Obesity and Cardiovascular Risk Factors

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Abstract

Excess bodyweight is an important risk factor for mortality and morbidity from cardiovascular diseases. Obesity and overweight have reached epidemic proportions and it could reverse life-expectancy gains in high-income nations. The aim of this review is to give an update of the present knowledge in cardiovascular consequences of obesity for physicians and other health workers.

Methods: In MEDLINE electronic database, a comprehensive search was performed on combinations of both medical subject headings and keywords from 2005 to January 2013. It involved the use of such keywords as overweight, obesity, body weight, combined with the terms prevalence, "cardiovascular risks factors", "cardiovascular disease", atherosclerosis and management. After a brief analysis of the obesity definition, metabolic syndrome and body fat distribution, the cardiovascular complications of obesity will then be reviewed. This will be followed by a discussion on the atherosclerosis pathogenesis in obesity and the management strategies of obesity.

Results: The quality of the manuscripts was assessed and of the 1450 articles identified, 65 studies were selected for this work. The main criteria were: systematic reviews, international consensus guidelines and scientific statements from the major organizations on cardiovascular disease and obesity.

Conclusions: Obesity is becoming a worldwide epidemic in both children and adults. It is directly linked to cardiovascular risk, and it is now considered as a major, independent risk factor for atherosclerosis. Comprehension of the mechanisms leading to obesity, and those linking obesity with cardiovascular disease is crucial for the design of therapeutic strategies targeting atherosclerosis prevention. Accordingly, obesity should be considered as a disease requiring treatment and more importantly prevention in the general population.

Keywords: Obesity; Cardiovascular risk factors

Introduction

Excess bodyweight is an important risk factor for mortality and morbidity from cardiovascular diseases (CVD), causing early 3 million deaths every year worldwide. Many studies have shown that adiposity, as measured by body mass index [BMI], has increased in recent decades in many populations (Figure 1). Obesity and overweight have reached epidemic proportions and it could reverse life-expectancy gains in high-income nations [1-4].

Figure 1: Prevalence of obesity in some countries.

Finucane et al. [5] estimated 1980-2008 trends in mean BMI for 199 countries and they found that mean BMI for men and women increased 0.4 kg/m² and 0.5 kg/m² per decade respectively [5]. The study showed that in high-income countries, male BMI rose most in the USA (1.1 kg/m² per decade), followed by the UK (1.0 kg/m² per decade), and Australia (0.9 kg/m² per decade), and least in, Switzerland, Italy, and France, with increases ranging 0.3-0.4 kg/m² per decade.

Moreover, in 2008, male BMI was higher in North America (28.4 kg/m²) and Australia (27.6 kg/m²) than in sub-Saharan Africa (apart from southern Africa) and in east, south, and southeast Asia, ranging 20.6-22.9 kg/m².

On the other hand, worldwide, prevalence of obesity was 9.8 % in men and 13.8 % in women in 2008, which were nearly twice the 1980 prevalence of 4.8 % for men and 7.9 % for women. Additionally, the prevalence of obesity in 2008 was highest in North American men, 29.2 % and lowest in South Asia in both men (1.4 %) and women (2.9 %).

In the World Health Organization (WHO) European Region the prevalence of obesity has risen threefold or more since the 1980s, including countries with traditionally low rates [6,7].

Regarding mortality, Berrington et al. [8] examined the relationship between BMI and all-cause mortality in a pooled analysis of 19 prospective studies, predominantly designed to study cancer, which included 1.46 million white (non-Hispanic) adults and 160,087 deaths [8].

They concluded that for non-Hispanic whites, both overweight and obesity were associated with increased all-cause mortality, and all-cause mortality was generally lowest within the BMI range of 20.0 to 24.9.

Nevertheless, the impact of obesity on life expectancy may be more complex than is commonly recognized. It is possible that the principal impact of obesity is on disability-free life expectancy rather than on life expectancy itself. This has substantial implications for the health of individuals and the future burden on the health care system [9].

The progression of this epidemic of obesity, in tandem with cardiovascular disease is predicted to slow or reverse the decline in mortality that has been noted in most Western countries over the past 30–40 years [10,11].

