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REVIEW

"Obesity paradox" in coronary artery disease

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Abstract

Obesity used to be among the more neglected public health problems, but has unfolded as a growing medical and socioeconomic burden of epidemic proportions. Morbid obesity is linked to traditional cardiovascular risk factors like, hypertension, hyperlipidemia and diabetes, and suspected to incur increased morbidity and mortality in the Western and even third world populations. This patient cohort is also at greater risk to develop coronary artery disease. Recent population-based registries revealed that 43% and 24% of all cases of coronary revascularization were carried out in overweight and obese patients, respectively. However, despite evidence of a positive correlation between obesity and increased cardiovascular morbidity, some authors have described a better clinical outcome in overweight and obese patients, a phenomenon they coined "obesity paradoxon". Thus, there is an ongoing debate in light of conflicting data and the possibility of confounding bias causing misconception and challenging the "obesity paradox". In this review article we present the current evidence and throughly discuss the validity of the "obesity paradoxon" in a variety of clinical settings.

Key words: Coronary stent; Obesity paradox; Mortality; Body mass index

Core tip: Obesity is one of the leading health problems within the last years and is associated with several cardiovascular risk factors resulting in increased prevalence of coronary artery disease as well as atherosclerotic disease in head vessels and peripheral artery system. Despite these positive correlations there are reports describing a protective effect in patients undergoing coronary revascularization. This review will enlight the potential causes and bias regarding this "obesity paradoxon" in several clinical setting and will present the latest data.

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INTRODUCTION

Epidemiologic data on obesity, traditionally defined

as a body mass index (BMI) > 30 kg/m^2, range in the Western population with a prevalence of up to 36.5%[1]. Prevalence in United States is up to 70% that is much higher than 40 years ago (25%)[2]. Obesity and associated disorders like arterial hypertension, dyslipidemia, diabetes mellitus and sleep apnoea syndrome are linked to increased morbidity and mortality[3,4]. Common recommendation is weight loss to modify cardiovascular risk as an attempt for primary and secondary prevention of cardiovascular disease in overweight and obese patients[5-7]. Obesity is associated with increased atherosclerotic diseases, especially coronary artery disease by reduced insulin sensitivity, enhanced free fatty acid turnover, increased basal sympathetic tone, a hypercoagulable state, and finally by promotion of systemic inflammation[8,9]. Population-based data revealed that 43% and 24% of all coronary revascularization were carried out in overweight and obese patients, respectively[10]. Clinical outcome speculations should indicate that these patient cohorts would be associated with worse outcomes as compared to normal weight patients. Nevertheless, despite proven evidence of a causative association between morbid obesity and increased cardiovascular morbidity, previous studies have described the phenomenon of "obesity paradoxon", reporting a protective effect of obesity with regards to postoperative morbidity and mortality in patients receiving a surgical of interventional revascularization[11]. The observation of better clinical outcome is not only restricted to coronary revascularization but also in other clinical settings like acute myocardial infarction and heart failure[12,13]. With this review article we would like to give an overview and summary on the evidence of an "obesity paradoxon" in coronary artery disease.

STABLE CORONARY ARTERY DISEASE

Correlation of BMI with clinical endpoints in the setting of interventional coronary revascularization was first reported in 1996 from a single-center experience in patients (n = 3571) receiving balloon angioplasty[14]. In-hospital outcomes revealed higher rates of mortality (2.8% *vs* 0.9% *vs* 3.7%; P < 0.001) in normal weight and obese patients as compared to overweight patients. Similar differences were seen in need for blood transfusion (11.9% *vs* 7.4% *vs* 8.4%; P = 0.003) and rise in creatinine > 1 mg/dL (3.6% *vs* 1.8% *vs* 1.8%; P = 0.018); whereas rates for myocardial infarction were not different (3.5% *vs* 3.4% *vs* 4.7%; P = ns). A total of 3634 patients from the multicenter BARI registry undergoing elective revascularization [2108 by interventional procedure (PCI) and 1526 by surgery (CABG)] between 1988 and 1991 were evaluated for BMI at study entry[15]. Body mass index (BMI) was associated with increased risk of a major in-hospital event just in the PCI arm. However, at five year follow-up there was a correlation between mortality and BMI only in the CABG arm. While these results from the BARI trial suggested an inverse correlation of BMI with in-hospital outcome after PCI and no such difference with long-term follow-up, Gruberg *et al*[11] revealed an inverse correlation during 12-mo follow-up in 9633 patients that had been evaluated between 1994 and 1999 for mortality (10.6% *vs* 5.7% *vs* 4.9%; P < 0.0001); conversely rates of myocardial infarction (7.4% *vs* 7.0% *vs* 6.7%; P = 0.66) and target vessel revascularization (20.2% *vs* 22.0% *vs* 22.4%; P = 0.16) were not different.

