Epidemiological, clinical, and mechanistic preclinical studies conducted in the field of cardiovascular medicine have led to remarkable progress in our understanding of nonmodifiable and modifiable risk factors for cardiovascular disease (CVD). For instance, although the prevalence of CVD had reached devastating levels in the 1950s, proper focus on the major CVD risk factors first identified at the time, such as smoking, hypertension, and high cholesterol levels, has allowed these risk factors to be targeted both at the clinical level and through public health policies. As a consequence, coronary heart disease mortality has decreased by ≈50% over the past 50 years. Ford et al have suggested that better screening and medical management of these CVD risk factors and the medical procedures developed to treat the various acute manifestations of CVD have had a favorable impact on its related mortality rates. However, the current overconsumption of processed and energy-dense food products of poor nutritional value combined with our sedentary lifestyle have contributed to the emergence of new drivers of CVD risk: obesity and type 2 diabetes mellitus (Figure 1). It has been proposed that our medical progress at tackling CVD could be offset, at least to a certain extent, by the dramatic consequences of our toxic lifestyle, which includes poor nutrition or excess caloric consumption and a sedentary lifestyle, both leading to obesity and type 2 diabetes mellitus.

Thus, the mosaic of modifiable CVD risk factors has evolved over the past 50 years with, on the one hand, less influence of smoking, and of untreated hypertension and high cholesterol, as well, but, on the other hand, an increased prevalence of sedentary overweight/obese patients having either type 2 diabetes mellitus or a constellation of metabolic abnormalities linked to insulin resistance: the so-called metabolic syndrome.

The exploding obesity epidemic has put this emerging risk factor at the front of CVD risk assessment and management. Accordingly, the American Heart Association has published several position papers to document and emphasize the health hazards of obesity. At the population level, although it is clear that more obesity is associated with more type 2 diabetes mellitus and with a greater risk of developing a variety of cardiovascular health outcomes, this condition (obesity) is very complex and heterogeneous as a phenotype. The present review article will discuss to what extent the individual variation in regional body fat distribution is one of the key variables explaining the metabolic heterogeneity of obesity and its related cardiovascular risk. Because numerous comprehensive review articles have been previously published on this topic, the reader will be referred to many of these earlier articles in the initial sections of this narrative review. Furthermore, to repeat concepts, findings, and issues already addressed in previous review articles, a succinct overview of the old literature on body fat distribution will be provided to focus instead on recently published studies on the topic.

Defining Obesity: Beyond the Body Mass Index

Obesity is generally defined by an excess of body fat and is most often estimated by the ratio of weight over height, the most commonly used anthropometric index being the body mass index (BMI) expressed in kilograms per meter squared. Many prospective studies have reported a J-shaped curve between the BMI and mortality/morbidity. On the basis of this relationship, many organizations have proposed BMI categories defining underweight, normal weight, overweight, and several stages of obesity. Significant relationships between BMI and various health outcomes have been reported in all ethnic groups. Although studies that have examined the association between anthropometry to risk factors have led to the proposal of using lower BMI thresholds to define overweight/obesity in East and South Asians, cohort studies using mortality as an end point do not appear to consistently support the need for lower BMI thresholds for the Asian population.

Despite the clear evidence linking obesity to various health outcomes including CVD, obesity has at times been a puzzling condition for clinicians because it is quite heterogeneous. More than 2 decades ago, we reported that equally overweight or obese individuals having the same amount of total body fat could nevertheless be characterized by markedly different risk factor profiles. Through imaging techniques such as computed tomography, we documented that the subgroup of obese patients with metabolic abnormalities such as insulin resistance and the high triglyceride–apolipo-
protein B–low high-density lipoprotein–cholesterol atherogenic dyslipidemia were characterized by an excess of abdominal visceral adipose tissue (Figure 1), whereas those obese patients who had a “normal” metabolic risk profile were characterized by low levels of visceral adipose tissue and by subcutaneous obesity.19 Many years later, the term metabolically healthy obese subjects was even coined to describe these obese patients without features of the metabolic syndrome.20,21 Clearly, irrespective of the terminology used to describe such metabolic heterogeneity among equally obese patients, it obviously represents a challenge to the CVD risk assessment and clinical management of overweight/obese patients.

