Overview of Epidemiology and Contribution of Obesity to Cardiovascular Disease

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ABSTRACT

The prevalence of obesity has increased worldwide and is a source of concern since the negative consequences of obesity start as early as in childhood. The most commonly used anthropometric tool to assess relative weight and classify obesity is the body mass index (BMI); BMI alone shows a U- or a J-shaped association with clinical outcomes and mortality. Such an inverse relationship fuels a controversy in the literature, named the ‘obesity paradox’, which associates better survival and fewer cardiovascular (CV) events in patients with elevated BMI afflicted with chronic diseases compared to non-obese patients. However, BMI cannot make the distinction between an elevated body weight due to high levels of lean vs. fat body mass. Generally, an excess of body fat (BF) is more frequently associated with metabolic abnormalities than a high level of lean body mass. Another explanation for the paradox is the absence of control for major individual differences in regional BF distribution. Adipose tissue is now considered as a key organ regarding the fate of excess dietary lipids, which may determine whether or not body homeostasis will be maintained (metabolically healthy obesity) or a state of inflammation/insulin resistance will be produced, with deleterious CV consequences. Obesity, particularly visceral obesity, also induces a variety of structural adaptations/alterations in CV structure/function. Adipose tissue can now be considered as an endocrine organ orchestrating crucial interactions with vital organs and tissues such as the brain, the liver, the skeletal muscle, the heart and blood vessels themselves. Thus, the evidence reviewed in this paper suggests that adipose tissue quality/function is as important, if not more so, than its amount in determining the overall health and CV risks of overweight/obesity.

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Epidemiology

The prevalence of obesity has increased dramatically worldwide over the last decades and has now reached epidemic proportions. For instance, the global prevalence of obesity has nearly doubled between 1980 and 2008. According to the World Health Organization, 35% of adults worldwide aged >20 years were overweight (34% men and 35% women) in 2008.

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The prevalence of overweight and obesity combined (body mass index; BMI ≥ 25 kg/m²) was 68.8% in 2010 with a mean BMI of 28.7 kg/m² in the US population. In Canada, the prevalence of obesity has more than doubled since 1980, by another 8% between 1988 and 1994 with similar increases between 1988–1994 and 1999–2000. In contrast, data from the last decade (1999–2010) suggest that the prevalence of obesity may have plateaued in the USA. According to the latest National Health and Nutrition Examination Survey (NHANES), the age-adjusted obesity prevalence was 35.7% in the United States in 2010 with no sex differences. Extreme obesity (grades 2 and 3) was associated with an increased mortality risk, with a hazard ratio of 1.18 (95% CI, 1.12–1.25). However, when analyzed separately, obesity grade 1 (Table 1) was not associated with an increased mortality risk, with a hazard ratio of 0.97 (95% CI, 0.90–1.04), compared to normal weight. In contrast, severe obesity (grades 2 and 3) was associated with an increased mortality risk (hazard ratio of 1.34 – 95% CI, 1.21–1.47). Childhood obesity also seems to impact mortality rate in early adulthood. Increased BMI in children has been positively associated with the risk of premature death in a population of American Indians born between 1945 and 1984 and followed between February 1966 and December 2003. According to the authors, this association could be partly mediated by the development of glucose intolerance and hypertension, but not hypercholesterolemia. Another study performed in older children also found a close relationship between BMI at adolescence and all-cause mortality rate assessed during adulthood. Indeed, after a follow-up of 31.5 years, it was reported that a BMI above the 95th percentile assessed during adolescence predicted increased adult mortality rates in both men (80% increase) and women (~100% increase) when compared to those who had a BMI between the 25th and 75th percentiles during their teenage years. Even among adolescents who had less severe obesity (between the 85th and 95th percentiles), such moderate obesity was associated with a 30% increase in all-cause mortality assessed during adulthood. Such an increased mortality rate observed in adults who were obese at childhood appears to be largely independent from adult BMI.

### Abbreviations and Acronyms

- BF = Body fat
- BMI = Body mass index
- CHD = Coronary heart disease
- CRP = C-reactive protein
- CV = Cardiovascular
- CVD = Cardiovascular disease
- DM = Diabetes mellitus
- FFAs = Free fatty acids
- HDL = High-density lipoprotein
- HF = Heart failure
- HTN = Hypertension
- II = Interleukin
- LDL = Low-density lipoprotein
- LV = Left ventricular
- LVH = Left ventricular hypertrophy
- LVM = Left ventricular mass
- MI = Myocardial infarction
- NHANES = National Health and Nutrition Examination Survey
- NSTEMI = Non-ST segment elevation myocardial infarction
- TGs = Triglycerides
- TNF = Tumor necrosis factor
- VLDL = Very low-density lipoprotein
- WC = Waist circumference
- WHR = Waist-to-hip ratio

