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Evidence Based Obesity Paradox

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Abstract

The presence of the "obesity paradox" was presented in publications in almost all major CVD, diabetes mellitus (type 2 DM), in patients with renal pathology and after revascularization of the coronary arteries and transcatheter aortic valve replacement. However, the vast majority of studies are retrospective. At the same time, the comparison groups were formed on the basis of the BMI value, although later publications also took into account the percentage of adipose tissue and waist circumference. However, in the formation of groups, as a rule, no other risk factors were taken into account and, moreover, no division of patients into groups were carried out, taking into account cardiovascular risk, followed by a comparison of the same risk groups of patients with normal or elevated BMI. The purpose of our review was to draw the attention of physicians and researchers that despite the biological possibility of the existence of a positive effect of adipose tissue on cardiovascular diseases, the presence of a large number of errors identified in analysis of the works of researchers "obesity paradox" require to reconsider the existence of this phenomenon in accordance with the recently formulated principles of "exact medicine".

Keywords: Obesity Paradox; Body Mass Index; Risk Factors; Cardiovascular Diseases; Obese People; Prognostic

Introduction

Obesity is a major independent risk factor for cardiovascular diseases (CVD) such as hypertension, coronary heart disease, atrial fibrillation, and heart failure [1,2]. Currently the WHO defines obesity as an increase of adipose tissue, which harms the health and further suggests BMI as a rough guideline for assessing normal and overweight, and obese, but individuals with the same BMI can have different degree content of adipose tissue [3]. Therefore, the ideal definition of obesity should include the percentage of adipose tissue. Universal indicators for the determination of increased adipose tissue to verify obesity>35% (30%) in women and > 25% in men. There are also specific to race, age and sex standards, which are indicated in scientific publications [4].Despite the fact that BMI is widely used, easy to operate, inexpensive, this method has its limitations. The benefit of BMI in determining obesity is criticized for its inability to separate adipose tissue, muscle and skeletal weight, making it an inaccurate method of determining excess adipose tissue at the individual level [5-7].

Given that BMI does not distinguish between fat, muscle and skeletal mass, individuals with the same BMI may have different body composition and, more importantly, metabolic parameters [7]. On the other hand, it is known that normal BMI parameters are combined with excessive accumulation of adipose tissue and an increase in cardiovascular risk. These individuals are defined as "obesity with normal BMI" (normal weight). This group includes persons with high fat content or with an increased waist circumference, but normal BMI, who have an increased risk of metabolic disorders, coronary heart disease (CHD), and death. Based on the determination of total obesity by BMI, it is expected that more accurate ways to estimate obesity will better predict the risk of death [3].

However, at the population level, BMI continues to be used to predict adverse outcomes, in particular in the Ortega, *et al.* study on more than 60,000 subjects, BMI has been shown to be a more accurate method of assessing cardiovascular risk than other obesity indices (% adipose tissue, fat and non-fat mass indices). Taking into account these data, BMI continues to be the gold standard in the assessment of total body weight, as it allows a comprehensive study on the effect of fat mass and non-fat mass on the development of cardiovascular disease [8].

But recently, it has been shown that many CVD have a better prognosis in people who are overweight or obese compared to those with normal body weight, and this pattern has been called the "obesity paradox". However, this is more related to overweight and I degree obesity and less typical to II degree obesity and above [3].

The "obesity paradox" has been described in many CVD and even in some other forms of pathology, such as end-stage renal failure, in patients with immunodeficiency virus and in various pulmonary diseases [9].

The term "obesity paradox" first appeared in the biomedical literature in 2002 in the title of Gruberg, *et al.* [10]. Originally Gruberg, *et al*. suggested that among patients with coronary artery disease people with overweight and obesity would have worse outcomes after percutaneous coronary intervention compared with patients with CAD and normal body weight.