Figure 1. Some of the alterations in the metabolic risk profile that have been found to be related to abdominal obesity assessed by anthropometry and later to excess visceral adiposity/ectopic fat assessed by imaging techniques. This constellation of metabolic abnormalities increases the risk of type 2 diabetes mellitus and of various cardiovascular outcomes. CVD indicates cardiovascular disease; HDL, high-density lipoprotein; LDL, low-density lipoprotein.

Regional Body Fat Distribution and the Metabolic Heterogeneity of Obesity: The Pioneers

In 1947, a French physician from Marseille, Jean Vague, reported in a French medical journal that his obese patients with diabetes or clinical signs of CVD had a central distribution of body fat (he referred to it as male-type or android obesity), whereas he suggested that the typical female body fat pattern of lower gynoid fat accumulation was rarely associated with complications.22 In 1956, Vague published his observations and proposed his hypothesis in the English scientific literature.23 These findings were initially received with skepticism by the medical community. Although some sparse supporting evidence was published over the next decades, it took >35 years before these early clinical observations received support from more modern epidemiological and clinical studies. In the early 1980s, 2 groups of investigators, one from Sweden and the other from the United States, produced almost at the same time solid evidence that a simple index of regional body fat distribution, the ratio of waist-to-hip circumference or waist-to-hip ratio (WHR), was more strongly correlated to metabolic complications and to cardiovascular outcomes than the BMI.24–28 For instance, independently of the BMI, a high WHR was found to be predictive of an increased risk of dyslipidemia, hypertension, CVD, and type 2 diabetes mellitus. Such converging observations really spurred the interest of the medical/scientific community, and they were followed by a stream of metabolic and prospective studies confirming the genuine relationship of body fat distribution to health outcomes.19,29–37 Indeed, most of these studies confirmed the notion that the regional distribution of body fat was much more important than excess adiposity per se in driving the CVD risk associated with a given excess of body weight/fat. Thus, although the BMI was found to be an adequate index of adiposity to describe populations, these studies suggested that this simple anthropometric index of total adiposity had to be accompanied by indices of body shape (such as the waist circumference or the WHR) to discriminate these overweight/obese patients with a high-risk body fat pattern.

From Anthropometry to Imaging

The rationale for the use of waist circumference or the WHR was simple: the greater the waistline for a given BMI or a given hip girth, the greater would likely be the relative amount of abdominal fat.38 Despite its added value in determining risk associated with a given BMI, these anthropometric measures have their limits and are of little help to understand the mechanism(s) by which body fat patterning could affect health risk. For instance, as shown in Figure 2, an enlarged waist circumference could be due to increased abdominal subcutaneous or visceral adipose depots (or both).

The use of imaging techniques such as computed tomography (initially) and MRI have represented remarkable advances in our ability to precisely and reliably quantify individual differences in body fat distribution and to selectively distinguish subcutaneous adiposity from visceral adipose tissue. With these techniques, Tarui’s team in Japan34 and Sjöstrom et al39 in Sweden have documented the substantial variation in regional fat accumulation at any BMI value. Thus, it became evident that our ability to store fat in various adipose tissue compartments could markedly differ from 1 individual to
another. For instance, although the bulk of our body energy is stored in subcutaneous adipose tissue, some individuals can accumulate substantial amounts of adipose tissue in their abdominal cavity. When present, such an excess of intra-abdominal or visceral adipose tissue has been reported to be quite detrimental and associated with a constellation of metabolic abnormalities including insulin resistance, hyperinsulinemia, glucose intolerance, type 2 diabetes mellitus, an atherogenic high triglyceride–apolipoprotein B–small, dense low-density lipoprotein–low-high-density lipoprotein–cholesterol dyslipidemia, inflammation, altered cytokine profile, impaired fibrinolysis, and increased risk of thrombosis, and endothelial dysfunction, as well (Figure 1).29–31,40–47 Obviously, such associations with cardiometabolic risk markers could provide a link for the body fat distribution–CVD association. Numerous comprehensive review articles have been published on this issue, and the reader is referred to these earlier articles.29–31,40–47 Recent large cohort studies such as the Framingham Heart Study and the Jackson Heart Study that have extensively used computed tomography imaging technology have generated robust and convincing evidence that excess visceral adiposity (along with other markers of excess ectopic fat deposition such as excess heart, liver, and intrathoracic fat, etc) is significantly correlated with various cardiometabolic abnormalities in a manner that is independent from the concomitant variation in the amount of total or subcutaneous fat.48–54 Even in patients with type 2 diabetes mellitus, studies by Sam and colleagues have documented that there is a highly significant relationship between visceral adiposity and plasma lipoprotein levels,55 and inflammatory markers, as well.56 Such association was independent of patients’ metabolic control.