Obesity assessment

The most commonly used anthropometric tool to assess relative weight and classify obesity is the BMI, which is expressed as the ratio of total body weight over height squared (kg/m²). Individuals with a BMI <18.5 kg/m² are considered to be underweight, whereas those with a BMI between 18.5 and 24.9 kg/m² are classified as having normal or acceptable weight. Individuals with a BMI ranging from 25 to 29.9 kg/m² are classified as overweight while obesity is 6.3% in 2010 for grade 3 (severe) obesity while reaching 15.2% for grade 2 obesity (Table 1). The age-adjusted prevalence of overweight and obesity combined (body mass index; BMI ≥ 25 kg/m²) was 68.8% in 2010 with a mean BMI of 28.7 kg/m² in the US population. In Canada, the prevalence of obesity is lower than in the United States reaching 27 and 25% respectively in both sexes while South East Asia shows the lowest prevalence (14% overweight in both sexes and 3% for obesity). In the United States, the prevalence of obesity has increased by 8% between 1976 and 1980, by another 8% between 1988 and 1994 with similar increases between 1988–1994 and 1999–2000. In contrast, data from the last decade (1999–2010) suggest that the prevalence of obesity may have plateaued in the USA. According to the latest National Health and Nutrition Examination Survey (NHANES), the age-adjusted obesity prevalence was 35.7% in the United States in 2010 with no sex differences. Extreme obesity has more than doubled since 1988–1994 NHANES, shifting from 2.9 to 6.3% in 2010 for grade 3 (severe) obesity while reaching 15.2% for grade 2 obesity (Table 1). The age-adjusted prevalence of overweight and obesity combined (body mass index; BMI ≥ 25 kg/m²) was 68.8% in 2010 with a mean BMI of 28.7 kg/m² in the US population. 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The age-adjusted prevalence of overweight and obesity combined (body mass index; BMI ≥ 25 kg/m²) was 68.8% in 2010 with a mean BMI of 28.7 kg/m² in the US population. In Canada, the prevalence of obesity is lower than in the United States reaching 27 and 25% of Canadian men and women, respectively. It is also relevant to mention that in Canada, 29% of men and 41% of women reach cut off values for waist circumference (WC; above 102 cm in men and 88 cm in women) suggesting the presence of abdominal obesity, with mean WC values of 95.1 cm for men and 87.3 cm for women. Such growing numbers are a source of concern since the negative consequences of obesity start as early as in childhood. Some experts predict a decrease life expectancy at birth in the US during the first half of the 21st century. Each year, 28 million individuals are dying from the consequences of overweight or obesity worldwide. High BMI is associated with the development of cardiovascular (CV) risk factors such as hypertension (HTN), dyslipidemia, insulin resistance, and diabetes mellitus (DM) leading to CV diseases (CVD), such as coronary heart disease (CHD) and ischemic stroke. The development of these comorbidities is proportionate to the BMI and obesity is considered as an independent risk factor for CVD. Several studies have documented that a high BMI is significantly associated, in both men and women, with manifestations of CVD such as angina, myocardial infarction (MI), heart failure (HF) and sudden death. The higher incidence of CVD events in obese patients seems to be related to endothelial dysfunction and subclinical inflammation in addition to the worsening of CVD risk factors. Overall, obesity is associated with an increased mortality rate, but obesity grades must be considered in risk stratification. In a recent meta-analysis including 2.88 millions of individuals, all obesity grades combined were associated with an increase in mortality rate, with a hazard ratio of 1.18 (95% CI, 1.12–1.25). However, when analyzed separately, obesity grade 1 (Table 1) was not associated with an increased mortality risk, with a hazard ratio of 0.97 (95% CI, 0.90–1.04), compared to normal weight. In contrast, severe obesity (grades 2 and 3) was associated with an increased mortality risk (hazard ratio of 1.34 – 95% CI, 1.21–1.47). Childhood obesity also seems to impact mortality rate in early adulthood. Increased BMI in children has been positively associated with the risk of premature death in a population of American Indians born between 1945 and 1984 and followed between February 1966 and December 2003. According to the authors, this association could be partly mediated by the development of glucose intolerance and hypertension, but not hypercholesterolemia. Another study performed in older children also found a close relationship between BMI at adolescence and all-cause mortality rate assessed during adulthood. Indeed, after a follow-up of 31.5 years, it was reported that a BMI above the 95th percentile assessed during adolescence predicted increased adult mortality rates in both men (80% increase) and women (~100% increase) when compared to those who had a BMI between the 25th and 75th percentiles during their teenage years. Even among adolescents who had less severe obesity (between the 85th and 95th percentiles), such moderate obesity was associated with a 30% increase in all-cause mortality assessed during adulthood. Such an increased mortality rate observed in adults who were obese at childhood appears to be largely independent from adult BMI.
such an inverse relationship fuels a controversy over whether patients with massive obesity and introduced grade 4 obesity take into consideration the rapidly expanding subgroup of patients with massive obesity and introduced grade 4 obesity corresponding to a BMI ≥50 kg/m² and grade 5 as a BMI ≥60 kg/m². 

