REVIEW ARTICLE

Overweight and grade I obesity in patients with cardiovascular disease: to treat or not to treat?

Maciej Haberka[1], Katarzyna Stolarz-Skrzypek[2], Danuta Czarnecka[2], Zbigniew Gąsior[1], Magdalena Olszanecka-Glinianowicz[3]

1 School of Health Sciences, Department of Cardiology, Medical University of Silesia, Katowice, Poland
2 1st Department of Cardiology, Interventional Electrocardiology and Hypertension, Jagiellonian University Medical College, Kraków, Poland
3 Health Promotion and Obesity Management Unit, Department of Pathophysiology, Medical University of Silesia, Katowice, Poland

KEY WORDS

coronary artery disease, heart failure, hypertension, obesity paradox, overweight

ABSTRACT

Obesity is a significant public health problem, associated with several comorbidities and complications. At the same time, the results of studies suggest that the relationship between obesity and survival in subjects diagnosed with cardiovascular disease is a U-shaped curve with a significantly worse prognosis among underweight and morbidly obese individuals. The association between overweight or grade I obesity and cardiovascular mortality is not clear, and numerous studies have shown an unexpected and paradoxical inverse relationship with better prognosis in this patient group, the so-called "obesity paradox". In the current review, we discuss the most important and most reliable studies regarding the prognosis and clinical course in patients with overweight or grade I obesity and essential hypertension, coronary artery disease, or heart failure, focusing on data for and against the obesity paradox.

Introduction Overweight and obesity are one of the major public health problems, commonly observed in clinical practice. The World Health Organization (WHO) estimates that over 1.4 billion adults worldwide were diagnosed with overweight and obesity in 2008, and that the prevalence of these diseases increased in both developed and developing countries. The mean body mass index (BMI) increased in men (0.4 kg/m^2) and women (0.5 kg/m^2) between 1980 and 2008.[1] According to the results of the latest WOBASZ study, representative of adult Polish population, overweight is diagnosed in 40.4% of men and 27.9% of women, while obesity in 20.6% and 20.2%, respectively.[2]

Obesity, especially visceral obesity, is a cause of numerous diseases including type 2 diabetes, dyslipidemia, hypertension, and other cardiovascular diseases (CVDs), sleep apnea syndrome, nonalcoholic fatty liver disease, infertility in men and women related to hormonal disturbances, and some cancers. Although it is well known that obesity is associated with an increased risk of mortality, a number of studies have found that the relationship between obesity and survival is a U-shaped curve with a steep increase in mortality among underweight (BMI ≤20 kg/m^2 or BMI ≤18 kg/m^2) and morbidly obese subjects (BMI ≥40 kg/m^2) with different points of increased mortality among studies (FIGURE 1).[3] It should be emphasized that a special review in the advisory document of the American Heart Association showed that the evidence supporting the effect of overweight (BMI, 25.0–29.9 kg/m^2) or even grade I obesity (BMI, 30.0–34.9 kg/m^2) on the risk of cardiovascular mortality is inconclusive.[4] A systemic meta-analysis by Flegal et al.[5] revealed that all-cause mortality among overweight subjects is significantly lower, and among subjects diagnosed with grade I obesity is not higher, compared with normal-weight subjects in the general population. The debate on the "obesity paradox" (OP) in selected CVDs continues.

The lack of significant associations between obesity and cardiovascular risk and all-cause mortality among hemodialysis patients with a BMI below 20 kg/m^2 was first described by Degoulet et al.[6] in 1982. In 1996, Ellis et al.[7] reported a similar observation in patients with coronary artery disease (CAD) scheduled for percutaneous coronary intervention (PCI). Since then, an unexpected and paradoxical negative relationship between mortality or cardiovascular endpoints

Correspondence to:
Maciej Haberka, MD, PhD, Katedra i Klinika Kardiologii, Śląski Uniwersytet Medyczny, ul. Ziołowa 45/47, 40-635 Katowice, Poland, phone: +48-32-252-74-07, fax: +48-32-252-30-32, e-mail: mhaberka@op.pl
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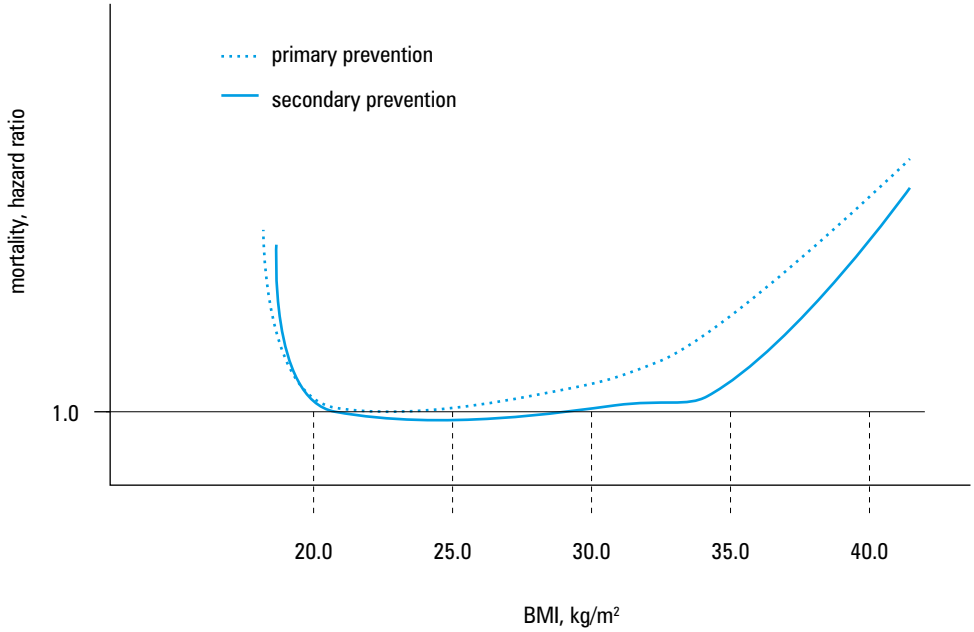

