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An Overview and Update on Obesity and the Obesity Paradox in Cardiovascular Diseases☆

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ABSTRACT

Obesity increases a number of cardiovascular disease (CVD) risk factors, but patients with many types of CVD may have a better prognosis if classified as overweight or obese, a phenomenon known as the "obesity paradox". This paradoxical benefit of a medically unfavorable phenotype is particularly strong in the overweight and class I obesity, and less pronounced in the more severe or morbidly obese populations (class II–III and greater). Rather than an obesity paradox, it is possible that this phenomenon may represent a "lean paradox", in which individuals classified as normal weight or underweight may have a poorer prognosis with respect to CVD, as a result of a progressive catabolic state and lean mass loss.

Cardiorespiratory fitness (CRF) is a fundamental part of this discussion. A greater CRF is associated with lower CVD risk, regardless of body mass index (BMI). Also, the assessment of body composition compartments (i.e., fat mass, fat-free mass, lean mass) and the presence of metabolic derangements may be better indicators of CVD risk than BMI alone.

The focus of this review is to summarize the current evidence of the obesity paradox. Moreover, we discuss the utility and limitations of BMI for cardiometabolic risk stratification, in addition to concepts such as "metabolically healthy obesity" (MHO) and the "fat but fit" phenomenon, which describe patients who are diagnosed with obesity using BMI, but without major metabolic derangements and with greater CRF, respectively. Finally, we propose that obese patients presenting with an excess body fat, yet without metabolic abnormalities, should still be viewed as an "at risk" population, and as such should receive advice to change their lifestyle to improve their CRF and to prevent the development of impaired fasting glucose, diabetes mellitus and other CVD risk factors as a form of primary prevention.

Contents

Abbreviations and Acronyms: AF, Atrial Fibrillation; BF%, Body Fat Percentage; BMI, Body Mass Index; BP, Blood Pressure; CABG, Coronary Artery Bypass Graft; CHD, Coronary Heart Disease; CRF, Cardiorespiratory Fitness; CV, Cardiovascular; CVD, Cardiovascular Disease; DM, Diabetes Mellitus; HF, Heart Failure; HTN, Hypertension; LDL, Low-density Lipoprotein; LV, Left Ventricular; MET, Metabolic Equivalent; MetS, Metabolic Syndrome; MHO, Metabolically Healthy Obesity; MI, Myocardial Infarction; NWO, Normal Weight Obesity; PA, Physical Activity; PAH, Pulmonary Arterial Hypertension; PCI, Percutaneous Coronary Intervention; WC, Waist Circumference.

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Introduction

The prevalence of overweight and obesity has reached epidemic proportions in Western countries,[1] and is the second leading cause of preventable death following tobacco use.[2] Although the etiology of the obesity epidemic has been intensely debated, it is widely accepted that increased body weight and overall adiposity are the result of a chronic positive energy balance, with energy intake exceeding energy expenditure.[3] Obesity is a major independent risk factor for cardiovascular (CV) disease (CVD), such as hypertension (HTN), coronary heart disease (CHD), atrial fibrillation (AF) and heart failure (HF).[3,4]

While obesity increases a number of the established CVD risk factors, it has been shown that many types of CVD may have a better prognosis in the overweight or obese population compared to their leaner counterparts,[3] and this phenomenon is referred to as the "obesity paradox". An obesity paradox is seen in many forms of CVD,[5] in addition to other diseases, such as end-stage renal disease, human immunodeficiency virus and various pulmonary diseases.[6,7] Although the obesity paradox has been observed for most CVD, it most likely applies to the overweight and class I obesity, and less for class II and greater (Table 1).[4]

The focus of this review is to evaluate the current evidence regarding the obesity paradox in CVD and to understand its clinical implications. Concepts such as the "fat but fit" phenomenon, "normal weight obesity" (NWO) and "metabolically healthy obesity" (MHO) will also be discussed, as well as the critical importance of physical activity (PA), cardiorespiratory fitness (CRF) and metabolic derangements in the overweight and obese.

Utility of BMI

Overweight and obesity are generally defined by Body mass index (BMI) in clinical practice (Table 1).[4] The modern definition of BMI comes originally from the Quetelet index in 1832, named after a Belgian astronomer and statistician who used height and weight to assess individuals in the French and Scottish armies.[8] However, the World Health Organization defines obesity as excess body fat that impairs health, and further suggest that BMI is a rough guide of body composition since individuals with similar BMI may present with different degrees of fatness.[9] For such reason, the ideal definition of obesity should include an assessment of body composition to determine body fat percentage (BF%). Universal cut-off values for BF% are, however, lacking, but the most commonly used BF% for the definition of obesity are BF% >35% in women and >25% in men.[10,11] Race, age and sex-specific cut-off values have also been proposed in the literature.[12]

Table 1
Weight Classification by BMI.

