Rev Esp Cardiol. 2011;64(2):140–149

Update: Systemic Diseases and the Cardiovascular System (I)

Obesity and the Heart

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ARTICLE INFO

Article history:
Available online 28 January 2011

Keywords:
Obesity
Body mass index
Coronary artery disease
Bariatric surgery

ABSTRACT

Excess weight is the most prevalent cardiovascular risk factor and certainly the factor that improves the least over time among those with established cardiovascular disease. The association between obesity and cardiovascular disease is complex and not limited to the standard risk factors like hypertension, dyslipidemia, and type 2 diabetes mellitus. In recent years, multiple studies have shown that obesity may cause cardiovascular diseases via multiple disease mechanisms like subclinical inflammation, endothelial dysfunction, increased sympathetic tone, atherogenic lipid profiles, enhanced thrombogenic factors and also through obstructive sleep apnea.

Despite the overwhelming data linking obesity to cardiovascular disease, several studies have shown a paradoxical association between obesity and prognosis among those with coronary disease and heart failure, which may be due to limitations of the way we currently define obesity. There is abundant data suggesting that measuring central obesity or total body fat content might be more appropriate than using the body mass index alone.

The management of obesity is challenging and studies using lifestyle modification alone or with pharmacologic agents generally have limited success and high levels of weight regain. Bariatric surgery has proven to be an effective and safe way to induce and maintain significant weight loss but is limited to those with medically complicated obesity or people who are severely obese.

Obesidad y corazón

Palabras clave:
Obesidad
Índice de masa corporal
Enfermedad coronaria
Cirugía bariátrica

RESUMEN

El exceso de peso es el factor de riesgo de enfermedad cardiovascular más prevalente y ciertamente el factor que menos mejora en sujetos con enfermedad cardiovascular establecida. La asociación entre obesidad y enfermedad cardiovascular es compleja y no se limita a factores mediadores tradicionales como hipertensión, dislipemia y diabetes mellitus tipo 2. En años recientes, diversos estudios han demostrado que la obesidad podría causar enfermedad cardiovascular mediante otros mecanismos como inflamación subclínica, disfunción endotelial, aumento del tono simpático, perfil lipídico aterogénico, factores trombogénicos y apnea obstructiva del sueño.

A pesar de la gran cantidad de datos que relacionan la obesidad con la enfermedad cardiovascular, varios estudios han demostrado una asociación paradójica entre la obesidad y el pronóstico en pacientes con enfermedad cardiovascular establecida. Esto se ha atribuido a la manera en que se define actualmente la obesidad. La evidencia indica que sería más apropiado medir la grasa corporal total y usar marcadores de obesidad central, en vez de sólo usar el índice de masa corporal.

El manejo de la obesidad es usualmente un reto. Los cambios de estilo de vida o los agentes farmacológicos tienen un efecto pequeño en la pérdida de peso y no previenen la recurrencia. Se ha probado que la cirugía bariátrica es un medio efectivo y seguro para inducir y mantener una pérdida de peso significativa, pero su uso está limitado sólo a pacientes con obesidad clínicamente complicada o con obesidad mórbida.

INTRODUCTION

Obesity has become one of the major threats to health throughout the world. Its prevalence has increased in almost every continent and has probably increased in all the developed countries. Obesity, together with excess weight, is currently the most prevalent cardiovascular risk factor in individuals with established coronary heart disease.[1] Obese individuals have poor quality of life and shorter life expectancy than normal-weight individuals. Epidemiological studies have shown that obesity is a major cardiovascular disease risk factor, including coronary heart disease, heart failure, atrial fibrillation, ventricular arrhythmias and sudden death. It is also considered a causal factor in hypertension, diabetes mellitus type 2, osteoarthritis, obstructive sleep apnea (OSA), dyslipidemia, gastroesophageal reflux, non-alcoholic fatty liver disease and many forms of cancer.[2] The

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1885-5857/$ – see front matter
doi:10.1016/j.rec.2010.10.011

Abbreviations

BMI: body mass index
OSA: obstructive sleep apnea
CRP: C-reactive protein

treatment of obesity places an immense economic burden on the health care system. The continuous increase in its prevalence has alerted public health officials, epidemiologists, and economists.[3]

In this article we discuss the fundamental aspects of the pathophysiology of obesity and its relation to cardiovascular disease, and summarize recent evidence that associates obesity with different forms of cardiovascular disease apart from coronary heart disease, such as atrial fibrillation, heart failure, and sudden death. We also review the current controversy on the way obesity is diagnosed. The diagnosis of obesity is usually based on estimates of the body mass index (BMI) and on the values used to define excess weight and obesity. The distribution of body fat has also been associated with cardiovascular events, and it may be more appropriate to measure total body fat and its distribution to determine the risk of obesity-associated cardiovascular disease.[4] In this update, we summarize the best evidence related to the management of obesity, including the use of surgery.