Capewell et al. [12] have reported that in the United States four of the six major risk factors for coronary heart disease (total cholesterol, prevalence of smoking, blood pressure and physical activity levels) improved between 1988 and 2003 [12]. Although, the rate of decline of all-cause and CVD mortality might be faster still if it was not for the increasing prevalence of diabetes, for which there is a clear association with heart disease. Examples of factors driving mortality down include population-wide changes such as reductions in the prevalence and intensity of smoking. However, Stewart et al. have predicted that over the next decade the negative effects of increasing levels of obesity will outweigh the benefits from reductions in the prevalence of smoking [12–14].

However, there is the possibility of improved medical interventions in some of the pathways linking obesity to CVD, for example, hypertension and dyslipidemia may blunt the impact of obesity on adverse health outcomes [15].

The aim of this review is to give an update of the present knowledge in cardiovascular consequences of obesity for physicians and other health workers.

Methods

In MEDLINE electronic database, a comprehensive search was performed on combinations of both medical subject headings and keywords from 2005 to January 2013. It involved the use of such keywords as overweight, obesity, body weight, combined with the terms prevalence, “cardiovascular risks factors”, “cardiovascular disease”, atherosclerosis and management.

The quality of the manuscripts was assessed and of the 1450 articles identified, 65 studies were selected for this work. The main criteria were: systematic reviews, international consensus guidelines and scientific statements from the major organizations on cardiovascular disease and obesity.

After a brief analysis of the obesity definition, metabolic syndrome and body fat distribution, the cardiovascular complications of obesity will then be reviewed. This will be followed by a discussion on the atherosclerosis pathogenesis in obesity and the management strategies of obesity.

Discussion

Definition of obesity and metabolic syndrome

In the most widely used classification of body mass, body weight is expressed in terms of body mass index (BMI). In adults, obesity is defined by a BMI ≥ 30 kg/m², which is further subdivided into grades (Table 1) [16].

Obesity has been defined by the American Heart Association as a major modifiable risk factor of cardiovascular disease (CVD). The improvement in risk factor recognition and management that developed through the years in cardiology may be challenged by today's youth who will carry their elevated risk of CVD for many more years [10].

However, obesity is a remarkably heterogeneous condition, where the distribution of the adipose tissue could be more important in determining cardiovascular risk than total body weight.

It appears that obesity as defined solely by BMI cannot always discriminate between the individuals at higher risk of developing CVD. Actually, non-obese overweight patients with excess visceral adiposity, thus at higher risk, would not be detected on the basis of BMI alone. For these reasons, measurement of the waist circumference and a set of metabolic markers have been proposed to detect individuals with the metabolic syndrome (Met S) and higher risk of developing CVD.

Waist circumference

The optimal level for measurement of waist circumference is midway from the lower rib margin to the anterior superior iliac crest, in the standing position. Thus, the WHO thresholds for waist circumference are the most widely accepted and two action levels are recommended: A) Action level 1, waist circumference ≥ 94 cm in men and ≥ 80 cm in women represents the threshold at which no further weight should be gained. B) Action level 2, waist circumference ≥ 102 cm in men and ≥ 88 cm in women represents the threshold at which weight reduction should be advised [17].

These thresholds have been calculated based on Caucasians and it is apparent that different cut-off points for anthropometric measurements are required in different races and ethnicities (Table 2) [18–26].

Table 1:

Underweight	BMI < 18.5 kg/m ²
Normal or acceptable weight	BMI 18.5–24.9 kg/m ²
Overweight	BMI 25–29.9 kg/m ²
Obese	≥ 30 kg/m ²
Grade 1:	BMI 30–34.9 kg/m ²
Grade 2:	BMI 35.0–39.9 kg/m ²
Grade 3:	BMI ≥ 40 kg/m ²
‘Super’ obese:	BMI ≥ 50 kg/m ²

Metabolic syndrome

With respect to the MetS, is often encountered in individuals with obesity and is characterized by a clustering of cardiovascular risk factors including central adiposity, insulin resistance, systemic hypertension, dyslipidemia, pro-inflammatory and pro-thrombotic state [27].

Various diagnostic criteria have been proposed by different organizations over the past decade. The first formalized definition of the metabolic syndrome was proposed in 1998 by a consultation group on the definition of diabetes for the World Health Organization (WHO) [28]. The other major criteria came from the National Cholesterol Education Program Adult Treatment Panel III (ATP III) in 2001 [29].