FIGURE 1 Association between body mass index (BMI) and all-cause mortality in primary and secondary prevention

TABLE 1 Major potential factors and explanations of the obesity paradox in cardiovascular diseases

1 Suboptimal methods used in studies
– retrospective design with a single body mass index assessment, no control group
– lack of information regarding: nutritional status, body fat percentage, fat distribution, intentional or unintentional weight change, cardiopulmonary fitness, physical activity, or other comorbidities affecting clinical prognosis
– differences in clinical characteristics of the study groups and other underlying causes of worse prognosis in normal weight or underweight patients (eg, age, alcohol abuse, smoking, cancer, chronic obstructive pulmonary disease, or other risk factors)
– relatively short time of follow-up (obesity as a "long-time killer")
2 Overweight and obesity with various clinical phenotypes
– type of obesity with different fat distribution or fat depots
– novel obesity categories: normal-weight obesity, fat but fit, or healthy obese
– degree of vascular and metabolic complications of obesity
– high or low cardiopulmonary fitness and physical activity, muscle mass and strength
– potential role of genetic factors and selected polymorphisms
3 Early symptoms in obese subjects suggesting cardiovascular diseases and early introduced and aggressive treatment (pharmacotherapy, hospitalization, and invasive procedures); higher doses of evidence-based drugs affecting clinical prognosis
4 Potential protective and adaptive role of adipose tissue in patients with severe, chronic, and systemic diseases

and overweight or obesity has been described in numerous studies performed in populations with various types of CVDs.[8-10] Despite some variations, a standard term used in the last decade to describe this phenomenon is "obesity paradox" (TABLE 1). It should be noted that no paradox was observed among morbidly obese subjects or patients with obesity complications such as type 2 diabetes.

The large number of studies providing data on the OP in various diseases does not allow us to discuss all aspects of this complex issue. Therefore, this review will focus on the most common forms of CVDs based on the reliable evidence.

Esssential hypertension Preliminary studies showed that the OP may occur in patients diagnosed with essential hypertension. However, data on the OP in hypertensive patients are limited. The Hypertension Detection and Follow-up Program (10,908 participants) found that the cardiovascular death rate was 50% higher in both men and women with a BMI of less than 21.96 kg/m^2 compared with those with a BMI of 26.4 to 28.8 kg/m^2.[8] In addition, a subanalysis of the results obtained in 800 participants of the European Working Party on High Blood Pressure in the Elderly Trial showed a U-shape relation between BMI and cardiovascular and noncardiovascular endpoints.[8] However, a subanalysis of the results of the Systolic Hypertension in the Elderly Program performed in 3975 subjects without a history of cancer, stroke, and myocardial infarction (MI) showed no associations between BMI and death and stroke prevalence in the group treated with placebo. Moreover, in subjects treated with low-dose antihypertensive drugs, the U-shaped relation between nutritional status and mortality showed the lowest probability of death for a BMI cut-off point of 26.0 kg/m^2 for men and 29.6 kg/m^2 for women.[11] Recently, a subanalysis of the data from the INternational VErapamil SR Trandolapril STudy, involving 22,572 elderly patients diagnosed with essential hypertension and CAD, revealed that the incidence of the primary outcome of death, nonfatal MI, and nonfatal stroke was lower among overweight and obese subjects compared with normal-weight ones.[12] In contrast, a higher risk of the primary outcome, all-cause and CVD mortality, and nonfatal stroke in underweight individuals compared with normal-weight ones was observed. However, it should be noted that underweight patients were older, were current smokers, and frequently had end-stage chronic kidney disease, heart failure (HF), MI, stroke, and

peripheral vascular disease.[13] The recent International Database of Ambulatory Blood Pressure in Relation to Cardiovascular Outcome (IDACO) consortium enrolled 8467 participants randomly recruited from 10 populations, including a population sample from southern Poland (n = 326). The study population consisted of 5363 Europeans (63.3%), 1666 Asians (19.7%), and 1438 South Americans (17.0%). The IDACO consortium studied the independent effect of BMI and the conventional and ambulatory blood pressure measurement on the prediction of both fatal and nonfatal outcomes. During a 10.6-year follow-up, it was found that a BMI of less than 20.7 kg/m^2 was associated with higher all-cause mortality and a BMI exceeding 30.9 kg/m^2, with higher rate of cardiovascular endpoints.[14] The IDACO results are in line with the current recommendations suggesting that weight reduction should be part of hypertension therapy in subjects diagnosed with overweight and obesity.

