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Cardiovascular disease in obesity: A review of related risk factors and risk-reduction strategies

Louis J. Aronne, MD,* W. Virgil Brown, MD, Kathy Keenan Isoldi, MS, RD, CDE

Weill-Cornell Medical College of Cornell University, New York, NY (Dr. Aronne); The Comprehensive Weight Control Program, 1165 York Avenue, New York, NY 10028 (Dr. Aronne and Ms. Isoldi); Emory University School of Medicine, Atlanta Veteran's Affairs Medical Center, Atlanta, GA (Dr. Brown)

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Abstract. Cardiovascular disease (CVD) is the number one cause of mortality in men and women. Currently, two thirds of US adults are overweight or obese. CVD and obesity are closely linked and together take a substantial toll on the health of individuals and the community. It is creating a growing burden on public health and financial difficulties in both personal and institutional funding of health care. A review of recent scientific literature reveals that modest weight loss of 5% to 10% ameliorates cardiometabolic risk factors and improves health outcomes. To date, successful weight-loss interventions have been elusive. The choice of weight-loss medications is limited, and the risks of surgical intervention demand that this option be reserved for those patients with extreme obesity. Research has elucidated an improved understanding of the mechanisms leading to obesity and disease. The potential role of hormones, such as leptin and adiponectin, in altering metabolism and vascular disease is better understood. The endocannabinoid system is now recognized as a potentially viable pathway to modulate appetite and energy, lipid, and glucose metabolism.

Cardiovascular disease (CVD) is the number one cause of mortality in the United States, and has been every year since 1900, with the exception of 1918 when a flu epidemic caused a high mortality toll. It is estimated that one in three adults in this country suffers from one or more types of CVD. Prevalence of CVD in the United States is expected to create an annual financial burden of more than $430 billion in 2007, due to both direct and indirect health-care costs.[1]

Prevalence of overweight and obesity has skyrocketed during the past few decades, and this is contributing to the overall cost of health care. The economic burden due to overweight and obesity in this country for direct costs, expressed in 2002 dollars, is estimated at $92.6 billion.[2] An increase in worksite injuries in obese employees has contributed to the indirect financial burden incurred from excessive body weight gain. Using data from the Duke Health and Safety Surveillance System, researchers report a clear linear relationship between body mass index (BMI; calculated as kg/m^2) and rates of workers' compensation claims, resulting in loss of productivity and increased absenteeism.[3]

The financial concern is only a small part of the total burden of overweight and obesity created by excessive weight gain. Obese individuals are at greater risk of developing heart disease, hypertension, cerebrovascular disease, type 2 diabetes mellitus, osteoarthritis, many forms of cancer, gallstones, nonalcoholic fatty liver disease, sleep apnea, and asthma.[4,5] Additionally, obese individuals are often stigmatized, experience depression, are targets of discrimination, and have lower scores on health-related quality-of-life surveys.[4–6]

Recent data estimate that two thirds of the adult US population are overweight, with a BMI $\geq$25 kg/m^2; >32%

* Corresponding author.
E-mail address: ljaronne@med.cornell.edu
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of adults meet the criteria for obesity, with a BMI ≥30 kg/m^2; and 4.8% are in the extreme obesity category, defined as a BMI ≥40 kg/m^2.[3] Unfortunately, the rise in obesity prevalence has not been confined to adults. Obesity has been on the rise in toddlers, children, adolescents, and teens, promoting the onset of risk factors for chronic disease in our youth. In the 1970s, obesity prevalence in children aged 2 to 19 years remained steady, at approximately 5%.[7] However, since 1980, there has been more than a threefold increase in obesity in the population under 20 years of age, with current estimates reporting a prevalence of 17.1%.[3]

Increases in incidence of insulin resistance, the metabolic syndrome, type 2 diabetes mellitus, nonalcoholic fatty liver disease, dyslipidemia, hypertension, left ventricular hypertrophy, atherosclerosis, "bowed legs," asthma, and obstructive sleep apnea have been reported, coinciding with rising childhood obesity rates.[8] The belief that development of CVD begins in childhood has been supported by recent data. Precursors to CVD have been identified in youth and young adults. Researchers have reported the appearance of fatty streaks and fibrous plaque—precursors to atherosclerosis—in the aorta and coronary arteries of adolescents and young adults during autopsies performed after accidental death.[9]

