

Obesity paradox and cardiovascular risk

Paradoja de la obesidad y riesgo cardiovascular

Ana Daniela Torres Quezada¹, Juan Pablo Garcés Ortega², Rina Elizabeth Ortiz Benavides³

SUMMARY

Obesity, traditionally defined as excess body fat, is a non-communicable chronic inflammatory disease highly prevalent in both sexes, in all age groups, and in different regions globally, which is frequently associated with an increased risk of metabolic and cardiovascular morbidity and mortality. During the last decades, evidence has been growing that suggests the existence of a phenomenon that is currently known as the “obesity paradox”, which exposes that individuals who are overweight or obese have a lower risk of mortality from all causes, an effect that extends to those patients with cardiovascular diseases (CVD), in whom mortality from CV causes is also decreased. However, the published data on the existence or not of this phenomenon are contrasting, so this research seeks to summarize the available epidemiological evidence on the real effect of overweight and obesity on the cardiovascular risk (CVR) of individuals with excess body fat.

Keywords: *Obesity paradox, obesity phenotypes, cardiovascular risk, overweight, body mass index.*

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ORCID: 0009-0005-4896-2502¹

ORCID: 0000-0002-3587-415X²

ORCID: 0000-0003-1804-491X³

Catholic University of Cuenca. Cuenca-Ecuador.

E-mail: ana.torres@ucacue.edu.ec

Catholic University of Cuenca. Cuenca-Ecuador.

E-mail: jgarces@ucacue.edu.ec

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RESUMEN

La obesidad, tradicionalmente definida como un exceso de peso corporal, se trata de una enfermedad crónica inflamatoria no transmisible altamente prevalente en ambos sexos, en todos los grupos etarios y en diferentes regiones a nivel global, la cual es asociada frecuentemente con un mayor riesgo de morbi-mortalidad metabólica y cardiovascular. Durante las últimas décadas, ha ido en crecimiento la evidencia que sugiere la existencia de un fenómeno que actualmente es conocido como la “paradoja de la obesidad”, el cual expone que los individuos con sobrepeso u obesos, tienen menor riesgo de mortalidad por todas las causas, efecto que se extiende a aquellos pacientes con enfermedades cardiovasculares (ECV), en quienes la mortalidad por causas CV también se encuentra disminuida. Sin embargo, son contrastantes los datos publicados sobre la existencia o no de este fenómeno, por lo que la presente investigación busca resumir la evidencia epidemiológica disponible sobre el efecto real del sobrepeso y obesidad en el riesgo cardiovascular (RCV) de individuos con exceso de peso corporal.

Palabras clave: *Paradoja de la obesidad, fenotipos de obesidad, riesgo cardiovascular, sobrepeso, índice de masa corporal.*

Catholic University of Cuenca. Cuenca-Ecuador.

E-mail: rortiz@ucacue.edu.ec

*Corresponding author: Rina Elizabeth Ortiz Benavides, MD, MSc, PhD. Maestría en obesidad y sus comorbilidades – Universidad Católica de Cuenca, Avda. de las Américas y Humboldt. E-mail: rortiz@ucacue.edu.ec

INTRODUCTION

Obesity is a morbid condition, traditionally defined as excess body weight, estimated in clinical practice through the body mass index (BMI). This is an anthropometric measure that evaluates the relationship between body mass and height (1). From a pathophysiological perspective, obesity results from an energy imbalance, where energy intake is higher than the energy expended, and the excess energy is stored in adipose tissue. However, it is known that body weight gain is multifactorial, where not only the abnormal intake of high caloric food is related to energy imbalance. Habits that lead to a reduction in physical activity at work or home, as well as certain environmental, socioeconomic, and even genetic/epigenetic factors, seem to play a fundamental role in the development of obesity (2-4).

Obesity is a highly prevalent morbid condition in both sexes, in different age groups, and in different regions, particularly in Western countries, where lifestyles and environmental conditions are characterized by obesogenic conditions. The maladaptive impact of obesity on cardiovascular structure, function, hormonal communication, and hemodynamics has played an important role in different cardiovascular diseases (CVD). Among these, we can find arterial hypertension (AHT), coronary heart disease, heart failure (HF), atrial fibrillation (AF), sudden cardiac attacks, and, therefore mortality (5,6).