The researchers were surprised by the results, as patients with normal BMI had unexpectedly the highest risk of re-hospitalization due to complications, as well as an increased risk of cardiovascular death, which persisted for 1 year. Complications after the intervention were higher in patients with normal BMI compared to those who had overweight or obese. Initially, in most studies that demonstrated the "obesity paradox", only BMI was used to diagnose obesity and overweight, and therefore the existence of the "obesity paradox" was doubted, based on the existing limitations in the meaning of BMI, as mentioned above. However, later in a number of studies it was shown that in addition to BMI and the percentage of adipose tissue, the waist circumference also demonstrates the presence of the "obesity paradox", especially in people with CVD [9]. Currently, the "obesity paradox" was registered in almost all major CVD, diabetes, in patients with renal pathology and after revascularization of the coronary artery, prosthetics of the aortic valve. However, the vast majority of studies are retrospective. At the same time, the comparison groups were formed on the basis of the BMI value, although later publications also took into account the percentage of adipose tissue and waist circumference. Our aim was to emphasize that in the formation of groups, as a rule, no account was taken on other risk factors and, moreover, no division of patients into groups, taking into account cardiovascular risk, followed by a comparison of the same risk groups of patients with normal or elevated BMI, as is customary in accordance with the recently formulated principles of "exact medicine" [11].

Methodology

We performed a systematic electronic search in the Medline/PubMed, Web of Science, SciELO, and LILACS databases of studies published up to July 2019 to identify articles that studied the "obesity paradox". We studied both original studies that directly identified the "obesity paradox" based on the analysis of BMI, percentage of adipose tissue or waist circumference, and the meta-analyses, that have appeared to date, which included a whole set of studies on the problem of "obesity paradox" in general or in a particular pathology and also criticisms of the problem .The main key words were "obesity paradox", biases and errors.

Arterial hypertension

Patients with obesity have a higher prevalence of arterial hypertension (AH) compared to those with normal weight. In addition, obesity adversely affects the risk factors for coronary heart disease and leads to an increase in myocardial mass, regardless of blood pressure. However, several studies demonstrate the presence of the obesity paradox in AH patients. Uretsky, *et al.* [12] conducted the largest of these studies in which evaluated the impact of obesity on outcomes in 22 576 patients with hypertension and coronary artery disease on the background of drug therapy. Despite the overall deterioration in blood pressure control over the next 2 years, the overall mortality rate in people with obesity was 30% lower in overweight and obese groups compared to those who were normal weight. Other studies have shown the same results, or demonstrated a U-shaped relationship between BMI and the risk of death from all causes, cardiovascular and non-cardiovascular death, since an increase in the risk of death was noted in both low and extremely high BMI (grade III-II of obesity) [13].Thus, on the basis of such a simplified analysis of the data obtained, the authors conclude that overweight and moderate obesity in patients with hypertension apparently have a positive impact on the prognosis compared to those without obesity [9].

Coronary heart disease

Obesity is associated with risk factors for coronary heart disease and increases the prevalence of this disease, although some studies show that the risk of developing coronary heart disease is not increased in individuals with "metabolic healthy" obesity [14-17]. However, as with arterial hypertension, many studies using different criteria for obesity, including BMI [18-27], percentage of adipose tissue [19-21], and sometimes even waist circumference [20], revealed a paradox of obesity in persons with coronary artery disease. Romero-Corral, *et al.* [18] performed a meta-analysis of 40 cohort studies involving more than 250,000 patients with CHD, and reported that patients with CHD who are overweight and obese have a lower risk of total and cardiovascular death compared to patients with CHD with reduced or normal body weight. However, in patients with grade II obesity (BMI - from 35 to 40 kg/m2), these authors identified an increased risk of cardiovascular death without increasing overall mortality. Recently, some studies have shown an increased risk of death in CHD patients with obesity at normal weight or central obesity at normal weight, in which the reference values of the percentage of adipose tissue or the waist circumference are increased, compared with those in which the BMI was within the normal range [17,22,23]. However, some researchers consider these conclusions to be justified only in people with low exercise tolerance [20]. A number of studies have also noted the relationship between less obesity and a worse prognosis [21], which may represent both the "thin paradox" and the "obesity paradox" [19,24,25]. In other studies it was demonstrated that low values of body fat percentage (<25% in men and <35% in women) and low BMI [19,26], both jointly and separately, are independent predictors of the worst outcomes. In particular, in a study involving 581 patients with coronary artery disease, it was shown that only people with low BMI (<25 kg/m2) and low percentage of adipose tissue had a high mortality rate compared to other groups [19]. More recently, it has been observed that a low percentage of adipose tissue and a low non-adipose mass are associated with worse survival, while patients with high muscle mass and a high percentage of adipose tissue had better