The American Heart Association has proposed additional obesity subgroups to take into consideration the rapidly expanding subgroup of patients with massive obesity and introduced grade 4 obesity. 

Adiposity markers are graded into 3 categories: grade 1 (BMI ranging from 30 to 34.9 kg/m²), grade 2 (BMI ranging from 35.0 to 39.9 kg/m²), and grade 3 (BMI ≥40 kg/m²). The American Heart Association has proposed additional obesity subgroups to take into consideration the rapidly expanding subgroup of patients with massive obesity and introduced grade 4 obesity corresponding to a BMI ≥50 kg/m² and grade 5 as a BMI ≥60 kg/m². 

It has also been recently pointed out that BMI was not very discriminant in order to distinguish lean from fat body mass particularly among patients with a BMI ≥30 kg/m². 

Generally, an excess of body fat (BF) is more frequently associated with metabolic abnormalities than a high level of lean body mass. BMI alone seems to present a U- or a J-shaped association with clinical outcomes and mortality. Such an inverse relationship fuels a controversy in the literature, named the ‘obesity paradox’, which associates better survival and fewer CVD events in patients with mildly elevated BMI afflicted with chronic diseases. 

Although obesity as defined by the BMI influences CV risk, one may argue that other adiposity indices should be taken into consideration by the clinician in the risk stratification of a given patient. Obesity assessed with the BMI presents some limitation in the prediction of CV mortality. Among patients who have CVD, it has been reported that overweight or mildly obese patients show better outcomes in terms of CV and total mortality, with a paradoxical association between BMI and survival. However, reasons for this “obesity paradox” remain unclear and some of them including the issue of selection bias are illustrated in Fig 2. 

Even with a worse perceived health, poorer adherence to lifestyle behaviour, more co-morbidities and risk factors, overweight and obese cardiac patients appear to nevertheless present a better prognosis than normal weight individuals. One explanation for this paradox could be found in BF distribution. For instance, markers of absolute and relative accumulation of abdominal fat accumulation, such as elevated WC and waist-to-hip ratio (WHR) have been associated with an increased risk of MI, HF and total mortality in patients with CVD. In the Trandolapril Cardiac Evaluation register, increased mortality (23%) was observed among patients with an antecedent of CVD presenting abdominal obesity. 

This relationship remained after exclusion of DM and HTN from the multivariate analyses, underlining the importance of abdominal obesity as an independent factor of all-cause mortality in patients with CVD. 

An increase in both WC and WHR predicted an increased risk of CVD in men and women; a 1 cm increase in WC and a 0.01 unit increase in WHR were respectively associated with a 2% increase and 5% increase in risk of future CVD events. 

Of importance, a lower lean body mass also appeared to partially explain this obesity paradox, underlining the importance of going beyond the measurement of relative weight in risk assessment (Fig 2).

Indeed, overweight and obese individuals may show strikingly different CVD risk factor profiles on the basis of their BF distribution (Fig 2). Excess abdominal visceral adipose tissue, irrespective of the BMI, has been associated with a constellation of diabetogenic and atherogenic abnormalities such as insulin resistance, increased triglycerides and apolipoprotein B levels, low high-density lipoprotein cholesterol and an increased proportion of small dense low-density lipoprotein (LDL) and high-density lipoprotein (HDL) particles, the latter lipid abnormalities being generally described as the atherogenic dyslipidemia (Fig 3). On the contrary, low levels of visceral adipose tissue and subcutaneous obesity are associated with a low risk metabolic risk profile. 

Table 1 - Classification of body weight.

