The Relationship Between Obesity and Coronary Artery Disease

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Abstract

Obesity continues to be a growing issue in the United States with an estimated prevalence of 72 million people. There are major health implications associated with obesity including its relationship with hypertension, diabetes mellitus type 2, the metabolic syndrome, and dyslipidemia, all independent risk factors for CAD. Despite the increased risk of developing CAD, in recent years an “obesity paradox” has been described in which moderately obese individuals with established cardiovascular disease, including CAD, appear to have mortality similar to their normal weight counterparts. This review discusses the relationship between obesity and CAD, including the increased risk of hypertension, diabetes mellitus, the metabolic syndrome, and dyslipidemia along with a discussion of the obesity paradox and the benefits of weight reduction.

Running header

Obesity and coronary artery disease
**Abbreviations**

BF: Body fat  
BMI: Body mass index  
CABG: Coronary artery bypass graft  
CAD: Coronary artery disease  
CI: Confidence interval  
COPD: Chronic obstructive pulmonary disease  
CV: Cardiovascular  
CVD: Cardiovascular disease  
DM: Diabetes mellitus  
ESRD: End stage renal disease  
HDL-C: High density lipid cholesterol  
HTN: Hypertension  
IRO: Insulin-resistant obese  
LDL-C: Low density lipid cholesterol  
LMI: Lean mass index  
MetS: Metabolic syndrome  
MHO: Metabolically healthy obese  
MI: Myocardial infarction  
PCI: Percutaneous coronary intervention  
RR: Relative risk  
STEMI: ST elevation myocardial infarction  
TG: Triglycerides
**Introduction**

Obesity, defined as a body mass index (BMI) $\geq 30$ kg/m$^2$, constitutes a major problem in the United States (US) with an overall prevalence estimated at 72 million people.$^{(1, 2)}$ Due to the numerous health implications associated with obesity, it is currently estimated to be the second leading caused of preventable death.$^{(2, 3)}$ Obesity is associated with increased risk of hypertension (HTN), diabetes mellitus type 2 (DM), the metabolic syndrome (MetS), and dyslipidemia, all risk factors for coronary artery disease (CAD).$^{(4, 5)}$ Obesity, however, is not homogeneous in its effect, with a subset of obese individuals that are relatively insulin sensitive, labeled metabolically healthy obese (MHO), who have a more favorable cardiovascular (CV) profile compared to insulin-resistant obese (IRO) individuals.$^{(6-11)}$

The relationship between obesity and CAD is further complicated by the idea of the “obesity paradox” where mildly obese individuals have similar or lower mortality to their normal weight counterparts. This review discusses the relationship of obesity and CAD, including the possible mechanisms through which obesity increases CAD risk, the MHO individuals, along with a discussion of the “obesity paradox” in CAD and its implications in patient management including weight loss.

**Obesity and its association with CAD risk factors**

Obesity is associated with increased risk of HTN, DM, MetS, and dyslipidemia.$^{(4, 5)}$

Through its affect on these diseases, obesity increases the risk of developing CAD. In the following section we describe the relationship between obesity and CAD.
Obesity's relationship with HTN has been well described in the literature in large studies such as the Framingham cohort and the Physician's Health Study.\(^{12-14}\) The Framingham cohort demonstrated that 34\% of HTN in men and 62\% of HTN in women aged 35-75 years was attributable to excess weight (defined as a BMI ≥25 kg/m\(^2\)).\(^{12}\) The Physician's Health Study described an 8\% increase in risk of incident HTN with each 1-unit increase in BMI during a median follow-up of 14.5 years.\(^{13}\) Weight loss, on the other hand, decreases the risk of HTN. An analysis of the Framingham cohort demonstrated that sustained weight loss of 1.8 kg or more was associated with a long term HTN risk reduction of 22\% in middle-aged patients and a 26\% reduction in older patients.\(^{14}\) The mechanism for the association between obesity and HTN is likely multifactorial. \(^{1} \text{(Table 1)}\) Through the production of angiotensin, a precursor of the renin-angiotensin-aldosterone system, adipose cells have a endocrine effect on a known pathway for the pathogenesis of HTN.\(^{15}\) Beyond adipose cell’s endocrine effect, there is an increase in circulating blood volume and total peripheral resistance seen with increasing BMI, which may lead to HTN.\(^{16}\)