Coronary artery disease It should be emphasized that the OP in subjects with CVDs was first described in CAD. So far, numerous studies have shown the OP in various CAD populations, including patients with stable or unstable angina and acute coronary syndrome as well as those receiving pharmacotherapy, undergoing PCI, or surgical coronary revascularization. The results of a meta-analysis including cohort studies, which enrolled 250,152 patients with CAD, found a higher risk of CVD and all-cause mortality in underweight subgroups and lower in patients with overweight and grade I or II obesity than in normal-weight subgroups, while the risk of CVD mortality was significantly higher and all-cause mortality risk was similar in morbidly obese compared with normal-weight subgroups.[15] The OP was also found in the CAD population referred for coronary revascularization. The results of a meta-analysis including 22 studies (10 with participation of subjects undergoing PCI), which enrolled 214,278 patients with CAD, revealed a lower risk of short- and long-term mortality after PCI among obese subjects compared with normal-weight subjects.[16] In addition, a meta-analysis of 11 prospective randomized studies showed a lower risk of mortality and CVD events among obese subgroups during a 2.1-year follow-up. All the studies included in this meta-analysis excluded subjects with terminal illness and malignancy.[17] In addition, the results of a prospective 5-year follow-up study, which enrolled 4880 consecutive patients undergoing elective PCI, showed a lower risk of mortality in overweight subjects (BMI ≥27.5 kg/m^2 and <30 kg/m^2) compared with normal-weight subjects, regardless of age, left ventricular function, and the presence of hypertension and diabetes.[18]

Recent studies have frequently focused on visceral obesity and used waist circumference (WC) or waist-to-hip ratio (WHR) measurements. The results of a meta-analysis including 6 studies (15,923 patients with CAD) revealed that mortality risk is directly proportional to WC and WHR values and inversely proportional to BMI values.[19] It should be stressed that the OP was not observed in patients treated with PCI and drug-eluting stent implantation.[20]

The other important potential mechanism explaining the OP in CAD is a more aggressive treatment of CAD and its risk factors in obese compared with normal-weight patients.[21] In addition, overweight and obese subjects are diagnosed with CAD at a younger age and receive treatment earlier than normal-weight subjects, which are usually older and have more comorbidities. The analysis of data from the National Cardiovascular Data Registry (NCDR) Acute Coronary Treatment and Intervention Outcomes Network (ACTION) Registry, including 50,149 patients diagnosed with morbid obesity, showed that in this group, the incidence of ST-segment elevation MI was observed at a younger age but CAD severity was lower and left ventricular systolic function was better. However, morbid obesity was an independent risk factor of higher mortality during hospitalization.[22]

The results of a retrospective analysis of patients with non-ST-segment elevation MI (NSTEMI) in the CRUSADE study (Can Rapid Risk Stratification of Unstable Angina Patients Suppress Adverse Outcomes with Early Implementation of the American College of Cardiology/American Heart Association Guidelines) demonstrated that obese subjects were younger, had a higher prevalence of all cardiac risk factors, and a higher prescription rate of cardioprotective drugs at baseline.[23] It should be noted that obese patients with NSTEMI were more aggressively treated, and this resulted in a lower incidence of death and reinfarction in subjects diagnosed with grades I and II obesity than in normal-weight subjects. Additionally, patients diagnosed with all grades of obesity were more frequently treated with PCI and received antiplatelet drugs, statins, β-blockers, and angiotensin-converting enzyme inhibitors.[24]

Heart failure Despite considerable progress in cardiovascular therapy, the prevalence of congestive HF (CHF) has been increasing, resulting in high mortality rates.[25] Obesity is an important risk factor predisposing to hypertension, type 2 diabetes, left ventricular hypertrophy, and—in the long term—CHF.[3] However, it has also been shown that in established CHF, obesity is not associated with worse prognosis.[26] The current European Society of Cardiology guidelines do not address this issue directly, and they are not consistent with data from clinical trials or do not provide clear recommendations for clinical practice.

The first systematic review, including 9 observational studies with a total number of participants of 28,209 and a mean follow-up of 2.7 years, revealed that both overweight and obesity are associated with a lower risk of mortality adjusted for baseline risk factors.[27] In addition,

