Obesity and Cardiovascular Disease
Risk Factors, Paradox and Impact of Weight Loss

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Abstract
Obesity has reached global epidemic proportions in both adults and children and is associated with numerous comorbidities, including hypertension (HTN), type II diabetes mellitus, dyslipidemia, obstructive sleep apnea and sleep-disordered breathing, certain cancers and major cardiovascular (CV) disease. Because of its maladaptive effects on various CV risk factors and its adverse effects on CV structure and function, obesity has a major impact on CV diseases, such as heart failure (HF), coronary heart disease (CHD), sudden cardiac death, and atrial fibrillation, and is associated with reduced overall survival. Despite this adverse association, numerous studies have documented an obesity paradox in which overweight and obese people with established CV disease, including non-obese patients.

This review summarizes the adverse effects of obesity on CV disease risk factors and its role in the pathogenesis of various CV diseases, review the obesity paradox and potential explanation for these puzzling data, and concludes with a discussion regarding the current state of weight reduction in the prevention and treatment of CV diseases.

Introduction
Obesity has been increasing in epidemic proportions in both adults and children. In adults, overweight is defined as a body mass index (BMI) 25 to 29.9 kg/m² and obesity as BMI>30 kg/m². Other indexes that have been used less commonly but waist circumferences (WC), waist-to-hip ratio (WHR), and weight-to-height ratio³. A recent study of nearly 360,000 participants from 9 European countries showed that both general obesity and abdominal adiposity are associated with risk of death and support the importance of WC or WHR in addition to BMI for assessing mortality risk⁴. Recent evidence indicates that obesity is associated with more morbidity than smoking, alcoholism, and poverty, and if current trends continue, obesity may soon overtake cigarette abuse as the leading cause of preventable death in U.S⁵. Should we fail to stop the obesity epidemic, it has been predicted that we may soon witness an abrupt end, or even a reversal, of the steady increase in life expectancy⁶. The paper reviews the metabolic consequences of obesity as well as its pathological effects on blood pressure and CV structures and function contributing to its role in HTN and HF as well as to its role in increasing CHD and atrial fibrillation(AF). We also review the evidence for the obesity paradox in these disorders as well as PAD. Finally, we discuss the current evidence for the potential risks and benefits of purposeful weight loss.

Pathophysiology
The adipocyte acts as an endocrine organ, and plays a substantial role in the pathogenesis and complications of obesity⁷. Increase level of leptin, and adipocyte derived hormone that controls food intake and energy metabolism, may be particularly related with CV disease. Recently, increase concentration of both CRP and leptin were associated with increased risk of major CV events, but leptin seems to be more robust predictor⁸.
Effects of obesity on Hemodynamics and CV structure and Function:

Obesity has many adverse effects on hemodynamics and CV structure and function.\(^9\)

Fig:1. Pathophysiology of Obesity and Cardiomyopathy.

Clinical Consequence of Obesity:

Obesity, HTN, and the obesity paradox:

Typically HTN leads to thickening of ventricular walls without chamber dilation, a process referred to as CR when LV mass is not increased or concentric LVH when LV mass is increased, whereas obesity is characterized as increasing chamber dilation without marked increased in wall thickness, a process that leads to eccentric LVH.

Despite having a higher prevalence of HTN in obesity, recent data have shown an obesity paradox. Uretsky-et-al\(^{10}\) investigates the effects of obesity on CV outcomes in 22,576 treated hypertensive patients with known CHD. During 2-year follow up, all-cause mortality was 30% lower in overweight and obese patients, despite less effective blood pressure control in these patients compared with the normal weight group. A previous study also showed decreased stroke risk and total mortality among overweight patients compared with lean patients. The association between BMI and major CV events was U-shaped, whereas non-CV mortality decrease with increasing BMI. In aggregate, these studies suggest that although obesity may be a powerful risk factor for HTN and LVH, obese hypertensive patients may paradoxically have a better prognosis, possibly because of lower systemic vascular resistance and plasma renin activity compared with more lean hypertensive patients.\(^{11}\)

Obesity Paradox in Cardiovascular and non-cardiovascular patients:

Cardiovascular:-

a) HTN
b) Heart Failure
c) Coronary Heart Disease-
   1. Percutaneous revascularization
   2. CABG
   3. Treatment referrals
d) Peripheral Arterial Disease
e) Echocardiography referrals

Non-Cardiovascular:-

a) Elderly
b) End stage Renal disease and dialysis
c) Advanced Cancer
d) COPD
e) Rheumatoid Arthritis
f) Human immunodeficiency virus/acquired immune deficiency syndrome

Obesity, HF, and the obesity paradox

In a study of 5881 Framingham heart study participants, Kenchaiah et al. showed that during a 14 year follow up, for every 1 kg/m\(^2\) increment in BMI, the risk of HF increased in 5% in men and 7% in women. In fact a graded increase in the risk of HF was observed across in categories of BMI. In a study of 74 morbidly obese patients, nearly one-third had clinical evidence of HF and the probability of HF increased dramatically with increasing duration of morbid obesity.

