Obesity and cardiovascular risk: the new public health problem of worldwide proportions

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Obesity could be considered a new global health epidemic above all others, especially when it is characterized by central fat distribution. This is illustrated by dramatic provisional data, indicating a continuous increase in the trend of overweight and obese individuals in several countries, including the USA and countries in Europe. Several epidemiological, pathophysiologival and clinical studies clearly indicate that two of the major independent risk factors for cardiovascular disease or events are being overweight, and obesity. Accordingly, weight loss and prevention of weight gain has to be considered one of the most important strategies to reduce the incidence of cardiovascular disease.


The World Health Organization (WHO) refers to obesity as 'the global epidemic'. Obesity and related disorders are leading causes of morbidity and premature mortality in industrialized countries. The prevalence of obesity and being overweight in industrialized and many developing countries is estimated to range from 40 to 60% [1]. In the USA, the most recent data (1999-2000) from the National Health and Nutrition Examination Survey (NHANES) indicate that an estimated 64.5% of adults (67.2% men and 61.9% women) are overweight and 30.5% of adults (27.5% men and 33.4% women) are obese. These data represent a prevalence approximately 8% higher than the age-adjusted overweight estimates obtained from NHANES III (1988–1994) and indicate that the obese population increased by 7.6% between 1988 and 1994 (p < 0.001) [2]. According to data taken between 1990 and 2000, the Behavioral Risk Factor Surveillance System indicates that the percentage of people with a body mass index (BMI) of 40 almost tripled in the USA (0.78–2.2%). Currently, more than 44 million Americans are considered obese, an increase of 74% since 1991 (FIGURE 1) [3]. Moreover, the prevalence of obesity has also risen in some minority populations, with the highest rates in some Native American groups, Hispanics and African-Americans and in populations with lower education and income levels [4,5].

At the same time, over 50% of adults in Western Europe were considered overweight or obese, which represents a dramatic increase of 10 to 40% in European countries in the last decade. According to the WHO, the prevalence of obesity among the adult population in Europe varies from 10 to 20% for men and from 10 to 25% for women. The economic costs of obesity are in the range of 2 to 7% of total healthcare costs [5]. This indicates the importance of the obesity problem and its impact on public health.

There are many disorders commonly associated with obesity, such as cardiovascular disease (hypertension, coronary artery disease [CAD] and heart failure), cerebrovascular disease, respiratory disease (breathlessness, sleep apnea and hypoventilation syndrome), renal dysfunction, cancer and metabolic disease (dyslipidemia, insulin resistance and Type 2 diabetes mellitus) (TABLE 1). Accordingly, obesity has to be considered an emerging internal medicine problem. This review will focus on the relationship between obesity and cardiovascular disease,
greater than 27.3 kg/m² for women and 27.8 kg/m² for men [7]. These definitions were based on the gender-specific 85th percentile values of BMI for people aged 20 to 29 years. In 1998, the National Institutes of Health (NIH) Expert Panel on the identification, evaluation, and treatment of overweight and obesity in adults adopted the WHO classification for overweight and obesity [8]. This classification defines underweight BMI as less than 18.5, normal BMI as 18.5 to 24.9, overweight BMI as 25.0 to 29.9, and obese BMI greater than or equal to 30 (TABLE 2). Moreover, the WHO distinguishes between Caucasians and the Asian population. Asians have a greater health risk than Caucasians, despite the fact that they have lower BMI measures [9]. It also has to be underlined that the BMI gives no information about body-fat distribution. This is very important, since central fat distribution is already considered an independent risk factor for cardiovascular disease [10-12]. Therefore, waist-hip ratio (WHR) or waist circumference alone have been extensively used to better define the type of obesity [11]. The WHO classification indicates an increasing risk for comorbidity including hypertension, Type 2 diabetes mellitus and cardiovascular disease in subjects with higher BMIs in comparison with subjects with normal BMIs. In view of this, men with waist circumference greater than 40 inches (102 cm) and women with waist circumference greater than 35 inches (88 cm) are at higher risk of comorbidity (TABLE 2).