The present review article will make the point, however, that such robust association cannot be considered as evidence of a cause-and-effect relationship between excess visceral adiposity/ectopic fat and the above constellation of metabolic abnormalities. Nevertheless, it has become clear that an excess of visceral adipose tissue could be considered as a good marker of an altered cardiometabolic risk profile predictive of increased risk of type 2 diabetes mellitus and CVD.

**Estimating Visceral Adiposity From Anthropometry Requires the Measurement of Both the BMI and the Waist Circumference**

Because there is considerable variation in visceral adiposity at a given BMI value, we proposed, >15 years ago, that the measurement of waist circumference could represent a simple and inexpensive marker of visceral adiposity.38 Thus, we suggested that a larger waistline for a given BMI would predict a greater accumulation of visceral adipose tissue. However, this initial finding was first interpreted by some as evidence that waist circumference could represent a convenient and simple anthropometric marker of visceral adiposity. Results presented in Figure 2 clearly indicate that it cannot be the case. For instance, in a convenience sample of men used in some of our cardiometabolic studies, waist circumference was found to be even better correlated with total body fat mass or subcutaneous adiposity than with the amount of visceral adipose tissue. Therefore, it is important to keep in mind that waist circumference is, above all, an index of total adiposity that cannot distinguish visceral from subcutaneous abdominal adiposity.
Excess Visceral Adiposity: A Culprit or a Marker of Other Primary Abnormalities?

The next step was to understand how excess visceral adiposity could be linked to cardiometabolic risk variables and to CVD outcomes. Several studies have supported the “portal free fatty acid” hypothesis first put forward by Björntorp who proposed that an expanded visceral fat depot would, through its lively lipolysis (which is resistant to the antilipolytic effect of insulin), expose the liver to high concentrations of free fatty acids, impairing liver metabolism and contributing to the hyperglycemic, hyperinsulinemic, hypertriglyceridemic state of visceral obesity.33,70–72 However, the portal hypothesis has been questioned by studies that have shown that ≈80% of free fatty acids found in the portal circulation are from systemic adipose tissue.73 Thus, there must be alternate scenarios for the link between excess visceral adiposity and diabetogenic/atherogenic metabolic abnormalities (Figure 5).

In this regard, it has also previously been proposed that other primary factors may affect both visceral fat deposition and cardiometabolic outcomes. For instance, excess visceral adiposity could be the consequence of an activated hypothalamic-pituitary-adrenal axis leading to an increased control of carbohydrate and lipid metabolism by glucocorticoids.74 Because visceral adipocytes have more glucocorticoid receptors than subcutaneous adipose cells, such an activated hypothalamic-pituitary-adrenal axis may promote preferential fat deposition in the visceral adipose depot while at the same time inducing insulin resistance in the liver and in the skeletal muscle.74

