

Obesity – is it really so bad for a patient with coronary heart disease?

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ABSTRACT

According to American Obesity Medicine Association obesity is a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences. Obesity has been renowned as a risk factor of cardiovascular, endocrinological, orthopedic and many other diseases. But for the last two decades, there have

been many reports of beneficial influence of overweight or obesity on patients with coronary heart disease. This phenomenon got a name of obesity paradox. It's existence is a matter of lively discussion in medical world, and even if true, the protecting mechanisms of obesity need much deeper understanding.

Keywords: Obesity, body mass index, acute coronary syndrome

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INTRODUCTION

According to American Obesity Medicine Association, obesity is a chronic, relapsing, multifactorial, neurobehavioral disease, wherein an increase in body fat promotes adipose tissue dysfunction and abnormal fat mass physical forces, resulting in adverse metabolic, biomechanical, and psychosocial health consequences [1]. It is believed, that obesity and its complications cause 300 000 deaths annually in the United States of America alone, and that obesity is second only to smoking as a preventable cause of death. BMI (Body Mass Index), defined as body mass divided by the square of body height (results expressed in kg/m² units), is the most commonly used method to assess patients nutritional status. It gained popularity due to the simplicity of acquiring data, as body mass and height are routinely assessed on every hospital visit. Obesity is a growing international health issue. Results of a global analysis published in 2011 indicate that Nauru population has the highest mean BMI (33.9) in the world, while the USA ranks first among high-income countries [2]. Citizens with BMI over 25 account for 71.3% of the American population and almost 4 in 10 Americans are obese (39.7%) [2]. In the EU more than half of the population is either overweight or obese (59.1% of men and 44.7% of women) [3]. Polish statistics are no different- In 2014 45.7% of women and 62.2% of men were at least overweight, with 15.6% and 18.1% respectively classified as obese [4]. There is a clear positive trend visible within the last 20 years – in 1996 only 38.8% of women and 47.8% of men were overweight or obese. Although an assumption that a person with BMI 30 or more is obese, is mostly correct, the proportion between fat and fat-free mass is immeasurable using this tool. As a result, the correlation between the BMI and body fat mass is variable and dependent on body composition and its proportions. According to Swinburn et al. the Polynesians have, on average, lower body fat mass than the Australians of European origin with the same BMI [5]. What is more, the percentage of fat tissue raises with time to reach it's peak between 60-65 years of age for both sexes [6]. Women compared to men of the same BMI tend to have higher fat mass percentage [6]. Even if fat and fat-free proportions between same BMI individuals would be considered irrelevant, BMI is not an effective tool in measuring the magnitude of obesity and cardiovascular risk associated with it, as those parameters depend not only on fat mass percentage but also on adipose tissue distribution [7]. Abdominal obesity is a strong predictive factor for future cardiovascular complications for both sexes. An underestimated yet important aspect which may influence the BMI results is proper measurements taking and accurate BMI calculation. When asked to self-report, all patients regardless of gender tend to

minimalize their body mass and this trend intensifies with both age and BMI [8].

Another parameter, which correlates with cardiovascular risk and is more accurate in abdominal obesity assessment, is waist to hips ratio (WHR). Based on WHR, obesity can be categorized as either android (proper abdominal type) or gynoid (hips-, buttocks- and thighs-oriented type). Abdominal obesity is an independent negative predictive factor for cardiovascular complications. Recommended value of WHR should not be greater than 0,8 and 0,94 for women and men respectively.. Another parameter defining abdominal obesity is waist circumference- less than 80 cm in women and 94 cm in men is associated with lower cardiovascular risk [9]. Methods mentioned above are based on simple anthropometric measurements, and don't reflect accurately the amount and the distribution of body fat. Unfortunately, the more precise methods, such as bioimpedance, computed tomography with planimetric and volumetric assessment, MRI, ultrasonic or isotopic methods, or even the skin fold measurements are more time- and money-consuming, and thus used mainly for academic purposes [10].