<table>
<thead>
<tr>
<th>Classification</th>
<th>BMI Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>BMI &lt;18.5 kg/m²</td>
</tr>
<tr>
<td>Normal or acceptable weight</td>
<td>BMI 18.5–24.9 kg/m²</td>
</tr>
<tr>
<td>Overweight</td>
<td>BMI 25–29.9 kg/m²</td>
</tr>
<tr>
<td>Obese</td>
<td>BMI ≥30 kg/m²</td>
</tr>
<tr>
<td>Grade 1</td>
<td>BMI 30–34.9 kg/m²</td>
</tr>
<tr>
<td>Grade 2</td>
<td>BMI 35.0–39.9 kg/m²</td>
</tr>
<tr>
<td>Grade 3</td>
<td>BMI ≥40 kg/m² (severe, extreme, or morbid obesity)</td>
</tr>
<tr>
<td>Grade 4</td>
<td>BMI ≥50 kg/m²</td>
</tr>
<tr>
<td>Grade 5</td>
<td>BMI ≥60 kg/m²</td>
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considerable evidence to support the notion that regional fat accumulation is much more important in CVD risk stratification than excess total adiposity per se. On that basis, a simple anthropometric index of total adiposity such as the BMI should be refined by measuring additional indices of fat distribution namely WC, WHR or waist-to height ratio to discriminate higher-risk individuals.32,33 Visceral adiposity can be measured accurately by computed tomography, magnetic resonance imaging, and with less precision by dual energy x-ray absorptiometry. Imaging cardiometabolic studies recently conducted in large cohort studies (Framingham Heart Study and the Jackson Heart Study) have shown that excess visceral adiposity accompanied by excess ectopic fat deposition such as excess heart, liver, and intrathoracic fat was significantly associated with cardiac and metabolic abnormalities, and that such relationship was independent from the amount of total or subcutaneous adipose tissue.34–36 Unfortunately, these imaging techniques are not available for large scale use to physicians. Since abdominal obesity is of importance in CVD risk stratification, measuring WC in addition to the BMI may represent the best alternative measurement for the health care professional. It is low cost, easy to perform and shows a reasonable association with visceral adiposity for a given BMI unit (Fig 2).25,37,38 Based on experts consensus, the World Health Organization has proposed sex-specific cut-off values associated with increased CVD risk: 94 cm in men and 80 cm in women for increased risk, and 102 cm in men and 88 cm in women for substantially increased risk.39 Many other techniques (air displacement plethysmography, bioelectrical impedance,
skinfold thickness, X-ray absorptiometry, hydrostatic weighing, etc.) may also be used to assess adiposity and body composition.Obesity and CVD

Obesity has numerous consequences on the CV system. Chronic accumulation of excess body fat leads to a variety of metabolic changes, increasing the prevalence of CVD risk factors but also affecting systems modulating inflammation. In addition to its contribution as an independent CVD risk factor, obesity promotes alterations in other intermediate risk factors such as dyslipidemia, HTN, glucose intolerance, inflammatory state, obstructive sleep apnea/hypoventilation, and a prothrombotic state, as well as probably many additional unknown mechanisms. Obesity also induces a variety of structural adaptations/alterations in CV structure/function. Indeed, among the 5,881 participants followed for 14 years in the Framingham Heart Study, 496 subjects developed HF. Obese subjects were 2 times more at risk of developing HF than normal weight individuals. An increased risk of 5% for men and 7% for women for every unit increase in BMI was observed after adjustment for established risk factors suggesting a direct link between excess body fat and cardiac dysfunction (Fig 3).
Cardiac adaptations to obesity

Chronic excessive accumulation of body fat causes adaptations of the CV system aiming at maintaining whole body homeostasis. Increased cardiac output and a decrease in peripheral resistance are of importance in this adaptive state. Stroke volume, the major determinant in the increased cardiac output in the obese patient, increases due to the augmentation of circulating blood volume.\(^{43,44}\) Expanded blood volume contributes to increase heart preload shifting the Frank-Starling curves to the left. Over the long term, such an increase in cardiac burden induces ventricular remodelling with enlargement of the cardiac cavities and increased wall tension which may eventually lead to left ventricular (LV) hypertrophy (LHV).\(^{45,46}\) Ventricle thickening is accompanied by a decrease in diastolic chamber compliance, eventually resulting in an increase in LV filling pressure leading to LV diastolic dysfunction which may be normalized with weight loss\(^{47}\) or aerobic exercise training.\(^{48}\) Early in the development of the disease, LHV adapts to LV chamber enlargement and systolic function is preserved. However, when LVH is getting more important than LV dilatation, impairment in systolic function will eventually be observed.\(^{49}\) In addition to LVH, muscular degeneration, increased total blood volume, diastolic and systolic dysfunctions are the main precursors of HF in obesity. In addition, several co-morbidities associated with obesity may exacerbate or predispose obese patients to HF, such as HTN, sleep apnea and DM.\(^{11}\) For instance, severe obesity has been known for more than 25 years to be a strong and independent predictor of increased LV mass (LVM), LV wall thickness, LV internal dimension, poorer LV systolic function and greater diastolic dysfunction,\(^{49,50}\) and those cardiac adaptations to obesity are also modulated by the duration of the obesity.\(^{50}\) The process behind LV remodelling is still not completely understood. Recently, Neeland and colleagues\(^{51}\) performed a large clinical prospective study to investigate the impact of body composition on LV function assessed by magnetic resonance imaging. In a multi-ethnic cohort of 2710 participants presenting normal weight (24%), overweight (32%) and obesity (44%), obesity, as expected, was associated with higher LVM, end-diastolic volumes, wall thickness and concentricity. However, these alterations in CV structure/function were dependent upon individual differences in BF distribution. Excess visceral adiposity was independently associated with the concentric LV remodelling (including increased LV wall thickness, increased LV mass/volume ratio – 3D measure of concentric geometry of the left ventricle and smaller LV end-diastolic volume) in addition with lower cardiac output and increased peripheral resistance (Fig 3). In contrast, gluteal-femoral adiposity was associated with eccentric LV remodelling (increased LV end-diastolic volume with reduced LVM, concentricity and wall thickness), a higher cardiac output and lower systemic vascular resistance.\(^{51}\) These results are in accordance with another study performed in an obese cohort of 5,998 participants (Multi-Ethnic Study of Atherosclerosis), where higher LVM-to-volume ratio was linearly correlated with adiposity measurements such as the WHR, WC, and estimated fat mass.\(^{52}\) It should be emphasized that changes in cardiac structure associated with obesity are not only observed in the adult population. It is also not uncommon to observe cardiac changes in the youth. Alterations may even be present early in life; obese children as young as 2 years old might present larger LV cavity compared to normal weight children.\(^{53}\) Clinical studies have reported greater epicardial fat, left atrial and LV enlargement in obese children compared to lean controls. However, the impact of such early cardiac changes on later clinical outcomes in adulthood such as incident HF is still lacking in the literature.\(^{54}\)