Obesity is an independent risk factor for both DM and MetS, with the prevalence of DM being closely related to the rise in obesity.\(^{17, 18}\) The Behavioral Risk Factor Surveillance System demonstrated that the prevalence of DM increased 33\% throughout follow up, a rise related with increasing rates of obesity.\(^{18}\) DM increases the risk of CAD through its association with endothelial dysfunction and dyslipidemias, both initial steps in the atherogenic process. \(^{1} \text{(Table 1)}\) Through these mechanisms, DM is one of the strongest CAD risk factors, characterized by very high 10-year risk of CV events.\(^{15, 19}\) Additionally, DM is a common cause of renal dysfunction, an independent risk factor for CAD.\(^{15}\) Similarly
MetS increases the risk of CAD and is defined by HTN, dyslipidemia, impaired fasting glucose, and central obesity, all risk factors for CAD.(20-24)

The exact mechanisms linking obesity with insulin resistance and other factors influencing risk of DM and CAD are unclear.(5) (Table 1) Research shows that adipose tissue functions as an endocrine organ and has been associated with elevated levels of circulating proinflammatory cytokines and fat related hormones.(22, 25, 26) A number of inflammatory responses are found to occur with obesity including increased clotting factors such as fibrinogen, von Willebrand factor, and factors VII and VIII; and increasing plasminogen activator inhibitor type-I that are associated with decreased fibrinolysis, all which may lead to increasing CAD.(22, 25, 26) Elevated levels of tumor necrosis factor alpha in obesity have also been implicated in the development of insulin resistance.(15, 27) Finally, leptin levels are higher in obesity and chronically elevated leptin levels have been related to negative CAD outcomes and are associated with in-stent restenosis.(28) Other potential mechanisms for the increase in CAD risk associated with DM include decreased insulin-mediated vasodilation, increased insulin-mediated renal sodium reabsorption, insulin related sympathetic nervous system stimulation, and increased vasoconstriction related to elevated circulating free fatty acids.(25, 26)

Obesity, in addition to increasing the risk of HTN and DM, also increases the risk for dyslipidemia. Higher BMI is associated with lower levels of high-density lipoprotein cholesterol (HDL-C), high levels of triglycerides, in addition to small, dense, atherogenic
low-density lipoprotein cholesterol (LDL-C), all potentially increasing the risk for CAD.(20, 21, 29, 30) (Table 1)

**The metabolically healthy obese**

Among individuals who are obese, there is a subset of MHO individuals that are relatively insulin sensitive and have a more favorable lipid and inflammatory profile compared to IRO individuals.\(^6\)\(^-\)\(^11\) Those with MHO compared to IRO appear to have earlier onset of obesity, fasting plasma insulin levels within normal range, a normal distribution of the excess fat, and other family members with MHO.\(^7\), \(^8\) These individuals also appear to have less visceral adipose tissue and more favorable lipid profiles including lower plasma triglyceride (TG) and higher HDL-C levels then their insulin-resistant counterparts.\(^8\) Compared to normal weight counterparts, MHO persons appear to have higher burden of subclinical CV Disease (CVD) \(^31\) and markers of CAD \(^32\), while their CV risk profile is intermediate between a healthy non-obese individual and someone with IRO.\(^33\) Thus, while MHO may increase the risk of CVD, how it impacts CAD is still unclear and further research needs to be performed to more fully understand the relationship between MHO and CAD.

**The obesity paradox**

Despite the increased risk of developing CAD and its risk factors, epidemiologic data from recent years has described an “obesity paradox”. The obesity paradox refers to the finding that despite an increased risk of developing CVD in the obese, once CVD has been established, overweight and mildly obese individuals may have a decreased or similar
outcomes and mortality compared to their normal weight counterparts. This paradox has been described in a number of CV diseases such as CAD, heart failure, and atrial fibrillation (1, 5, 34-43), though conflicting data exists in the literature among certain subgroups of CAD individuals (35, 44, 45). The following is a discussion of the obesity paradox in CAD cohorts and its implication.

