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The Impact of Obesity on Risk Factors and Prevalence and Prognosis of Coronary Heart Disease—The Obesity Paradox

Alban De Schutter[a], *Carl J. Lavie*[a,b,*], *Richard V. Milani*[a]

[a]*Ochsner Heart and Vascular Institute, Ochsner Clinical School–University of Queensland School of Medicine, New Orleans, LA*
[b]*The Department of Preventive Medicine, Pennington Biomedical Research Center, Louisiana State University System, Baton Rouge, LA*

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ABSTRACT

Obesity is associated with a host of cardiovascular risk factors and its prevalence is rising rapidly. Despite strong evidence that obesity predisposes to the development and progression of coronary heart disease (CHD), numerous studies have shown an inverse relationship between various measures of obesity (most commonly body mass index) and outcomes in established CHD. In this article we review the evidence surrounding the ≪obesity paradox≫ in the secondary care of CHD patients and the CHD presentations where a paradox has been found. Finally we discuss the impact of cardiorespiratory fitness and a number of mechanisms which may offer potential explanations for this puzzling phenomenon.

Obesity and Coronary Heart Disease (CHD) in primary prevention

Obesity is an increasing public health problem in the United States (US) and much of the developed world. Being overweight is defined by National Institutes of Health as a body mass index (BMI) ≥ 25 kg/m^2 and obesity as a BMI ≥ 30 kg/m^2. By these criteria, in 1960 approximately one in every ten Americans was obese, a number which has since tripled.[1] At the same time the proportion of the population which was overweight remained constant; currently the majority of the population is overweight or obese. Perhaps most concerning, morbid obesity (defined as ≥40 kg/m^2) has increased in prevalence from 1% of the population to 6%. The importance of obesity as a public health problem is difficult to underestimate; by some accounts[2] it is destined to take over smoking as the leading cause of preventable death in the US and it may halt[3] the improvements in life expectancy at a national level.

While in all likelihood obesity is a risk factor for CHD in itself, it is most importantly associated with a cluster of conditions that contribute directly and indirectly to the development and progression of CHD.[4,5] Obesity is associated with insulin resistance and type 2 diabetes mellitus (DM2),[6] through dietary indiscretion and endocrine activity of adipose tissue. This is illustrated by the fact that the increase in prevalence of DM2 has closely followed the rise of obesity.[7] DM2 is possibly the strongest CHD risk factor; it is characterized by the same 10-year risk for cardiovascular (CV) events as the population with known CHD.[8] It is also associated with endothelial dysfunction and dyslipidemias, both crucial to the initial steps in atherogenesis. In addition DM2 is one of the

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* Address reprint requests to Carl J. Lavie, M.D., FACC, FACP, FCCP, Medical Director, Cardiac Rehabilitation, Director, Exercise Laboratories, John Ochsner Heart and Vascular Institute, Ochsner Clinical School - The University of Queensland School of Medicine, 1514 Jefferson Highway, New Orleans, LA 70121-2483.
E-mail address: clavie@ochsner.org (C.J. Lavie).

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Abbreviations and Acronyms

BF = body fat

BMI = body mass index

CABG = coronary artery bypass graft

CHD = coronary heart disease

CO = central obesity

CRF = cardiorespiratory fitness

CV = cardiovascular

DM2 = diabetes mellitus type 2

FFM = fat-free mass

HDL-C = high-density lipoprotein cholesterol

HF = heart failure

HTN = hypertension

PCI = percutaneous coronary intervention

STEMI = ST-segment elevation myocardial infarction

TGs = triglycerides

US = United States

WC = waist circumference

WHR = waist-to-hip ratio

most common causes of renal dysfunction, which is an independent risk factor for CHD itself. In fact guidelines require cholesterol-lowering treatment to be as aggressive in DM2 as in individuals with known CHD, effectively treating the disease as equivalent to CHD.

Adipose tissue is an endocrine organ,[9] and, especially, central adiposity, has been associated with elevated levels of circulating proinflammatory cytokines, most notably interleukin 6 (produced by adipocytes) which stimulates platelet activity and secretion of C-reactive protein. In addition, elevated levels of tumor necrosis factor alpha in obesity have been implicated in the development of insulin resistance. Angiotensinogen produced by adipose cells is a precursor of the renin–angiotensin–aldosterone system and is likely implicated in the pathogenesis of obesity related hypertension (HTN). Fat cells produce plasminogen activator inhibitor 1, which shifts homeostasis away from physiologic fibrinolysis, increasing thrombosis.