In 2005, both the International Diabetes Federation (IDF) and the American Heart Association/National Heart, Lung, and Blood Institute (AHA/NHLBI) attempted to reconcile the different clinical definitions. In spite of this effort, their separate recommendations contained differences related to waist circumference [18, 30]

Recently, IDF and AHA/NHLBI representatives held discussions to attempt to resolve the remaining differences

Table 2: Current Recommended Waist Circumference Thresholds for Abdominal Obesity by Organization.

Population	Organization (Reference)	Men	Women
Europid	IDF (4)	≥94 cm	≥80 cm
Caucasian	WHO (7)	≥94 cm (increased risk) ≥102 cm (still higher risk)	≥88 cm (increased risk) ≥88 cm (still higher risk)
United States	AHA/NHLBI (ATP III)* (5)	≥102 cm	≥88 cm
Canada	Health Canada (8,9)	≥102 cm	≥88 cm
European	European Cardiovascular Societies (10)	≥102 cm	≥88 cm
Asian (including Japanese)	IDF (4)	≥90 cm	≥80 cm
Asian	WHO (11)	≥90 cm	≥80 cm
Japanese	Japanese Obesity Society (12)	≥85 cm	≥90 cm
China	Cooperative Task Force (13)	≥85 cm	≥80 cm
Middle East, Mediterranean	IDF (4)	≥94 cm	≥80 cm
Sub-Saharan African	IDF (4)	≥94 cm	≥80 cm
Ethnic Central and South American	IDF (4)	≥90 cm	≥80 cm

*Recent AHA/NHLBI guidelines for metabolic syndrome recognize an increased risk for CVD and diabetes at waist-circumference thresholds of ≥ 94 cm in men and ≥ 80 cm in women and identify these as optional cut points for individuals or populations with increased insulin resistance.

between definitions of metabolic syndrome. Both sides agreed that abdominal obesity should not be a prerequisite for diagnosis but that it is 1 of 5 criteria, so that the presence of any 3 of 5 risk factors constitutes a diagnosis of metabolic syndrome. This would result in the common definition shown in Table 3. Table 2 shows current international recommendations proposed for thresholds of abdominal obesity to be used as one component of the metabolic syndrome [27]. Table 2 also lists waist circumference thresholds currently being recommended in several different populations and ethnic groups. Although some uncertainty about the Met S exists, it remains useful in identifying CVD risk.

Body fat distribution: Metabolically healthy obesity and non-obese individuals at increased risk for CVD.

Although it is well recognized that obesity is a health hazard, its heterogeneity has remained a challenge in clinical practice [31]. For instance, whereas there is a clear link between obesity and complications such as dyslipidemia, hypertension, and type 2 diabetes, not every obese patient is characterized by these risk factors.

Hamer et al. [32] have provided evidence that one can find individuals with a diagnosis of clinical obesity defined on the basis of their BMI but without the expected cardiovascular disease risk factors. The proportion of obese individuals who were nevertheless metabolically healthy represented about 22% of the sample of obese participants examined in this cohort. Thus, we need to identify them in clinical practice because they do not share the risk burden of their peers. On the other hand, there was also a subgroup of non-obese individuals who were characterized by metabolic risk factors (about 25 % of participants with a BMI < 30 kg/m²) and who were at increased risk for CVD and total mortality. Thus, the BMI don't seems to be the optimal anthropometric variable to estimate the health hazards of obesity [32].

There is now emerging evidence from several computed tomography and magnetic resonance imaging studies that excess visceral adiposity and liver fat content are two key drivers of cardio metabolic risk associated with a given level of total body fat. It is therefore very likely that obese individuals who are metabolically healthy have low levels of visceral adipose tissue and of liver fat, whereas non-obese metabolically unhealthy individuals probably have increased levels of visceral fat. Cross-sectional analyses of large metabolic/imaging studies have revealed considerable individual variation in visceral adiposity fat at any BMI level [33-36].

Nevertheless, adiposity indices are powerful correlates of deteriorated levels of intermediate risk factors. These strong associations between body fatness variables and risk factors are not trivial and have important public health implications. Therefore, we should help patients to lose weight and improve their lifestyle habits [37].

One simple clinical approach that has been proposed to identify the subgroup of individuals with an excess of visceral adipose tissue is the simultaneous measurement and interpretation

Table 3: Criteria for Clinical Diagnosis of the Metabolic Syndrome.