There are numerous studies describing the obesity paradox in CAD in a variety of cohorts including hospitalized registries (46, 47), revascularized populations (48, 49), post-coronary artery bypass graft surgery (CABG) programs (50), ambulatory settings (51, 52), and high-risk patients undergoing stress testing (53, 54). Das and colleagues demonstrated the obesity paradox in a cohort of 50,000 patients with ST-segment elevation myocardial infarction (STEMI) (49). They described that individuals with moderate obesity (BMI between 30-35 kg/m$^2$) had the lowest mortality compared to other weight groups (49). Similarly, another study of individuals presenting with both STEMI and non-STEMI, found that in-hospital, adjusted mortality was lowest amongst those with morbid obesity (BMI $\geq 40$ kg/m$^2$) when compared to those with a BMI <40 kg/m$^2$ (46).

In post-revascularization patients, those receiving either percutaneous coronary intervention (PCI) or CABG, data on the obesity paradox is inconsistent. The Do Tirofiban and ReoPro Give Similar Efficacy and Outcomes Trial (TARGET), a study of over 4,800 individuals designed to compare the use of tirofiban and abciximab in planned PCI with bare metal stents, demonstrated that there was no difference in 30-day and 6-month outcomes of death and MI among obese and non-obese patients, supporting the obesity paradox (44).
However, among individuals younger than 65 years, those who with a BMI >32 kg/m² had a significantly higher rate of target vessel revascularization at 6 months compared with more lean patients.(44) Another study demonstrated that patients who underwent PCI of single de novo lesion for stable or unstable angina or inducible ischemia found that a BMI >30 kg/m² was an independent predictor of target vessel revascularization and major adverse cardiac event (MACE) at 1 year in those receiving BMS but no paclitaxel-eluting stents.(45) Finally, a study of 6,068 individuals undergoing CABG developed a propensity model that demonstrated that over a 12 year span, mortality was similar between those with a normal BMI and those who are moderately obese (BMI between 32 to 36 kg/m²), but higher among the morbidly obese patients (BMI ≥36 kg/m²).(55) These studies support that individuals with CAD and moderate obesity may have similar outcomes to normal weight individuals, but that outcomes worsen among morbidly obese.

This statement is supported by a large systematic review and meta-analysis of 40 cohort studies and over 250,000-pooled participants with CAD completed by Romero-Corral and colleagues.(35) In their study, they describe that when evaluating all individuals with CAD (PCI, MI and CABG), moderately obese individuals (BMI 30-35 kg/m²) and those with morbid obesity (≥ 35 kg/m²) had no increased risk for total mortality (relative risk (RR)=0.93, 95% confidence interval (CI) 0.85-1.03 and RR= 1.10, 95% CI 0.87-1.41, respectively). (Figure 1) However, in regards to CV mortality, while moderately obese patients had no increase in CV mortality (RR= 0.97, 95% CI 0.82-1.15) compared to the normal weight group, those with severe obesity had the highest risk (RR= 1.88, 95% CI 1.05-3.34). (Figure 2) When stratified by MI, PCI, or CABG, only obese and severely obese
patients in the CABG group had significantly higher total mortality than normal weight patients.\(^{(35)}\) (Figure 1) This systematic review and meta-analysis by Romero-Corral is important in the discussion of obesity and CAD as it demonstrates that obese patients do not have a significantly higher risk unless further stratified as moderate obese and morbid obesity. Furthermore, only CV mortality is worsened among the severely obese. What was not seen was an inverse association between obesity and death in patients with CAD, and thus caution should be used in discounting obesity as a risk factor for CAD progression and complications.