survival rates. Intermediate survival rates were also observed in other groups [21]. "Overweight paradox" was also demonstrated in the group of patients with coronary heart disease in comparison with thin persons with coronary heart disease [24,25]. In addition, patients with ischemic heart disease reveal the presence of "obesity paradox", not only based on BMI, but also on the percentage of adipose tissue and waist circumference, with the best prognosis observed in patients with ischemic heart disease and overweight in contrast to patients with more severe obesity [27]. However, most studies of the "obesity paradox" in CHD, as in other types of CVD, represent a retrospective analysis or meta-analysis, in which the division into groups occurs only on the basis of BMI or other indicators, for example, the percentage of fat or muscle tissue, as well as on the basis of the waist circumference [20-23,25]. At the same time, a significantly smaller number of prospective observations in which the "obesity paradox" was also observed did not take into account other risk factors that could affect the results of the observation when divided into risk groups [19,24]. In particular, in the review of Lavie CJ, *et al.,* devoted to the "obesity paradox", it is indicated that the formation of comparison groups not only on the basis of weight, but also taking into account the level of physical endurance (fitness) significantly leads to the disappearance of the "obesity paradox" [25].

Heart failure

Since obesity is the cause of significant disorders in the structure and function of LV [13,28], an increase in the spread of heart failure (HF) in obesity is not surprising. The study Kenchaiah, *et al.* [29] studied 5,881 participants in the Framingham study and demonstrated a 5% increase in the prevalence of HF in men and a 7% increase in women for each increase in BMI by 1 kg/m^2. However, in the study that included 550 individuals without diabetes, an increase in BMI was not associated with escalate in the risk of HF, while the presence of other metabolic disorders increased the risk of developing HF by 2.5 times [30]. In this study, a 6-year follow-up revealed, that patients with normal weight and metabolic syndrome had a greater risk of developing HF, than metabolic healthy obese persons. Although a study from Norway showed, that metabolically healthy obese individuals have an increased risk of developing HF [15]. Alpert, *et al.* [31] also demonstrated a very close relationship between morbid obesity and the development of HF. In meta-analysis of observational studies in patients with HF, including 28 209 patients., Oreopoulous, *et al.* [32] showed, that compared with patients with normal BMI, patients with HF with overweight or obesity had lower rates of cardiovascular (19% and 40%, respectively) and total mortality (16% and 33%, respectively) in the observation for an average of 2.7 years. The "obesity paradox" with heart failure was also found when considering only BMI, body fat percentage and waist circumference [9,28,33-35].In a retrospective study by Lavie, *et al.* [2] , which included 209 patients with systolic heart failure, the presence of the "obesity paradox" was demonstrated, taking into account only BMI and the percentage of adipose tissue. In fact, for every 1% increase in adipose tissue, there was a 13% decrease in cardiovascular events. Clark, *et al.* showed, that the increase in BMI and waist circumference were also associated with better survival in patients with heart failure, while the best survival was observed in individuals with high BMI values and waist circumference [2].

Atrial fibrillation

The prevalence of atrial fibrillation (AF), as well as obesity, is increasing, and is expected to increase 2.5-fold over the next 30 years [13]. The increase in AF may be partially related to the obesity epidemic, its adverse hemodynamic effects and impact on the structure and function of LV and left atrium [13,36]. In a meta-analysis of 16 studies involving 120,000 patients, Wanahita, *et al.* [37] demonstrated that patients with obesity have an increased risk of AF by 50%. However, as in patients with hypertension, coronary artery disease and HF, persons with AF, taking into account only overweight or obesity, have a much better prognosis than patients with AF with BMI within the normal values [9]. There may be a number of explanations for this. First, a greater proportion of patients with AF in cohort studies tend to be overweight or obese were significantly younger while those patients who have normal BMI tend to be significantly older. Second, there appears to be a greater use of rhythm control strategies and anticoagulation in patients with high BMI, potentially to account for a greater proportion of persistent AF in groups with a higher BMI. Third, patients with high BMI tend to have higher blood pressures facilitating greater use of appropriate cardiac medications. Fourth, patients with an apparently normal BMI may have other medical conditions which lead to a relatively catabolic or pro-inflammatory state and that increased BMI provides a metabolic reserve in this case. Fifth, cardiorespiratory fitness is being increasingly recognized as a major factor in reducing AF [38].