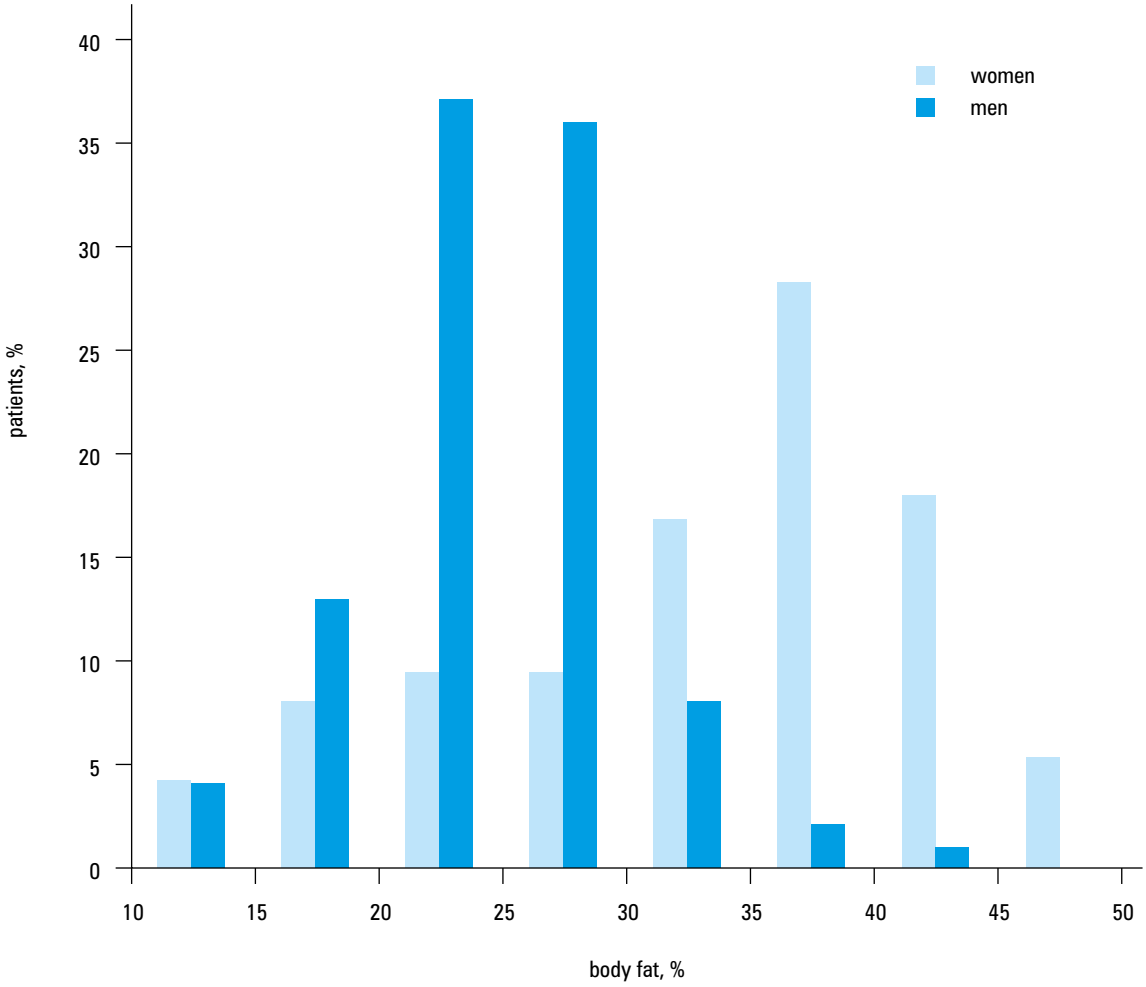

FIGURE 2 Body fat percentage in men and women with overweight (body mass index, 25.0–29.9 kg/m²); data from a study group of 300 patients aged 45–75 years (unpublished)

a lower rate of hospital mortality was also found in a large cohort of 108,927 patients with acute decompensation of CHF during a single hospitalization among obese subjects independently from other prognostic risk factors. The OP was observed in HF groups with both systolic dysfunction and preserved systolic function.[28] A recently published study provided results showing lower mortality in obese HF patients with a complex cardiopulmonary condition, namely, pulmonary hypertension (PH). The significant association was independent of the type of PH and was found in both precapillary and unproportional postcapillary PH.[29] A number of studies suggested that the survival in HF is dependent on its etiology (ischemic vs. nonischemic); however, it is still unknown whether it is related to nutritional status or etiology itself (eg, concomitant CAD).[30]

The great majority of studies used only BMI values to assess nutritional status, which is an important limitation and therefore some researchers explain the paradox simply as the BMI paradox (FIGURE 2). However, Lavie et al.,[31] in a group of 209 patients diagnosed with HF from a mild to moderate functional impairment, found that not only BMI values but also body composition parameters including fat mass and percentage were inversely correlated with a clinical prognosis of HF. Moreover, the observation that, increased WC (an intermediate parameter of visceral fat accumulation) was associated with better outcomes in patients with advanced CHF is particularly controversial. It is in contrast to the associations reported in other cardiovascular conditions, including the studies on CAD that confirmed the presence of the OP.[32]

It is well known that cardiac natriuretic peptides, including B-type natriuretic peptide (BNP) and N-terminal proBNP, play an important role in the salt-water homeostasis, and that they are typically increased in patients with CHF and provide diagnostic and prognostic information. Numerous studies have shown an inverse association between circulating natriuretic peptides levels and BMI values in general and CHF populations. It is related to a natriuretic handicap and impaired natriuretic response in obesity. However, several interfering factors (eg, drugs) and the complex pathogenesis of CHF are the reasons for the lack of data explaining whether lower levels of natriuretic peptides are markers of better prognosis in obese subjects diagnosed with CHF. This paradoxical inverse relation between obesity and natriuretic peptides is explained largely in patients with advanced and severe CHF by malnutrition–inflammation complex syndrome.[33] Moreover, the increased expression of the natriuretic peptide receptor gene found in obese subjects diagnosed with hypertension compared with normotensive obese subjects may also partially explain the lower circulating levels of natriuretic peptides in obesity.[34]