Weight class	BMI (kg/m^2)
Underweight	<18.5
Normal weight	18.5–24.9
Overweight	25.0–29.9
Obesity	
Class I	30.0–34.9
Class II	35.0–39.9
Class III	40.0–49.9
Class IV	50.0–59.9
Class V	≥60

Although BMI is commonly used, simple to apply and inexpensive, this measurement does have its limitations. The utility of BMI to assess obesity has been criticized for its inability to differentiate between fat, muscle and skeletal weight,[2] therefore being an inaccurate measurement for adiposity at the individual level. Because of this inability to distinguish between fat mass, fat-free mass and lean mass, individuals with similar BMI may have vastly different body compositions and perhaps more importantly, very different metabolic profiles.[13] On the other hand, BMI within the normal range does not preclude increased fat mass and increased cardiometabolic risk.[13] These patients are classified as NWO, which describes patients with high total BF% or waist circumference (WC), but normal BMI, who have been shown to have increased metabolic syndrome (MetS), CHD and mortality risk.[14,15]

Based on the BMI estimation error when assessing total adiposity,[16] it would be expected that more accurate measures of total adiposity would be stronger predictors of mortality than BMI. However, at the population level, BMI still predicts clinical outcomes. Ortega et al.[17] found that BMI was a stronger predictor of cardiovascular mortality than indicators of fat mass in >60,000 participants and evaluated BMI, BF%, fat mass index, fat-free mass and fat-free mass index, and concluded that BMI can be as clinically important or more important than total adiposity measures assessed using accurate, complex and expensive methods. Given these findings, BMI is likely to continue being a gold-standard of body composition assessment because of the combination of its utility in assessing the effects of both fat mass and fat-free mass in CV pathology and simplicity with widespread adoptions in literature as well as groups such as the World Health Organization. In addition to BMI and total BF%, measurements of adipose tissue distribution, such as WC and waist-to-hip ratio have also demonstrated an obesity paradox, especially in CHD.[14]

Recent studies have attempted to debunk the obesity paradox,[18,19] suggesting that the obesity paradox could be explained by the fact that the diagnosis of CVD in obese patients occurs earlier in life, therefore justifying the improved prognosis. However, such studies clearly confirmed the association between obesity and CVD, but they did not assess the effects of obesity and excess adiposity once CVD were diagnosed, which would have challenged the obesity paradox. Moreover, prior studies showing an improved prognosis in overweight and obese patients, especially in the setting of heart failure, were adjusted for a number of variables, including age,[20] making it therefore unlikely to explain the obesity paradox.[21]

Physiologic impact of overweight/obesity

Increasing adiposity is associated with neurohormonal activation and metabolic abnormalities, including renin-angiotensin-aldosterone