Obesity as a risk factor

Obesity as a risk factor of a coronary heart disease has been a widely accepted fact for a long time. It has been reported during the 26 years of observation in the Framingham Heart Study, that heavily obese men under 50 were 2,5 times more likely and obese women under 50 were 2 times more likely to develop an ischemic heart disease than their normal-weight counterparts [11]. Other large XX century studies, like the Manitoba Study [12], or the Harvard School of Public Health Nurses Study [13] provided similar results. The positive correlation between the increasing BMI and cardiovascular complications can also be observed in more up to date, XXI century studies [14]. Obesity is an independent risk factor of cardiovascular diseases in itself, but is also connected to other common comorbidities like hypertension, hyperlipidemia, insulin – resistance or diabetes – each of those being a strong risk factor for CHD. Diabetes type 2, which is strongly correlated with obesity, is one of the strongest risk factors of ischemic heart disease. It is a cause of exacerbation of dyslipidemia, renal impairment and endothelial dysfunction – significant factors of atherosclerosis. In a Finnish study diabetic patients without previous myocardial infarction had as high a risk of myocardial infarction as nondiabetic patients with previous myocardial infarction during a 7-years observation [15]. High BMI is associated with left ventricle hypertrophy (LVH) (increasing of left ventricular wall thickness, end-diastolic volume and ejection volume of left ventricle) [16,17]. Obese patients are diagnosed with LVH 4 times more frequently (RR 4,19) than normal weight individuals

– patients with LVH are much more susceptible for developing systolic and diastolic heart failure [18,19]. Apart from causing a great increase in general cardiovascular risk, obesity proves to be a diagnostic obstacle in cardiological patients. A vast amount of subcutaneous and epicardial fat influences the ECG pattern [20], impairs acoustic window in echocardiographic examination, and doubles the required radiation doses during coronarographies [21]. Despite a well-established

position of obesity as a risk factor in development of cardiovascular diseases, obesity paradox is being repetitively described in various research results in recent years. It is a hypothesis which holds that obesity and overweight may, counterintuitively, be protective and associated with similar or even better survival, when compared to normal- or under-weight patients. It has been reported in a number of cardiovascular diseases (Table 1)

Table 1. Diseases and procedures in which the obesity paradox has been reported or is suspected [22]

Cardiovascular diseases	Cardiovascular interventions
Chronic Heart Failure	PCI in course of CHD
Acute Heart Failure	PCI in course of AMI
Heart Failure with preserved ejection fraction	TAVI
CHD with comorbidities	Endarterectomy of jugular arteries
Unstable Angina/ NSTEMI	CABG
STEMI	Valvular cardiac surgery
Stroke, TIA	Vascular surgery
Diabetes mellitus with comorbidities	Heart transplantation
Atrial fibrillation	Cardiological rehabilitation

Flegal et al. analyzed an all-cause mortality in a meta-analysis on a group of 2,88 million patients, and concluded that mortality rate was statistically lower for overweight group (HR 0,94) and not worse in stage 1 obesity group, when compared to normal weight patients [23].

Heart Failure

As it has been stated before, obesity is connected to LVH, which might lead to full spectrum heart failure (HF). However, obese patients with HF are reported to have much better prognosis than similarly ailed, but normal weight patients [24]. In a study conducted by Curtis et al. on a group of almost 8 thousand patients with heart failure, there has been reported much lower all-cause mortality risk for overweight and obese patients (HR 0,8 and 0,81 respectively) when compared to normal weight patients during 37 months observation [25]. In another study it has been concluded after a multivariable analysis, that high ratio of adipose tissue to fat-free mass and high BMI were second best independent prognostic factors in heart failure patients, inferior only to low natriuretic peptide concentration [26].