Despite the known adverse effects of obesity on both systolic and particularly diastolic CV function in the epidemiological data showing a strong link between obesity, generally defined by BMI criteria, and HF, many studies have suggested that obese HF patients had a better prognosis.

In a recent meta-analysis of 9 observational studies (n=28,209) in which patients were followed up for an average of 2.7 years, Oreopoulos et al. showed that compared with individuals without elevated BMI, overweight and obese HF patients had reductions in CV (-19% and -40%, respectively) and all-cause (-16% and -33%, respectively) mortality. They have suggested that excess body weight may confer some protective effects on HF mortality. Because advanced HF is a catabolic state, obese patients with HF may have more metabolic reserve. Cytokines and neuroendocrine profiles of obese patients also may be protective. Adipose tissue produces soluble tumor necrosis factor-alpha receptors and could
play a protective role in obese patients with acute or chronic HF by neutralizing the adverse biological effects of tumor necrosis factor-alpha. Additionally, overweight and obese patients with acute and chronic HF have lower levels of circulating atrial natriuretic peptides. Obese patients with HF may have attenuated sympathetic nervous system and renin-angiotensin responses.

Because obese patients typically have high levels of atrial pressure, they may have a better prognosis in advanced HF and may tolerate higher levels of cardio protective medications.

**Obesity, CHD, and the Obesity Paradox**

Obesity plays a major role in adversely affecting major CHD risk factors, including HTN, dyslipidemia and diabetes mellitus (DM), is the major component of metabolic syndrome, and is probably an independent risk factor for atherosclerosis and CHD events. Although recent studies indicate that the various measures to define obesity are not all created equally regarding overall CV disease risk, the consensus is that compared with the traditional BMI assessments, the more refined modalities (e.g: WC, WHR, waist-to-height ratio, and so on) do not add significantly to the BMI assessment from clinical standpoint, although this has not been assessed for the obesity paradox.

Nevertheless, as with HTN and HF, many studies have also reported an obesity paradox in CHD, including in patients treated with revascularization. In a recent systematic review over 250,000 patients in 40 cohort studies followed up for 3.8 years, Romero- Corral et al. reported that overweight and obese CHD patients have a lower risk for total and CV mortality compared with underweight and normal-weight CHD patients. However, in patients with a BMI >35 kg/m2, there was an excess risk for CV mortality without any increase in total mortality.

**Obesity and Stroke**

Numerous studies have reported an association between BMI and stroke. In fact, for each I-U increase in BMI, there was an increase of 4% in the risk of ischemic stroke and 6% for hemorrhagic stroke. This increased risk of stroke may be attributable to a higher prevalence of HTN, a pro-thrombotic / pro-inflammatory state that accompanies excess adipose tissue accumulation, as well as increased AF.

**Obesity and Sleep Apnea**

Obesity is a classic cause of alveolar hypoventilation and the obstructive sleep apnea (OSA) syndrome. In fact, OSA may contribute to the pathogenesis of HTN and increased inflammation and CRP. Clearly, patients with OSA have increased risk of HTN, dysrhythmias, pulmonary HTN, HF, MI, Stroke, and overall mortality.

**Obesity and Venous disease**

The combination of increased intravascular volume and high volume lymphatic overload, as well as reduced physical activity, often lead to venous insufficiency and edema with increasing obesity. Additionally, obesity is associated with an increased risk for venous thromboembolism and pulmonary embolism, especially in women.

**Status of Weight Reduction**

Considering that some long term studies have shown that weight loss in overweight and obesity is associated with increased mortality coupled with many CV studies showing a better prognosis with a higher BMI, it has been suggested that purposeful weight loss may not be beneficial and may even be detrimental in patients with CV diseases.

In contrast, however, other studies assessing mortality based on body fat and lean mass rather than BMI or weight alone have suggested that subjects losing body fat rather than lean mass have a lower mortality. Clearly lifestyle interventions, including exercise training and at least mild weight reduction with caloric restriction, showed a nearly 60% reduction in the risk of developing DM, which was considerably better than that noted in patients treated with metformin.

The most studies non-pharmacologic therapy in CV disease for weight reduction has been cardiac rehabilitation and exercise training, which resulted in a 37% reduction in the prevalence of metabolic syndrome. In HTN weight reduction has resulted in significant decreases in arterial pressure.

**Conclusion**

Overwhelming evidence supports the importance of obesity in the pathogenesis and progression of CV disease. Although an obesity paradox exists, in that overweight and obese patients with established studies have shown that weight disease seem to have a more favorable prognosis than leaner patients, the constellation of data still support purposeful weight...
reduction in prevention and treatment of CV disease. Further research is needed in all of these areas, and if the current obesity epidemic continues, we may soon witness an unfortunate end to the steady increase in life expectancy.

**References**