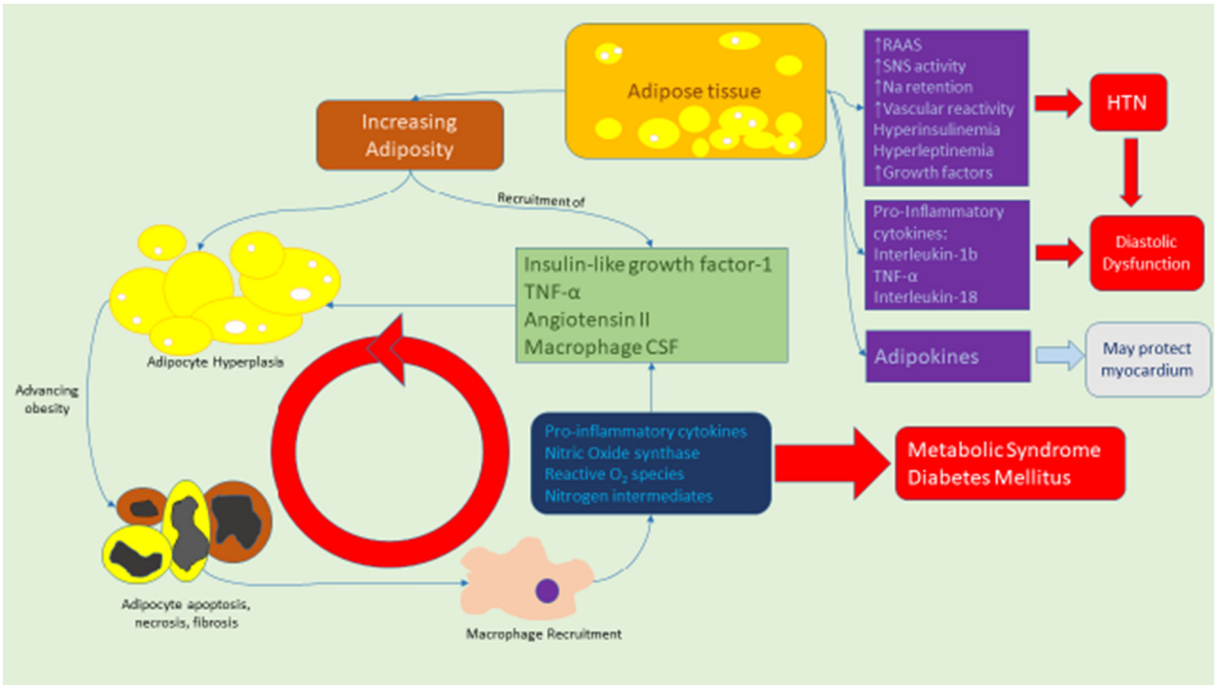

Fig. 1. Physiologic impact of adipose tissue. CSF = Colony stimulating factor; HTN = Hypertension; Na = Sodium; RAAS = Renin angiotensin aldosterone system; SNS = Sympathetic nervous system; TNF = Tumor necrosis factor.

system activation, sympathetic system activation, hyperleptinemia and dysregulation of growth factors, such as insulin-like growth factor.[2] These homeostatic aberrations induce increased sodium retention, vascular reactivity and hyperinsulinemia, and each contribute to the development of HTN in obesity.[22] Adipose tissue, while previously viewed as a storage depot, is now recognized as an endocrine organ. Adipocytes synthesize a number of hormones or active molecules called adipokines, which may have a protective effect on the myocardium.[13,23] However, adipose tissue also produces pro-inflammatory cytokines, such as Interleukin-1b, tumor necrosis factor-α and Interleukin-18, which induce diastolic dysfunction in preclinical animal models (Fig. 1).[13,24–26]

With increasing adiposity, adipocyte hyperplasia is mainly driven by the recruitment of adipogenic progenitors and growth factors, such as insulin-like growth factor-1, tumor necrosis factor-α, angiotensin II and macrophage colony stimulating factor.[22] As obesity advances, the hypertrophied adipocytes undergo apoptosis, cell necrosis and fibrosis, which further induce a low-grade systemic pro-inflammatory state and adipose tissue dysfunction.[22] Once the inflammatory response is initiated, it is intensified by macrophage recruitment to adipose tissue, leading to insulin resistance.[22] These macrophages also produce pro-inflammatory cytokines, inducible nitric oxide synthase, reactive oxygen species and nitrogen intermediates that are thought to promote insulin resistance leading to MetS and diabetes mellitus (DM).[22]

Overweight and obesity adversely impact cardiac structure and function; both systolic, and especially, diastolic ventricular function, increasing the prevalence of HF (Fig. 2).[4] Although obesity is associated

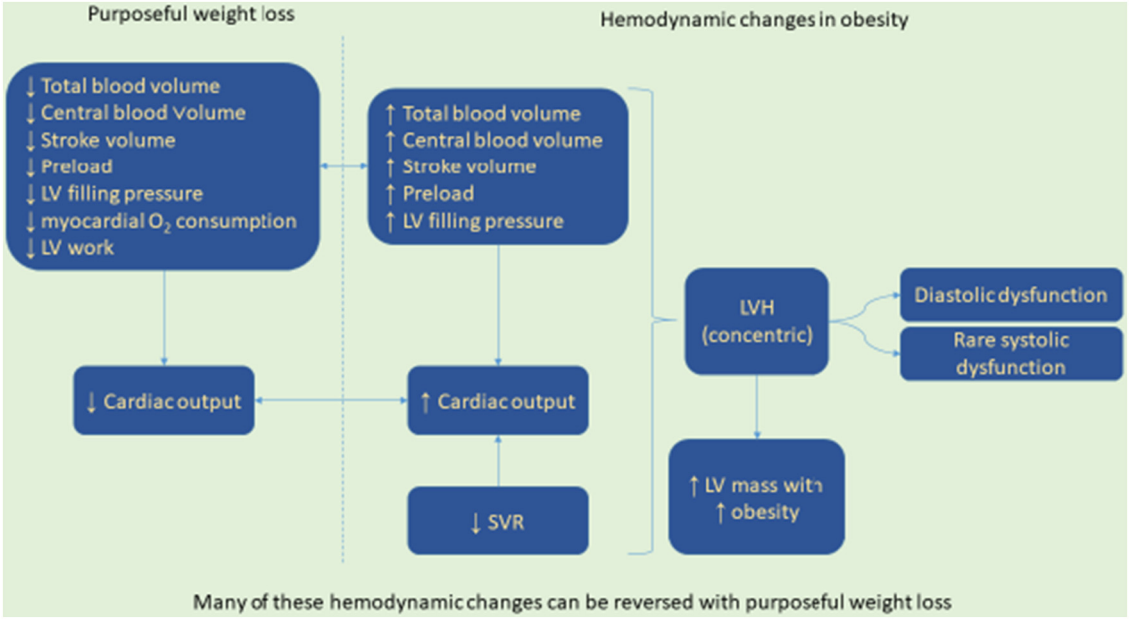

Fig. 2. Hemodynamic changes in obesity. LV = Left ventricular; LHV = Left ventricular hypertrophy; SVR = Systemic vascular resistance.

with excess adiposity, the increase in body weight is typically also paralleled by an increase in lean mass, with higher blood flow requirements, that translates into higher total and central blood volume, stroke volume and cardiac output.[4] Blood flow in adipose tissue is, in fact, very low compared to many other organs and lean mass, and therefore would not be sufficient to account for the increased cardiac output seen in obese patients.[2] Class II-III obesity also has increased venous return, which leads to increased preload and left ventricular (LV) filling pressure (which leads to elevated pulmonary arterial and right heart pressures).[4] The sustained increase in cardiac output due to increased preload seems to be responsible for an initial dilation of the left ventricle, followed by a hypertrophic compensatory response.