**Potential mechanisms for the obesity paradox**

While the mechanism for the potential protective effect of obesity among those with CAD remains unclear, there have been several possibilities proposed.\(^{(36, 56-58)}\) (Table 2) It has been speculated that before a CVD event, positive caloric balance leading to adiposity may result in pathogenic adipose tissue responses that cause metabolic diseases, increasing cardiovascular disease risk. Paradoxically, during a time of negative caloric balance, as may occur during a CV event, adipose tissue may respond with enhanced function, which may improve clinical outcomes.\(^{(36, 56)}\) Additionally, individuals with higher body fat (BF) leading to their obesity may have increased muscular strength which has been associated with better prognosis and survival in several populations.\(^{(57, 58)}\)

Another potential mechanism for the obesity paradox may lie in the treatment and management of patients based upon BMI. Patients with a BMI above normal may be more likely to be treated with American College of Cardiology (ACC)/American Heart Association
(AHA)-recommended medications then normal or lower BMI individuals. Additionally, obese patients were also shown in one study to undergo more diagnostic and revascularization procedures than patients with low or normal BMI. Thus, obese individuals may receive more aggressive treatment such as better medical management and more revascularization then their normal weight counterparts, leading to better outcomes. Finally, there has been some criticism that the paradox only occurs due to the inaccurate nature of using BMI to define obesity. Critics argue that a more meaningful measure of obesity, as shown by various studies, should be measured via waist circumference, waist/hip ratio, or BF.

Others have proposed that fitness is more important than obesity in improving mortality among CAD patients. Fitness alters the relationship between adiposity and all-cause mortality in patients with CAD and only those with low levels of fitness seem to have an obesity paradox. A study by McAuley et al. described that in a population with CAD referred for exercise stress testing, fitness altered the obesity paradox. Overweight and obese men with moderate fitness had mortality rates similar to the highly fit normal-weight reference group. (Figure 3) In fact, in most CV disorders, patients with high fitness have lower mortality than those with lower fitness and fitness appears to improve CV mortality when added to other traditional risk factors. Fitness, also appears to predict the development of some of the risk factors for CAD such as HTN, MetS, and dyslipidemia. Therefore, using adiposity to assess mortality risk in patients with CAD may be misleading unless fitness is considered. These studies are limited by confounders such as smoking history, undiagnosed chronic disease, the catabolic effects of
illness, or having a shorter duration of follow up than is optimal which may both affect the ability to be fit while also affecting CV mortality. Despite the findings of the obesity paradox, current data does not support increasing weight among individuals with CAD, but appear to indicate that fitness is an important part of preventing obesity.(56, 72-76)

**Weight loss and CAD**

While obesity appears to demonstrate improved mortality benefit in those with CAD, there is still significant evidence supporting weight loss as a way to reverse CAD risk factors, including HTN, DM, and dyslipidemia and potentially reduce mortality.(36, 74, 75, 77-86) Weight loss has been associated with marked improvements in arterial pressure and LV geometry, potentially improving HTN.(86) Additionally, exercise, a potential tool for weight loss, has been associated with increases in cardioprotective HDL-C, increased insulin sensitivity, and a decrease in the prevalence of MetS and DM.(78-80)

Weight loss also appears to impact mortality in CAD.(36, 74, 75, 77) Lavie et al demonstrated that in a cohort of overweight and obese individuals with CAD who underwent cardiac rehabilitation after a CV event, greater weight loss lead to improvements in metabolic profiles, exercise capacity and a trend towards lower mortality.(36) In a study of 1,500 CAD patients, intentional weight loss produced a lower incidence of CAD events over 4-year follow-up.(74) Similar findings have also been demonstrated in other studies, including a reduction in all-cause and CV mortality with weight loss through cardiac rehabilitation and exercise programs(77) and a decrease in major CV events with weight loss, including even in individuals with a BMI < 25 kg/m².(75)
Despite these findings, others have described increased mortality with weight loss (87) and the benefit of weight loss, except among the morbidly obese, is unclear. (1, 88-90) What is certain is that fitness is important to improve prognosis among CAD patients (81-83) and, therefore, physical activity, exercise training and fitness improvements, with potentially accompanying purposeful weight loss, should be incorporated into treatment plans of overweight or obese patients with CAD. (84, 85)