TABLE 2 Diseases and patient groups with a possible obesity paradox

cardiovascular diseases well evidenced with higher probability of the obesity paradox
heart failure
coronary artery disease (heterogeneous study groups with various cardiovascular risk and treatment)
cardiovascular diseases with weak, uncertain or discrepant evidence
atrial fibrillation
peripheral artery disease, stroke
hypertension
noncardiovascular diseases with a possible obesity paradox mostly explained by disease severity
end-stage renal disease
HIV/AIDS
cancer
chronic obstructive pulmonary disease
elderly patients

Weight reduction is associated with several benefits including decreased preload and afterload, sympathetic stimulation, blood pressure, and left ventricular hypertrophy as well as an improvement in the symptoms of HF (New York Heart Association, NYHA). However, unintentional weight loss, especially in cachectic HF patients, is always a disturbing symptom and a marker of a worse HF prognosis. Nonetheless, data from the Spanish Registry of Heart Failure (RICA) revealed that a moderate weight loss (≥5% during a 12-month follow-up, no special interventions) observed in 20.8% of the patients was not associated with a higher risk of mortality and rehospitalizations.[35] On the other hand, Melenovsky et al.[36] showed that the loss of fat mass, but not free fat mass, is related to poor prognosis, especially in patients with right HF. Additionally, it has also been shown that in patients randomized to cardiac resynchronization therapy with defibrillator function (the CRT-D arm of MADIT-CRT) with mild symptoms (NYHA class I or II), unintentional weight loss at 1-year follow-up was significantly associated with an increased risk of all-cause mortality. However, the main limitations of this study are the arbitrary cut-off of only a 2-kg weight loss in a complex population of HF patients treated with diuretics and a relatively unstable body composition.[37]

Cardiopulmonary fitness seems to be another important factor that alters clinical prognosis in patients including those diagnosed with CHF. The results of a controlled study, HF-ACTION, investigating the outcomes of exercise training among 2331 hemodynamically stable patients with HF in 82 cardiovascular centers in the United States with a median follow-up of 30 months demonstrated that, compared with standard care, additional aerobic exercise training (36 supervised sessions and home training) was not associated with a reduction in the primary and secondary clinical endpoints, and a modest but significant reduction in all-cause mortality or hospitalization and cardiovascular mortality or HF hospitalization was observed. Moreover, as expected, systematic aerobic exercise training results in the improvement of numerous functional and exercise tolerance parameters as well as the quality of life, regardless of the nutritional status (BMI) and weight loss.[38,39] This observation suggests that the main therapeutic goal in subjects diagnosed with CHF is the improvement of cardiopulmonary fitness independently of its effect on body mass.

Potential factors and explanations of the obesity paradox in cardiovascular diseases Although the OP is well established in certain CVDs (HF), the underlying patomechanisms are not clear. There are several explanations provided by both supporters and opponents of the concept of the OP. The major limitation of studies are the methods used for assessing nutritional status, fat distribution, or phenotype. Most studies with even large cohorts were a post hoc or retrospective analysis including single baseline BMI values as a marker of obesity with no control assessment and no prospective follow-up, which was related to mortality databases (TABLE 2).

The summary of the potential explanations and data for and against the OP is presented in the online supplementary material.

Overweight and grade I obesity in patients with cardiovascular disease: to treat or not to treat? As described above, BMI is not a specific and sensitive predictor of CVD risk and outcomes associated with obesity. Thus, the diagnosis of overweight and grade I obesity on the basis of the BMI WHO criteria is insufficient to make a decision about treatment in patients with a diagnosis of CVD. Beside the BMI calculation, the WC and body composition should be measured using at least the bioimpedance method. In addition, the assessment should include the presence of obesity complications such as hypertension, type 2 diabetes, and dyslipidemia.

The data assessing the effect of intentional weight reduction on survival are limited. Some studies showed that during 3 months of a cardiac rehabilitation program and exercise in overweight or obese subjects with CAD, there was no significant effect on mortality even among those with a higher weight loss. However, the weight loss was followed by a significant improvement of risk factors, such as a decrease of the body fat percentage, peak oxygen consumption, low-density lipoprotein cholesterol or triglyceride levels, and an increase in high-density lipoprotein cholesterol levels, as well as lowering of glucose and C-reactive protein levels. Morever, both the baseline BMI and body fat predicted the OP in this study.[26] This observation was confirmed by a 6-year-follow-up study performed in 377 patients with CAD aged from 30 to 85 years. The authors showed that even a slight weight loss was significantly associated with a lower rate of the composite outcome (mortality + fatal and nonfatal MI, fatal and nonfatal stroke, unplanned revascularization and

hospitalization for CHF) after adjustment for age, sex, smoking, dyslipidemia, diabetes, hypertension, MI, and obesity status (hazard ratio [HR], 0.62; $P = 0.018$]. The beneficial effects on weight loss were observed in both groups with a BMI of less than 25 (HR, 0.32; $P = 0.035$) and BMI of 25 kg/m^2 or higher.[56]