### Obesity & cardiovascular disease

#### Epidemiological aspects

Whether or not obesity represents an independent risk factor for cardiovascular disease is somewhat academic [13-15]. Although many authors refer to an association between obesity and cardiovascular disease, others have denied it. Such

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**Table 1. Obesity and comorbidities.**

<table>
<thead>
<tr>
<th>Category</th>
<th>Disorder</th>
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<tr>
<td>Metabolic disease</td>
<td>Insulin resistance</td>
</tr>
<tr>
<td>Respiratory disease</td>
<td>Breathlessness</td>
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<tr>
<td>Cardiovascular disease</td>
<td>Hypoventilation syndrome</td>
</tr>
<tr>
<td>Orthopedic disease</td>
<td>Osteoarthritis</td>
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<tr>
<td>Gall bladder disease</td>
<td>Gallstones</td>
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discrepancy represents two different ways to consider the relationship between obesity and cardiovascular risk.

In fact, some authors consider obesity as a condition characterized by an amplified cardiovascular risk, through a concomitant association with hypertension, diabetes mellitus and dyslipidemia [16]. In contrast, others report that obesity is an independent risk factor, especially if it is characterized by central fat distribution [14,17-19].

Despite this apparent contrasting interpretation, the more remarkable epidemiological studies point out that:

- The incidence of cardiovascular disease goes up with increasing body weight [12]
- The total mortality for cardiovascular disease is higher for higher quintiles of BMI [14], even when adjusted for smoking habit and history of previous cardiovascular disease [18]
- There is a higher prevalence of overweight and obese subjects among patients with myocardial infarction. In other words, obese patients are affected by myocardial infarction more precociously than lean ones [17]
- Increase in body weight is associated with a high incidence of ischemic stroke [20] and increased total and cardiovascular mortality [12,13]
- The presence of obesity in adolescence seems to be predictive of cardiovascular events in adulthood, even if a normal body weight has been reached by this time [21]

Several epidemiological studies have also been carried out, to analyze the role of central fat distribution in the incidence of cardiovascular disease and on mortality connected to it. These suggest that central obesity may be considered one of the major independent cardiovascular risk factors [11,13,20]. American Heart Association Guidelines include weight loss as one of the most important procedures in both the primary and secondary prevention of cardiovascular disease [22]. Accordingly, since cardiovascular events occur after a long observation period, it is necessary to address pathophysiological study to evaluate intermediate end points. In fact, some abnormalities in cardiovascular structure and function may be detectable early in obese subjects. In the authors' opinion, the recognition of silent left ventricular dysfunction may be able to improve the cardiovascular prevention strategy.

<table>
<thead>
<tr>
<th>BMI (kg/m²) and class</th>
<th>Waist circumference</th>
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<tbody>
<tr>
<td></td>
<td>Men = 102 cm</td>
</tr>
<tr>
<td>25–29.9</td>
<td>Overweight</td>
</tr>
<tr>
<td>30–34.9</td>
<td>Obesity class I</td>
</tr>
<tr>
<td>35–39.9</td>
<td>Obesity class II</td>
</tr>
<tr>
<td>&gt; 40</td>
<td>Obesity class III</td>
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Modified from [18].