Measure	Categorical cut points
Elevated waist circumference*	Population- and country-specific definitions
Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator†)	≥150 mg/dL (1.7 mmol/L)
Reduced HDL-C (drug treatment for reduced HDL-C is an alternate indicator†)	≤40 mg/dL (1.0 mmol/L) in males; ≤50 mg/dL (1.3 mmol/L) in Females
Elevated blood pressure (antihypertensive drug treatment in a patient with a history of hypertension is an alternate indicator)	Systolic ≥130 and/or diastolic ≥ 85 mm Hg
Elevated fasting glucose‡ (drug treatment of elevated glucose is an alternate indicator)	≥ 100 mg/dL

HDL-C indicates high-density lipoprotein cholesterol.

*It is recommended that the IDF cut points be used for non-Europeans and either the IDF or AHA/NHLBI cut points used for people of European origin until more data are available.

†The most commonly used drugs for elevated triglycerides and reduced HDL-C are fibrates and nicotinic acid. A patient taking 1 of these drugs can be presumed to have high triglycerides and low HDL-C. High-dose Ω-3 fatty acids presumes high triglycerides.

‡Most patients with type 2 diabetes mellitus will have the metabolic syndrome by the proposed criteria.

of elevated waist circumference and plasma triglyceride concentrations, a phenotype referred to as “hypertriglyceridemic waist”. It is suggested that hypertriglyceridemic waist could have been helpful to identify non-obese metabolically unhealthy individuals with an excess of visceral adipose tissue [38]. Many studies have shown that this simple phenotype could discriminate a large proportion of individuals with excess visceral fat and that this condition was also predictive of an increased CVD risk [39-41].

Finally, another powerful modulator of CVD risk associated with a given BMI is the level of physical activity and fitness. Although cardio respiratory fitness has a genetic component, it is also a marker of participation to vigorous physical activities [14]. Blair et al. have shown that the so-called “fat and fit” individuals are at substantially reduced risk for clinical outcomes such as type 2 diabetes and CVD despite their high level of adiposity [42].

Indeed, these studies have demonstrated that a high level of cardio respiratory fitness is even more important as a cardio protective factor than low adiposity. In this regard, some authors, have reported that fat and fit individuals were also characterized by low levels of visceral adipose tissue and of inflammatory markers [43,44]. Thus, metabolically healthy obese subjects probably have less visceral adipose tissue fat and may be more fit, and these two factors could largely explain the absence of increased CVD risk despite their clinical obesity defined on the basis of the BMI.

Thus, obesity assessed only by the BMI cannot properly estimate CVD and all-cause mortality risk. Furthermore, the therapeutic objective of achieving a normal BMI to prevent cardio metabolic diseases may also be questioned on the basis of the emerging evidence. In this regard, it have been recently proposed that increased participation in vigorous physical activity to reduce visceral adiposity fat and to maintain a proper level of insulin sensitivity may be more important than achieving a “healthy” body weight defined by the BMI. Therefore, evidence support that obesity should be assessed using waist circumference as measure of visceral fat.

Cardiovascular complications of obesity

Obesity and cardiovascular disease.

Obesity and stroke: Numerous studies have reported an association between BMI and stroke. Indeed obesity is considered as a potential modifiable risk factor for stroke and the independence of this relationship from cholesterol, systemic hypertension and diabetes was identified. Each 1-Unit increase in BMI was associated with a increase of 4% in the risk of ischemic stroke and 6% for hemorrhagic stroke. However, stroke severity for ischemic stroke was not associated with BMI. The increase of stroke in obesity may be predicted by the pro-thrombotic and pro-inflammatory state that so often accompanies excessive adipose tissue accumulation [45].

Coronary heart disease (CHD): In adults, it has been shown that visceral obesity is associated with maximal density of macrophages in atherosclerotic lesions, reduced coronary flow reserve and insulin resistance and MetS is associated with lipid-rich plaque. However, obesity was associated, with lower all-cause and cardiovascular mortality after unstable angina or non-ST-segment elevation myocardial infarction treated with early revascularization. This has been described in the literature as the ‘obesity paradox’ and it may reflect the lack of discriminatory power of BMI to adequately reflect body fat distribution [46, 47].

Congestive heart failure: Elevated BMI predisposes to congestive heart failure [CHF] by promoting hypertension, diabetes, and CHD. It is estimated that there is an increase in the risk of CHF of 5% for men and 7% for women for each increment of 1 Unit of BMI. In contrast, once the patient presents with CHF, the presence of obesity may not adversely affect the patient's outcome. Indeed, among patients with CHF, subjects with higher BMI are at decreased risk for death and hospitalization (“obesity paradox”) compared with patients with a normal BMI [45, 48].