There are no data on the effect of intentional weight loss on mortality among subjects diagnosed with hypertension, HF, and CAD who underwent percutaneous transluminal coronary angioplasty or coronary artery bypass grafting. The reason for limited data in this area may be the difficulty in obtaining a weight loss of 5% to 10% and its long-term maintenance in a large population. However, this is not an argument for not treating overweight and grade I obesity in these patients. Our study revealed that both overweight and obesity are associated with systemic low-grade inflammation.[57] Furthermore, we reported that inflammation is an early event in abdominal fat accumulation.[58] Moreover, our results of a 5-year follow-up study revealed that the yo-yo effect has a modest effect on systemic microinflammation and seems not to abolish the benefit achieved via a weight loss program.[59] It is also known that a moderate weight reduction of 5% to less than 10% in overweight or obese subjects is associated with significant improvements in CVD risk factors at 1 year, but a larger weight loss had a greater benefit.[60] It has also been shown that a change of diet and increased physical activity regardless of weight loss improves CVD risk factors.[61] The benefits of weight reduction on the cardiovascular system included a decrease of blood volume, stroke volume, cardiac output, pulmonary capillary wedge pressure, left ventricular mass, resting oxygen consumption, systemic arterial pressure, filling pressure of the right and the left side of the heart, resting heart rate and QT_c interval, as well as improvement of left ventricular diastolic and systolic dysfunction.[3]

All the above data indicate that, in each case, the decision should be considered individually with the assessment of potential patient benefits including the effect of weight loss on comorbidities and quality of life, and potential risk associated with old age. The American Heart Association still recommends the cut-off point for WC of 88 cm or higher for women and 102 cm or higher for men. However, the results of a meta-analysis showed that WC cut-off points associated with high mortality among patients diagnosed with CAD are lower.[44] Thus, the International Diabetes Federation criteria for the cut-off points for central obesity (≥80 cm for women and ≥94 cm for men) should rather be considered. The WC measurements should also be performed in normal-weight subjects with CVD. In addition, the patient's readiness to make lifestyle changes to achieve weight loss should be evaluated. If a decision to start treatment is made, it should be recognized that both diet and physical activity are important. In normal-weight subjects with central obesity and in overweight subjects, an increase in physical activity adapted to their physical capacity should be primarily recommended. In addition, the regular consumption of meals and restricted consumption of animal fats and simple carbohydrates should be recommended without a substantial reduction of energy content. In grade I obesity, both the physical activity and energy deficit should be recommended. The safety energy deficit is from 500 to 750 kcal/d relative to total energy expenditure calculated individually (an average of 1200–1500 kcal for women and 1500–1800 for men).[62] In patients with CVD, we should not use starvation and ketogenic diets such as very low-calorie diets, liquid-protein diets, and high-protein diets because of the risk of QT_c interval prolongation associated with potentially life-threatening arrhythmias.[3] However, to prevent a muscle mass loss and sarcopenic obesity development, the protein intake should be about 1.0 g/kg. An important part of the diet in subjects with CVD is also a balance between consumption of fatty acids n3 and n6; therefore, vegetable oils and regular fish consumption should be advised. The results of a recently published meta-analysis revealed that an increased intake of linoleic acid in subjects after acute coronary syndromes was associated with higher mortality from all and cardiovascular causes.[62] It has also been shown in a pooled analysis of cohort studies, that a low dietary fiber intake is associated with a higher relative risk of death from coronary heart disease.[63] Thus, the minimum daily fiber intake of 25 g (wholegrain cereals, legumes, vegetables, and fruits) should be recommended.

A regular training program including aerobic, endurance, and resistance exercises helps preserve fat-free mass and maintain weight,[64] and is important for improving the overall physical functioning and cardiorespiratory fitness. It should be emphasized that the results of a recently published meta-analysis revealed that physical activity-based interventions are more important to reduce mortality risk than weight loss.[65] According to the 2008 Physical Activity Guidelines of the Department of Health and Human Services, the amount of physical activity needed to develop a moderate level of cardiorespiratory fitness is 150 minutes of moderate-intensity exercise per week, which can be accumulated at doses of 10 minutes or more. This amount of physical activity is achievable by the most unfit individuals.[66]

Conclusions The OP was shown in a number of cohorts studies and meta-analyses with various outcomes and reliability of evidence depending on the cardiovascular disease. The current interest is focused mainly on CHF subjects in whom the paradoxical survival benefit is most probable and on the potential explanations of the mechanisms responsible for the OP in this group. To confirm the OP in CVD studies with a precise assessment of the nutritional status, dual-energy X-ray absorptiometry or computed tomography

is needed. These studies should take into account the duration of obesity, all obesity complications and their treatment, as well as physical functioning and cardiorespiratory fitness. It should be emphasized that the OP cannot be the argument against professional treatment of overweight or grade I obesity in subjects diagnosed with CVD. However, in each case, the decision should be made individually with the assessment of potential benefits, including the effect of weight loss on comorbidities and quality of life, and potential risks associated with old age.

Supplementary material online Supplementary material is available with the online version of the article at www.pamw.pl.

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ARTYKUŁ POGLĄDOWY

Nadwaga i otyłość I stopnia u pacjentów z chorobą sercowo-naczyniową – leczyć czy nie leczyć?