**Obesity & hypertension**

It is well known that obesity and hypertension are two associated conditions, and that weight gain is probably the most important modifiable risk factor contributing to hypertension [23]. In particular, some specific characteristics of obesity, such as the degree, duration and type of fat distribution may influence this association. In view of this, in 1956, Vaugh reported that central fat distribution correlated to a high prevalence of hypertension [24]. Nevertheless, the pathophysiology of obesity-associated hypertension includes some multifactorial mechanisms. It shows specific hemodynamic adaptations (increased intravascular and cardiac volumes, cardiac output and inadequate vascular resistance) [25], hyperactivity of the sympathetic nervous system [26], insulin resistance [27], alterations of the hormonal mechanisms controlling sodium balance [28] and abnormal renal sodium handling [29], hyperactivity of the renin system [30], leptin resistance [31] and natriuretic peptide downregulation [28,29]. Therefore, the increase in blood pressure is the result of a continued interaction between these mechanisms. Studies in humans show that weight gain raises blood pressure and that weight loss reduces blood pressure in both normotensive and hypertensive subjects [17,26,29]. The hemodynamic changes in obese hypertensive subjects show a mixed profile resulting from the interplay of the individual components of obesity and hypertension. In obese hypertensive subjects, intravascular volume, total peripheral resistance and cardiac output are all elevated. However, due to the effect of obesity, total peripheral resistance is less elevated than would be expected in lean hypertensive patients and may be completely normal in some obese hypertensive patients [25,30]. The reason for this has not been completely understood. It is known that insulin resistance determines the inhibition of glucose transport and phosphorylation of glucose to glucose-6-phosphate, which activates calcium (Ca) ATPase transcription, increasing cellular Ca efflux and decreasing vascular resistance. This mechanism leads to an increase in peripheral vascular resistance [31]. The significance of the relationship between obesity and hypertension is well explained by Willet and colleagues, who demonstrated that the risk of hypertension among people with a BMI of 26 was two to three times higher than that of the leanest group and indicated that people with a BMI of 29 had an
correlation between serum levels of leptin and body fat mass has been found [34,35]. Additionally, leptin has multifunctional actions on the cardiovascular and renal system. It increases sympathetic activity, renal sodium excretion and insulin sensitivity, and inhibits glucose-mediated insulin secretion controlling hyperinsulinemia [29,36]. Therefore, leptin resistance might have an effect on sodium retention, intravascular expansion (association with hypertension) and insulin resistance in obese patients. Finally, increasing interest has to be attributed to the role of some cytokines [37,38] synthesized by adipocytes, such as transforming growth factor (TGF)-β1. TGF-β1 overproduction has been reported to be an important pathophysiological factor in essential hypertension and related to hypertensive target organ disease [39-41].

Obesity & CAD

Many epidemiological studies have shown obesity to be an important risk factor for ischemic heart disease. Some disorders responsible for the future development of coronary heart disease may be found early on in obese subjects. The main role may be attributed to the atherogenic lipid pattern (elevated levels of low-density lipoprotein-cholesterol [LDL-C], triglycerides and low levels of high-density lipoprotein-cholesterol [HDL-C]) and coagulatory system with a prothrombotic-hypofibrinolitic profile. The European Concerted Action on Thrombosis and Disabilities (ECAT) study has underlined that a prothrombotic-hypofibrinolitic profile can be considered predictive of ischemic heart disease [42]. It is well known that obesity is characterized by an increase in coagulation activity and by a reduction in fibrinolitic activity. In fact, circulating levels of fibrinogen, Factor VII, plasminogen activator inhibitor (PAI) and tissue plasminogen activator (t-PA) are positively correlated with the BMI and WHR and negatively with left ventricular function [43]. Other authors have documented the relationship among visceral fat (quantified by computed tomographic [CT] scanning) fibrinogen, PAI 1 and Factor VII [44,45]. Additionally, it is necessary to underline that mild weight loss can improve coagulation and fibrinolysis alterations and this may be associated with a lower incidence of coronary heart disease [46]. Furthermore, alterations of endothelial function and the prevalence of the angiotensin-converting enzyme (ACE) deletion allele homozygotic (DD) genotype also play a major role. Endothelial dysfunction has to be considered as a ‘promoter’ of atherogenic vascular damage, and has been recently recognized in many diseases, such as arterial hypertension, diabetes mellitus, hypercholesterolemia and central obesity [47,48]. In a recent study, Perticone and colleagues demonstrated that in obese young people there is an inverse relationship between WHR and endothelial-dependent vasodilatation. In addition, the authors have observed that in obese young people (age < 40 without cardiovascular risk factors) it is possible to detect higher levels of plasmatic endothelin. This finding strictly correlates with the left ventricular mass and interventricular septum thickness. An inverse correlation is evident when ejection fraction and rapid ventricular filling are taken into account [49].

increased risk [32]. Regarding the renin-angiotensin system (RAS) and atrial natriuretic peptide (ANP) regulation, it has been shown that delayed suppression of RAS exerts a delayed urinary sodium excretion, and blunts the ANP response to saline load [28]. This statement is supported by the elevated RAS values found in obese subjects and in the offspring of obese hypertensive parents. A significant relationship between RAS plasmatic values and left ventricular mass was evident in these patients [33]. The weight loss in obese subjects may ameliorate the ANP suppression and increase the ANP activity inducing natriuresis and diuresis.