In this regard, it is well known that obesity represents an important risk factor for CVD-related morbidity and mortality (7,8). However, in recent decades it has become evident that, epidemiologically, not all obese subjects have the same risk of developing cardiovascular events. This opened the way to a new era in nutritional research, focused on what is now known as the "Obesity Paradox", a phenomenon that reveals the possible cardioprotective role of obesity. Studies have shown that overweight or obese subjects with established CVD often have a better prognosis compared to their leaner counterparts with the same CVD (5,6). To explain this phenomenon, it has been proposed that in each BMI category, different metabolic profiles are associated with

different degrees of cardiovascular risk (CVR). It is in this way that the existence of different obesities or phenotypes of obesity is proposed, of which the most common are: the metabolically healthy obese (OBMS) and the metabolically obese/sick or unhealthy normal-weight (NPME), which have a prevalence of 7.27 % and 19.98 %, respectively. This prevalence varies according to the parameters for defining and measuring each phenotype (8-10). OBMS is the obese phenotype without metabolic syndrome and with lower CVR, while NPME is a phenotype defined by a normal BMI but with obesity-related metabolic complications (11).

So far, the available data on the real impact of obesity phenotypes on CVR increase are contrasting. Some authors claim that OBMS is a benign condition with no associated short-term risk; however, other studies document that this obesity phenotype does have a significantly negative impact on long-term CV health (8,12,13). In a prospective study of 8 years of follow-up, it was reported that CVR was not increased in the OBMS group compared to normal weight subjects without dysmetabolic factors (12). Because of this uncertainty, the present review aims to summarize the available evidence on the real effect of overweight and obesity on CVR in individuals with excess body weight.

Obesity Paradox in cardiovascular disease

Traditionally, BMI has been used as an anthropometric marker for the estimation of morbidity and mortality in clinical practice, where a value above 30 kg/m² (obesity) is associated with an undeniably higher risk of cardiovascular morbidity and mortality (14,15). However, several studies have shown that some overweight and obese patients have a better cardio-metabolic prognosis compared to normal-weight subjects, a phenomenon known as the "obesity paradox" (6).

In the early 2000s, Gruberg et al. (16), were the first researchers to describe that overweight or obese individuals had a better prognosis when affected by CVD regardless of gender and smoking compared to their lean counterparts. Subsequent studies have provided further evidence on the apparent protective role of excess fat for overall mortality and cardiovascular mortality in patients affected by various CVD,

such as coronary heart disease, heart failure (HF), atrial fibrillation (AF), and even in other types of chronic noncommunicable diseases such as end-stage chronic kidney disease, chronic obstructive pulmonary disease, and type 2 diabetes mellitus. In this regard, Flegal et al. (17), conducted a systematic review and meta-analysis that included more than 90 observational studies, analyzing 2.88 million subjects, which found that being overweight is associated with lower overall mortality (OR=0,94 IC95 %=0,91-0,96; p<0,05).

However, the possible molecular mechanisms that explain the obesity paradox in CVD are still not completely clear. It is known that overweight individuals produce more stable receptors for tumor necrosis factor-alpha in their adipose tissue and have a greater metabolic reserve, which confers certain cardio-metabolic protection (5,6,18,19). Additionally, overweight or obese subjects with HF have reduced circulating levels of B-type natriuretic peptide (BNP). This allows them to develop symptoms in a shorter period, compared to patients with lower weight, which leads to a timely diagnosis and approach that would reduce the risk of morbidity and mortality. It has been observed that these low levels of BNP in overweight subjects are associated with greater development of lean mass, a factor that also confers protection (20). Likewise, it is necessary to consider that those overweight or obese patients who ended up developing CVD could have avoided them if they had prevented weight gain. Meanwhile, individuals with normal weight who develop CVD may have developed them due to pathophysiological mechanisms different from those associated with obesity, either due to genetic predisposition, sociodemographic factors, lifestyles, or other biological factors specific to the thin individual (5,6,19).