Maciej Haberka[1], Katarzyna Stolarz-Skrzypek[2], Danuta Czarnecka[2], Zbigniew Gąsior[1], Magdalena Olszanecka-Glinianowicz[3]

1 Wydział Nauk o Zdrowiu, Katedra i Klinika Kardiologii, Śląski Uniwersytet Medyczny, Katowice
2 I Klinika Kardiologii i Elektrokardiologii Interwencyjnej oraz Nadciśnienia Tętniczego, Uniwersytet Jagielloński, Collegium Medicum, Kraków
3 Zakład Promocji Zdrowia i Leczenia Otyłości, Katedra Patofizjologii, Śląski Uniwersytet Medyczny, Katowice

SŁOWA KLUCZOWE

choroba wieńcowa, nadciśnienie tętnicze, nadwaga, niewydolność serca, paradoks otyłości

STRESZCZENIE

Otyłość jest ważnym problemem zdrowotnym związanym z wieloma chorobami towarzyszącymi oraz powikłaniami. Jednocześnie, wyniki badań sugerują, iż krzywa zależności między stopniem otyłości a śmiertelnością u osób z rozpoznaną chorobą sercowo-naczyniową ma kształt litery U, z wyraźnie gorszym rokowaniem u osób z niedowagą i ciężką otyłością. Związek między nadwagą lub otyłością I stopnia a śmiertelnością z przyczyn sercowo-naczyniowych jest niejasny, a liczne badania wykazały nieoczekiwaną i paradoksalną odwrotną zależność z lepszym rokowaniem w tej grupie pacjentów – tzw. paradoks otyłości. W niniejszej pracy przedstawiamy najważniejsze i najbardziej wiarygodne badania dotyczące rokowania i przebiegu klinicznego wśród pacjentów z nadwagą lub otyłością I stopnia oraz nadciśnieniem tętniczym, chorobą wieńcową lub niewydolnością serca, opisując wyniki przemawiające za i przeciw istnieniu rzeczywistego paradoksu otyłości.

Adres do korespondencji:
dr n. med. Maciej Haberka,
Katedra i Klinika Kardiologii,
Śląski Uniwersytet Medyczny,
ul. Ziołowa 45/47, 40-635 Katowice,
tel.: 32-252-74-07, fax: 32-252-30-32,
e-mail: mhaberka@op.pl
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SUPPLEMENTARY MATERIAL ONLINE

Data supporting the obesity paradox (OP) **1** Body mass index (BMI) is an imperfect diagnostic parameter that does not always reflect the body fat accumulation and fat distribution. In addition, most OP studies used only a single BMI measure, which is their major limitation. However, BMI is recognized by the World Health Organization as a diagnostic parameter of the nutritional status used in most research studies (not only OP-related studies), including large randomized clinical trials. Thus, we do not neglect its results owing to the use of BMI only, and we trust in its conclusion regarding, for example, cardiovascular pharmacotherapy in obese subjects. In addition, a great majority of the main cardiovascular-related guidelines recommend the use of BMI for the diagnosis of obesity and treatment-related decisions in everyday clinical practice.[40-42]

2 Waist circumference better identifies high-risk subjects, and should be measured in routine clinical practice, especially in overweight and normal-weight subjects together with the BMI calculation. However, it should be noted that this indirect parameter of visceral fat distribution is related to metabolic risk but it does not reflect the general amount of fat.[3,43-46]

3 There are studies showing that obesity parameters other than BMI (fat mass percentage and waist circumference) are also inversely associated with clinical endpoints in patients with congestive heart failure (CHF).[31,32]

4 There are no data from prospective observational studies that an intentional weight loss in patients with heart failure (HF) and diagnosed with overweight or grade I obesity is followed by lower mortality or better clinical outcomes. Although it translates into an improvement in metabolic disease control and functional status. However, it has been shown that regular physical activity results in better outcomes in HF patients irrespective of their nutritional status or weight loss.[35,38,39]

5 Obese subjects usually have a higher probability of hospitalization and earlier treatment, and they usually have higher arterial pressure that tolerates more aggressive pharmacotherapy compared with normal-weight individuals. However, subjects diagnosed with grade II obesity (BMI ≥35 kg/m^2) may have a lower rate of coronary catheterization and revascularization procedures owing to a perceived high risk of periprocedural complications.[34,47]

6 Cardiopulmonary fitness (CPF) and leisure-time physical activity are important overlooked issues. The available data suggest that a higher level of fitness even in obese patients strongly reduces the cardiovascular risk ("fat but fit").[38,39,48] Neither clinical studies nor everyday practice supports the hypothesis that all obese subjects have higher and all normal-weight subjects have lower CPF. Thus, CPF cannot simply explain the OP or cannot be used as an argument against the OP.

7 There are numerous studies that focused on the OP for almost 2 decades. Despite large study groups and increasing quality of clinical trials, we still do not have a hypothesis simply explaining the OP in all cardiovascular diseases (CVDs). There are several factors partially explaining the OP, suggesting a lower (CAD) or higher (HF) probability of a better prognosis in subjects diagnosed with overweight or grade I obesity.

8 The most reliable evidence suggests that the OP occurs in a selected group of subjects diagnosed with CHF and severe chronic disorders in a narrow range of BMI values (25–35 kg/m^2), only (see the section on Heart Failure). The guidelines on CVD prevention may not be suitable for all patients.