PATHOPHYSIOLOGY OF OBESITY AND CARDIOVASCULAR DISEASE

The association between obesity and different forms of cardiovascular disease is complex, probably due to the different physiopathological mechanisms involving a large number of interacting factors (Fig. 1). Obesity can cause coronary atherosclerosis through well-described and accepted mechanisms, such as dyslipidemia, hypertension, and diabetes mellitus type 2.[5,6] However, recent evidence has shown that the association between obesity and cardiovascular disease[7] could include many other factors, such as subclinical inflammation, neurohormonal activation with increased sympathetic tone,[8] high leptin and insulin concentrations,[9] OSA and increased free fatty acid turnover, and may also be due to fat deposits in specific areas of the body with a direct role in the pathogenesis of coronary atherosclerosis, such as subepicardial fat (Table 1).[10]

Metabolic Factors

Excess visceral fat, associated with central obesity, is the metabolically most active adipose tissue that causes increased insulin resistance, high triglyceride concentrations, changes in the size of low-density lipoprotein (LDL) particles and low concentrations of high-density lipoproteins (HDL).[11,12] The mechanisms by which excess fat causes insulin resistance are complex, certainly involving different physiopathological pathways, and are mediated by cytokines, other inflammatory mediators and elevated leptin levels. Insulin resistance causes diabetes mellitus type 2, a condition that alone can initiate or accelerate the atherogenic process by several additional mechanisms, such as hyperglycemia.[13]

Leptin is an important hormone in the induction of satiety. Resistance to leptin in obese humans is shown by increased serum leptin concentrations. It is a multiple-action hormone, whose possible effects include increased sympathetic activity that promotes thrombosis and increases blood pressure and heart rate. Leptin is a cytokine and is therefore also involved in the inflammatory process. Voluntary weight loss, especially the reduction of adipose tissue, leads to decreased circulating leptin.[14]

Activation of the Sympathetic System

Direct measures of muscle sympathetic nerve activity and catecholamine concentrations suggest that obesity is associated with increased sympathetic activity.[15,16] However, these studies are at variance with other clinical and experimental reports.[17] Patients with morbid obesity, who usually have elevated sympathetic tone, commonly present OSA.[18] Although OSA causes increased sympathetic activity, this disorder has not been taken into account in the majority of studies on sympathetic activity and obesity in humans, and thus it remains unknown whether the association between sympathetic activity and obesity is totally or partially mediated by sleep apnea. Increased sympathetic activity may be related to fat accumulating in the central region of the body, rather than to the BMI itself, or to a prolonged sedentary lifestyle or stress.[19]

Endothelial Dysfunction

Increased BMI and body fat content, especially central obesity, have been associated with endothelial dysfunction.[20] The mechanisms by which obesity can induce endothelial dysfunction are not well defined. The endothelium is a complex organ with endocrine functions. It regulates smooth muscle cell proliferation, platelet function, vasomotor tone and thrombosis. Endothelial dysfunction induces chemotaxis of adhesion molecules and the differentiation of monocytes into macrophages. This is considered a key process in atherogenesis. Endothelial dysfunction also promotes platelet aggregation and decreases nitric oxide bioavailability, which promotes thrombosis by decreasing the ratio between plasminogen activator inhibitor-1 (PAI-1) and plasminogen activator.[21] Some experimental studies point out that sustained weight loss improves endothelial function.[22,23]

Systemic Inflammation

Inflammation has emerged as a powerful predictor, and a possible etiological factor, of cardiovascular disease.[24] Elevated C-reactive protein (CRP) has been associated with an increased risk of myocardial infarction, cerebrovascular disease, peripheral arterial disease and coronary heart disease death in apparently healthy men and women.[25,26] It has also been suggested that obesity is an inflammatory state. A positive association has been observed between BMI and CRP in adults and children.[27] The mechanisms by which obesity leads to elevated CRP have not been fully explained. Interleukin-6 (IL-6) is a cytokine that stimulates the production of CRP in the liver. IL-6 is produced and released by adipose tissue into the bloodstream and a strong correlation has been demonstrated between serum CRP concentrations and IL-6 content in adipose tissue in humans.[28] Of note, the release of proinflammatory cytokines (such as IL-6) by adipose tissue may be influenced by leptin. Experimental studies in rats suggest that CRP can induce atherosclerosis and is not only an indirect marker of vascular inflammation.[29,30]

Changes in Hemostatic Factors

Obesity is associated with various changes in the coagulation and fibrinolytic systems. Obese individuals have increased concentrations of fibrinogen, factor VII, factor VIII, von Willebrand factor and PAI-1 and increased platelet adhesion than lean