Postprocedural clinical events like arterial hypotension, pulmonary congestion, impairment of renal function, as well as bleeding events, access site complications and mortality rates were more frequently seen in underweight patients than in overweight or obese ones. Different from previous all-comers trials, the Scottish Coronary Revascularisation Register included only patients (n = 4880) receiving elective PCI between 1997 and 2006 without a history of previous known coronary artery disease. During five years of follow up BMI between 27 and 30 kg/m^2 was correlated with lower all-cause mortality as compared to other weight groups. Introduction of a blanking time (< 30 d) to exclude periprocedural events and an adjustment to different baseline data did not impact on outcomes of their study[16]. These results could be confirmed in the APPROACH registry in 31021 patients treated medically (n = 7801), by PCI (n = 7017) or by CABG (n = 15601)[17]. In the first group, mortality rates were lower in overweight and obese patients as compared to normal ones. Similar findings were found in both the CABG and PCI group. Interestingly, the use of bare-metal stents (BMS), or any metaanalysis of these single trials revealed an inverse relationship between BMI and clinical outcome after stenting[18]. In contrast to the above-mentioned results from the balloon angioplasty and BMS era, some other studies from that time do not support the "obesity paradoxon" in patients with both, BMS or DES. Poston *et al*[19] revealed in 1631 patients that normal weight patients were older than the non-normal weight ones at the time of hospital admission[18]. During one year follow-up mortality and risk for repeat procedures was not different between groups. In the TAXUS trials, 1307 patients were stratified according to BMI and use of stent type (BMS *vs* DES)[20]; restenosis rates with use of BMS were higher in obese and overweight patients as compared to normal weight ones (29.2% *vs* 30.5% *vs* 9.3%, respectively; P = 0.01). Although rates for major cardiac events were also significant different in favour of normal weight patients, clinical event rates were not different in patients receiving DES. These findings were underlined by the results of the German DES.DE registry[21]. At 98 sites in Germany 5806 patients receiving DES in an all-comers design were included and followed over 12 mo. Similar to previous trials baseline comorbidity index was higher in obese patients as compared to overweight and normal weight patient are in-hospital events were similar in all three

Table 1 Overview of literature addressing the "obesity paradox" in patients suffering from stable coronary artery disease undergoing coronary angiography and/or revascularization

Ref.	Year	*n*	Follow-up (mo)	Mortality	Myocardial infarction	Target vessel revascularization	Renal insufficiency	Vascular complications
Ellis *et al*[14]	1996	3571	12	+	-	-	+	+
Gurm *et al*[15]	2002	3634	60	+	NA	NA	NA	-
Gruberg *et al*[11]	2002	9633	12	+	-	-	+	-
Poston *et al*[19]	2004	1631	12	-	NA	-	NA	NA
Nikolsky *et al*[20]	2005	1301	12	-	-	-	NA	NA
Romero-Corral *et al*[18]	2006	250152	45	+	NA	NA	NA	NA
Oreopoulos *et al*[17]	2009	31021	46	+	NA	NA	NA	NA
Hastie *et al*[16]	2010	4880	60	+	NA	NA	NA	NA
Akin *et al*[21]	2012	5806	12	-	-	-	-	-

NA: Not available.

groups. One-year follow-up revealed no differences in rates of death (3.3% *vs* 2.4% *vs* 2.4%; $P = 0.17$), myocardial infarction (2.8% *vs* 2.3% *vs* 2.3%; $P = 0.45$), target vessel revascularization (10.9% *vs* 11.7% *vs* 11.6%; $P = 0.56$) and major bleeding (2.5% *vs* 2.1% *vs* 2.8%; $P = 0.53$) between normal weight, overweight and obese patients, respectively (Table 1).