Finally, the role of leptin in obese subjects must be outlined. It has been demonstrated that leptin plasma levels are more elevated in obese patients than lean subjects [34] and a strong
Moreover, endothelial function may also be evaluated by the analysis of adhesion molecules. They are expressed and amplified when an endothelial injury occurs. Among these molecules an important role has been attributed to endothelium-bound E-selectin, an endothelium specific molecule that is able to mediate the initial phase of adhesion of leukocytes to the endothelium [52,53]. Soluble E-selectin has recently been indicated as an early marker of endothelial damage [52,53]. However, the predictive role of adhesion molecules for cardiovascular disease or events is still questioned today. In fact, although data from the Atherosclerosis Risk Communities Study (ARIC) [54] and from Blanksberg and colleagues [52], indicate a strong association between vascular cell adhesion molecule (VCAM)-1, intracellular adhesion molecule (ICAM)-1 and E-selectin and CAD, a recent meta-analysis by Malik does not demonstrate a significant role for selectin molecules in cardiovascular risk [55]. The association between obesity and regional endothelial dysfunction has been reported in some recent studies. These indicate that BMI is independently associated with both coronary endothelial dysfunction in patients with normal or mildly diseased coronary arteries [54], and with an increased risk of recurrent coronary events in subjects following acute myocardial infarction [57].

Another interesting aspect concerning the relationship between obesity and CAD is the role of ACE polymorphism and its association with endothelial dysfunction. It is known that this gene polymorphism is characterized by three genotypes. These are deletion (D) allele, and insertion (I) allele homozygotes (DD and II), and DI heterozygotes. The D allele would be responsible for a high rate of ACE stimulating angiotensin II synthesis. Nevertheless, contrasting data have been reported about the ACE DD genotype association with frequency of myocardial infarction in populations studies [58,59].

In a recent study the authors observed that central obese subjects with DD genotype were characterized by higher levels of soluble E-selectin, left ventricular mass, carotid wall thickness and depressed left ventricular function [60]. These data indicate that the association between DD genotype and higher levels of soluble E-selectin may be considered an early marker for cardiovascular damage in central obese subjects (Table 3, Figure 2).

Further epidemiological prospective data are necessary to confirm the higher susceptibility to develop cardiovascular disease or events within this subset of central obese subjects.

Table 3. Correlation coefficient in multiple regression analysis: data only from patients with DD genotype.

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<th>Partial correlation coefficient</th>
<th>Multiple correlation coefficient</th>
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<tr>
<td></td>
<td>LVM/h</td>
<td>LVEF</td>
</tr>
<tr>
<td>E-selectin</td>
<td>0.602&lt;sup&gt;2&lt;/sup&gt;</td>
<td>-0.710&lt;sup&gt;8&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Explanatory variables were left ventricular mass/height (LVM/h), left ventricular ejection fraction (LVEF), age, Body Mass Index (BMI) and 24 h mean blood pressure (MBP/24 h). The first value for partial coefficient, for example, is the correlation coefficient between E-selectin and LVM/h after adjustment for age, BMI and MBP/24 h. *p < 0.05, Modified from [60].

Obesity & heart failure

Heart failure is a frequent cause of death in morbidly obese subjects [61,62]. The finding that being overweight and obesity are independent risk factors for congestive heart failure has been underestimated in the past. Previously, only extreme obesity was independently linked to heart failure. Data from the Framingham Heart Study demonstrated that elevated BMI was associated with an increased risk of heart failure and there was no threshold in this relationship [63]. This was evident in both men and women of all levels of obesity. Therefore, being overweight or obese represents an independent risk factor for congestive heart failure. A 34% higher risk in overweight and a 104% higher risk in obese subjects compared to patients of normal weight has been found. The attributable risk of heart failure due to being overweight was 14% for women and 8.8% for men. The corresponding risk due to obesity was 10.5% in men and 13.5% in women. Nevertheless, recent studies indicate that in patients with severe chronic systolic heart failure, obese patients have a better survival prognosis [64-67]. The authors suggest that a heightened catabolic state is associated with a lower body weight, related to higher levels of cytokines, particularly tumor necrosis factor and increased cortisol–dehydroepiandrosterone balance [68,69]. Naturally, cachexia and wasting appear to be independent predictors of increased mortality in subjects with advanced heart failure [70].

