Chapter 10

Obesity and Coronary Artery Disease

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Abstract

The impact of obesity can be better understood by studying the growing medical and socioeconomic burden of this often neglected public health epidemic. Traditionally associated with cardiovascular risk factors like hypertension, hyperlipidemia, and diabetes mellitus, morbid obesity has increasingly contributed to mortality among Western as well as Third World populations. Contemporary evidence has also consistently linked this patient cohort with a greater risk to develop coronary artery disease. Recent population-based registries indicate that 43 and 24% of all cases of coronary revascularization were performed in overweight and obese patients, respectively. In this context, although popular thought has reaffirmed the positive correlation between obesity and increased cardiovascular morbidity, some authors have opined a better clinical outcome in overweight and obese patients, a phenomenon they termed "obesity paradoxon." Conflicting data and the possibility of confounding bias have festered an ongoing debate challenging this "obesity paradox." In this review article, we present updated evidence and discuss the validity of the "obesity paradoxon" in a variety of clinical settings.

Keywords: coronary stent, obesity paradox, mortality, BMI

1. Introduction

Obesity has traditionally been defined as a body mass index (BMI) value >30 kg/m^2, and its prevalence in the Western world, according to recent epidemiological data, could be as high as 36.5% [1]. Evidence of the growing prevalence of obesity can be inferred from the USA, where almost 70% of the population has been classified as obese; a significant increase from the 25% reported forty years ago [2]. The clinical relevance of obesity and its cluster of associated disorders, like arterial hypertension, dyslipidemia, diabetes mellitus, and sleep apnea syndrome, are demonstrated by its persistent link to an increased morbidity as well as

mortality [3, 4]. It is for this reason that initiatives detailing the primary and secondary prevention of cardiovascular disease in overweight and obese patients have laid specific emphasis on the significance of weight loss so as to modify cardiovascular risk [5–7]. Obese patients have an increased preponderance to develop atherosclerotic disease, especially coronary artery disease, which is characterized by a reduced sensitivity to insulin, enhanced free fatty acid turnover, increased basal sympathetic tone, a hyper-coagulable state, and finally with promotion of systemic inflammation [8, 9]. Population-based data suggest that 43 and 24% of all coronary revascularization in recent years were carried out in overweight and obese patients, respectively [10]. It has been speculated that the obese patient cohort is somehow associated with a clinical outcome far worse than that of a normal weight patient, and this theory is further substantiated by the existence of evidence describing the causative association of morbid obesity in cardiovascular disease. Interestingly, contemporary studies have recently elucidated the role of an "obesity paradoxon," describing the protective effect of obesity (when considering postoperative morbidity and mortality) in patients receiving either surgical or minimally invasive coronary revascularization [11]. This observation suggesting a better clinical outcome for obese patients is not only restricted to the clinical setting of coronary revascularization, as similar data have also been reported in cases of an acute myocardial infarction and heart failure [12, 13].

In this review article, we attempt to present an overview and summarize the evidence documented on "obesity paradoxon" in coronary artery disease.

2. Stable coronary artery disease

The correlation of BMI with clinical endpoints in the setting of interventional coronary revascularization from a single-center experience in patients (n = 3571) receiving balloon angioplasty was first reported in 1996 [14]. A detailed study of the in-hospital outcomes suggested 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. This bias could also noted in the patients' need for blood transfusions (11.9% vs. 7.4% vs. 8.4%; $p = 0.003$) and their corresponding rise in creatinine value >1 mg/dl (3.6% vs. 1.8% vs. 1.8%; $p = 0.018$). Interestingly, the rates of myocardial infarction did not reflect any such patient group preference (3.5% vs. 3.4% vs. 4.7%; p = n.s.). The multicenter BARI registry evaluated the BMI of 3634 patients undergoing elective revascularization [2108 by interventional procedure (PCI) and 1526 by surgery (CABG)] at study entry between 1988 and 1991 [15]. Initial analyses of the results elicited a correlation between the body mass index and an increased risk of a major in-hospital event in the PCI arm. At the five-year follow-up interval, this correlation between BMI and mortality existed only in the CABG arm. The final results from the BARI registry suggested an inverse relationship between BMI and in-hospital outcome post-PCI without any major difference in long-term follow-up. Interestingly, although the study by Gruberg et al. [11] did indicate an inverse relationship in the 9633 patients evaluated between 1994 and 1999 at the 12-month follow-up for mortality (10.6% vs. 5.7% vs 4.9%:

$p < 0.0001$), 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%: $p = 0.16$) did not vary significantly. Certain post-procedural clinical events like arterial hypertension, pulmonary congestion, impairment of renal function, bleeding events, access site complications, as well as those leading to mortality were seen more often in underweight patients as compared to the overweight and obese patient cohort.