ACUTE CORONARY SYNDROME

In contrast to stable coronary artery disease an acute myocardial infarction is characterized by a proinflammatory state with different forms of hemodynamic, rhythmogenic and hemostatic disturbances. The phenomenon of an "obesity paradoxon" has also been evaluated in this patient population; yet, data on a potential link between BMI and clinical events in patients with acute myocardial infarction are scarce and inhomogenous in the literature. Data from the PREMIER and TRIUMPH registries including 6359 patients with acute coronary syndrome were taken to look for any relationship between BMI with survival rate[22]. Similar to patients with stable coronary artery disease there was an inverse relationship between BMI and rate of mortality (9.2% *vs* 6.1% *vs* 4.7%; $P < 0.001$) without any interactions of demographic data like age and sex. Similar findings were revealed in the KAMIR registry involving 3824 patients with ST-elevated myocardial infarction[23]. Baseline characteristics were characterized by the fact that normal weight patients were older, had more impairment of left ventricular ejection fraction, and a higher comorbidity index. Nevertheless, normal weight in this scenario was associated with higher mortality. In contrast of these trials several other trials showed no inverse relationship between BMI and clinical outcome[24,25]. Our group analyzed 890 patients suffering from ST-elevated myocardial infarction including patients with cardiogenic shock and followed them up to 12 mo; clinical events were not significantly different between all three weight groups, again challenging an obesity paradox. These findings were also seen in patients suffering from cardiogenic shock[26] (Table 2).

RATIONALE FOR THE "OBESITY PARADOX"

Self-reported obesity increased by 37% from 13.6% to 18.6% among men aged 35-49 since 1970. Simultaneously, epidemiology of other cardiovascular risk factors like arterial hypertension and diabetes increased[27,28]. However, mortality attributed to coronary events declined during the last 40 years mainly due to decreased cholesterol levels and damaging smoking habits with greatest reduction seen in overweight and obese patients, and to some degree as a result of more frequent revascularization[29-31]. Nevertheless, overweight and obesity, as part of the metabolic syndrome, are still linked to other cardiovascular risk factors, endothelial dysfunction, and inflammation and are often associated with an increased risk of suffering from atherosclerosis.

The key question to answer is how to explain better survival rates from coronary events despite increasing rates of obesity in light of above mentioned correlation. There is an ongoing debate whether the phenomenon of "obesity paradoxon" is real in the space of coronary artery disease[10-26].

Close examination of the current literature revealed that some published and most often retrospective data just claimed a U-shaped nonsignificant trend towards lower survival among underweight patients, compared with normal or mildly overweight patients; this however might predominantly result from a technical bias, that cannot be completely corrected by statistical means.

Detailed analyses reveal that up to 2% of patients who were underweight were likely to suffer from comorbid conditions, including malignancies, heart failure, malnutrition, multiorgan dysfunction, and happened to be significantly older than the normal and obese patients[10,11,15]. There is clear evidence that elderly and frail patients have worse clinical outcomes after any coronary event regardless of reperfusion or reperfusion strategy[32,33]. It is important to recognise that increasing age with its concomitant comobidity index results in weight change[34,35]. Chronic diseases might lead to gradual weight-loss, which is not taken

Table 2 Overview of literature addressing the "obesity paradox" in patients suffering from acute coronary syndrome including cardiogenic shock undergoing coronary revascularization