Experts predict that the health detriment imposed on children by excess body fat can result in today's youth being the first generation in more than 2 centuries to experience a reduction in life expectancy.[10,11] Data reported by Fontaine and colleagues[12] highlight the influence of excess body weight on the life expectancy of young adults. They reported that young white men aged 20 years with a BMI >45 kg/m^{2}are estimated to cut their life expectancy by 13 years, and white women in the same weight category are expected to lose 8 years of life. Young black men and women aged 20 years with severe obesity are estimated to reduce their life expectancy by 20 years and 5 years, respectively.[12] The need to curb obesity and prevent the financial and health burdens carried at both the individual and the community levels is apparent. This dire need for action has prompted the Robert Wood Johnson Foundation to commit to a $500 million initiative over the next 5 years to support research aimed at finding superior obesity prevention and treatment interventions to reverse the obesity epidemic in children.[11]

A large part of the increase in disease risk attributable to obesity, including CVD, is the effect of excessive fat mass on cardiometabolic risk factors, stemming from inflammatory processes. This article will review the connection between obesity, inflammation, increased cardiometabolic risk factors, and development of CVD. Current recommendations and realistic options for obesity treatment and CVD prevention will be discussed.

CVD risk factors

Dyslipidemia, hypertension, insulin resistance, and inflammatory markers are well-recognized as predictors of CVD risk. Elevated concentrations of total cholesterol and low-density lipoprotein cholesterol (LDL-C), as well as low concentrations of high-density lipoprotein cholesterol (HDL-C), are associated with risk for coronary heart disease (CHD). Prevalence rates of hypercholesterolemia (≥200 mg/dL), elevated LDL-C (≥130 mg/dL), and low HDL-C (<40 mg/dL) are estimated at 48.4%, 32.5%, and 16.7%, respectively, in US adults.[1] Several studies have found that elevations in LDL-C particle number are strongly associated with CHD and that the LDL particles are often small and more dense with reduced cholesterol content (measurements ≤25.5 nm), causing an underestimation of the number of LDL and underestimating their power as an independent risk factor.[13]

In addition, hypertension is quite common in US adults and contributes to development of CVD. It is estimated that one in three US adults has high blood pressure.[1] Prehypertension, defined as an untreated systolic blood pressure (BP) of 120 to 139 mm Hg, or an untreated diastolic BP of 80 to 89 mm Hg, affects an estimated 37% of the US adult population.[1]

As part of the Framingham Heart Study, Wilson and colleagues[14] investigated the long-term outcomes of overweight and obesity in risk factor development for CVD, as well as disease outcomes in >5000 men and women. Researchers prospectively followed participants aged 35 to 75 years for up to 44 years. Strong correlations were found between overweight and obesity and development of hypertension, angina pectoris, total CHD, and total CVD (Table 1).[14]

Recent evidence supports that atherosclerosis results from mechanisms other than dyslipidemia and lipid storage and is, in fact, initiated and promoted by an inflammatory process as well. It was observed decades ago that white blood cells adhere to the intact endothelium of early-stage atherosclerotic lesions. In animal studies, just 1 week after starting an atherogenic diet, proinflammatory cytokines and oxidized lipoproteins induced the release of vascular cell adhesion molecule-1; this adhesion molecule promotes adhesion of monocytes and lymphocytes to the intimal surface of the endothelium. Chemokine release promotes penetration of leukocytes into the vessel wall.[15]

Inflammatory mediators of disease

There is a strong association between fat-mass accumulation and disease promotion. Fat mass functions as an endocrine organ, secreting adipokines and free fatty acids (FFAs) that influence lipid metabolism, insulin sensitivity, vascular homeostasis, BP regulation, metabolism, inflammation, angiogenesis, and regulation of energy balance.[16] Metabolic and immune pathways are interconnected. Preadipocytes have been found to act as macrophages, therefore, fat mass influences innate immune function.[17,18] Obesity overactivates the immune system, creating a state of chronic low-grade inflammation.[16]