The Scottish Coronary Revascularization Register offers another perspective to this debate. In contrast to previous all-comers trials, this study included only those patients ($n = 4880$) undergoing elective PCI between 1997 and 2006, and without any known history of coronary artery disease. Patients evaluated to have a BMI in the range between 27 and 30 kg/m^2 were linked with lower all-cause mortality after 5 years of follow-up as compared to other weight groups. The introduction of a blanking time (<30 days) to exclude periprocedural events as well as an adjustment to different baseline data did not impact the outcome of their study [16]. These conclusions were reaffirmed in the APPROACH registry, where a collective of 310,121 patients were treated conservatively ($n = 7801$), by PCI ($n = 7017$), or by CABG ($n = 15,601$) [17]. Lower mortality rates were recorded among overweight and obese patients as compared to normal weight patients in the cohort treated conservatively. These findings were also consistent for the CABG as well as the PCI group. An interesting corollary to these results centered around the use of bare-metal stents (BMS) as well as a discussion on the meta-analysis of these single trials, suggesting an inverse relationship between BMI and the clinical outcome after stenting [18]. The results from studies of the balloon angioplasty and the BMS era are in stark contrast to other studies conducted in this timeframe, wherein patients receiving any of the two stents, DES or BMS, did not observe the "obesity paradoxon." An additional note in this context is summarized by the study of Poston et al. conducted in 1631 patients, suggesting that normal weight patients were older than obese or overweight patients at the time of hospital admission [18]. The 1-year follow-up mortality and risk for procedure revision were comparable in both groups.

In the TAXUS trials, of the 1307 patients stratified according to BMI and type of stent used (BMS versus DES) [20], higher rates of BMS in-stent restenoses were observed in obese and overweight patients than in normal-weight patients (29.2% vs. 30.5% vs. 9.3%; $p = 0.01$). The patients receiving DES had major cardiac event (MACE) rates skewing in favor of normal weight patients, and however, the clinical event rates in these different patient groups did not vary significantly. Subsequent results obtained from the German DES.DE registry would also validate these findings [21]. A total of 5806 patients assimilated from 98 sites in Germany were included in this registry for DES patients and followed up over a period of 12 months. The results would summarize suggestions made in previous trials, stating that the baseline comorbidity index was higher in obese patients as compared to overweight and normal weight patients, while the rates of in-hospital events were similar in all three groups. The follow-up after 1 year indicated no significant variability in mortality rates (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

Author	Year	*n*	Follow-up (months)	Mortality	Myocardial infarction	Target vessel revascularization	Renal insufficiency	Vascular complications
Ellis et al. [14]	1996	3571	12	+	–	–	+	+
Gurm et al. [15]	2002	3634	60	+	n.a.	n.a.	n.a.	–
Gruberg et al. [11]	2002	9633	12	+	–	–	+	–
Poston et al. [19]	2004	1631	12	–	n.a.	–	n.a.	n.a.
Nikolsky et al. [20]	2005	1301	12	–	–	–	n.a.	n.a.
Romero-Corral et al. [18]	2006	250, 152	45	+	n.a.	n.a.	n.a.	n.a.
Oreopoulos et al. [17]	2009	31, 021	46	+	n.a.	n.a.	n.a.	n.a.
Hastie et al. [16]	2010	4880	60	+	n.a.	n.a.	n.a.	n.a.
Akin et al. [21]	2012	5806	12	–	–	–	–	–

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

(2.5% vs. 2.1% vs. 2.8%; $p = 0.53$) between normal weight, overweight, and obese patients, respectively (**Table 1**).