Coronary Heart Disease

The first time the obesity paradox was mentioned in a context of long survival of patients after coronary interventions, was in 1996 in a one

center study on a group of 3571 patients. The authors observed much higher in-hospital mortality in normal-weight and obese patients when compared to overweight patients (in-hospital mortality 2.8% vs 0.9% vs 3.7% for normal weight, overweight and obese respectively). Similar observations were made when the need for emergency blood transfusions (11.9% vs 7.4% vs 8.4%) and serum creatinine concentration elevation > 1 mg/dL (3.6% vs 1.8% vs 1.8%) were analyzed. There was no difference in after-PCI AMI rate (3.5% vs 3.4% vs 4.7%; P = ns) [27].

In a study performed on a subpopulation of the Scottish Coronary Revascularization Register, which included 4880 patients undergoing an elective PCI for a first time were included, the authors described much better 5-year survival in a group of patients with a BMI in the range of 27,5 and 30 (HR 0,59) [28].

In a retrospective study on a subset of patients from Western Denmark Heart Registry with angiographically confirmed CHD, the patients with BMI ranging from 27,5 to 30 had the lowest mortality rate in 10-years observation period, compared to other weight groups (HR 0,82) [29].

Similar data can be acquired from meta-analyses involving hundreds of thousands of patients. In a meta-analysis prepared by Bundhun PK et al (22 studies, 242 377 patients after PCI) in-hospital, 12 months and ≥ 1 year (long-term)

mortality risks were significantly lower in the overweight and obese groups with RR: 0.67 and RR: 0.60 respectively in the in-hospital follow-up, RR: 0.62 and 0.57 at 12 months, and RR: 0.70, and RR: 0.80 respectively for the long-term follow-up after PCI. Overweight and obese groups of patients were younger (59,3 years for obese 63,0 years for overweight and 65,5 years for normal weight patients) and had higher rate of comorbidities such as diabetes mellitus, hypertension or dyslipidemia than the normal weight group [30].

In the APPROACH study 31021 patients with CHD were divided in one of three subgroups based on the course of their treatment – pharmacological treatment, percutaneous intervention and cardiac surgery. The lowest mortality was observed: in the pharmacologically treated group - in overweight patients (HR 0,72), in PCI group – in patients with class II obesity patients (HR 0,65) and in CABG group – in class I obesity patients (HR 0,75) [31].

However, although so many studies have reported the obesity paradox, not all researchers tend to agree.

In the TAXUS study there has been reported a much higher rate of restenosis in obese and overweight patients who had undergone a PCI with a bare metal stent (BMS) implantation as compared to normal weight patients (29.2% vs 30.5% vs 9.3%). There was no such relation in patients who received an antiproliferation drug eluting stents (DES) [32].

In a German DES.DE registry, where 5806 patients from 98 centers after DES implantation were observed for a year, there was no significant difference between normal weight, overweight and obese subgroups in mortality rate (3.3% vs 2.4% vs 2.4%; $P = 0.17$), as well as in major adverse cardiac and cerebrovascular events (MACCE) rate (7.1% vs. 5.6% vs. 5.5%; $p = 0.09$) and target vessel revascularization (TVR) in survivors rate (10.9% vs 11.7% vs 11.6%; $P = 0.56$) [33].

Cardiac surgery

Obesity is a known factor contributing to wound infections and other local complications after coronary artery bypass grafting [33]. However in a study conducted by researchers of University Clinical Hospital in Białystok on patients with left main coronary artery disease treated with coronary artery by-pass grafts, the overweight and mildly obese patients had better survival ratio, than normal weight and heavily obese patients. The Parsonnet score was significantly higher in obese patients. They were also more likely to have diabetes mellitus or hypertension. The serum creatinine levels were the highest and blood morphology results were the lowest in the most obese subgroup of the patients. The most obese patients required extracorporeal circulation during surgeries more often. In the most

obese group of patients impaired wound healing (60% vs 23,1%, 19,4%, 11,1%) and postoperative sternal dehiscence (40% vs 10,3%, 6,9%, 5,5%) were observed much more frequently than in less obese patients. What is important, proper body mass along with class II and III obesity were associated with the highest mortality rates in comparison to overweight and class I obesity group (18,9% and 20% vs 9,7% and 2,5%). The most obese patients were hospitalized again more frequently [34].

