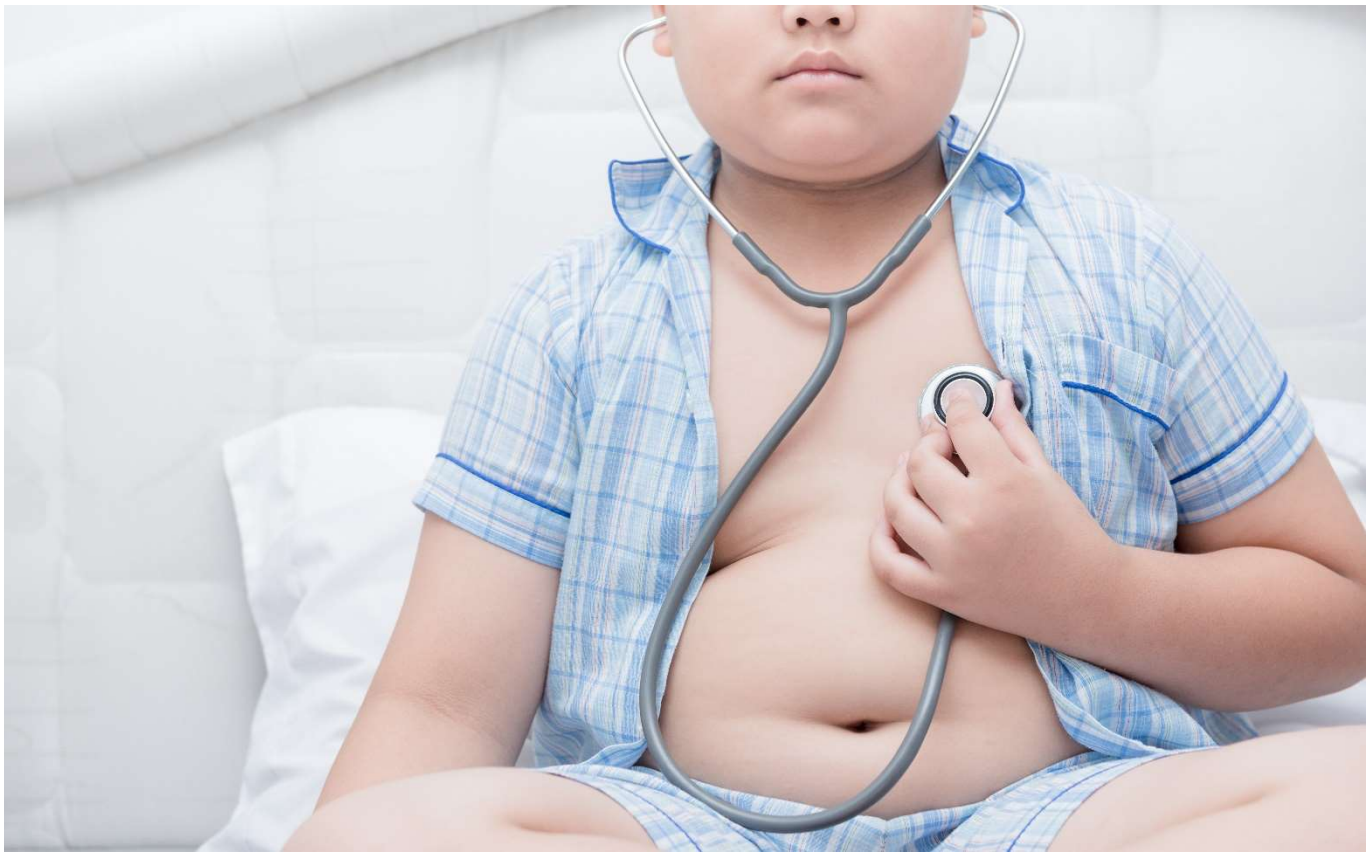

OBESITY - RISK OR PROTECTION FACTOR? OBESITY PARADOX IN CARDIOVASCULAR DISEASES

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ABSTRACT

Obesity, by definition, is a chronic disease which is the result of excessive accumulation of fatty tissue and characterized by increasing body mass index (BMI) ≥ 30 kg/m^2. It is classified as a civilization disease. According to World Health Organization (WHO) in 2016 worldwide, there were 650 million obese people. As evidenced, obesity increases the probability of developing cardiovascular diseases such as hypertension, heart failure and coronary artery disease. Interestingly, a lot of studies have been carried out and results of these studies indicate that obesity, which is an important risk factor for cardiovascular disease, may also act as a favorable prognostic factor. Obese patients with chronic diseases, for instance heart failure or patients with coronary artery disease, who underwent percutaneous coronary intervention, have better results of treatment compared to patients with normal body weight. This phenomenon, which is based on the paradoxical relationship of increased body mass with lower mortality, is defined as the obesity paradox. We present a review of the literature, which will allow understanding the problem of this phenomenon, its pathophysiology and results of the patients with cardiovascular disease connected with obesity paradox.