In the heart itself, many additional alterations are observed along with increased adiposity. In healthy individuals, epicardial fat depot is distributed on the heart surface, close to the coronary arteries. With obesity, outside of the intracellular accumulation of fat, a higher amount of extracellular fat deposition builds up in the epicardium. The proximity of epicardial fat and coronary arteries might be associated with the atherosclerosis burden.\(^{55,56}\) Also, epicardial fat deposition is correlated with the amount of visceral fat.\(^{57}\) The potential link between fat accumulation on the heart surface and risk of CVD is far from being fully understood. However, epicardial fat seems to produce potential pro-inflammatory adipocytokines and macrophage signals that may be involved in the development of CHD.\(^{55}\) For instance, in visceral obesity, epicardial fat could influence blood vessels by its action as a paracrine organ while secreting locally pro-atherosclerotic molecules (such as interleukin or IL-1β, IL-6 or tumor necrotic factor-α) and less adiponectin compared to subcutaneous fat.\(^{58}\) Fat infiltration within the heart may cause direct damage that may lead to HF.\(^{59,60}\) In fact, myocytes degeneration may be caused by a progressive accumulation of fat between muscle fibers (Fig 3). Secondary to this infiltration, a restrictive cardiomyopathy may develop impairing heart contraction. In this context, fat accumulation produces small irregular aggregates or bands of adipose tissue that might range between the myocardial cells. This phenomenon may contribute to muscular cell atrophy as a result of the increased pressure produced by these fat depots creating cardiac dysfunction.\(^{61}\) This myocardium degeneration is also known as adipositas cordis (Fig 3).\(^{5}\)

Contribution of obesity to CVD

Atherosclerosis is a degenerative process starting early in life and progressing throughout lifetime. Progression of atherosclerosis is related to age, but many chronic inflammatory conditions such as obesity and diabetes may exacerbate its development.\(^{62}\) The relationship between obesity and development of CVD is now overwhelmingly clear. As discussed earlier, large prospective studies such as the Framingham Heart Study, the Manitoba Study, and the Harvard School of Public Health Nurses Study and many others have documented obesity as an independent predictor of CVD.\(^{13,14,63}\) In a recent large study, the potential relationship between BMI categories and the incidence of non ST-segment elevation MI (NSTEMI) were assessed retrospectively. The study included a cohort of 111,847 patients with unstable angina and NSTEMI. Obesity was the strongest factor associated with NSTEMI at younger age followed by tobacco use. Respectively, for all BMI categories (overweight,
involved in the evolution of the atheroma differ between lean and obese individuals. In the future, experts predict that the current growth rate of obesity (an estimated 7% increase in men and 10% increase in women in 2020) will lead to an increase in the number of CVD events of ~14% in 2035. This is not surprising since in studies involving young patients who died from non-cardiac causes, obesity was one of the major predictors of extended fatty streaks and advanced lesions (fibrous plaques and plaques with calcification or ulceration) in the right coronary artery and in the abdominal aorta. In young adults, obesity through lifetime is positively related to atherosclerosis development as measured by carotid intimal-medial thickness. This finding supports the notion of a potential cumulative cardiovascular effect of childhood obesity on adult CV outcomes. From a pathophysiological point of view, young individuals with visceral obesity seem to have more infiltrated macrophages (macrophages/mm²) in their atherosclerotic lesions. It was reported that young obese individuals are more subject to endothelial dysfunction. For instance, obesity, particularly abdominal obesity, has been associated with decreased endothelial dependent vasodilation even in the absence of established CVD risk factors. Endothelium-dependent vasodilation is considered as an early marker of atherosclerosis development, probably via its relationship with nitric oxide. Outside endothelial dysfunction, the early development of atherosclerosis in obesity is also probably related to the resistance of blood vessels and their inflammation.