Central (visceral) or peripheral (subcutaneous and/or hip) distribution is another factor that could influence the paradoxically better overall and cardiovascular survival observed in overweight patients compared to lean counterparts (21). Another key factor in paradoxical obesity is the existence of individuals who could well be considered overweight or obese based on their BMI, but whose excess weight is the result of a high percentage of hypertrophic muscle tissue resulting from regular anaerobic physical activity (22). Other factors such as

genetic polymorphism, intrauterine exposure to toxic substances, contamination by endocrine disruptors, air pollution, and even intestinal microbiota also play a determining role in the predisposition to obesity. These factors influence the distribution of adiposity and the cardio-metabolic risk of each phenotype (23,24). Similarly, the obesogenic environment driven by the consumption of high-caloric food and epigenetic modifications that affect the transcription of obesity-related genes is other factors influencing the obesity paradox (25,26).

Coronary heart disease

Although the presence of paradoxical obesity in cardiovascular diseases has been suggested, its existence in coronary heart disease is still under discussion, since studies have failed to demonstrate the protective effect of excess weight on cardiovascular mortality (27). However, it has been evidenced that in obese patients, acute myocardial infarction (AMI) is associated with less severe and complex coronary artery disease, compared to non-obese subjects, suggesting the presence of the obesity paradox in coronary artery disease (28). Thus, in a study of patients who suffered AMI, it was observed that in those with morbid obesity, the unadjusted mortality rate was 3.5 %, while in non-obese subjects it was 5.5 %, this difference being statistically significant (p <0,0001). After adjustment, the odds of mortality remained lower in morbidly obese compared to non-morbidly obese patients (29). Similarly, Bucholz et al. (30), conducted a retrospective study involving 124,981 patients with AMI, reporting longer survival in overweight and obese subjects, even after accounting for younger age and more intensive pharmacological treatment. Likewise, in a systematic review conducted by Romero-Corral et al. (31), which analyzed 250 152 patients with coronary artery disease, it was found that the total mortality risk of coronary artery disease was (RR 0.87 [95 % CI 0.81–0.94]) and of cardiovascular mortality was (RR 0.88 [95 % CI 0.75–1.02]) was lower in overweight and moderately obese patients.

Given these findings, it is important to consider that, epidemiologically, obese and overweight patients who develop coronary artery disease tend to be younger and have a higher left ventricular ejection fraction compared to normal-weight

patients, factors that favor a better prognosis for the patient (16,32,33). Likewise, it should also be taken into account that patients with excess weight usually have more regular access to cardioprotective drugs such as aspirin, statins, or beta-blockers, which could partially explain the reduced hospitalization times and low mortality (34,35).

Heart failure

HF is another very frequent CVD in obese patients; however, these patients seem to have a better prognosis than lean subjects, both in men and women, even when adiposity has been estimated with other anthropometric methods, such as abdominal circumference, hip circumference, or triceps skinfold thickness (36-38). In this context, Littnerova et al. (39), conducted a longitudinal study in 5 057 patients with acute HF, where they found that, after 32 months of follow-up, overweight/obese patients had lower long-term mortality than normal-weight patients (HR 1.36; [IC 95 % 1.26-1.48]). Likewise, Zamora et al. (40), reported that those individuals with elevated BMI who did not have diabetes as a comorbidity had lower cardiovascular and all-cause mortality after 4 years of follow-up (HR 0.76; [IC 95 % 0.58-0.99]). In the same manner, in Curtis et al. (41), which included 7 767 patients with stable HF, it was observed that after 37 months of follow-up, both in overweight patients and in patients with stable HF, it was observed that after 37 months of follow-up, both in overweight patients and patients with (HR 0.88; [IC 95 % 0.80-0.96]) and obese (HR 0.81; [IC 95 % 0.72-0.92]), there was lower mortality for all causes. Similar results were achieved by other authors (42-44).

Several mechanisms have been proposed that could explain the protective role of obesity in HF. Thus, as discussed in the case of coronary heart disease, patients with HF and obesity are usually younger than their thin counterparts. This added to the fact that they can be diagnosed in earlier stages of the disease, due to the presentation of a clinical picture characterized by dyspnea, edema, and/or decreased left ventricular ejection fraction. This phenomenon allows, in one way or another, this group of patients to be treated promptly, with a consequent reduction in the risk of long-term morbidity and mortality (39,40,42-48).