3. Acute coronary syndrome

The essential difference between stable coronary artery disease and an acute myocardial infarction is the existence of a pro-inflammatory state with different forms of hemodynamic, rhythmogenic, and hemostatic disturbance in the latter. Although the "obesity paradoxon" phenomenon has been evaluated in the patient population, there is lack of homogenous data establishing a potential link between BMI and clinical events in patients with acute myocardial infarction. Data analyses of the 6359 acute coronary syndrome (ACS) patients included in the PREMIER and TRIUMPH registries drawn to establish a relationship between BMI and survival rate yielded novel results [22]. BMI and mortality rates shared an inverse relationship (9.2% vs. 6.1% vs. 4.7%; $p < 0.001$) irrespective of demographic age and sex distribution. The KAMIR registry yielded similar results in its 3824 ST-elevation myocardial infarction patient collective [23]. The baseline characteristics defined an older group of normal weight patients, with impairment of left ventricular ejection fraction and having a higher comorbidity index. The study eventually summarized that normal weight patients were associated with higher mortality rates.

An attempt to reaffirm this inverse relationship between BMI and clinical outcome in this scenario, however, was not possible in many other similarly conducted trials [24, 25]. Our research working group analyzed data from 890 patients diagnosed with ST-elevated myocardial infarction and followed them up for a duration of 12 months. This group also constituted patients diagnosed with cardiogenic shock. Interestingly, results indicated that clinical events did not vary significantly between all three weight groups, thus challenging the premise of the "obesity paradox" [26] (**Table 2**).

Author	Year	N	Follow-up (months)	Mortality	Myocardial infarction	Target vessel revascularization	Renal insufficiency	Vascular complications
Kosuge et al. [25]	2008	3076	hospital	–	n.a.	n.a.	n.a.	n.a.
Kang et al. [23]	2010	3824	12	+	–	–	n.a.	n.a.
Camprubi et al. [24]	2012	824	hospital	–	n.a.	n.a.	n.a.	n.a.
Bucholz et al. [22]	2012	6359	12	+	n.a.	n.a.	n.a.	n.a.
Li et al. [27]	2013	1429	12	–	–	–	n.a.	n.a.
Shehab et al. [28]	2014	4379	1	–	–	–	n.a.	n.a.
Akin et al. [26]	2015	890	12	–	–	–	–	–

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

4. Rationale for the "obesity paradox"

The growing incidence of obesity can be construed from data suggesting an increase of 37% from 13.6 to 18.6%, in the cases of self-reported obesity, among men aged 35–49 since 1970. Epidemiological factors attributed to the development of obesity and cardiovascular disease like arterial hypertension and diabetes mellitus are also on the rise [29, 30]. Recent efforts directed to reducing cholesterol levels and prevention of damaging smoking habits have helped sustain a decline in mortality from an acute coronary event. Frequent vessel revascularization has also possibly played a role in this positive development [31–33]. This, however, does not discount the influence of the metabolic syndrome and its link to various cardiovascular risk factors. Overweight and obese patients are derivatives of this syndrome, and the continual process of endothelial dysfunction and inflammation is often associated with the risk of developing atherosclerosis.

Evidence of this correlation constitutes an interesting paradox where better survival rates in an acute coronary event are real despite an increased incidence of obesity. This pertinent question has festered an ongoing debate as to the existence of the "obesity paradoxon" phenomenon in the spectrum of coronary artery disease [10–26].

An examination of current literature indicates that certain published data, essentially that comprising retrospective information, have claimed a U-shaped nonsignificant trend to suggest lower survival among underweight patients as compared to normal or mildly overweight patients. This, however, could be the result of a technical bias, which unfortunately cannot be fully corrected by statistical means.

A detailed analysis of these patient groups has suggested that up to 2% of patients who are underweight are likely to suffer from comorbid conditions, including malignancies, heart failure, malnutrition, and multi-organ dysfunction (MODS). This patient group also happens to constitute a significantly older age group demographic as compared to normal and obese patients [10, 11, 15], and clear evidence has linked elderly and frail patients to significantly poorer clinical outcomes regardless of management or reperfusion strategy [34, 35].

An interesting highlight in this respect is the influence of increasing age with its concomitant comorbidities on weight change [36–38]. The possibility of chronic disease leading to gradual weight loss had not been factored into presented trials. Another important confounding observation was the increased tendency of obese patients receiving diagnosis and treatment at an earlier stage in comparison with lean patients.