In study conducted by Benedetto U et al. on 13963 patients undergoing cardiocirculatory procedures, among whom 3296 maintained proper body weight, 6662 were overweight, 3821 were obese and 211 morbidly obese, the obesity paradox was not confirmed. Para-surgical mortality rates were almost equal in all subgroups. In prolonged observation being overweight had no impact on late mortality risk (HR 1.05; 95% CI, 0.9-1.08; $P = 0.4$) as opposed to obesity and morbid obesity, where mortality risk was elevated - hazard ratio, 1.22; 95% CI, 1.07-2.66; $P = .006$ for obese patients; hazard ratio, 1.36; 95% CI, 0.74-2.49; $P = .3$ for morbidly obese patients [35].

Acute myocardial infarction (AMI)

In 2006 one of the large studies confirmed, that obesity is the strongest NSTEMI risk factor. Age at the moment of NSTEMI diagnosis was respectively 3.5; 6.8; 9.4 and 12 years lower in overweight, class I, class II, and morbidly obese patients accordingly compared to proper BMI patients [36]. In metaanalysis including 36803 patients, overweight and obesity strongly correlated with an increased heart attack risk (OR = 1.27 and OR = 1.22 respectively) [37]. However, results of some studies seem to confirm obesity paradox also in acute myocardial infarction group. Analysis presented by Buchholz et al. based on 6359 hospital records of patients hospitalized due to AMI in USA in 2003-2004 (PREMIER registry) and 2005-2008 (TRIUMPH registry) showed that there is a negative correlation between increased BMI and one-year-mortality (normal, 9.2%; overweight, 6.1%; obese, 4.7%; morbidly obese; 4.6%; $P < .001$) which persisted in multivariable adjustment. At 1 year, patients with higher BMIs had a 20% to 68% lower mortality, when compared with patients with a BMI of 18.5. No interactions between age ($P = .37$), sex ($P = .87$), or diabetes mellitus ($P = .55$) were registered [38]. Multiple meta-analysis seem to confirm obesity paradox in heart attack patients. Wang L., et al showed that pooled RRs of overweight and obese patients compared to normal weight patients were 0.72 for in-hospital mortality, 0.39 for short-term mortality, 0.66 for medium-term mortality and 0.68 for long-term mortality. No statistically significant difference was observed when risk of death was assessed in obese patients compared to overweight patients [39]. Niedziela et al. reported that in 26

studies and 218,532 patients with acute coronary syndrome (ACS) group characterized by the highest risk of mortality was Low BMI group-RR 1.47. Lower mortality compared with those with normal BMI was observed in overweight, obese and severely obese patients - RR 0.70, RR 0.60 and RR 0.70, respectively [40]. JACSS study (Japanese Acute Coronary Syndrome Study) evaluated 3076 patients who underwent PCI in course of ACS. Highest in-hospital mortality was reported in patients with BMI <20 and the lowest in patients with BMI >30. In-hospital mortality reached 9,2% vs. 4,4% vs. 2,5% vs. 1,8%, $p < 0,001$ in underweight, normal weight, overweight and obese patients. Multivariable analysis revealed no statistically significant difference in in-hospital mortality but age, Killip class on admission, renal insufficiency and final TIMI flow grade emerged as independent predictors [41]. A group of 50149 patients from National Cardiovascular Data Registry (NCDR) National Cardiovascular Data Registry (NCDR) was randomized into following groups of BMI: underweight 1.6%, normal weight 23.5%, overweight 38.7%, class I obese 22.4%, class II obese 8.7%, and class III obese 5.1%. Study revealed that extreme obesity correlated with younger age at STEMI presentation (median age 55 years for class III obese vs. 66 years for normal weight); a higher prevalence of hypertension, diabetes, dyslipidemia; a lower prevalence of smoking, a less extensive atherosclerotic changes in coronary arteries and higher left ventricular ejection fraction. When risk-adjusted in-hospital mortality was compared, III class obese patients presented with significantly higher mortality rates, when compared to class I obese patients (adjusted odds ratio: 1.64) [42].