LV mass markedly increases with the severity of obesity by a concentric pattern which commonly leads to diastolic dysfunction.[4] Diastolic dysfunction in the obese progresses with increases in body mass; there is reported to be up to 12% prevalence in class I obesity, 35% in class II obesity and 45% in class III obesity.[27] Many of these changes can be reversed with purposeful weight loss.[23] However, systemic vascular resistance is reduced in obese patients, which facilitates increased cardiac output,[4] representing a potential protective mechanism in obese patients in the setting of heart failure, which is, on the contrary, associated with increased systemic vascular resistance.[28]

CVD risk of obesity

Certainly, obesity is associated with worsening physiologic parameters that promote the development and progression of CVD, including dyslipidemia, high blood glucose, low-grade systemic inflammation and the MetS/DM.[2,29] Overweight and obese patients consistently have a higher prevalence of CHD, and the Framingham study showed that 23% of CHD in men and 15% of CHD in women was attributable to excess adiposity.[30] Another analysis of patients from the Framingham cohort study with follow-up of up to 48 years concluded that all-cause mortality increased as the number of years lived with obesity increased, with a clear dose-dependent pattern; for every 2 additional years with obesity, CVD mortality risk increased by 7%.[31] Khan et al.[19] performed a study with 3.2 million person-years follow-up from 1964 to 2015, and confirmed that obesity is associated with a significantly increased risk of CVD morbidity and mortality compared with normal BMI. Incident CVD events were significantly higher in the overweight or obese compared to normal weight individuals.

HF

The Framingham study[32] was the largest to assess the risk of HF in obesity; every 1 kg/m^2 increase in BMI increased the risk of HF by 7% in women and 5% in men. While obesity significantly increases the risk of HF,[29] Pandey et al.[33] have demonstrated that the increase in HF with reduced ejection fraction is lower compared to the markedly increased risk for HF with preserved ejection fraction. Furthermore, the risk of HF associated with obesity is independent of other risk factors as well as CRF levels.[34] Despite this increased risk for HF, many large studies have demonstrated an obesity paradox in HF patients, as overweight and obese patients have a better short- and intermediate-term prognosis compared with leaner patients with similar degrees of HF after adjustments for confounders.[4]

A meta-analysis of 9 observational studies, including nearly 30,000 patients by Oreopoulos et al.[35] showed that overweight and obese patients with HF had reductions in CVD mortality (19% and 40%, respectively) and all-cause mortality (16% and 33%, respectively) compared to HF patients without elevated BMI. Sharma and colleagues[36] reported a meta-analysis (n = 22,807) showing that adverse events, mortality and re-hospitalizations were highest in the low (normal or underweight) BMI and lowest in the overweight groups. Clark et al.[37,38] showed that higher BMI and WC were associated with better event-free survival in HF, with the best survival in those with both high BMI and high WC. Shah et al.[39] evaluated patients with decompensated HF across four continents and found that every 5 kg/m^2 increase in BMI was associated with an 11% decrease in 30-day mortality and a 9% decrease at 1 year. However, a study from the Cleveland clinic in patients with systolic HF showed that the survival paradox of high BMI disappeared following adjustment for confounders.[40,41] Recently, obesity has been associated with the severity of HF exacerbation yet presented with lower in-hospital mortality.[42]

HF is associated with a chronic catabolic state, resulting in fat mass, as well as lean mass loss (i.e. cachexia), which carries a devastating prognosis in HF; 50% of those with cachexia (defined as nonintentional documented weight loss of at least 7.5% of previous normal weight over 6 months) had died at 18-month follow-up.[43] Advanced HF is exceptionally associated with cachexia, perhaps explaining why heavier advanced HF patients demonstrate an obesity paradox, likely due to increased metabolic reserve.[4] Adipose tissue promotes soluble tumor necrosis factor-α receptors which could neutralize tumor necrosis factor-α and therefore have a protective impact.[23] The obese patients also have higher levels of circulating lipoproteins, which may bind and detoxify lipopolysaccharides responsible for the release of inflammatory cytokines.[23] Because obesity is usually associated with greater blood volume and higher blood pressure (BP), obese patients with HF may be able to tolerate higher doses of cardioprotective medications.[4] Finally, the increased amount of lean mass seen in obese patients may improve CRF, which is associated with improved outcomes in this population.[44,45]