A recent survey of >130,000 patients suggested that patients with higher BMI adhere more sincerely to guidelines with regard to the use of standard drugs such as aspirin, beta-blockers, acetylcholinesterase inhibitors, angiotensin II receptor blockers, as well as lipid-lowering drugs and are increasingly likely to undergo invasive diagnostic and therapeutic interventions [15, 18, 21]. Additionally, overweight and obese subjects tended to be more stable at presentation, with the general constellation describing a patient lacking hemodynamic compromise, having a lower Killip class and also a preserved or less impaired ventricular function, which in turn proffers a better prognosis to the existing clinical scenario. These preliminary results present a clear challenge to the "obesity parodoxon" phenomenon.

Novel theories explaining the post-PCI "obesity paradoxon" hypothesize that obese patients have "larger vessels" somehow instituting a beneficial effect. A further consolidation of this hypothesis naturally suggests that post-PCI outcome is significantly worse in patients with smaller vessels [39, 40]. The pharmacology of antithrombotic drugs is another interesting topic of discussion in this regard. The use of a standard dose rather than weight-adjusted dosages precludes accurate measurement of the pharmacokinetic and pharmacodynamic effects of these medications in each patient. For example, the standard dose could very well be too high for an underweight patient (as calculated by BMI) resulting in significant bleeding events and is associated with a higher mortality rate [41]. Similarly, the sheath-to-artery size ratio varies in different BMI groups, and this could influence the rates of vascular complications [15]. These superficial differences observed in the context of a periprocedural event can reflect on the perceived improved survival noted among overweight patients [11, 42].

An absolute limiting factor in most studies centers around the use of BMI as a measure of obesity. The inadequate documentation of obesity distribution questions the plausibility of several results as this vital information has a significant impact in the clinical scenario. For example, central obesity has been associated with a poorer clinical outcome [43]. Other parameters such as waist circumference, waist-to-hip ratio, and weight change have not found mention in several of these trials [44–47]. Additionally, the inherent limitation of all these trials hypothesizing the "obesity paradoxon" is that they are an observational retrospective registry.

The failure to analyze potentially confounding variables such as physical inactivity, unintended weight loss, the influence of socioeconomic factors, as well as the short follow-up of these registries may have contributed to additional bias. Any existing relationship between obesity and in-hospital and short-term survival may have been lost, and the longer patients were followed. The possible buildup of the detrimental effects of obesity overtime could also have been studied in an extended follow-up period, perhaps establishing a link to increased late mortality [48, 49].

The "obesity paradoxon" hypothesis hinges on certain questionable data. The proponents of this theory claim that replete adipose tissue plays the role of an endocrine organ [50] producing soluble tissue necrosis factor receptor and hence ensues the protective effect [51].

Conversely, higher levels of thrombotic factors as well as elevated plasminogen activator inhibitor-I in patients who are morbidly obese (BMI > 40 Kg/m^2) probably contribute to the higher adjusted rates of post-PCI mortality seen in this patient group [52].

The suggestion, in early studies, that there exists an inverse relationship between underweight patients and outcomes in heart failure is what heralded the concept of "obesity paradoxon." However, an in-depth analysis of recently published data questions any such claim in the setting of coronary artery disease and modern coronary intervention. In fact, there is insufficient evidence or even proof of concept to veer away from the classic relationship between risk factors, confounding variables and prognostic outcomes. These association studies are limited not only by the lack of pathophysiological underpinnings, but also hindered by the use of descriptive notions and confounding variables with unknown impact to substantiate their results. While analyzing the neutralizing results of the German DES.DE Registry [21], the perception of obesity demonstrating a protective effect on outcomes post-PCI is seriously held in doubt and the provocative construct of an "obesity paradoxon" debased, as this hypothesis was never really substantiated in the clinical setting of coronary artery disease and PCI.

Finally, the support expressed by associative studies (in light of little or no statistical and biological evidence) leading to the hypothesis of an "obesity paradox" has been effectively debunked by the interpretation of recent clinical data. A contrarian concept would only hold traction if supported by plausible pathophysiology. In the context of coronary artery disease and PCI, there are hardly any convincing explanation and certainly no clinical data to justify an "obesity paradoxon."

Conflict of interest

No conflict of interest for all authors.

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