As previously mentioned, the concentrations of BNP are lower in individuals who co-morbidly present overweight and acute or chronic HF, which leads to an earlier clinical presentation with a consequent better prognosis (49). In addition, it is important to note that chronic HF promotes a persistent catabolic state causing cardiac cachexia, which could be remedied by the additional nutritional support provided by obesity (46,50). In this regard, one study found that, in a group of patients with HF, only obese subjects were able to maintain muscle protein balance. In non-obese individuals, higher protein catabolism was observed and, therefore, an increased release of amino acids (51). It should also be taken into account that obese patients usually also suffer from hypertension, which is why they are treated with cardioprotective drugs more intensely than their normal-weight counterparts (52).

Atrial Fibrillation

The association between obesity or overweight and AF has been widely documented and reconfirmed with different anthropometric measures to estimate adiposity, apart from BMI. It has also even been observed that excess weight represents a risk factor for the progression of paroxysmal AF to permanent AF and recurrences (53-55). However, different longitudinal studies have demonstrated the presence of the obesity paradox in subjects with AF, since overall mortality and mortality due to CV causes is lower in obese than in normal-weight subjects. In this sense, Wang et al. (56), conducted a study in 2016 of patients with AF for 12 months, observing that the odds of all-cause mortality and CV mortality were higher in the low weight category (HR 1.57 [IC 95 % 1.02-2.42] and HR 2.01 [IC 95 % 1.76-3.43], respectively) and normal weight (HR 1.53 [IC 95 % 1.76-3.43] and HR 1.53 [IC 95 % 1.03-2.28], respectively) comparing with the overweight category. Likewise, Inoue et al. (57), also conducted a study in 6 379 patients with non-valvular AF, finding lower all-cause mortality in overweight patients (HR 0.60 [IC 95 % 0.37-0.95]; $p=0.029$), after a 2-year follow-up. In the same manner, Sandhu et al. (58), followed 17 913 patients with AF for 1.8 years, reporting a lower risk of all-cause mortality in overweight patients (HR 0.67 [IC 95 % 0.59-0.78]) and obese (HR 0.63 [IC 95 %

0.54-0.74]) compared to subjects with normal BMI; they also found a 31 % reduction in the risk of all-cause mortality and a 28 % reduction in the risk of stroke or systemic embolism in women with high abdominal circumference. Similar results were reported by other authors (59-61). Concerning age, the protective action of obesity in older patients has also been demonstrated, as shown by Yanagisawa et al. (62), in a sample of 413 individuals ≥ 70 years with AF, where obesity was associated with lower mortality (HR 0.35 [95 % CI 0.13-0.89]) and lower need for hospitalization compared to lean counterparts.

In contrast to these findings, other studies reveal that weight loss may rather have a beneficial effect on the onset and progression of AF. In this regard, Berkovitch et al. (63), showed that for every 5 kg of weight loss, the risk of developing AF was reduced by up to 12 % in asymptomatic middle-aged subjects; whereas, Pathack et al. (64), in a prospective study conducted over 12 months, reported that patients with a progressive weight loss of more than 10 % were up to 6 times more likely to maintain sinus rhythm. Thus, the available evidence on the true effect of excess weight on AF patients is discordant, so the estimation of the beneficial factor of the obesity paradox should be personalized in this type of patient.

Obesity Paradox: Defining Different Subtypes of Obesity

The contrasting evidence on the controversial role of obesity in the estimation of CVR could be explained in part by the existence of different phenotypes of obesity. This is based more on the distribution of body fat than on the total percentage of adipose tissue. In this sense, obesity has classically been defined based on BMI, a nutritional anthropometric measure that does not allow estimation of the level of ectopic fat. Similarly, it is not able to differentiate fat mass from lean mass, which promotes the placement in the same category of subjects with anthropometric characteristics, metabolic profiles, inflammatory profiles, or levels of physical activity associated with a good or bad state of health (65). Thus,

the cut-off point defined for discrimination between non-overweight and overweight could allow the overlapping of both categories. This is because the former could include subjects who, although they have a “normal” BMI, are a body fat percentage higher than that of individuals classified as overweight or obese.

In resonance with the above, it has been proposed that the apple body shape in individuals classified as normal weight, where fat is distributed mainly in the visceral adipose tissue, is associated with an adverse cardio-metabolic profile. While the pear body shape in overweight subjects, where the highest percentage of fat is distributed in the subcutaneous tissue and hips, is associated with a healthier cardio-metabolic profile (66). Thus, it is hypothesized that there are different types of obesity phenotypes, each of which could individually explain the phenomenon of paradoxical obesity.