BACKGROUND

Obesity is defined by World Health Organisation (WHO) as an excessive accumulation of fatty tissue that may influence health condition. It can be found in International Statistical Classification of Diseases and Related Health Problems (ICD-10). One of the methods of classification of obesity is Body Mass Index (BMI). It equals body mass in kilograms divided by square of height in meters. For overweight, it has value over 25 and for obesity, it is bigger than 30. In the years 1980-2008 number of obese people in the world has doubled [1]. High BMI is an essential risk factor for many non-communicable diseases like cardiovascular diseases, diabetes mellitus, musculoskeletal disorders and some of the neoplasms [2]. High BMI relates to over 100 million years of healthy life lost due to premature death or disability (DALYs – disability-adjusted life years) [3]. However higher value of BMI does not combine with higher mortality in every group. Analysis of some patients with cardiovascular diseases has revealed that those with overweight or moderate obesity had a longer time of survival compared to patients with normal weight. Diagrams of survival depending on BMI among them form a "U" shape with the most favorable score for 25kg/m^2, which is a lower threshold for overweight. This phenomenon is called an obesity paradox [4, 5].

OBESITY PARADOX IN CORONARY ARTERY DISEASE AND ACUTE CORONARY SYNDROME

Coronary artery disease (CAD) is a disorder of blood flow to cardiomyocytes due to changes in the coronary arteries. Progressing CAD may lead to the occurrence of acute coronary syndrome when part of heart muscle dies. In many types of research overweight and obesity were proved to be modifying risk factors for CAD [6]. Therefore observation of longer survival of the overweight among patients suffering from CAD may seem paradoxical. This conclusion was submitted by Romero-Corral et al. after meta-analysis of 40 studies including 250, 152 people. Patients after the percutaneous coronary intervention, coronary artery bypass graft or myocardial infarction were taken into consideration. Then they were divided into groups according to their BMI. The highest risk of death occurred among patients with underweight and class II obesity. It had intermediate value for a class I obesity and was the lowest for overweight [7]. In studies conducted by Levi et al. [8] 570 patients suffering from CAD were split due to body fat (BF) and lean mass index (LMI). Patients with lower BF (men <25%, women <35%) and LMI (men <18.9 kg/m^2, women<15.4 kg/m^2) had lower 3-year-survival as opposed to those with higher values. In another meta-analysis [9] studied 15,923 patients chosen in order to the same criteria as in the previously mentioned Romero-Corral. researches. This time aside from BMI, WHR (waist to hip ratio) and WC (waist circumference), which are a measure of central obesity, were used as obesity parameters. High WHR and WC values were related to increased number of deaths. But the connection between BMI and number of deaths was opposite and showed lower mortality for higher BMI. It may indicate the incorrect use of BMI as a parameter of body fat [10]. Paradoxical protective influence of obesity was also noticed in patients who have undergone myocardial infarction. 50,149 patients hospitalized due to STEMI (ST elevation MI) were split according to BMI [11]. The lowest mortality occurred among patients with class I obesity, but it did not diverge significantly from values for patients with normal body weight, overweight and class II obesity. Patients with class III obesity (BMI>40 kg/m^2) had the highest mortality. In MERLIN-TIMI studies patients in one-year period after undergoing an acute coronary syndrome were observed. Dependence between BMI, WC and WHR and recurrence of another myocardial infarction was investigated. It was noticed less frequently among overweight patients in first thirty days of observation but did not vary significantly in the one-year period between groups divided according to BMI. The higher risk of recurrence was detected in a group with lower BMI but high WC [10].

OBESITY PARADOX IN HEART FAILURE

The existence of the obesity paradox, sometimes called as the reverse epidemiology of obesity, has also been demonstrated in heart failure. This is particularly interesting due to several reasons. One of them is the fact that a high BMI index increases the risk of heart failure, which has been demonstrated, among others, in the Framingham Heart Study [12]. Another interesting mechanism is an inverse relationship between adiponectin concentration and BMI. Adiponectin is a cytokine produced by adipocytes that form adipose tissue. The low concentration of this cytokine correlates with a higher risk of cardiovascular disorders and higher mortality. Accordingly, obese patients with heart failure with the more developed adipose tissue should be included in the group of high risk. Meanwhile, some studies show that these people paradoxically have a better prognosis.