All these data have been well explained by Lave and colleagues, who discuss the relationship between body composition and prognosis in chronic heart failure as the ‘obesity paradox’ [71].

Several pathophysiological and clinical aspects may be useful to explain the higher susceptibility of obese subjects to develop left ventricular dysfunction and heart failure. In fact, long-standing obesity is associated with left ventricular remodeling and overt heart failure, particularly predilection and clinical left ventricular hypertrophy, dilatation [62,72-74], and impaired systolic function [73]. These abnormalities may also occur in the absence of hypertension or CAD. These characteristics have been labeled as ‘obesity cardiomyopathy’ [74]. It is well known that hypertensive subjects show ‘concentric hypertrophy’ due to elevated peripheral resistance, increased ventricular afterload and wall stress [75]. Obesity is characterized by an increase in intravascular volume and cardiac output, proportional to excess body weight and high filling pressure and stroke volume [76]. The increase in adipose tissue blood flow is primarily responsible for this high-output state.
It has also been demonstrated that a reduction in left ventricular ejection fraction at rest and absence of the normal increase in ejection fraction during exercise may be detectable early on in obese patients. This is consistent with a 'preclinical systolic dysfunction' [77,78]. Regarding diastolic function, prolongation of isovolumetric relaxation time [79], and abnormalities in left ventricular filling [80,81] in the absence of systolic dysfunction has been found in healthy obese patients. All these findings determine the appearance of an 'eccentric cardiac hypertrophy'. Obesity-associated hypertension was characterized by a doubled percentage of left ventricular hypertrophy compared with hypertensive nonobese patients [82].

The concomitant existence of obesity and hypertension results in a 'eccentric–concentric' hypertrophy [72]. In fact, the double association produces a rise in left ventricular stroke work resulting from the increased afterload determined by hypertension and increased preload associated with obesity [73]. The combination of obesity and hypertension increases the risk for congestive heart failure and sudden death [83]. The hypertrophic alterations, together with pathologic changes like mononuclear cell infiltration around the senoatrial node and fat throughout the conduction system [84], may lead to cardiac arrhythmias [85].

**Benefits of weight loss**

Some data describe the benefits of weight loss as being better than any other intervention. Studies have demonstrated that a weight loss of 1 kg produces a 1 mmHg reduction in systolic blood pressure and a 0.5 mmHg reduction in diastolic blood pressure [86]. Other studies show that a 5 to 10% weight loss can cause a 4 to 8 mmHg reduction in blood pressure, a 1 to 6 mg/dl increase in HDL-C, a 4 to 20 mg/dl reduction in total and LDL-C and a 18 to 30% reduction in fasting glucose levels [87]. Though most weight loss occurs due to reduction in caloric intake by 300 to 500 calories/day for those people with a BMI of 27 to 35 and by 500 to 1000 calories per day for those with a BMI over 35 (10% weight loss in 6 months), it is also necessary to increase physical activity. It reduces risk of cardiovascular disease and diabetes, in addition to benefiting weight loss [8].

**Guidelines for the assessment & treatment of overweight & obese subjects**

According to the Clinical Guidelines Evidence Report, assessment and management are the two primary stages in the treatment of overweight and obese patients. Assessment encompasses determination of the degree of obesity and overall health status. Management includes weight loss, maintenance of body weight and measures to control other risk factors. A lifelong effort is necessary to fight a chronic disease such as obesity, but many studies support the benefits of weight loss for reducing blood pressure, lowering blood glucose and decreasing dyslipidemia (Figure 3)[8].