Other possibly important key players are gonadal steroids. Indeed, very informative metabolic studies conducted in transsexual subjects have documented the remarkable influence of steroid hormones on body fat distribution and related cardiometabolic risk. Female-to-male transsexual patients receiving appropriate steroid hormone replacement therapy were found to lose gluteofemoral fat and gain visceral adipose tissue, whereas the
reverse phenomenon was observed for the male-to-female transsexual patients.75–77 We also know that viscerally obese men have lower sex hormone–binding globulin and testosterone levels and that such a profile is also predictive of an increased cardiometabolic risk.78,79 Thus, excess visceral adiposity may indeed be a marker of a disturbed hormonal milieu affecting both regional fat distribution and cardiometabolic risk. Other possibilities involve increased local conversion of steroids by abdominal adipose cells through enzymes such as 11beta-hydroxysteroid dehydrogenase80 or overactivation of the endocannabinoid system,81,82 which have been associated with excess visceral adiposity. Among environmental/behavioral factors associated with visceral adipose tissue deposition, smokers have been shown to have more abdominal adipose tissue and to be characterized by more insulin resistance despite the fact that they tended to have lower BMI values than nonsmokers.83 There is also evidence from randomized trials that dietary fructose may promote selective deposition of visceral adipose tissue.84,85 Finally, another important correlate of individual differences in visceral adiposity is ethnicity. For instance, more than a decade ago, we reported substantial differences in the proportion of visceral adipose tissue between black versus white adults, the former group having less visceral adipose tissue than whites.86 Several studies have also reported this finding of greater susceptibility of whites to visceral adipose tissue deposition than blacks.87–90 As a consequence, we reported that such a difference in visceral adiposity largely explained the higher plasma triglyceride and apolipoprotein B levels in whites than in blacks.86 Another ethnic group that has received attention recently is the Asian population, which appears to be more prone to visceral adipose tissue deposition at lower BMI values.91 This factor could contribute to the explanation, at least in part, of why Asians may be more susceptible to developing type 2 diabetes mellitus at lower BMI values than whites.16 Ethnic-specific data with extensive imaging of body fat distribution phenotypes will be needed to define what is high-risk abdominal obesity all over the world. In brief, excess visceral adiposity could, on the one hand, play a role in the development of a diabetogenic/atherogenic metabolic profile but, on the other hand, represent a reliable marker of more primary abnormalities affecting energy partitioning and cardiometabolic risk. In the end, both factors (the expanded visceral adipose depot and the altered neuroendocrine and hormonal profile) may act as a diabetogenic/atherogenic duo driving insulin resistance and related cardiometabolic risk.

Figure 5. The lipid overflow-ectopic fat model. Excess visceral fat accumulation may be causally related to the features of insulin resistance, but it may also be a marker of a dysfunctional adipose tissue not being able to appropriately store the energy excess. Under this model, the body’s ability to cope with the surplus of calories (resulting from excess caloric consumption, a sedentary lifestyle, or, as often the case, a combination of both factors) may ultimately determine the individual’s susceptibility to develop features of the metabolic syndrome. There is evidence suggesting that, if the extra energy is channeled into insulin-sensitive subcutaneous adipose tissue (able to expand through hyperplasia), the subject in positive energy balance will nevertheless be protected against the development of the metabolic syndrome. However, in cases where the adipose tissue is absent, deficient, or insulin resistant with a limited ability to store the energy excess (hypertrophic adipose tissue), the triglyceride surplus will be deposited at undesirable sites such as the liver, the heart, the skeletal muscle, and in visceral adipose tissue, a phenomenon described as ectopic fat deposition. Factors associated with a preferential accumulation of visceral fat and with features of insulin resistance include, among others, smoking, the well-documented genetic susceptibility to visceral obesity and a permissive neuroendocrine profile related to a maladaptive response to stress. The resulting metabolic consequences of this defect in energy partitioning include visceral obesity, insulin resistance, an atherogenic dyslipidemia, and a prothrombotic, inflammatory profile, which are features defining the metabolic syndrome. This constellation of abnormalities can be detected by the metabolic syndrome clinical criteria, the 2 simplest being the simultaneous presence of an elevated waist girth and fasting triglyceride levels, a condition that has been described as hypertriglycerideremic waist. FFA indicates free fatty acid. Adapted from Després and Lemieux40 with permission from the publisher. Copyright © 2006, Nature Publishing Group.
Excess Visceral Adiposity: The Most Visible Marker of Ectopic Fat Deposition?