Hypertension: The majority of patients with high blood pressure are overweight, and hypertension is more frequent in obese subjects. A 10 kg higher body weight is associated with a 3.0 mm higher systolic and 2.3 mm Hg higher diastolic blood pressure. These increases translate into an estimated 12% increased risk for CHD and 24% increased risk for stroke. This increase in blood pressure is greatest when the obesity is of abdominal distribution [45, 49].

Arrhythmias: Obese subjects have an increased risk of arrhythmias and sudden death, even in the absence of cardiac

dysfunction, and the risk of sudden cardiac death with increasing weight is seen in both genders. In the Framingham study, the annual sudden cardiac mortality rate in obese men and women was estimated to be approximately 40 times higher than the rate of unexplained cardiac arrest in a matched non-obese population. Prolonged QTc interval was observed in approximately 30 % of subjects with impaired glucose tolerance, and there is a positive association between BMI and QTc [45, 50].

The relationship between obesity and cardiovascular disease is associated with atherosclerosis and altered cardiac function by different mechanisms as insulin resistance, diabetes mellitus, adipokines, dyslipidemia, ventricle hypertrophy, fatty heart and endothelium dysfunction.

Atherosclerosis pathogenesis and altered cardiac function in obesity

The relation between obesity and CVD is indeed complicated. Some investigators suggest that the connection is indirect and dependent on the increased prevalence of diabetes, hypertension and dyslipidemia, whereas others have demonstrated an independent association between obesity (especially abdominal obesity) and CVD risk. The relationship between obesity and CVD appears to develop at a relatively young age and is associated with atherosclerosis [51].

Obesity and insulin resistance: Obesity leads to insulin resistance via various, frequently inter-related, mechanisms. Infiltration of fat into the pancreatic islet cells amplifies the age-related decline in the islets' capacity to maintain the increased insulin output demanded by insulin resistance, and so glucose intolerance and premature type 2 diabetes mellitus readily develop [52].

Furthermore adipose tissue-derived products or adipokines are believed to be actively involved in the regulation of insulin sensitivity in peripheral tissues. Obesity-related modifications in adipocytes function induce a paracrine suppressive effect on adiponectin expression, a powerful insulin sensitizer, down regulated in obesity. In addition up regulation of proinflammatory adipokines in obesity like interleukin (IL)-1, -6 and tumor necrosis factor- α (TNF- α), also contributes to blunted insulin-signaling in peripheral tissues.

Obese individuals have decreased insulin receptor expression and decreased tyrosine kinase activity in skeletal muscle cells and adipocytes. Both insulin receptor expression and its tyrosine kinase activities are restored by weight loss, which also improves insulin sensitivity [54].

In abdominal obesity, omental and mesenteric adipose depots liberate high concentrations of non-esterified fatty acids (NEFA) directly into the portal vein with direct negative effects on liver metabolism of glucose. NEFA also directly stimulate insulin secretion by pancreatic β -cells, while they compete with glucose use by skeletal muscles as energy substrate, further aggravating insulin resistance [55].

Obese individuals have insulin resistance in adipose tissue (light resistance), liver (light resistancer) and skeletal muscles

(severe resistance). Indeed, while in lean subjects, glucose uptake occurs primarily in skeletal muscles, in obese occurs in adipocytes and that increase obesity. The transfer of nutrients to adipose tissue may cause hypertrophy and hyperplasia of fat tissue.

Obesity and diabetes mellitus: Most of type 2 diabetic patients are overweight supporting the hypothesis that excess adipose tissue mass may play an important role in the pathogenesis of the disease. Around 90% of individuals who develop type 2 diabetes mellitus have BMI higher than 23.0 kg/m². First, it develops glucose intolerance and if obesity persists, type 2 diabetes mellitus .

An increase in type 2 diabetes may have significant impact on public health and could reverse in the future, the trend toward decreasing CVD mortality [54].

Obesity and adipose tissue function: Initially, adipose tissue was believed to be a passive depot for storing excess calories. More recently, however, studies have revealed that visceral adipose tissue is metabolically active organ capable of synthesizing and releasing into the bloodstream an important variety of peptides and non-peptide compounds molecules implicated in cardiovascular pathophysiology.