CHD

The major effect of obesity on CHD risk is attributable to atherogenic dyslipidemia and MetS/DM.[2] This is supported by evidence from the INTERHEART study,[46] which assessed 30,000 patients in 52 countries, finding that over 90% of the risk for acute myocardial infarction (MI) was attributable to nine modifiable risk factors; dyslipidemia being the leading factor, which could account for approximately 50% of the risk of developing acute MI. Despite having relatively normal total low-density lipoprotein (LDL) plasma levels, obese individuals typically have an increased proportion of small, dense LDL-cholesterol, which is more easily oxidized, and therefore more atherogenic than larger, more buoyant LDL cholesterol particles.[2]

However, once CHD is diagnosed, overweight and obese patients present with a more favorable prognosis. A meta-analysis of 40 cohort studies with >250,000 patients reported overweight/obese with CHD have lower risk of total and CVD mortality compared with underweight and normal weight CHD patients.[47] An additional large meta-analysis of 89 studies including >1.3 million CHD patients also confirmed an obesity paradox,[48] which was evident during early follow-up even in patients with severe obesity. Such protective effects, however, seemed to disappear after approximately 5 years. Further, those with CHD and moderate/severe obesity had higher mortality during long-term follow-up. Romero-Corral et al.[47] reported more favorable CVD and total mortality outcomes in overweight/mildly obese (BMI = 25–35 kg/m^2) patients than normal weight and underweight individuals. An obesity paradox has also been demonstrated following ST-elevated MI, with findings that suggest a poorer prognosis in thinner elderly patients.[49] However, the majority of the studies lack an assessment of body composition and functionality, as well as levels of PA and CRF, which are major determinants of prognosis.[50]

Following revascularization

The prevalence of patients undergoing percutaneous coronary intervention (PCI) or coronary artery bypass graft (CABG) surgery who are overweight or obese may be as high as 70%.[2] A review of 26 PCI studies found that underweight patients had the highest rates of all-cause death, CVD death and MI with mean follow-up of approximately 1.7 years compared with normal BMI.[51] In the same study, overweight

patients had the lowest risk of these outcomes, with significant reductions in all-cause and CVD mortality by 32% and 22%, respectively.

A 10-year analysis of patients undergoing CABG (n = 9862) found that obesity was not associated with increased morbidity or mortality,[52] however, patients with BMI > 40 kg/m^2 had greater need for postoperative re-exploration. A 2014 analysis of 12 CABG studies in >60,000 patients found worst survival rates in underweight patients, who had a 2.7-fold higher mortality than patients with normal BMI.[51] It is important to note that the severely obese had a 4-fold higher risk of CVD death after CABG.

HTN

The Physicians' Health Study demonstrated a strong association between higher BMI and the risk of HTN with approximately 8% increase per 1-unit increase in BMI.[53] Interestingly, several studies have demonstrated that patients with HTN who are overweight or obese have a better prognosis than leaner patients with HTN, even in those with less optimal BP control and more LV geometric abnormalities.[2] Patients with obesity and HTN typically respond favorably to diuretics and calcium channel blockers, given that obese patients are usually in a state of volume overload and often have relatively lower plasma renin activity.[2] Uretsky et al.[54] investigated outcomes in 22,576 patients with HTN and known CHD, finding that despite worse control of BP, all-cause mortality was 30% lower in overweight and obese HTN patients compared with their leaner counterparts.

One study has shown that the obesity paradox is also apparent in patients hospitalized for HTN emergency. Agarwal et al.[55] assessed 281,560 HTN emergency hospitalizations finding that overall mortality was 2.75% with significantly lower in-hospital mortality in those with obesity ($p < 0.001$). In-hospital mortality has also been demonstrated to be lower in patients with pulmonary arterial HTN (PAH) and obesity (3.5%) compared to the non-obese (8.1%) from a 9-year nationwide study.[56] Multiple other studies have also demonstrated an obesity paradox in PAH, including one which demonstrated significantly higher survival in obese patients with PAH during long-term follow-up.[57,58]

AF

Along with obesity, the prevalence of AF has been increasing and is expected to increase 3.5-fold during the next 30 years.[59] Obesity is an independent risk factor for AF,[60] and obese patients have been shown to have a 50% increased risk for developing AF.[61] Another study showed that every 1-unit increase in BMI has been associated with an almost 4% increased risk of AF.[62] Obesity may also be a risk factor for progression of paroxysmal to persistent AF, which carries higher morbidity and mortality.[3]

Multiple controlled cardiac imaging studies have demonstrated an association between pericardial fat and AF, and nearly all of these studies showed that greater volume or thickness of pericardial fat were associated with a higher prevalence of paroxysmal and persistent AF.[60] Further, a recent meta-analysis has suggested that the associations of AF with pericardial fat were stronger than those with abdominal or overall adiposity.[63]

An obesity paradox has been demonstrated in patients with AF, in which overweight/obese have nearly 50% reduced CVD and all-cause mortality compared with AF patients with normal BMI.[3] Multiple recent studies have demonstrated AF patients to have lower risk of all-cause mortality in the overweight/obese versus normal BMI in long-term follow-up, including a study by Pandey et al.,[64] which demonstrated a 35% lower risk of all-cause mortality among Class I obese patients with AF as compared with normal BMI patients. Table 2 summarizes a list of conditions which have been associated with an obesity paradox, in addition to AF.