Assessment of overweight or obese subjects should include the evaluation of BMI, waist circumference and all medical risks. It is necessary to pay much more attention when evaluating very muscular patients because BMI may overestimate the degree of fitness in these subjects. Overall risk must take into account the potential presence of other risk factors. Some conditions associated with obesity place patients at a high risk for subsequent mortality. These require aggressive modification. There are several conditions associated with obesity. Although these disorders are less lethal, they still require some treatment. It is understood that an attempt to treat patients for weight loss must go together with a patient's readiness to make life-style changes.

Therapy is recommended for patients with a BMI greater than or equal to 30. It is also recommended for patients with a BMI between 25 and 29.9, or those who have a high waist circumference and two or more risk factors. Individuals that may decide to change must be informed about the necessity to make effective life-style modifications, which encompass diet and physical activity. When goals of therapy are not achieved after 6 months, careful consideration can be given to pharmacotherapy in patients with a BMI greater than or equal to 30, or a BMI greater than or equal to 27 who have additional risk factors. The only two drugs approved for long-term use known to the authors are orlistat ( Xenical®, Roche Pharmaceuticals, NJ, USA) and sibutramine (Meridia®, Abbott Laboratories, IL, USA). Currently, while their efficacy is appreciable, they are both lacking predictor response. Additional effects of both drugs on weight loss is about 10% when used in combination with an hypocaloric diet [88].
Table 4. New obesity drugs in development.

<table>
<thead>
<tr>
<th>Agonists</th>
<th>Antagonists</th>
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<tr>
<td>Dopaernergic agents</td>
<td>Fatty acid synthesis inhibitors</td>
</tr>
<tr>
<td>Noradrenergic agents</td>
<td>Endocannabinoid receptor antagonists</td>
</tr>
<tr>
<td>Serotinergic agents</td>
<td>Ghrelin antagonists</td>
</tr>
<tr>
<td>Glucagon-like peptide-1</td>
<td>Tyrosine phosphatase-IB inhibitors</td>
</tr>
<tr>
<td>Insulin mimetics and/or</td>
<td>Neuropeptide Y receptor antagonists</td>
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<tr>
<td>sensitizers</td>
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<tr>
<td>Leptin, leptin analogs and/or</td>
<td>Melanin-concentrating hormone receptor antagonists</td>
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<tr>
<td>sensitizers</td>
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<tr>
<td>Melanocortin-4 receptor</td>
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<tr>
<td>agonists</td>
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Therapy aims to achieve reduction in body weight and at the same time, to maintain a lower body weight in the long-term. A weight loss of 10% of body weight is the target recommended in a period of 6 months. A weight loss of 1 to 2 pounds each week is considered satisfactory. The goal is to maintain the weight which is achieved through combined changes in diet and physical activity. If patients do not lose weight, the goal is the prevention of further weight gain.

Expert opinion

Data presented in this review clearly indicate that obesity has to be considered one of the major cardiovascular risk factors for cardiovascular disease today [12-14,17-19].

It is necessary to emphasize that, although during the first phase of obesity cardiovascular damage can be considered reversible if an appropriate weight reduction is achieved, in a short time it becomes irreversible. This finding, related to a missed correction of obesity, determines intervention of other cardiovascular risk factors, such as the hyperactivity of the renin–angiotensin–aldosterone system associated with hypertension, hyperinsulinemia, diabetes mellitus and dyslipidemia. All these factors lead more quickly to fatal or non-fatal cardiovascular events. Obesity presents many risk factors, some of which are modifiable by weight reduction. In this way, weight loss represents an important intervention in cardiovascular prevention [19]. It is already known that bodyweight reduction and its association with pharmacological therapy is able to improve the cardiovascular risk profile. For a long time, weight loss has been recommended as a procedure of primary prevention of cardiovascular disease. Unfortunately, few prospective data are available on the effects of weight loss on cardiovascular mortality. The results of the British Regional Heart Study demonstrate that a switch from a condition of obesity to a normal body weight caused a reduction of almost a third of the cardiovascular mortality [19]. At the same time, subjects that decreased body weight, also being obese, achieved reduced cardiovascular mortality in comparison with obese patients that did not lose weight. The favorable effects of weight loss are also documented by some trials of secondary prevention in patients with stable cardiovascular disease. For example, a meaningful reduction of cardiovascular events was observed in patients with recent myocardial infarction and of total mortality in subjects in which an appreciable weight reduction was achieved [6]. In the Lifestyle Heart Trial, it was shown that lifestyle modifications, including effective body weight reduction, were associated with a significant regression of coronary lesions in subjects affected by CAD [91]. These findings were documented by angiography. In conclusion, it is important to point out that an objective of primary importance for reduction of cardiovascular risk is represented by body-weight reduction. This must be achieved through the combination of an appropriate and rational caloric restriction, regular and continued physical activity, suitable programs of socialization and psychobehavioral therapy, and finally with the aid of drugs.