Diabetes

Obesity is closely related to the risk of developing type 2 diabetes. The risk of its development increases by 20% with an increase in BMI per 1 kg/m^2. At the same time, the risk of diabetes is not increased with BMI < 27.2 kg\m^2, but it sharply increases to 100% with BMI 27.2-29.4 kg\m^2, and with obesity (BMI> 29.4 kg\m^2) the risk of diabetes is 300% [39]. However, Kwon, *et al.* conducted a systematic review and meta-analysis of the results of sixteen studies in order to calculate the relationship only between BMI and the risk of total and cardiovascular mortality in patients with type 2 diabetes and concluded that in patients with diabetes there is also a "paradox of obesity" with respect to total and cardiovascular mortality [40]. Han SJ and Boyko EJ identified 17 studies investigating the association between obesity defined by BMI and mortality in diabetes that included more than 1,000 subjects who were followed for more than 4 years. Eleven studies showed that being overweight or obesity was associated with lower mortality rate. Four studies reported an inverse relationship between BMI and mortality rate. It is assumed that these results are based on the same errors in the construction of studies that are listed in our review [41].

Patients after coronary artery revascularization

Among patients with overweight or obesity, the prevalence of percutaneous coronary interventions (PCI) or coronary artery bypass grafting (CABG) can reach 70%. Long-term follow-up showed that the risk of total and cardiovascular mortality decreased in people with obesity and normal weight. 10-year follow-up of CABG survivors (n = 9862) revealed that obesity was not associated with increased morbidity or mortality, but patients with a BMI of 40 kg /m^2 had a greater need for re-hospitalization. In 2014 have helded analysis of the results of 12 studies in patients after CABG (60, 000 patients) found, that the risk of cardiovascular death was 4 times higher in patients with obese compare to normal BMI [3].

Patients after transcatheter aortic valve implantation (TAVI)

The published meta-analysis of the data showed the presence of the "obesity paradox" even after transcatheter aortic valve implantation due to its stenosis. Patients with obesity and overweight in single-factor analysis had significantly better indicators of 30-day and long-term survival compared with patients with normal BMI [42].

The mechanisms underlying the "obesity paradox" in CVD are not very clear, the potential biological benefits of excess fat stores during disease periods are well known [43,44]. However, it is important to present evidence that studies of the "obesity paradox" suffer from a number of methodological errors:

- Most studies are retrospective analysis, the results of which have low evidential value [45].
- The comparison of groups in the retrospective analysis was carried out without taking into account other risk factors, as well as the degree of general cardiovascular risk, but only on the basis of BMI (within the normal values, overweight, obesity) in persons with the same leading disease [46].
- Weight loss associated with disease progression (such as cachexia in heart failure) can also lead to a distortion of the study results when divided into groups based only on weight and body composition. Heavy patients with reduced weight due to illness automatically fall into the group of thin [43,47-48].
- In people with obesity, CVD develops at a more younger age than in patients with normal weight, but age not always have taken into account in comparing groups of patients, what can also lead to errors [49-50].
- Among people with obesity, such a harmful habit as smoking is less common, due to which patients with obesity can have a better prognosis compared to smoking patients with normal weight [43,51-56].
- In persons with obesity, the parameters of lipid and glucose metabolism can be both within the normal range, which is called "metabolic healthy obesity", and significantly go beyond the reference values ("metabolic unhealthy obesity"). Exactly the same deviations in the parameters of the metabolic profile can be observed in persons with normal weight. At the same time, metabolic disorders significantly worsen the prognosis in persons with CVD, so their presence should also be taken into account when dividing into comparison groups [57].
- A lower level of atrial natriuretic peptide in people with obesity and HF indicates that persons with obesity have a lighter degree of heart failure than those with normal weight [9].
- The reduced reactivity of the renin-angiotensin-aldosterone system in people with obesity and HF may contribute to improved prognosis in such individuals [9].
- Higher blood pressure in people with obesity, makes use more pharmaceuticals, which can improve the prognosis [9].
- Different etiology of diseases, which led to the development of HF (myocardial infarction, hypertension) , can result in a better prognosis. For example, the prognosis of systolic form of the HF (usually associated with CAD) less favourable, than diastolic form of the HF (usually associated with hypertension) [9].
- The increase in muscle mass and muscle strength in individuals who formally fall into the group of obese on the basis of increased BMI has a favorable effect on the prognosis [9].
- The unaccounted influence of physical fitness acquired during regular aerobic exercise (the so-called "fat but fit" phenomenon), which can cause a better prognosis [58,59].
- Only a few studies have data on some specific variables, such as alcohol or drug abuse, that may also have an impact on the prognosis [9].
- The presence of other uncertain now risk factors, that may also affect the results of studies [9,45]

The above errors are usually amplified when attention is limited to individuals who have developed the disease. Thus, the most pressing question today is whether the "obesity paradox" is the result of the actual protection provided by excess fat body, or whether organizational and statistical errors lead to distortion of results and have important clinical consequences? [43].

Some studies are debunking the "obesity paradox" due to the fact that CVD is diagnosed in individuals with obesity much earlier in life in comparison with individuals with normal body weight, which in turn explains the more favorable prognosis in individuals with obesity. Moreover, these studies have shown that with the exception of smokers and persons with concomitant pathology, the risk of developing CVD increases linearly in proportion to weight gain, or J-shaped, as shown in previous studies [49,50]. The relationship between smoking and the "obesity paradox" is the result of the widespread use of smoking, its deadly danger and its feedback on obesity. People who are overweight and obese are less likely to smoke than people who are normal weight, a negative relationship that becomes stronger when people with already developed CVD are selected; in this case both smoking and obesity become the risk factors. A stronger negative correlation between smoking and obesity in people with CVD, in turn, increases the risk of underestimating the risk of death associated with obesity [43].

Some authors believe that in addition to smoking, there are other, clearly unobservable risk factors that increase the relative mortality of patients with CVD among people without obesity [51-56]. In addition, the reverse causal relationship, which refers to cases in which weight, is the consequence, not the cause of the disease, can lead to erroneous conclusions. Low weight is often the result of diseases that can lead to loss of appetite or increase metabolism, which leads to higher mortality [47-48]. Given that weight loss tends to be more common among people suffering from disease and therefore their mortality is also higher, reverse causation poses a greater threat to an objective assessment of the risk of death from obesity when the analysis is limited to such individuals [43]. To reduce the impact of cause-and-effect feedback on the relationship between obesity and mortality, large groups of individuals had to be removed from the analysis. Excluded could be persons who have lost weight, persons with various diseases, and persons who died within the first few years. These exceptions eliminated up to 80% of deaths [60]. When such patients were included in the analysis of the relationship between obesity and mortality and accounted for almost 80% of the dead, erroneous data were certainly obtained.

Researchers Stokes A, Preston SH [43] decided to evaluate the Association between weight and mortality in individuals with CVD who would be resistant to bias associated with reverse causation and smoking. The study compared patients with CVD of the same age with normal and overweight, obesity. The authors showed that these shifts are amplified in the population with CVD, in which both the prevalence of the disease is higher and the negative correlation between BMI and smoking is stronger than in the general population. The results show that the simultaneous elimination of smoking and reverse causation leads to a striking disappearance of the "obesity paradox". The presence of overweight or obesity was associated with a slight 11% reduction in relative mortality compared to those with normal weight in the conventional model that used BMI in weight estimation. However, when the study groups were formed from those who had always been normal weight, never smoked, overweight/obesity was associated with a statistically significant increase in mortality by 51%.