Table 2
Conditions associated with an obesity paradox.

Congestive heart failure
Coronary heart disease
Following percutaneous coronary intervention
Following coronary artery bypass grafting
Hypertension
Hypertensive emergency
Pulmonary arterial hypertension
Atrial fibrillation
End-stage renal disease
HIV
Various pulmonary diseases (i.e. COPD)

Lean paradox

Some have argued that the observation of worse clinical outcomes in CVD in those with low BF% and low BMI may be suggestive of a "lean paradox" even more so than an obesity paradox.[3,65,66] Low BF% and low BMI are independent predictors of worse outcomes, and those with both have demonstrated increased mortality rates.[14]

Unintentional weight loss carries an extremely high burden of morbidity and mortality for most medical conditions, especially for HF.[4,67] None of the major HF societies recommend weight loss for HF patients, except for the recognition that class III obesity has a particularly poor prognosis.[4] Studies on the effects of weight loss are largely retrospective in nature and often lack uniform controls to define and/or delineate between "healthy" and "unhealthy" weight loss, leading to a range of both beneficial and harmful associations between studies. The current landscape of differing data contributes to the lack of weight-management specific recommendations, and large randomized trials that analyze the effects of intentional weight loss in CVD, particularly in HF patients, are needed.

When discussing the lean paradox, "lean" refers to those patients in lower BMI categories. "Lean mass" is distinctly different from this definition because it is intended to reflect a person's fat-free mass, including skeletal muscle. A decreased amount of lean mass or skeletal muscle mass defines sarcopenia, a condition independently associated with poor prognosis in a number of chronic diseases,[68] including HF.[69] Those with excess fat mass and reduced skeletal muscle mass are classified as having sarcopenic obesity, with a heightened metabolic and CVD risk that is worse than either obesity or sarcopenia alone.[45] Kamiya et al.[70] examined HF patients according to BMI and added the measurement of mid-upper arm circumference as a surrogate for muscle mass. Combining the assessment of BMI with arm circumference improved mortality prediction, and those with low BMI and low arm circumference had significantly higher mortality, whereas low BMI and high arm circumference did not, suggesting that muscle mass alters the relationship between adiposity and survival in HF.[71]

CRF and the "fat but fit" phenomenon

The importance of CRF has often been neglected for CVD risk stratification, despite the fact that it correlates with overall health status and is a potent predictor of an individual's future risk of CVD.[72] High levels of CRF largely neutralize the adverse effects of excess adiposity and other CVD risk factors, which has led to what is described as the "fat but fit" phenomenon.[73,74] Substantial evidence suggests that CRF remains very predictive and largely negates the adverse effects of body fatness, as well as other traditional CVD risk factors, including overweight/obesity, MetS, type II DM, and HTN.[14]

While many studies have demonstrated the effects of CRF and obesity on mortality independently, Barry and colleagues[75] assessed the joint association of CRF and weight status on mortality. It was shown that unfit individuals have twice the risk of death regardless of BMI, while fit, overweight and obese individuals have similar mortality risk

as their normal weight counterparts.[75] Many other studies support the notion that CRF is a stronger predictor of CVD outcomes than obesity,[75,76] and Pedersen[77] stated that higher CRF level independently reduces mortality regardless of BMI.

CRF level markedly alters the relationship between adiposity and prognosis in patients with CHD, and a cohort study of nearly 10,000 patients with CHD followed for almost 15 years showed that those with relatively good CRF had favorable prognosis regardless of body composition, including BMI, BF% and WC.[78] Evidence from 5 observational cohort studies indicated that CRF significantly alters the obesity paradox.[79,80] A meta-analysis of 33 studies with >100,000 patients showed that each 1 metabolic equivalent (MET) increase in CRF reduced all-cause and CHD/CVD events by 13% and 15%, respectively.[81] Maintaining or taking up PA, likely resulting in improved CRF, has been associated with substantial reductions in all-cause and CVD mortality risk in CHD patients.[82]

Lower CRF is a major predictor of mortality, regardless of BMI.[3,77] Increased PA and exercise training to maintain or improve CRF are effective, safe and proven strategies for primary and secondary prevention of CVD in all weight groups.[73] Pathak et al.[83] observed that every 1-MET increase in baseline CRF reduced the relative risk of arrhythmia recurrence by 20%. Importantly, CRF is also said to be one of the best predictors of health outcome, regardless of age, sex, ethnicity, body habitus, chronic disease risk factors or actual chronic disease.[2]