9 The recent guidelines on cardiovascular diseases (European Society of Cardiology: Prevention, CAD or HF, American Heart Association statement) noticed and provided a comment on a controversial and unexpected clinical prognosis (OP) in overweight or grade I obese patients with selected CVDs.[4,40-42,49]

The most important and intriguing, but unresolved, issue is the question of whether the higher volumes of adipocytes offer some cardiovascular protection. It was observed that adipose tissue of subjects with severe diseases changed morphological, endocrine, and metabolic properties, which may play an adaptive and protective role in survival. However, in catabolic state associated with several diseases, including CHF, adipose tissue is not only the energy reserve but also participates in neutralization of numerous toxic metabolites and is the source of cytokines, especially tumor necrosis factor α but also its soluble receptors that potentially may neutralize the action of proinflammatory cytokines. In addition, normal-weight subjects with CHF had more progressive muscle protein degradation and a greater reduction of circulating essential amino acid levels, while obese subjects with CHF had normal muscle protein balance and circulating essential amino acid levels.[50]

Finally, genetic predispositions and polymorphisms are known factors that reveal different effects on vascular and metabolic complications of obesity. Therefore, they may also influence clinical prognosis in obese patients. However, the available evidence does not allow to draw clear conclusions on its role in the OP and further research is needed.

Critical points in relation to the obesity paradox (OP)

1 A recently published review concerning the OP revealed that studies confirmed this paradox when BMI was used as an index of overweight or obesity. However, most studies using waist circumference (WC) and waist-to-hip ratio (WHR) do not support the OP. Furthermore, studies have also shown that greater WC and WHR values were

directly and positively associated with a higher rate of events and total mortality among CVD patients.[51,52]

2 The results of a 10-year follow-up of a large population (527,265 subjects aged from 50 to 71 years) have shown that the risk of death in apparently healthy subjects at the start of the study who had never smoked was increased by 20% to 40% among overweight subjects and 2- to 3-fold among obese ones. This study has also revealed that a preexisting disease was associated with both decreased weight and an increased risk of death. In addition, the analysis of BMI at the age of 50 years in relation to the risk of death showed that the results were stronger than those based on the current BMI after the exclusion of participants who died during the early years of the follow-up.[53] Thus, on the basis of this study, it may hypothesized that the OP is the effect of the current BMI assessment and other comorbidities.

3 The results of a meta-analysis including 6 studies and a total of 15,923 participants diagnosed with CAD showed that a 1-standard deviation (SD) increase in WC and WHR was associated with higher mortality, whereas a 1-SD increase in BMI was associated with lower mortality across all subgroups (normal-weight, overweight, obese). Furthermore, a direct and significant association with mortality for the second and third tertiles of central obesity parameters (WC: 84 cm and 96 cm for women; 89 cm and 99 cm for men; WHR: 0.86 and 0.93 for women; 0.94 and 0.98 for men, respectively) after adjustment for age, sex, smoking, diabetes, heart failure, and BMI was noted. An interesting observation is that central obesity is associated with increased mortality in the groups both with normal weight (hazard ratio [HR], 1.70; 95% confidence interval [CI], 1.52–1.89) and obesity (HR 1.93; 95% CI 1.61–2.32).[14] It may partially explain the OP observed in studies assessing BMI only. This hypothesis is also supported by the results of 2 meta-analyses, which found that central obesity parameters are better than BMI for detecting cardiovascular risk in both men and women.[43] WHR and WC are significantly associated with the risk of CVD events (in both men and women for a 1-cm increase in WC, the relative risk [RR] of a CVD event increased by 2% [95% CI, 1%–3%] overall after adjusting for age, cohort year, or treatment and for a 0.01 increase in WHR, the RR increased by 5% [95% CI, 4%–7%]).[44]

4 The results of a large cross-sectional study, which enrolled 13,601 subjects aged from 20 to 79.9 years, have shown that obesity diagnosed on the basis of BMI was present in 19.1% of men and 24.7% of women, while on the basis of the body fat percentage (>25% for men and >35% for women) in 43.9% of men and 52.3% of women. Furthermore, it has also been shown that a BMI of 30 kg/m^2 or higher had high specificity (95 [94–96] and 99% [98–100] for men and women, respectively [mean with 95% CI]), but poor sensitivity (36 [35–37] and 49 [48–50] for men and women, respectively) to detect obesity defined by the body fat percentage. In addition, in overweight women and men, BMI failed to discriminate between body fat percentage and fat free mass.[45] It has also been shown that the above results are the same among patients diagnosed with CAD.[46]

5 It should also be noted that the results of the MERLIN-TIMI 36 trial showed that obese subjects had a lower risk of the primary endpoint than normal-weight subjects at 30 days after acute coronary syndrome. However, the analysis covering the period from 30 days to 1 year showed no difference in the risk between the BMI groups. Thus, the OP may be reversed in a long-term follow-up. Increased WC indicates high-risk patients after acute coronary syndrome.[54]

6 The OP in patients with HF may be also associated with an earlier symptomatic presentation of this disease in obese subjects, and less severe symptoms are associated with most aggressive therapy early in this group with a better long-term prognosis.[55]

7 On the basis of observational cohort studies (30,104 patients with CVD), it has also been suggested that the OP persists among patients with low cardiorespiratory fitness regardless of BMI, WC, and body fat percentage. Thus, it was suggested that higher levels of fitness may modify the relationship between body fat and survival in patients manifesting the OP.[48]

8 Finally, higher mortality rates among underweight and normal-weight subjects may be influenced by factors such as smoking, alcohol abuse, cancer, chronic obstructive pulmonary disease, or end-stage chronic kidney disease and has been associated with a spontaneous reduction of body weight.[26]