These mediators or adipokines are actively implicated in the atherosclerotic process and include adiponectin, resistin, leptin, plasminogen activator inhibitor-1 (PAI-1), TNF- α , IL-6 and other less well-characterized molecules [56, 57].

Expression of some adipokines is elevated in obese and a reduction in fat mass is strongly correlated with a decrease in circulating proinflammatory adipokines levels. Indeed visceral fat depot seems to be more active than other body fat depots in producing a variety of these adipokines.

Among these mediators, leptin is an adipokine implicated in the regulation of appetite and increases blood pressure, sympathetic nerve activity, reactive oxygen species, platelet aggregation and arterial thrombosis. Clinical studies show that leptin is increased in obesity and is an independent CHD risk factor and a potentially useful biomarker in CVD.

Adiponectin, has insulin sensitizing properties and is down regulated in obesity. Firm evidence suggests that adiponectin has many anti-inflammatory and anti-atherogenic effects both on myocardium and vascular wall. Interestingly adiponectin plasma levels have been found to be more closely related to the amount of visceral than total fat.

On the other hand TNF- α , interleukina-6 and PAI-1 levels are up regulated in obesity and associated with visceral fat. Conclusively altered expression of adipokines in obesity might be partly responsible for the insulin resistance state and accelerated atherosclerosis in obese individuals [51].

Obesity and dyslipidemia: Obesity is characterized by impaired adipocytes trapping of fatty acids and excessive adipocytes lipolysis. These alterations lead to high circulating NEFA levels that result in increased hepatic lipogenesis.

Overwhelming of hepatic secretory capacity leads to hepatic steatosis by the newly synthesized triglycerides (TG) and increased VLDL circulating levels. An impaired lipoprotein lipase activity and enhanced cholesteryl ester transfer protein (CETP)-mediated lipid exchanged contribute to the observed HDL-C reduction in obesity.

Atherogenic dyslipidemia is clinically presented as elevated serum TG levels, increased levels of small dense low-density lipoprotein particles, and decreased levels of HDL-C. The use of WC ≥ 90 cm for men in combination with plasma TG levels ≥ 2 mmol/L has shown to be highly discriminatory for the development of CHD [51,58].

Ventricle hypertrophy and fatty heart in obesity: It has been long known that morbidly obese subjects develop obesity-related cardiomyopathy. Compared with subjects with a normal BMI, obese subjects had a doubling of heart failure (HF) risk. However it should be also noted that in HF patients higher BMI is not an adverse prognostic feature. Instead patients with low BMI seem to have poorer prognosis, a fact possibly dependent on HF-related cachexia ("obesity paradox").

Ample evidence suggests that obesity is associated with altered cardiac hemodynamics. Obesity is characterized by a hyperdynamic circulation in order to maintain metabolic demands in the excess adipose depots. Furthermore obesity-related hypertension imposes an elevated afterload to left ventricle, while obstructive sleep apnea disorders may also augment right ventricular afterload. This altered hemodynamic profile may lead to eccentric or even concentric left ventricle hypertrophy with impaired diastolic function parameters.

Probably the fatty heart is a metaplastic phenomenon. Cords of fat cells can gradually accumulate fat between muscle fibers or cause myocyte degeneration resulting in cardiac conduction defects. These cords of fat cells may also emanate from epicardial fat. Particularly interesting are the possible effects of epicardial fat on myocardium. Epicardial fat constitutes a visceral adipose depot and is a significant source of proinflammatory mediators, thus, clinical and imaging studies have demonstrated a strong correlation between epicardial fat mass and visceral adiposity [51,59].

Obesity, endothelium dysfunction and atherosclerosis: It is well established that higher BMI is associated with subclinical inflammation, reflected in increased C-reactive protein levels, and increased systemic oxidative stress. Evidence suggests that both insulin resistance and hyperinsulinemia lead to endothelial dysfunction. In insulin resistant individuals, insulin-mediated nitric oxide (NO) release is impaired and prostacyclin levels and potassium-mediated vasodilatation are reduced. Therefore an imbalance between vasodilatory and vasoconstrictive agents is favoured, and NO beneficial anti-inflammatory, antioxidant and antithrombotic effects are lost.

Proinflammatory cytokines increase expression of adhesion molecules on endothelial cells surface like intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 (VCAM-1)

which promote monocytes infiltration into subendothelial space.