**Conclusion**

Obesity is related to multiple risk factors of CAD including HTN, DM, MetS, and dyslipidemia, while also likely being an independent risk factor for CAD. Through multiple pathways including increased angiotensin, circulating blood volume, and total peripheral resistance excess weight increases HTN risk. (15, 16) Through changes in insulin sensitivity, obesity increases the risk of DM and MetS, which lead to changes in endothelial function, increased dyslipidemias, and other inflammatory responses all of which increase the risk of CAD. (15, 22, 25-28) Obesity also leads to an unfavorable lipid profile, leading to elevated CAD risk. (20, 21, 29, 30) Despite these findings, a subset of obese individuals remains insulin-sensitive, the MHO, and maintain a CAD risk profile that is intermediate between a healthy non-obese individual and someone with IRO. (33)

While obesity increases the risk for CAD, it appears that in those with established disease, a paradox exists where the moderately obese with CAD appear to have improved mortality then those with normal weight. Current standards including weight loss and a physical activity and exercise program remain the recommendation as they have been associated
with reductions in blood pressure, triglycerides, an increase in insulin sensitivity and
decrease in HDL-C.(77, 89) Therefore, physical activity as a means to improve fitness and health outcomes should be promoted throughout the healthcare system despite BMI.(91)

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References


Table 1: Potential mechanisms by which obesity increases coronary artery disease risk factors

<table>
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<th>Risk factor</th>
<th>Mechanism</th>
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| Hypertension | Production of angiotensin a precursor of the renin-angiotensin-aldosterone system  
Increase in circulating blood volume  
Increase in total peripheral resistance |
| Diabetes mellitus & metabolic syndrome | Dietary indiscretion that leads to obesity  
Endocrine activity of adipose tissue:  
Increased clotting factors: Fibrinogen, von Willebrand factor, factors VII and VIII  
Increased plasminogen activator inhibitor type-I  
Increased leptin  
Increased tumor necrosis factor alpha  
Endothelial dysfunction:  
Decreased insulin-mediated vasodilation  
Increased insulin-mediated renal sodium resorption  
Insulin related sympathetic nervous system stimulation  
Increased vasoconstriction related to elevated circulating free fatty acids  
Increased risk of dyslipidemia  
Increased risk of renal dysfunction |
| Dyslipidemia | Low levels of high-density lipoprotein cholesterol  
High levels of triglycerides  
High levels of low-density lipoprotein cholesterol  
Elevated total cholesterol |
Table 2: Potential mechanisms for the obesity paradox in coronary artery disease

A. Greater metabolic reserves
B. Less cachexia
C. Younger presenting age
D. More aggressive medical therapy
E. More aggressive diagnostic and revascularization procedures
F. Increased muscle mass and strength
G. Possible improved cardiorespiratory fitness despite obesity
H. Attenuated hormonal response including the renin-angiotensin-aldosterone system
I. Unmeasured confounders, including selection bias*

* Selection bias may occur in that obese individuals may develop coronary artery disease (CAD) due to weight, whereas the etiology of CAD in lean patients may be different and associated with worse prognosis.
Figure 1. Unadjusted and adjusted relative risks (RR) for total mortality in patients with coronary artery disease by different body mass index (BMI) groups compared to normal BMI for all groups together and by myocardial infarction (MI), percutaneous coronary intervention (PCI), and coronary artery bypass graft (CABG) subgroups. Reproduced with permission from Romero-Corral et al.(35)

Figure 2. Unadjusted and adjusted relative risk (RR) for cardiovascular mortality in patients with coronary artery disease by body mass index (BMI) groups compared to normal BMI groups. After grouping studies with adjusted risks, obese patients had no increased risk and severely obese patients had a significantly higher risk compared to normal BMI group. Reproduced with permission from Romero-Corral et al.(35)

Figure 3. 9,563 subjects with known or suspected coronary heart disease stratified by body mass index (BMI) category (A), waist circumference (WC), and body fat percent (BF) tertiles ((B) and (C) respectively) on all cause mortality. Normal BMI, low WC and low BF in the high fitness group were used as reference groups. Hazard ratios (boxes) and 95% confidence intervals (error bars represent values) after adjusting for age, baseline examination year, physical activity, smoking hyperlipidemia, diabetes and family history of cardiovascular disease. Reproduced with permission from McAuley et al.(65)