Five-year view

Some provisional data from the International Obesity Task Force indicate a dramatic problem related to the on-going worldwide increase of prevalence of obesity in next 20 years [101]. It is reasonable to state that in 2025 more than 60% of North American people will be characterized as having BMI's higher than 30 kg/m². In addition, according to Grundy, head of the National Cholesterol Education Program, obesity in this century will likely surpass smoking as the USA's leading cause of preventable death [86]. This should induce obesity experts and political authorities to promote awareness programs in order to reverse or attenuate this trend.

A constant effort must be made, not only to attain an optimal reduction of body weight, but also and above all to individualize measures by which this can be achieved and maintained. Undoubtedly this represents the challenge that will have to unite clinical research, sanitary authorities and politicians in the coming years. A further effort must be applied to the synthesis of new drugs able to improve weight loss in obese subjects. For these reasons, researchers concerned with the advance in understanding of pathophysiology of obesity must be encouraged. Several new targets for obesity treatment have arisen from the recent advancement in our understanding of the complex mechanism controlling energy homeostasis (Table 4). Some of these drugs are currently in preclinical or clinical trials, such as cannabinoid receptor-1 antagonists and leptin analogs. In the future, treatment should be aimed specifically at factors within the weight control circuitry that will act with greater efficacy, perhaps when used in combination, but will not cause side effects associated with past treatments. This should lead to more effective treatments for obesity in the future. With such understanding we can hope not only to develop safe and effective ways to help obese people to achieve and maintain a healthy weight, but also to understand how to prevent the development of obesity in those who are at risk.

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Key issues

- Obesity, one of the major cardiovascular risk factors, is increasing at an alarming rate.
- Hypertension, ischemic heart disease and cardiac failure are the most common cardiovascular diseases associated with obesity, especially when it is characterized by central fat distribution.
- Lifestyle modification and behavioral intervention are the most important preventive strategies, often associated with pharmacotherapy. However, the effects of available drugs on obesity are still unsatisfactory. Therefore, the effort in the coming years will be to find new drugs able to help achieve effective weight loss.

References

Papers of special note have been highlighted as:

* of interest
** of considerable interest


** This study clearly indicates the increase in prevalence of obesity and overweight in the USA and that this is a problem of public health importance.


** The first large prospective study that clearly indicates that central fat distribution may be considered one of the most important cardiovascular risk factors.


** The first large prospective study that indicates that obesity is clearly associated with CAD in women.


** Reports that hypertensive obese subjects were characterized by specific hemodynamic changes indicating these subjects are a particular subset of hypertensives.


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- Endothelial dysfunction is investigated in obese subjects by a technique able to detect coronary endothelial dependent or independent vasodilation.
- The first study indicating that obese subjects with endothelial dysfunction and DD genotype of ACE are a particular subset of subjects at higher risk for cardiovascular damage.

- The first study indicating that central obese subjects could be characterized by a dysfunction in the hormonal mechanisms that control saline balance.
- In this multicentre prospective study, an important relationship between haemostatic factors, coronary arteriosclerosis and coronary risk factors are reported in 3000 patients with angina pectoris. This indicates the relevant role of the prothrombotic-hypothrombinic profile in the development of cardiovascular events.


Cardiovascular alterations in obesity are well documented and utilized for the classification of cardiomyopathy of obesity.


The first study that indicates that it is also possible to detect a left ventricular dysfunction early in overweight subjects. This alteration is primarily related to the degree and duration of obesity.


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