Another possibility for the link between excess visceral adiposity and cardiovascular outcomes does not exclude the primary neuroendocrine and hormonal abnormality(ies) discussed above: excess visceral fat deposition could also be a marker of the relative inability of subcutaneous adipose tissue to expand as a protective metabolic sink.\(^{40,41}\) For instance, a given neuroendocrine or hormonal milieu or some intrinsic (possibly inherited) defect(s) in subcutaneous adipose tissue may limit its ability to expand through hyperplasia of adipocyte precursors,\(^{92}\) leading to insulin-resistant hypertrophic adipose tissue.\(^{93,94}\) Under such circumstances, the subcutaneous adipose tissue of a sedentary individual exposed to a diet rich in calories may have difficulties to properly expand, leading to a spillover and deposition of the energy excess at undesired sites such as the liver, the skeletal muscle, the heart, the liver, the pancreas, the kidney, etc, a phenomenon described as ectopic fat deposition (Figures 5 and 6). Although the lipid spillover hypothesis remains debated, considerable clinical and experimental data support this theory. For instance, fatless mice models lacking subcutaneous adipose tissue are characterized by ectopic fat deposition.\(^{95,96}\) Grafting adipose tissue to these fatless mice has been shown to improve their metabolic profile.\(^{95,96}\) On the other hand, another transgenic mouse model overexpressing adiponectin is characterized by a huge accumulation of subcutaneous adipose tissue and no evidence of ectopic fat deposition, and these mice are metabolically healthy despite their massive subcutaneous obesity.\(^{97}\) Many human forms of lipodystrophies are characterized by ectopic fat deposition and insulin resistance.\(^{98}\) Treated HIV lipodystrophic patients have excess visceral and ectopic fat and are at high risk for type 2 diabetes mellitus and for the development of the atherogenic dyslipidemia of the metabolic syndrome.\(^{99−101}\) Peroxisome proliferator–activated receptor gamma agonists inducing the growth of subcutaneous fat through the hyperplasia of subcutaneous adipose tissue have been shown to reduce ectopic fat deposition and improve insulin sensitivity,\(^{102}\) although some harmful cardiovascular side effects have compromised the use of this class of drugs in clinical practice.\(^{103}\)

Thus, the hypothesis that excess visceral adiposity may rather be an excellent marker of ectopic fat deposition and of related metabolic abnormalities appears reasonable and currently supported by considerable evidence, although further experimental work on this model is warranted. A key unanswered question is the respective contributions of these various ectopic fat depots including the expanded visceral adipose tissue to cardiometabolic risk. Numerous articles linking liver and epicardial fat to cardiometabolic risk have been published recently and will be discussed in the next sections.

Liver Fat in Visceral Obesity: A Key Ectopic Fat Depot

It had been known for a long time that nonalcoholic steatohepatitis is associated with the features of the metabolic
syndrome. However, it was not until the development of magnetic resonance spectroscopy that it had been possible to precisely measure with a noninvasive technique liver fat content in large cohorts. With the availability of magnetic resonance spectroscopy, very strong associations have been reported between liver fat content and features of the cardiometabolic risk profile predicting risk of type 2 diabetes mellitus and CVD. Although Liu et al have reported stronger correlations between cardiometabolic risk factors and visceral adipose tissue than with liver fat, some other studies have even suggested that the associations between visceral adiposity and diabetogenic and atherogenic metabolic complications could be entirely explained by the concomitant increase in liver fat content. These results can be explained by the fact that the liver is a key organ that is central to the control of carbohydrate and lipid metabolism.

For instance, it is a major site of insulin uptake and degradation. Some recent data suggest that a high liver fat content, largely associated with abdominal obesity (reflected by a high WHR), may result in a reduced hepatic extraction of insulin, leading to increased intrahepatic insulin exposure. In addition, hepatic glucose output is increased among subjects with a high liver fat content. This phenomenon contributes to glucose intolerance and largely explains the hyperglycemic state of patients with type 2 diabetes mellitus, because their hepatic glucose production also becomes resistant to the inhibitory effect of insulin. Furthermore, the fatty liver pumps out more triglyceride-rich lipoproteins through an overproduction of large VLDL1 particles. Increased lipid availability also protects apolipoprotein B against its local degradation in the hepatocyte, explaining the elevated plasma apolipoprotein B concentrations observed among individuals with a high liver fat content. Thus, a high liver fat content can, by itself, largely explain the hyperinsulinemic, hyperglycemic, hypertriglyceridemic, and elevated apolipoprotein B dysmetabolic state of visceral obesity without involving a specific contribution of visceral adipose tissue. From this evidence, it appears reasonable for the time being to conclude that both visceral adipose tissue and liver fat are key drivers of cardiometabolic risk associated with a given level of total body fat.