Ref.	Year	*n*	Follow-up (mo)	Mortality	Myocardial infarction	Target vessel revascularization	Renal insufficiency	Vascular complications
Kosuge *et al*[25]	2008	3076	Hospital	-	NA	NA	NA	NA
Kang *et al*[23]	2010	3824	12	+	-	-	NA	NA
Camprubi *et al*[24]	2012	824	Hospital	-	NA	NA	NA	NA
Bucholz *et al*[22]	2012	6359	12	+	NA	NA	NA	NA
Li *et al*[51]	2013	1429	12	-	-	-	NA	NA
Shehab *et al*[52]	2014	4379	1	-	-	-	NA	NA
Akin *et al*[26]	2015	890	12	-	-	-	-	-

NA: Not available.

into consideration in presented trials. Along these lines, another important confounding observation was the fact that obese patients tended to be diagnosed and treated at an earlier stage than lean patients[36]. Furthermore, the "obesity paradoxon" is clearly challenged by a recent survey on > 130000 patients, revealing that adherence to guidelines was better with higher BMI with regards to standard medication such as aspirin, b-blockers, acetylcholinesterase inhibitor and angiotensin Ⅱ receptor blockers, as well as lipid lowering drugs and also an increased likelihood of receiving invasive diagnostic and treatment[15,18,21]. Furthermore overweight and obese patients present in a much more stable status with lack of hemodynamic compromise, lower Killip class, and less impairment of ventricular function. Novel theories to explain the "obesity paradoxon" after PCI have included the suggestion that obese patients have "larger vessels" and outcome after PCI is worse in patients with smaller vessel[37,38]. Antithrombotic medications usually given as standard dosage and not weight adjusted, may be too high in normal weight and underweight patients according to their BMI, resulting in more bleeding events which are associated with higher mortality rate[39]. Similarly, sheath-to-artery size ratio is different in BMI groups resulting in different rates of vascular complications[15]. All these differences in periprocedural events can contribute to improved survival among overweight patients[11,40]. The fact that BMI alone was the only measure of obesity is containly a limiting factor. There is no information in several trials regarding the distribution of obesity that might be very important, as there is a worse outcome in patients with central obesity[41]. Moreover additional information regarding waist circumference, waist-to-hip ratio and weight changes are missing in several trials describing the "obesity paradoxon"[42-45]. Additionally, all trials supporting the "obesity paradoxon" suffer from the inherent limitation of an observational retrospective registry. Potentially confounding variables such as physical inactivity, unintended weight loss and even socioeconomic factors were not analyzed, and may be the source to further bias, not to mention the short follow-up of these registries. Eventually any potential relation between obesity and in-hospital and short-term survival may be lost the longer patients are followed. Therefore with extended follow-up a cumulative detrimental effect of obesity may manifest over time as increased late mortality[46,47].

It is sensible to ask what is left to support the so-called "obesity paradoxon", or is it just a paradoxical concept? Protagonists claim that adipose tissue is being recognized as an endocrine organ[48] that produces soluble tissue necrosis factor receptor with its protective effect[49]. Morbidly obese patients (BMI > 40 kg/m^2) certainly have higher adjusted rates of post-PCI mortality that might be due to higher levels of prothrombotic factors as well as elevated levels of plasminogen activator inhibitor- Ⅰ[50]. On aggregate, while early studies may have suggested an inverse relationship between being underweight with outcomes in heart failure, which led to the assumption of a "obesity paradoxon", the analysis of the published evidence denies any such "obesity paradoxon" in the context of coronary artery disease and modern coronary interventions. In fact there is no plausible concept to turn away from the classic relationship between risk factors, confounding variables and prognostic outcomes. The limitations of such association studies are not only the lack of a pathophysiologic underpinnings, but moreover the mere association with descriptive notions and the unknown impact of confounding variables. With respect to the neutralizing results from the German DES.DE Registry[21], the perception of obesity as a protective condition of outcomes after PCI is shattered and the provocative construct of an "obesity paradoxon" evaporates, as such hypothesis was never really substantiated in the clinical setting of coronary artery disease and PCI. Finally, as it turns out, associative studies with little to no statistical evidence lended support to invent a "obesity paradox" which was never supported by biological evidence and seems now shattered by new interpertation of recent clinical data. Any concept will eventually survive only if supported by plausible physiology. In the context of coronary artery disease and PCI there is hardly any plausible explanation and certainly no clinical data to justify an "obesity paradoxon".

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