Thus, common pathophysiological pathways relate obesity and processes leading to accelerated atherosclerosis; both involving inflammation and alterations in lipid metabolism. The pathophysiology of obesity, in contrast to atherosclerosis, involves free fatty acids (FFAs) and triglycerides, rather than LDL cholesterol. In obesity, chronic caloric excess induces the accumulation of dietary fatty acids in the adipose tissue until its storage capacity becomes saturated, leading to a spillover of lipids which are then stored in normally lean tissues such as the liver, muscles and in the intra-abdominal or visceral adipose depots. Such saturation in the storage capacity of lipids in subcutaneous adipose tissue and the resulting ectopic fat deposition induce a combined state of inflammation and insulin resistance. In addition, adipocytokines secreted by adipose tissue are also involved in modulating processes promoting atherosclerosis such as endothelial vasomotor dysfunction, hypercoagulability and dyslipidemia. Levels of many inflammatory mediators are altered in obesity. First, circulating C-reactive protein (CRP) and tumor necrosis factor (TNF) (production by adipose tissue) levels are increased, but other mediators (such as IL-6 and IL-1), and monocyte chemo-attractant protein-1) and hormones (such as adiponectin and leptin) are also known to potentially contribute to the inflammatory profile observed in obesity, particularly of abdominal obesity. Regarding the inflammatory process itself, monocytes and macrophages involved in the evolution of the atheroma differ between lean and obese individuals. Obesity leads to a shift in “alternatively” activated macrophages (recognized for their protective function in metabolic homeostasis) to “classically” activated macrophages (characterized by the production of pro-inflammatory factors such as IL-6 and nitric oxide synthase 2), a pro-inflammatory state that contributes to insulin resistance.

White adipose tissue itself also seems to be of importance in the inflammatory state of obesity. Excessive adipose tissue growth, as seen in obesity, requires increased blood supply and total adipose tissue blood flow is globally increased. However, perfusion per unit of adipose tissue decreases with increased adiposity. The difference in perfusion may represent a 35% reduction in relative perfusion when an obese individual is compared to a nonobese control. This miss-match in the perfusion leads to a relative diminution of oxygen supply to adipocytes, which contributes to cellular hypoxia, organ stress and dysfunction, pro-inflammatory responses and metabolic disease. In addition, under such state of hypoxia, cells secrete macrophages-attractive chemokines, which may lead to secretion of various pro-inflammatory factors, also called adipocytokines. On the other hand, in association with the lower blood supply or the chronic state of inflammation, multinucleates giant cells (fusion of many macrophages) are found in the expanded white adipose tissue of obese individuals. During their action of phagocytosis, these cells acutely secrete pro-inflammatory cytokines (II-1α, TNF-α). Activation of these giant macrophages is related to necrotic-like adipocyte death found in a higher proportion in obese individuals than in nonobese individuals.

### Abdominal obesity

In a state of a positive energy balance, excess FFAs should be preferentially stored in adipose tissue. Adipocytes expand in order to store energy and as the demand for lipid storage increases, pre-adipocytes located in the adipose tissue differentiate to become mature and participate to fat storage. When the adipose tissue has reached its maximal expansion capacity, a “spill over” of lipids from adipocytes occurs, resulting in an increase of circulating FFAs. Lipids then start to accumulate in ectopic sites (visceral adipose tissue, intrahepatic, intramuscular, renal sinus, pericardial, myocardial and perivascular fat, etc.), a phenomenon leading to lipotoxicity. In addition to its role as the main energy reserve of the body, adipose tissue is now considered as a key organ regarding its ability to control overall energy flux and partitioning in the body, as the fate of excess dietary lipids (storage in subcutaneous adipose tissue vs. accumulation in lean tissues) may determine whether or not body homeostasis will be maintained (metabolically healthy obesity) or a state of inflammation/insulin resistance will be produced, with deleterious consequences on the vascular wall and the myocardium. Adipose tissue can be categorized as an endocrine organ orchestrating crucial interactions with vital organs and tissues such as the brain, the liver, the skeletal muscle, the heart and blood vessels themselves. As mentioned earlier, depending on their location, fat depots present distinct metabolic properties, different states of inflammation or adipocytokines excretion, leading to major individual differences regarding the impact of obesity on cardiometabolic risk (from protective to neutral to increased risk). A important distinction should therefore be made between the various adipose depots; the non-ectopic fat (or subcutaneous fat) appears to be less metabolically deleterious, its primary role...
being energy storage, whereas excess ectopic fat defined as an excess lipid accumulation in the visceral adipose depots and in normally lean tissues (intrahepatic, intramuscular, renal sinus, pericardial, myocardial and perivascular fat) is clearly a health hazard. The first hypothesis explaining the close relationship between visceral obesity and metabolic complications involves the old «portal free fatty acid» theory. Related to its close proximity to the liver and drained by the portal circulation, excess visceral adipose tissue could alter lipoprotein metabolism mainly by inducing an overproduction of large triglyceride (TGs)-rich very low density lipoproteins (VLDLs). The expanded visceral adipose depot also contributes to an increased delivery of non-esterified FFAs and cytokines to the liver. This theory must be considered with some caution as the majority of FFAs (80%) found in the portal circulation appear to originate from the lipolytic activity of systemic adipose tissue. Thus, although there is a clear relationship between excess visceral adiposity and the flux of non-esterified FFAs to the liver, the precise role of this phenomenon to the disturbed hepatic metabolism remains debated. However, FFAs issued from the visceral adipose tissue are transformed into VLDLs that are subject to hepatic metabolism remains debated. However, FFAs issued from the visceral adipose tissue are transformed into VLDLs that are subject to hepatic metabolism. This theory must be considered with some caution as the majority of FFAs (80%) found in the portal circulation appear to originate from the lipolytic activity of systemic adipose tissue. Thus, although there is a clear relationship between excess visceral adiposity and the flux of non-esterified FFAs to the liver, the precise role of this phenomenon to the disturbed hepatic metabolism remains debated. However, FFAs issued from the visceral adipose tissue are transformed into VLDLs that are subject to hepatic metabolism.