Obesity and, more specifically, central obesity (CO) are essential components of the metabolic syndrome. MS is characterized by central obesity combined with certain diagnoses (including impaired fasting glucose, HTN, dyslipidemias), a combination shown to be strongly associated with early onset CHD, and future events.[10,11] Arterial blood pressure (BP) and prevalence of HTN, yet another risk factor for CHD, are elevated in obesity not only due to the endocrine effect but also due to increased circulating blood volume and total peripheral resistance.[12] Higher BMI and CO are associated with dyslipidemia, including low levels of high density lipoprotein cholesterol (HDL-C) and high levels of triglycerides (TGs) and higher levels of small, dense, atherogenic low density lipoprotein cholesterol.[13] Obesity is associated with poor self esteem and psychological stress, which in itself is an independent risk factor for CHD.[14]

Significant evidence supporting weight loss as a tool to reverse risk factors associated with obesity further underscores the importance of obesity in CHD. In particular, weight loss has been associated with a reduction in BP and TGs. Exercise, a frequently used tool in weight loss programs, has been associated with increased insulin sensitivity, decreases in proinflammatory cytokines and increases in cardioprotective HDL-C. In fact, purposeful weight loss through cardiac rehabilitation and exercise programs has directly been linked to a reduction in CV events and all-cause and CV mortality in randomized clinical trials.[15]

However, despite the evidence of causality between obesity and development of CHD, multiple studies have now indicated that obesity might be associated with a better prognosis in the secondary care of those afflicted with CHD,[16] in stark contrast with primary care.[17] This paradoxical effect has been coined the "obesity paradox". Aside from CHD, similar effects have been shown in many chronic diseases[18] including end stage renal disease,[19] heart failure (HF),[20] chronic obstructive pulmonary disease,[21] DM2,[22] HTN,[23] and atrial fibrillation.[4]

BMI paradox or obesity paradox

The obesity paradox has been most commonly described defining obesity by BMI, since it is a readily measured parameter in clinical practice. While the presentation of the CHD patient varies, the BMI–mortality curve is typically U-shaped, with increasing mortality at the extremes of obesity.[24] This relationship has been confirmed in many studies from all over the world,[25] with varying results in terms of optimal and most detrimental BMI range. In a large meta-analysis of 40 cohort studies by Romero-Corral[24] and colleagues with 250,000 patients with CHD, the authors noted an optimal adjusted mortality in the overweight (followed by the obese) subgroup. In contrast Das et al.[26] showed a BMI obesity paradox in a cohort of 50,000 patients with ST-segment elevation myocardial infarction (STEMI), favoring class I obesity (BMI 30–35 kg/m^2) with the lowest mortality. Dhoot et al.[27] noted an in-hospital, adjusted mortality benefit associated even with morbid obesity (BMI > =40 kg/m^2; when compared to <40 kg/m^2 aggregated) in 400,000 patients presenting with both STEMI and non-STEMI in 2009. Regardless of what the optimal BMI range is in which population,[28] one consistent result is that the typical National Institutes of Health range of ≪normal≫ BMI (20–25 kg/m^2) is not associated with the best outcome.

Despite its widespread use, BMI has received a lot of critique in terms of its accuracy to define obesity[29–32] in the CHD population. In fact it was suggested that its inaccuracy might be the cause of the obesity paradox, given the U shape of the adjusted BMI–mortality curve.[24,33] After all, BMI is an aggregate of varying amounts of fat free mass (FFM) and body fat (BF), each of which contributes in its own way to the metabolic profile of the subject. The overweight range, the nadir of the BMI-mortality curve found by Romero-Corral and colleagues in the meta-analysis, is a range where BMI correlates poorly with BF (r 0.17).[31] In addition, FFM enjoys a widespread acceptance as a positive prognostic factor. It is protective in the general population and by inference in the CHD population through its association with muscle strength,[34,35] nutritional status[36] and cardiorespiratory fitness (CRF). In 2009, researchers in Denmark[37] found an