Another study showed that a 1-MET increase in CRF by exercise stress testing over an average of 6.3 years in 13,345 men was associated with reductions in all-cause and CVD mortality of 15% and 19%, respectively, while BMI change was not associated with mortality following adjustment.[84] Another study showed that patients with relatively preserved CRF (6 METs) had an extremely low mortality rate of <1% per year, although the normal BMI group had a higher mortality rate.[85]

McAuley and colleagues[78] used data from the Aerobics Center Longitudinal Study and found that after adjustment, men in the middle and upper thirds of CRF had 28% and 35% lower risks of total mortality compared with men in the lower third of CRF, which did not change following adjustment for other measures of adiposity (BMI, WC and BF%). Except for the severely obese group showing 93% higher CVD mortality risk, higher adiposity did not seem to contribute to CVD mortality.[78] An analysis of obese patients from this trial also found that obese fit individuals had a markedly reduced risk (25% - 46% lower) of having CVD risk factors and a reduced risk of having MetS.[65]

CRF is a particularly important risk factor for HF and prior studies have demonstrated a dose-dependent, inverse association between CRF, exercise levels, and risk of HF.[86,87] The mortality benefits of higher levels of exercise and CRF have been demonstrated in patients with HF, including those with HF with preserved ejection fraction.[88,89] Low CRF annual mortality has been reported as high as 8.2% compared with 2.8% in those with high CRF.[90] While it has been suggested that obesity may only be protective in short- and medium- term follow-up, CRF has been shown to have more long-term protective effects. The Cooper Center Longitudinal study evaluated 66,371 participants and found that a single measure of CRF significantly improves classification of both 10- and 25-year risk for CVD mortality when added to traditional CVD risk factors.[91]

The relationship between PA, CRF and AF is more complex, as multiple longitudinal and case control studies have reported a particularly higher risk of AF among athletes who participate in endurance sports.[60] It has been shown that lean mass was the predominant anthropometric risk factor for development of AF, whereas obesity had no association when adjusted for lean mass.[92] Among healthy, nonathletic individuals, the association between PA and AF is less well established, and therefore PA within the optimal range may be beneficial and not have an increased risk of AF.[60] When CRF is assessed, rather than PA, higher CRF has been associated with greater arrhythmia-free survival in patients with existing AF.[60] The role of exercise for AF management is not well defined in current guidelines.

MHO

MHO is generally defined as BMI ≥ 30 kg/m^2 without HTN, glucose abnormalities or dyslipidemia.[7] Because there is no official definition for MHO, Ortega et al.[65] have proposed a definition, in short, BMI ≥ 30 kg/m^2 and meeting 0 of the MetS criteria (excluding WC). As discussed earlier, obesity is associated with multiple CVD risk factors, and some authors have argued that obesity should never be considered "healthy". Supporting this notion, a meta-analysis by Kramer et al.[93] found that in studies with ≥10 year follow-up, patients with MHO had a 24% increased risk of major CVD events compared to lean individuals who were also metabolically healthy. A study from Norway demonstrated that MHO patients also had an increased risk of HF.[94]

Mongraw-Chaffin et al.[95] found that in 12.2 years follow-up, almost ½ of their participants with MHO developed MetS (and subsequent increased risk of CVD). One extremely powerful study in 3.5 million patients found that MHO individuals had a higher risk of CHD, cerebrovascular disease and HF than normal weight metabolically healthy individuals.[96] However, this and many similar studies have been criticized for not including assessments of CRF or PA,[97] and some authors have strongly suspected that only MHO individuals with low PA and reduced CRF would have increased risk of CHD and most CVD.[98] This represents the "fat but fit" phenomenon, as discussed previously. It has also been argued that when CRF and other important confounders are considered, relatively fit individuals with MHO are not at significantly higher risk of CVD morbidity or mortality than metabolically healthy normal-weight individuals.[97]

It is possible that MHO patients with preserved CRF may not be at increased CVD risk. However, until this is confirmed, the current evidence may suggest that MHO should be treated as an "at risk" medical condition, such as pre-DM,[99] for which treatment primarily involves either lifestyle modification, medications, or both, in order to prevent the development of MetS/DM and its sequelae.[100] Perhaps MHO should be considered in a similar fashion, and efforts should be made in treating those with MHO before developing metabolic abnormalities and ultimately increased risk for CVD, as a form of primary prevention.