**High-density lipoproteins**

High-density lipoproteins (HDL) have a protective role on the vascular wall. There is a well-established negative correlation between HDL-cholesterol concentrations, apolipoprotein A1 levels (a significant protein contained in HDL) and CVD incidence. Although the protective effects of HDL on CV health were initially believed to be related to their ability to promote reverse cholesterol transport, it is now well documented that this lipoprotein class also has numerous additional properties which may be beneficial such as anti-inflammatory, antioxidant, and antithrombotic properties. In the visceral obese individual, HDL levels are decreased by the successive actions of cholesteryl ester transfer protein and hepatic lipase. As a consequence, HDL particles also become smaller and denser which can also affect their catabolism and their potentially protective properties. Also, it is possible that visceral obesity may be associated with compositional changes in HDL particles, making them less efficient regarding their protective action on cholesterol efflux. Dysfunctional HDL particles may also become pro-inflammatory instead of anti-inflammatory; they may display reduced antioxidant and anti-inflammatory properties which could contribute to diminish their ability to prevent LDL oxidation, thereby contributing to atherosclerosis. It is well known that low levels of HDL are associated with an increased risk of developing CVD, but high levels of HDL may not always be protective, since in a context of chronic inflammation, HDL may be less functional. Level of physical activity also has an influence on HDL quality. For instance obese exercise-trained individuals have been shown to be characterized by improved HDL redox activity compared to sedentary untrained individuals while presenting HDL functional proprieties which were similar to lean active individuals.

**Adipo(cyto)kines and CVD**

There is now overwhelming evidence that adipose tissue is a key organ in the production and in the regulation of endocrine and paracrine hormones modulating inflammation and other important metabolic processes. Cytokines produced by adipose tissue (or adipokines) have been classified in two main categories: 1) “healthy” adipokines (adiponectin and omentin) and 2) “unhealthy” adipokines (TNF-α, IL-6, plasminogen activator inhibitor-1, adipocyte fatty acid-binding protein, lipocalin-2, chemerin, leptin, visfatin, vaspins, resistin), which are upregulated in obesity. Adiponectin and omentin appear to play important roles in regulating endothelial function. The first suppresses TNF-α secretion, attenuates production of reactive oxygen species induced by high glucose, oxidized LDL and palmitate, stimulates endothelial cell migration and prevents cell apoptosis. On the other hand, omentin appears to promote nitric oxide production. Levels of plasma adiponectin are decreased in obesity.