**Epicardial-Pericardial Adipose Tissue: Contribution of the Fatty Heart**

Another site of ectopic fat deposition is the heart, which includes the myocardial fat and the adipose tissue surrounding the heart, as well, which can be classified into the epicardial and pericardial adipose tissue. An excellent and comprehensive review on this specific topic has been recently published. Several studies including data from the Framingham Heart Study have now revealed that the size of the epicardial or pericardial fat depot is significantly associated with the cardiometabolic risk profile. However, some studies that have reported these associations have failed to control for the concomitant variation in other critically important ectopic fat depots, such as the visceral adipose tissue and liver fat. Studies that have attempted to address this question have found that some cardiometabolic risk markers may be more affected by some ectopic fat depots than others. From a physiological standpoint, mechanistic studies will have to be conducted to fully answer this question. For instance, the relative contributions of the various ectopic fat depots (epicardial, liver, and visceral) as drivers of cardiometabolic risk may depend on the clinical or metabolic outcome considered. For example, it would intuitively make sense that outcomes such as atrial fibrillation or heart failure may be more closely related to some local markers of cardiac lipids and metabolism, such as cardiac steatosis or epicardial fat. On the other hand, visceral adipose tissue and liver fat may be key drivers of plasma markers of the cardiometabolic risk profile, such as insulin resistance, glucose intolerance, inflammation, and the high triglyceride–apolipoprotein B-low-density lipoprotein–cholesterol atherogenic dyslipidemia. Thus, under this model, excess visceral and liver fat would synergistically act to perturbate the metabolic milieu, whereas excess epicardial fat may represent a marker of the relative inability of the heart to handle the lipid spillover resulting from the saturation of subcutaneous adipose tissue, leading to a progressive reliance on free fatty acids as a substrate that could eventually contribute to the development of diastolic dysfunction and heart failure.

Increased epicardial fat may also contribute to an increased local release of cytokines/adipokines that may impair the vasodilatory response of coronary vessels under certain physiological stress conditions.

Clearly, most ectopic fat depots examined so far show correlations with cardiometabolic and clinical outcomes, and with most clinical manifestations of CVD, as well. Because all ectopic fat depots are interrelated, deciphering their respective roles in the pathophysiology of the various cardiovascular outcomes (eg, angina, myocardial infarction, atrial fibrillation, heart failure, stroke, aortic stenosis, etc) represents a very fertile area for future investigations in cardiology. Recently, Britton and Fox have proposed that ectopic fat depots could be classified into 2 subtypes: those with predominantly systemic effects and those with preferential local effects (Figure 6). Under this model, visceral adipose tissue, liver fat, and skeletal muscle intracellular lipids could modulate CVD risk mainly through their effects on the metabolic risk profile (systemic effects), whereas other ectopic fat depots, such as perivascular fat, epicardial fat, myocardial fat, intrathoracic fat, and renal sinus fat, may primarily have local toxic effects.

In addition, although coronary heart disease is a serious clinical condition, CVD has devastating consequences for patients and their families. Limited available evidence suggests that there is a link between abdominal obesity and the risk of stroke. There are also data suggesting that cognitive function in older adults could be related to body fat partitioning beyond excess adiposity per se. Aortic stenosis, which for a long time had been considered as a degenerative process related to aging, has also been related to some of the features of the metabolic syndrome resulting from abdominal obesity. With the aging of the population, the consequences of regional body fat distribution on other cardiovascular outcomes such as valvular disease, atrial fibrillation, and stroke will have to be further investigated to develop proper preventive approaches. The consequences of
regional body fat distribution thus represents an important area for future research.