Heart failure (HF) is defined as the condition in which occurs impairment of its function and, as a result, the heart cannot cover the body's need for the components delivered with blood: oxygen and nutrients. The paradoxical influence of obesity on longer survival of patients with heart failure has been proven in many studies, among others in French EPICAL study (Épidémiologie de l'Insuffisance Cardiaque Abancée Lorraine), as well as in CHARM (Candidate in Heart Failure-Assessment of Mortality and Morbidity), DIAMOND-CHF (Danish Investigations of Arrhythmia and Mortality on Dofetilide in Congestive Heart Failure), DIG (The effect of Digoxin on Mortality and Morbidity in Heart Failure) or ValHeFT (A Randomized Trial of the Angiotensin-Receptor Blocker Valsartan in Chronic Heart Failure) [13]. The exact pathomechanism, which could clearly explain the obesity paradox in heart failure, remains unknown. There are several theories about the probable causes of this phenomenon. One of them is associated with increased catabolism and limitation of anabolic processes in the people with heart failure. This hypothesis indicates the protective effect of the increased metabolic reserve resulting from the higher content of adipose tissue, which allows better survival of catabolic states, characteristic especially for exacerbations of heart

failure [14, 15, 16]. Another hypothesis concentrates on the production of soluble receptors for tumor necrosis factor alpha (TNF-α) by the adipose tissue which can neutralize the proinflammatory action of this factor [13, 14]. An interesting issue is also the inverse relationship between the concentration of natriuretic peptides and body weight. Natriuretic peptides participate in the regulation of cardiovascular homeostasis, their concentration increases in the case of increased tension on the heart cavities, and they are a clinically useful indicator of left ventricular dysfunction and the advancement of heart failure. Obese patients with HF have been shown to have a lower level of natriuretic peptides, which may be associated with an earlier occurrence and earlier diagnosis of heart failure with lighter symptoms. Therefore, such patients are treated earlier, which can be associated with a better long-term prognosis [13, 17].

OBESITY PARADOX IN HYPERTENSION

In the course of obesity, the concentration of leptin in the blood increases, which results in the activation of the adrenergic system, what may cause an acceleration of the heart rate and, consequently, increased blood pressure. Therefore, obesity is a well-known risk factor for hypertension. However, it has been proven that increased body weight is associated with better treatment results and lower mortality among people with this disease. It was confirmed in a study which involved 22,500 patients with hypertension and coronary artery disease. It showed that patients with a BMI higher than 25 kg/m^2 have a 30% lower risk of death compared to patients with normal body weight. The explanation for these surprising results may be lower peripheral vascular resistance and decreased plasma renin activity in obese patients compared to patients with lower weight, who suffer from hypertension [17, 18].

CONTROVERSIES SURROUNDING THE OBESITY PARADOX

Both the significance and the pathogenesis of the obesity paradox are not fully explained and are controversial among researchers. On the one hand, in many cases research results indicate that a higher BMI index has actually a protective role. It can occur as a result of adipose tissue endocrine function - the secretion of adiponectins with anti-inflammatory and anti-atherogenic effects, although other compounds in this group may have pro-inflammatory activity [19]. In addition, adipose tissue provides a metabolic reserve that facilitates surviving the predominance of catabolic processes associated with chronic disease [4]. The above arguments lead some researchers to the conclusion that patients with chronic diseases should not be recommended to reduce their weight [20].

Opponents of this theory point the wrong selection of factors whose occurrence results in the appearance of an apparent direct relationship between the increase in body weight and reduced mortality. One of them may be the fact that obese patients, after the diagnosis of the disease, are treated with a more aggressive therapy that provides better results [21]. In addition, some patients lose their weight during the course of the disease and if the studies take into consideration only patients with constant body weight, the results for both groups are very similar. Narrowing the study group to non-smokers, the mortality rate is significantly higher among obese and overweight people. This is due to the fact that smoking leads to a reduction in body weight and, at the same time, a poorer patient condition [22]. Additionally, the use of BMI in these studies is criticized because it does not characterize the distribution of body fat and the level of visceral obesity. In studies in which waist circumference (WC) or waist-hip ratio (WHR) was used, it was shown that the higher values of these two factors of overweight and obesity were associated with higher mortality [23].

CONCLUSIONS

Obesity is one of the basic modifiable risk factors for cardiovascular system diseases among the population. Therefore, it seems surprising that the BMI value above 25 is connected with a better prognosis in patients with heart failure, coronary artery disease or hypertension. This indicates potentially a protective effect of overweight and obesity on the condition of these patients. However, a broader approach and taking into consideration not only BMI but also other metabolic indicators such as WHR and WC are needed to fully evaluate the phenomenon of the obesity paradox. The association of the last two with prognosis in patients with the cardiovascular disease does not show any protective effect or it is observed solely in the short period after exacerbation of the disease. The possible differences in the treatment methods and intensity in different groups of patients also should be taken into account.

The obesity paradox is undoubtedly an interesting phenomenon that can affect the prognosis of people with cardiovascular disease. Determining its exact meaning will require further research on its pathomechanism and linking this phenomenon not only with the BMI index which is used to recognize overweight or obesity, but also other indicators used to the measurement of the distribution of body fat content such as WHR or WC.

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ABBREVIATIONS

BF – body fat
BMI – Body Mass Index
CAD – coronary artery disease
DALYs – disability-adjusted life years
HF – heart failure
ICD-10 – International Statistical Classification of Diseases and Related Health Problems
LMI – lean mass index
STEMI – ST elevation myocardial infarction
TNF-α – tumor necrosis factor alpha
WC – waist circumference
WHO – World Health Organization
WHR – waist to hip ratio

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