Metabolically Healthy Obesity

In the metabolically healthy obese phenotype (MBO) are those individuals with a high BMI who have a healthy metabolic profile. There is a non-atherogenic lipid profile, where there are low concentrations of pro-inflammatory cytokines, both in plasma and adipose tissue, where peripheral tissues are highly sensitive to insulin, and where there is a lower percentage of visceral adipose tissue and hepatic fat (67,68). In European populations, the incidence of this phenotype varies between 10 % and 30 %, being more frequently observed in the female sex and young individuals (69). This subgroup of patients has a CVR and mortality rate comparable to normal-weight individuals (70). However, other authors have observed that the MBO profile is not an entirely benign phenotype. Because, in studies with long evaluation periods of up to 30 years, it has been observed that these subjects have a higher CVR, a higher probability of chronic kidney disease, and non-alcoholic steatohepatitis (13,71–74). It has even been documented that some subjects who were initially MBO, over the years, acquired metabolic characteristics that turned them into sick individuals (75).

Normopoietic Metabolically Obese

The metabolically obese or diseased normal-weight phenotype (NPME) integrates those subjects with a BMI within the normal range, but who have CV risk factors characteristic of obese diseased subjects (76). Thus, NPME patients are characterized by a pro-atherogenic lipid profile, a pro-inflammatory adipokine profile, a higher amount of visceral adipose tissue, and hyperinsulinemia accompanied by insulin resistance (77). Individuals with this phenotype, whose prevalence can reach up to 20 %, are often characterized by being smokers, sedentary, older, and with obesogenic habits. Underdiagnosis of this phenotype is high because both the patient and the health professional typically underestimate the CVR of individuals with normal weight. In this situation, it has been proposed that in men with BMI > 23.8 kg/m² and women with BMI > 22.5 kg/ m², the abdominal circumference is measured, since it has been suggested that the diseased profile of this phenotype is attributable to excess visceral adipose tissue (11.78) < 25.0; overweight, 25.0-29.9; and obese, > or = 30.0 [calculated as weight in kilograms divided by height in meters squared].

Normal-weight Obesity

Normal-weight obesity (NWO) is a phenotype where the individual has a BMI within normal limits with a percentage of body fat mass above 30 %, however, they lack the sick metabolic profile characteristic of the NPME. This phenotype seems to be typical of women, in whom an intermediate pro-inflammatory state between normal-weight and pre-obese subjects has been reported. This early pro-inflammatory condition represents a prognostic factor for CVR and metabolic syndrome, so its diagnosis and timely approach should be emphasized in patients with NWO (79,80).

Sarcopenic obesity (SO)

Sarcopenic obesity (SO) is a phenotype of obesity that is difficult to characterize since there is no established consensus on the specific definition of this condition. However, SO

arises from the coexistence of decreased lean mass, skeletal muscle hyperfunctioning, and a high percentage of adipose tissue, phenomena that are associated with aging. Likewise, it has been shown that obesity and sarcopenia have a synergistic relationship since the metabolic, CVD, and mortality risk is higher in SO compared to that observed in each of these conditions in isolation. In this sense, both obesity and sarcopenia are pathologies that have some risk factors in common, such as a sedentary lifestyle; in addition, the chronic inflammatory state of obesity promotes loss of muscle mass, which further favors the sarcopenic state (81-83).

CONCLUSIONS

The obesity paradox is an epidemiological phenomenon in which excess weight seems to have a protective role in overweight or obese subjects. It also reduces the risk of all-cause and CVD death in patients with CVD such as coronary heart disease, heart failure, or atrial fibrillation. However, the evidence currently available is contrasting, with studies either reinforcing or refuting this axiom. It has been proposed that paradoxical obesity could be partially explained by the existence of phenotypes such as OBMS, NPME, NWO, and SO, each of which has anthropometric characteristics and cardio-metabolic and inflammatory profiles, which individualize CVR. In the absence of a universally shared definition of “obesities”, it is difficult to estimate the real burden of each phenotype and its role in the obesity paradox. Hence, more prospective studies with long follow-up periods, where adiposopathy is determined in different ways, are needed. In addition, the evaluation of all possible influencing and confounding factors in the relationship between excess weight and CVR, so that the existence of an obesity paradox can be confirmed.

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