**Body Fat Distribution: The Clue to the Apparent Obesity Paradox in Cardiology?**

Although it is commonly accepted that obesity, irrespective of body shape, is a risk factor for the development of various cardiovascular outcomes, the situation is less clear among patients who already have the disease. For instance, several studies have shown that obesity, as defined by the BMI, may rather be associated with increased survival and reduced mortality among patients with CVD.\(^{124,125}\) Such a finding may, at first glance, appear counterintuitive, because obesity is an established CVD risk factor. How could it become protective among CVD patients? Some recent studies that have controlled for body fat distribution may have shed light on this apparent obesity paradox in cardiology. For instance, when an index of abdominal obesity such as waist circumference was used, a totally different picture emerged; an elevated waistline was predictive of an increased mortality rate among CVD patients.\(^{126–128}\)

These results provide further evidence that CVD risk is more closely related to body shape and adipose tissue distribution than to the BMI or to an excess of total body fat. As previously discussed, excess subcutaneous fat may represent a helpful energy reserve for CVD patients not characterized by harmful ectopic fat. On the other hand, CVD patients with lower BMI values may nevertheless be characterized by high levels of visceral adipose tissue and ectopic fat, making them more vulnerable to clinical outcomes and death.\(^{58}\) On that basis, we have proposed that excess visceral adiposity/ectopic fat may be the clue to the obesity paradox in cardiology.\(^{58}\) Finally, a low BMI in CVD patients may also be reflective of reduced lean and bone mass, which are also protective, especially at an older age.\(^{129,130}\) Future cardiometabolic imaging studies in CVD patients are thus clearly warranted to test this hypothesis.

**Assessing and Managing High-Risk Obesity in Cardiology: Going Beyond Weight Loss as a Therapeutic Target?**

Considerable evidence supports the notion that obesity is not a homogeneous entity, because it can no longer be defined solely on the basis of excess total body fat. In the present review, we have emphasized that remarkable individual differences exist in regional body fat accumulation at any given BMI or level of total body fat. Such variation in regional adiposity is a key in determining the CVD risk...
With the use of computed tomography, we have reported that them to introduce the concept of the "fat and fit" individual. Such observations led to the recognition that low levels of cardiorespiratory fitness are a key confounding variable explaining part of the increased CVD risk of overweight/obese individuals (Figure 8). Such findings are promising and may eventually allow the identification of the subgroups of overweight/obese patients more likely to be characterized by excess visceral adiposity (Figure 5). On the basis of the available evidence, it is proposed that, beyond weight loss, which remains a legitimate therapeutic target, we should aim for (1) the improvement of cardiorespiratory fitness (as an objective marker of participation to vigorous physical activity/exercise) and (2) the reduction of waist circumference and circulating triglyceride levels as simple indices of abdominal obesity/ectopic fat.

**Conclusions**

There is now considerable evidence supporting the notion that obesity is a heterogeneous condition. Such heterogeneity appears to be explained, to a very significant extent, by individual differences in regional body fat distribution, particularly in visceral adipose tissue/liver fat accumulation. In addition to visceral adiposity and liver fat as key drivers of the cardiometabolic risk associated with overweight/obesity, other ectopic fat depots may also contribute to the risk of various cardiovascular outcomes, and further work should clarify their specific functions.

At any given BMI value, an elevated waist circumference is predictive of an increased level of abdominal fat. When observed along with elevated triglyceride levels, such elevated waistline is predictive of excess visceral adiposity. Simple markers of visceral/liver fat content such as waist circumference and circulating triglyceride levels may allow community cardiologists and primary care physicians to identify the subgroups of overweight/obese patients more likely to be characterized by excess visceral adiposity/ectopic fat and at increased cardiovascular risk (Figure 5). On the basis of the available evidence, it is proposed that, beyond weight loss, which remains a legitimate therapeutic target, we should aim for (1) the improvement of cardiorespiratory fitness (as an objective marker of participation to vigorous physical activity/exercise) and (2) the reduction of waist circumference and circulating triglyceride levels as simple indices of abdominal obesity/ectopic fat.

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