DISCUSSION

Despite extensive research, protective value of obesity among coronary disease patients remains unclear. Some scientists claim, that obesity paradox results mostly from lower age of morbidly obese patients with CVD [41] but this phenomenon persists when age is included in multivariable analysis [43].

Some scientists point out that obese patients receive better pharmacological treatment, undergo PCI more frequently and are kept under intensified supervision, but positive obesity influence remains stable even in those studies in which groups are unified in terms of those parameters [43].

Influence of endogenous cannabinoids which act as strong vasodilators may shed some light on this complex matter. Animal ischemia-reperfusion models reveal cardioprotective influence of endogenous cannabinoid receptor agonists. They delay necrosis along with diminishing risk of severe arrhythmia and sudden cardiac death [43]. Elevated tri-glycerides concentration in post-infarct scar

among obese patients may also minimize the risk of ventricular arrhythmias [44].

Obesity is associated with many modifiable risk factors such as: DM 2, hyperlipidemia, arterial hypertension or more extensive inflammatory mediators release. At the moment of diagnosis normal weight patients have limited possibilities to improve their health. Obesity paradox may result from the fact, that some obese patients after the heart attack lose weight using diet, physical activity or pharmacological treatment intensification and therefore improve their cardio-respiratory fitness (CRF). This strongly minimizes the risk of future complications. Moreover, regardless of other risk factors, genetical predisposition for coronary disease development may worsen the prognosis in normal weight patients group [45]. CRF is an important yet commonly overlooked parameter in obesity paradox research. In low CRF patients obesity paradox occurred more frequently whereas mortality rates were equal for overweight, obese and normal weight patients with high CRF [46,47]. One of the main flaws of all obesity paradox research is the fact, that BMI is highly unspecific in defining abdominal obesity and percentage of fat body mass. In studies which use WC and WHR as referring parameters in abdominal obesity diagnosis obesity paradox in cardiovascular diseases is rarely confirmed [48]. Despite that, BMI remains most commonly used obesity indicator mostly due to its simplicity, as body height and weight are routinely collected prior each hospital admission.

Obesity paradox may result from certain biases- lead time bias, confounding bias and publication bias. We speak about lead time bias when earlier detection is mistaken for prolonged survival. Obese patients are considered high risk patients in whom diagnosis and treatment of coronary artery disease is often rushed compared to normal weight individuals, which seriously influences treatment results. Diagnostic process in normal weight patients is often delayed and commonly starts along with symptoms occurrence therefore the disease is more advanced. Confounding bias takes place when some other factors interfere with analyzed parameters. If not included in multivariable analysis, they disturb study results. Such phenomenon takes place among smokers with coronary disease. Smoking is associated with an elevated risk of lung cancer, COPD and other lung diseases where low BMI is an important factor influencing mortality. Publication bias is defined as a situation, where positive research tends to be much more likely published compared to negative research. Such situation may take place in obesity paradox context, where worse prognosis of obese patients is a truth universally acknowledged and emerging contraindicating results might be considered an interesting subject [45].

CONCLUSIONS

Obesity has been renowned as a risk factor of cardiovascular, endocrinological, orthopedic and many other diseases. But for the last two decades, there have been many reports of beneficial influence of overweight or obesity on patients with cardiovascular diseases. This phenomenon got a name of obesity paradox. It's existence is a matter of a lively discussion in the medical world, and even if true, the protecting mechanisms of obesity need much deeper understanding. For now, the data available strongly suggest, that patients should be encouraged our patients to keep their weight under control and maintain a healthy lifestyle on a regular basis.

Conflicts of Interest

The authors declare no conflicts of interest.

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