Furthermore, T lymphocytes are also activated and further enhance macrophage atherogenic ability. Additionally, insulin has proliferative effects on vascular smooth muscle cells and insulin and promote extracellular matrix degradation and atheromatous plaque rupture.

Altered adipokines expression by adipose tissue is an additional factor responsible for perpetuating the vicious cycle of inflammation and endothelial dysfunction. Recent evidence suggests that leptin stimulates cholesterol uptake by macrophages, particularly in the presence of high glucose, triggering the formation of foam cells and the development of atheromatic lesions. Obesity-related hypoalbuminemia might also contribute to impaired endothelial function, increased vascular reactive oxygen species (ROS) production and overall proatherogenic effects. Finally increased release of proinflammatory cytokines by adipose tissue, like IL-6, IL-1 and TNF- α , sustains vascular wall inflammation and promotes proatherogenic genes expression [51,60,61].

Management strategies of obesity

It is now well understood that obesity, in particular abdominal adiposity, is associated with increased risk of CVD and diabetes mellitus. Obesity is one of the nine easily evaluated, modifiable risk factors (abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, consumption of fruits, vegetables, alcohol and physical activity), that account for more than 90% of AMI risk.

Evidence suggests that routine measurement of waist circumference in addition to BMI is a useful clinical marker for CVD risk assessment even in patients with normal weight [62].

Management strategies of major risk factors should be number one priority in obese patients (Table 4).

"Healthy" lifestyle modifications, like discontinuing smoking, decreasing fat and cholesterol content in diet, consuming vegetables and fruits and exercising regularly (at least 30 min of moderate activity a day) should also be encouraged. In cases of severe obesity drugs for weight loss or even surgical treatment of obesity can be tested. Nevertheless it should be noted that both drugs and surgery are often associated with adverse side-effects and complications [63,64]. The target behaviors for obesity prevention are summarized in Table 5 [65].

Limitations of the study. This study has several limitations.

Table 4: Recommended strategies of major risks factors.

WC	<102 cm (men) / <88 cm (women).
Blood pressure:	<140/90 mmHg (or <130/80 mmHg for patients with diabetes mellitus or chronic kidney disease).
Ratio of total cholesterol/ HDL-C:	<6.
Fasting plasma glucose:	<110 mg/dL (6 mmol/L)
HbA1c:	< 6.5%.

Table 5: Behavior Targets for Obesity Prevention.

Diet	Activity	Others
<p>To increase consumption of fruits, vegetables, legumes, whole grains and nuts.</p> <p>Limit calories from added sugars, solid fats, fruits and alcohol.</p> <p>To decrease consumption of sugar-sweetened beverages/soft drinks.</p> <p>To promote breastfeeding initiation, duration, and exclusivity.</p> <p>To decrease consumption of high-calorie, energy-dense foods.</p> <p>Accept ability to regulate energy intake rather than eating until the plate is empty.</p> <p>Ensure appropriate micronutrient intake to promote optimal linear growth.</p>	<p>To increase physical activity and promote an active lifestyle.</p> <p>Children: ≥ 60 min of physical activity per day.</p> <p>Adults: ≥ 150 min of moderate-intensity or 75 min of vigorous-intensity physical activity per week.</p> <p>To decrease television viewing.</p>	<p>Limit exposure of young children to heavy marketing of energy-dense, micronutrient-poor foods.</p> <p>Provide information and skills necessary to make healthy food choices.</p>

First, the obesity definition was based on BMI and waist circumference. Anthropometric measurements are useful indices in clinical practice, however they do not distinguish abdominal (visceral) fat from subcutaneous abdominal fat. Therefore more sophisticated methods for assessing body fat compartments could be useful, like magnetic resonance imaging, computerized tomography, or even ultrasound. They could add valuable information on cardiovascular risk stratification. Second, this review states BMI and waist circumference thresholds in different populations but obviously, there are many people in the world of mixed ethnicity. With respect to this, additional studies are needed. Finally, another powerful modulator of CVD risk associated with a given BMI is the level of physical activity/fitness and it was not included in this review.

Conclusions

Obesity is becoming a worldwide epidemic in both children and adults. It is directly linked to cardiovascular risk, and it is now considered as a major, independent risk factor for atherosclerosis. Comprehension of the mechanisms leading to obesity, and those linking obesity with cardiovascular disease is crucial for the design of therapeutic strategies targeting atherosclerosis prevention. Accordingly, obesity should be considered as a disease requiring treatment and more importantly prevention in the general population.

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