These two shifts had roughly the same meaning in the explanation of the "obesity paradox". The researchers interpret these data as evidence that the "obesity paradox" is the result of reverse causation and unaccounted effects of smoking, rather than a real biological phenomenon, as previous studies have shown [43].

Another likely explanation for the widespread data on the "obesity paradox" is that the control group with normal BMI is often represented by individuals with low risk of cardiovascular and general death and stable weight, as well as high risk individuals who have lost weight [46]. In addition, the study Stokes A. and Preston S.H. [43] it was shown that among patients with CVD, the majority of persons with normal weight at the time of the survey were previously overweight or obese. These individuals have a higher risk of death than those who have had a consistently normal weight throughout their lives. This appears to be due to the fact that weight loss in these individuals is the result of illness. The disease itself does not change the significance of other risk factors that predict death from CVD, such as hypertension or high fasting plasma glucose. These patients often experience weight loss and are associated with an erroneous bias in the analysis of mortality and its association with obesity.

Studies have also been conducted to assess the role of aerobic exercise (running, cycling, and fitness, walking with a heart rate increase of 20% or more during exercise) in the emergence of the "obesity paradox" among people with CVD. McAuley and Beavers analyzed five studies involving individuals with established or suspected coronary artery disease [58]. They found that in all cases, the "obesity paradox" persists in patients with low physical activity, while in patients with high physical activity, the "obesity paradox" disappears in three studies and remains in two out of 5 studies. Smoking is one of the key risk factors for deterioration of physical activity [59]. In this sense, the inclusion of risk factors such as smoking and low physical activity in the study of the "obesity paradox", mutually reinforcing, lead to significant changes in the results of the analysis of the impact of obesity on mortality. That is, habits represent a lot in the prognosis of the disease, regardless of body weight.

There is increasing evidence that not all people with obesity have an increased risk of metabolic disorders and cardiovascular disease, which has been called "metabolic healthy obesity." Approximately 25% or more people with obesity, although not necessarily morbid obesity (extreme obesity with BMI > 40kg/m^2 or more), were "metabolically healthy". They had no insulin resistance and had a normal lipid and glucose profile and a favorable risk of cardiovascular disease. In contrast, almost 23% of adults with normal weight had metabolic disorders comparable to glucose and lipid metabolism disorders in individuals with obesity, in particular insulin resistance, dyslipidemia including high triglyceride levels and low HDL levels. Typically, these individuals have lower physical activity and higher rates of visceral obesity [57]. The "obesity paradox" is mainly observed in older persons. Consequently, the protective effect of good nutrition in older persons who are overweight and obese and the negative effect of malnutrition among those who are not overweight are likely to contribute to this paradox. In addition, it is possible that people who are overweight and obese with really serious diseases simply do not live to an elderly age, and people with high nutrition, which is compared with patients with normal weight, have lighter and benign forms of the disease, which can also cause the "obesity paradox".

Due to the fact that many risk factors are closely interrelated errors can often occur in observational studies. The paradox arises when the results contradict expectations. This result is more likely when risk factors are negatively correlated and when one of the variables is missing or poorly measured. Future studies of the "obesity paradox" should recognize the greater threat to objective assessment due to the negative correlation between smoking and obesity.

Conclusion

Those studies that have been conducted to assess the presence of the "obesity paradox" suffer from a number of methodological errors. First of all, a simple division into comparison groups of patients based on BMI or other body composition parameters does not take into account the presence of other risk factors that can significantly affect the results of the retrospective study.

Moreover, patients have not divided into groups according to the degree of cardiovascular risk, which significantly distorts the results of retrospective analysis. The organization of prospective studies or more careful consideration of all currently known risk factors for CVD will significantly improve the results of the study effect of overweight and obesity on mortality in patients with CVD. Thus, despite the biological possibility of the existence of a positive effect of adipose tissue in cardiovascular diseases, the presence of a large number of errors identified in the analysis of the researchers works of the "obesity paradox", require to reconsider the existence of this phenomenon, it should be taken into account the possibility that the "obesity paradox" may be the result of improper design of studies to learn this phenomenon.

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