose tissue and mobilization of ectopic fat depots should eventually be considered. This issue clearly deserves more attention. It is therefore suggested that one key challenge of the field will be to select the right patient for the right drug. On that basis, it is very unlikely that an antiobesity blockbuster drug will be successfully developed for widespread use (122). Rather, as a general rule, patients receiving weight management medication should be properly selected, and health improvements rather than weight loss per se should be the main goal of therapy.

2. Thiazolidinedione

Thiazolidinediones (TZDs) act by stimulating adipogenesis, particularly in the subcutaneous compartments and recruit new small adipocytes, which can better accommodate excess dietary lipids (376, 631). Such treatment has a favorable effect on the comorbidities related to abdominal, visceral obesity, as reviewed elsewhere (570, 631, 633). These agents are ligands for the PPAR-γ, which is a key transcription factor in the regulation of adipogenesis (570). These mechanisms would account for most of the favorable effects of TZD treatment. However, the side effects of TZDs must be taken into account, specifically an increased risk of heart failure, which has been closely examined (220, 289, 399, 535, 643). Rosiglitazone was recently found to have little impact on ultrasound measures of saphenous vein graft atherosclerosis but significantly improved cardiometabolic risk variables in postcoronary artery bypass graft patients (40, 41). These results are consistent with a meta-analysis showing a protective effect of TZD treatment on carotid intima-media thickness or pulse wave velocity (610). Thus, in addition to their very significant impact on our understanding of the pathophysiology of the metabolic complications as-
sociated with abdominal obesity, TZDs appear as potentially valuable drugs to alter body fat distribution and improve cardiometabolic risk (633). The significant side effects of these compounds obviously have to be considered seriously, and under the current debate (329), their future in clinical practice is uncertain. Whether they could be combined with other drugs is also currently investigated (435, 642).

3. Growth hormone treatment

Whether growth hormone (GH) treatment is effective in treating visceral obesity has been uncertain as suggested by a few studies, and a critical analysis proposing that GH deficiency was secondary to obesity or visceral obesity (501, 577). Nevertheless, several studies including randomized placebo-controlled studies have now shown beneficial effects of GH therapy on visceral fat accumulation and related outcomes in various populations (33, 161, 412, 527, 528). Moreover, a recent meta-analysis suggested that GH therapy does decrease visceral adiposity and increase lean body mass while also having beneficial effects on the lipid profile in obese adults (370). These changes apparently do not include weight loss and generally increase fasting plasma glucose and insulinemia (370). GH-releasing hormone therapy has also been shown to have similar effects (593). The magnitude of the changes induced through therapy remains, however, a matter of controversy, and a clinical role for GH therapy in the treatment of visceral obesity remains uncertain (370, 412).

The effects of GH on visceral fat have been proposed to result from its well-known lipolytic properties (144, 333). In such situations, visceral adipose tissue lipolysis will be expected to be stimulated to a larger extent than peripheral adipose tissue lipolysis (14, 549). Serum concentrations of IGF-I and IGFBP-3 are recognized markers of the biological effects of GH, although other factors such as age and sex also need to be considered (100, 240). Interestingly, IGF-I and IGFBP-3 concentrations are more closely related to visceral adipose tissue accumulation than overall adiposity (100).

The effects of GH treatment on the metabolic profile are thought to occur partly through changes in inflammatory markers (160), which are possibly mediated through IGF-I (277). On the other hand, GH may also act by downregulating 11β-HSD-1 in adipose tissue (379, 418). This hypothesis stems from studies showing that fluctuations of GH and IGF-I levels through medication changes in patients with acromegaly correlate with corresponding changes in urinary glucocorticoid metabolites (379). In vitro studies show that 11β-HSD-1 o xo reductase activity is inhibited by IGF-I, but not GH (379). Moreover, the impact of GH/IGF-I on cortisol metabolism may be transient (514), and needs to be further confirmed. Finally, studies on the GH receptor (GHR) have recently shed light on the notion of a possible GH resistance in individuals with idiopathic abdominal obesity (141). Previous work had shown that adipocytes express the GHR as well as a truncated form, trGHR, the latter which could interfere with GH signaling (23, 479, 611). Recent work by Goodyer et al. (141) has shown that omental and subcutaneous adipose tissue GHR mRNA levels displayed significant negative correlations with a spectrum of indicators of obesity while in subcutaneous fat there was a significantly higher trGHR/GHR ratio with increasing adiposity. These results are consistent with the notion of a reduced sensitivity to GH in adipose tissues of obese individuals (141).

4. Steroid hormone therapies

With regard to steroid hormone therapies, it seems that the correction of the relative androgen deficiency in men and ovarian hormone (estrogen) deficiency in women leads to improvement of the metabolic profile, at least partly through modulation of body fat distribution. However, substitutive hormonal treatments obviously need to be considered in the context of their effects or side effects on other systems. For example, female hormone replacement therapy has been seriously reconsidered or even abandoned by many women following data indicating that the oral combination of equine estrogens and a progestin causes a 26% increase in the incidence of breast cancer at 5.2 yr of follow-up with a negative impact on cardiovascular events (480). On the other hand, the link between androgen replacement and favorable body composition/fat distribution changes is increasingly recognized in hypogonadal, aging males (43). Further studies are required to determine whether other androgen replacement modes such as DHEA, for example, could be suitable for metabolic improvements in men or women (287, 288, 598). Inhibitors of local cortisol generation by 11β-HSD-1 are currently considered as a potentially important avenue for future drug development (73, 184). In a recent study, addition of one of these inhibitors (INCB13739) to metformin therapy in patients with inadequate glycemic control was efficacious and well-tolerated, showing for the first time that decreasing local cortisol exposure through 11βHSD-1 inhibition improves hyperglycemia over 12 wk in patients with type 2 diabetes (469). Thus inhibition of local cortisol generation may offer a new potential approach to control abdominal obesity-related alterations and cardiometabolic risk factors in type 2 diabetes.