In 1994, the first protein selectively derived from adipocytes, leptin, was discovered. The primary role initially attributed to this protein was to control appetite by a central action inhibiting food consumption. More recently, it has become evident that leptin has numerous important biological functions and that some of them may have an impact on the CV system. In 2006, leptin was found to be a regulator of non-esterified FFAs oxidation by peripheral tissues. By its action on non-esterified FFAs oxidation, leptin was shown to prevent the accumulation of deleterious ectopic fat in peripheral organs i.e. heart, skeletal muscles, kidney, and pancreas. Fat accumulation in target organs may produce irreversible damages by the accumulation of ceramides (cytotoxic lipids), which may, through increased nitric oxide formation, cause apoptosis of lipid-laden cells (such as beta-cells and cardiomyocytes). Leptin was also suggested to have a potential role in inflammation according to the fact that leukocyte receptors were found on the protein, although the relationship between leptinemia and CVD remains debated. It is now considered that adipocytokines secreted by adipose tissue activate several pathways, some having protective roles whereas others...
can act in opposite directions. Some of these adipokines probably play an important role in atherosclerosis development and progression to CV outcomes. Adiponectin clearly exhibits anti-inflammatory, anti-atherosclerotic and potentially cardioprotective properties (including anti-apoptotic and anti-oxidant effects). More precisely, adiponectin inhibits the expression of TNF-α-induced endothelial adhesion molecules, inhibits macrophage-to-foam cell transformation, suppresses TNF-α expression in macrophages and adipose tissue, reduces intracellular cholesteryl ester content in macrophages and inhibits smooth muscle cell proliferation. Some clinical trials have shown that high levels of adiponectin are associated with lower risk of CVD and may be associated with lower atherosclerosis plaque development in men although such relationship remains debated as well. In addition, adiponectin may have a beneficial impact on the myocardium itself. For instance, by its action in promoting cell survival and inhibiting cell death, adiponectin may have a direct effect on cardiomyocytes acting as a “heart protector”. In contrast, in chronic HF, adiponectin levels are increased and such increased levels are associated with a worsened prognosis. Some authors have attempted to explain this paradox by a certain “adiponectin resistance” that may be found among patients with massive heart injuries. Under this model, higher levels of adiponectin may represent a counter-regulatory response necessary to promote anti-inflammatory and anti-oxidative processes to compensate for heart degeneration. Along the same line, omentin may also provide protective effects on the CV system by its vasodilation effect on vessels, its anti-inflammatory action (attenuation of CRP) and its action to prevent arterial calcification. Although the above evidence supports the relevance of increasing adiponectin levels therapeutically, whether or not pharmacotherapies substantially increasing circulating adiponectin levels translate into benefits in terms of cardiovascular outcomes is not established and very controversial. Indeed, studies with glitazones, a class of drugs producing robust and consistent increases in circulating adiponectin levels have all failed to show clear CV benefits. Thus, which features of subcutaneous adipose tissue “endocrine” secretions could be eventually targeted in abdominal obesity to reduce CVD risk remains unknown. However, as regular physical activity/exercise has been shown to be beneficial in terms of protection against CVD and as regular exercise has also been shown to mobilize ectopic fat and visceral adipose tissue, reducing sedentary time in the viscerally obese patients and regular endurance exercise training appears to represent important components of a lifestyle modification program to reduce CVD risk in patients with abdominal obesity.

**Conclusions**

Basic, clinical and population studies have provided robust evidence supporting the notion that obesity is associated with numerous alterations increasing the risk of CVD (Figs 1, 2). The pathophysiological processes linking obesity to atherosclerosis and CVD clearly involve a chronic inflammatory state. This inflammatory profile is usually the result of combined factors, such as visceral obesity and excess ectopic fat, insulin resistance, an atherogenic dyslipidemia and HTN. Such constellation of additional metabolic abnormalities found in patients with “at risk obesity” has often contributed to confuse the issue of obesity as a CVD risk factor in contrast to the “obesity paradox” (Fig 3). There is no doubt that obesity is associated with changes in CV structure and function. However, before weight loss interventions can be recommended, patients must be assessed for their adiposity-related risk. Unfortunately, healthcare providers and systems have not done a proper job of assessing excess adiposity even in its simplest form, such as measuring BMI. As an initial step, we need to emphasize further the importance of assessing adiposity in clinical practice. Although it can be argued that preventive approaches should focus on the entire population, the identification of “at risk” overweight/obese individuals in clinical practice nevertheless requires simple tools and strategies to better assess and manage these patients. We must therefore identify those individuals at highest risk of comorbidities in order to optimally use our limited health care resources. Under these considerations, the identification of individuals with excess visceral/ectopic fat is key so that these high risk patients could benefit from the support of health care professionals in their attempt to reshape their nutritional and lifestyle habits. In this regard, we know from decades of short term weight loss studies that although achieving weight loss is feasible over the short term, long term maintenance of a reduced body weight is a daunting task due to the fact that patients live in an obesogenic environment and do not have access to the long term support which has been found to be required to achieve long term success. Furthermore, the remarkable recent findings of the one study to permanently reduce body weight despite expensive resources and support suggest that we may have focussed too much on weight loss rather than on key upstream behaviors such as nutritional quality and inactivity/sedentary behavior/exercise. In addition, too many weight loss trials have been conducted in fairly low risk population of largely obese women participants with no cardiovascular outcomes. Maybe the time has come to consider a new paradigm where we use simple tools to redefine higher risk overweight/obesity (such as WC, TGs, nutritional quality and inactivity/activity level) and new therapeutic objectives: improving nutritional quality, reducing sedentary behaviors and increasing physical activity). Such a new model can be experimentally tested.

**Statement of Conflict of Interest**

All authors declare that there are no conflicts of interest.

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