Weight loss

Although an obesity paradox exists, it may not apply to more morbid obesity in which prognosis is adversely affected in CHD, cardiac revascularization (both PCI as well as CABG) and HF.[14] While arguments have been made for the "fat but fit" phenomenon, CRF assessment of the morbidly obese may be technically challenging. Many changes in cardiac performance and morphology associated with obesity are reversible with purposeful weight loss,[2] as purposeful weight loss reduces total and central blood volume, myocardial oxygen consumption, cardiac output, LV stroke volume, LV work and LV stroke work in patients with obesity.[101]

The role of purposeful weight loss in HF is controversial. However, obesity is associated with multiple complications following heart surgery, including poor wound healing, increased risk of infection, pulmonary complications and earlier high-grade acute rejection and 5-year mortality following heart transplantation.[102] The International Society for Heart and Lung Transplantation heart transplant candidacy guidelines support weight reduction to achieve optimal post-transplant outcomes.[103]

Support devices, such as LV assist devices, are very beneficial when used to provide the necessary time for successful weight loss as a bridge to heart transplantation.[23] However, with the exception of severe obesity, some studies have suggested that weight loss may be associated with increased mortality.[14,23] In HF, intentional weight loss might be one of the most effective strategies to improve abnormal hemodynamics and alterations in cardiac structure and function, however, major guidelines from the American Heart Association do not provide firm recommendations for weight loss in HF, owing to a lack of robust evidence.[104] These guidelines do, however, acknowledge the very

poor prognosis in patients with severe or morbid obesity. The European Society of Cardiology and Canadian Cardiovascular Society recommend purposeful weight loss in HF patients only with BMI ≥ 30 kg/m^2.[23] The European Society of Cardiology recommends management of overweight and obese patients with HF as per guidelines for general cardiovascular disease prevention, but acknowledges the gaps in evidence.[105] Obesity and more specifically measures of adiposity such as fat-mass index are major determinants of exercise intolerance in patients with HF, particularly in those with HF with preserved ejection fraction, independent of cardiac function abnormalities.[106] A landmark trial in obese patients with HF with preserved ejection fraction, in fact, showed that caloric restriction-induced weight loss was associated with improved CRF. Such improvements were mainly driven by changes in body composition as cardiac function did not change over the duration of the study.[107] However, the long-term effects of caloric restriction-induced weight loss on clinical outcomes are unknown.

Among patients with established AF, lifestyle interventions with sustained weight loss have been associated with reduction in the AF burden and symptom severity in a dose-dependent fashion.[60] Pathak et al.[108] demonstrated that AF patients with significant intentional weight loss over a 5-year follow-up (>10%) had 6-fold higher likelihood of arrhythmia free survival, as compared with those with modest to no weight change (<3%). Multiple authors have suggested that PA should be encouraged to improve CRF rather than weight loss to reduce mortality risk.[75,78] It has also been proposed that weight management in the elderly should be directed at increasing or maintaining lean body mass and muscular strength without increasing body fat (except in the underweight).[109]

Confounders

Mechanisms for an obesity paradox are not well understood, and it has been argued that this observation may be due to confounding variables,[18] or biases such as lead time, confounding or publication biases.[110] Typically, the overweight/obese patients are significantly younger than patients with normal BMI in most observational cohorts, and this may be an age confounder.[60] A lead time bias due to earlier detection of CVD in the overweight and obese population (due to higher pretest probability of disease and earlier diagnostic testing) could result in increased apparent survival.[110] Leaner individuals in contrast may have a lower pretest probability of disease and receive their diagnosis at a time of more advanced disease leading to a worse overall prognosis.[110] The fact that >50% CVD deaths occur in those without a previous diagnosis of CVD illustrates the difficulty with early diagnosis of CVD, and the possibility of lead time bias affecting the observation of an obesity paradox.[111]

Conclusion

There is much evidence to suggest that increased PA and CRF may be more important and effective treatment methods rather than weight loss alone for CVD, considering the fallibility of BMI. Although the use of BMI to assess adiposity is flawed, it is a good marker of excess body weight, and seems to be a better marker of CVD risk than more expensive, cumbersome and precise measurements of adiposity, as we recently described.[17]

Obesity is associated with multiple unfavorable physiologic and hemodynamic changes, many of which are reversible with purposeful weight loss. Certainly, describing the obesity paradox is not a promotion of overweight and obesity or a suggestion that weight gain is beneficial.[50] Obesity clearly increases CVD risk and many obese individuals with CVD can attribute much of their disease burden to excess weight. One of the main purposes for reporting the obesity paradox is to emphasize that physicians should likely be more concerned about the poor prognosis in their leaner or underweight patients with CVD, particularly those with low CRF and/or low muscle mass.[50] Also, those with MHO should be considered to have an "increased risk" medical condition in the least, and treatment should be initiated to prevent the development of metabolic derangement and further increased CVD risk.

Finally, weight loss in the obese seems to exert several beneficial effects on the CV system, as well as improving glucose metabolism abnormalities especially in the setting of increasing CRF. However, the confounding messages from numerous studies demonstrating the obesity paradox prevent clear guidance on the parameters of weight loss needed to combat an increasing obesity epidemic. Thus, large randomized trials investigating the effects of intentional weight loss are imperative to determine the measures that are critical to improving clinical outcomes.

Statement of Conflicts of Interest

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