B. Lifestyle (Nutrition, Physical Activity/Exercise)

Although the correlation is not close to unity, there is a highly significant positive association between the amount of total body fat and visceral adiposity (shared variance of ~50%) (118, 318, 443). Therefore, any intervention that will reduce total adiposity will likely induce some (albeit
variable) loss of abdominal fat. Whether weight loss generated by a lifestyle modification program will lead to preferential loss of visceral versus subcutaneous adipose tissue has been previously discussed in excellent reviews (82, 472, 476, 520), and a full coverage of this topic is beyond the scope of the present paper. As a general rule, studies examining the effects of weight loss modalities (diet, physical activity/exercise, pharmacologically induced weight loss) have all shown that the greater the initial amount/proportion of visceral adipose tissue, the greater is the loss of visceral relative to subcutaneous adipose tissue in response to weight loss (309, 578). Thus factors associated with the proportion of visceral adipose tissue (age, sex, ethnicity, initial level of physical activity/fitness, use of medications known to affect energy partitioning such as the TZDs, menopausal status, etc.) will affect the response of regional fat depots to lifestyle modification programs. Whether a similar caloric deficit induced by diet or by an exercise program will generate the same loss of visceral adipose tissue in a given individual is debated. As discussed in a previous section of this paper, the advantage of vigorous regular exercise over caloric restriction is that it could preserve or even increase lean muscle mass. Under such circumstances, a loss of visceral adipose tissue and a reduction in waist circumference could be found even in the absence of weight loss (as the loss of adipose tissue would have been compensated by an increase in lean tissue leading to no change in body weight), which could be predictive of improved cardiometabolic risk factors. Overall, it is fair to state that the visceral fat depot (as well as liver fat) appears to be readily mobilized when a lifestyle modification program is able to successfully produce a negative energy balance (82, 411, 472, 473, 476). The question as to which lifestyle factors optimize loss of visceral adipose tissue/ectopic fat and long-term benefits will require further studies.

VIII. CONCLUSIONS AND PERSPECTIVES

With the epidemic proportions achieved by the prevalence of obesity worldwide, it is crucial that we fully understand the factors driving the risk of chronic disease in overweight/obese patients. Widely published research over the last 30 years has identified the regional distribution of body fat as a key phenotype associated with the complications which had, in the past, been associated with excess total body fat per se. Considerable variation in body fat topography is observed with age, sex, genetics, ethnicity, hormonal factors, diet, level of physical activity/exercise, pharmacological agents, and other factors such as smoking and stress.

Although an increase in total body fat is associated with an increase in health risk, the amount of abdominal fat, particularly when located within the abdominal cavity, has been associated with an increased risk of comorbidities such as type 2 diabetes, CHD, stroke, sleep apnea, hypertension, dyslipidemia, insulin resistance, inflammation, and some types of cancer. This phenomenon is usually verified at any level of total body adiposity.

Observational and experimental studies have shed some light as to why excess visceral adipose tissue may only partly be causally related to atherogenic and diabetogenic cardiometabolic abnormalities. The notion that excess visceral adiposity may be a marker of dysfunctional subcutaneous adipose tissue leading to ectopic fat deposition (undesired lipid accumulation at the heart, liver, skeletal muscle, pancreas, etc.) is increasingly recognized (FIGURE 8). Although early investigations conducted in the 1960s had received modest scientific attention, the study of subcutaneous adipose tissue morphology and metabolism now benefits from renewed interest. Considerable progress should be expected from the combination of in vitro work with integrative physiology and metabolic studies. How regional adipose tissue morphology and metabolism responds or does not adequately handle energy surpluses or deficits should provide clues on how to manage the complications of visceral obesity. Meanwhile, designing new programs to help individuals reshape their nutritional and physical activity habits in a cost-effective manner combined with the possible development of new, safe pharmacological approaches to target excess visceral/ectopic fat should improve our ability to cope with the devastating consequences of this epidemic, which was unfortunately assessed with a suboptimal metric: the BMI. In this regard, the waist circumference measurement has been shown to add to the BMI, improving risk assessment at any BMI level, particularly when it is accompanied by the elevation of a simple blood marker: triglycerides (a condition that we first described as “hypertriglyceridermic waist”). It is hoped that this work will pave the way to the development of better, yet simple tools allowing primary care physicians to better assess their patient’s risk at any given adiposity level.

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PATHOPHYSIOLOGY OF HUMAN VISCERAL OBESITY


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ANDRÉ TCHERNOF AND JEAN-PIERRE DESPRÉS


Ryan AS, Nicklas BJ, Berman DM. Is weight loss the optimal target for obesity-related cardio-


