Editorial

Weighing in on obesity prevention and cardiovascular disease prognosis

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Considerable data has emphasized the importance of obesity in the overall development and prognosis of cardiovascular (CV) diseases (CVD) (1-3). Clearly, obesity has been increasing in epidemic levels in the United States (US) and most of the Westernized globe (4), with current statistics being especially alarming, including 39.6% of the US population now meeting criteria for obesity based on body mass index (BMI) criteria (BMI ≥30 kg/m^2) and even more alarming is that now 7.7% of the adult population meet criteria for severe, or class III, obesity, with BMI ≥40 kg/m^2 (5). Certainly, the marked increase in obesity is increasing almost all CVD, producing tremendous burden on our society and the healthcare system and could even threaten to reduce or reverse the welcome decline that has been occurring in CVD mortality trends during recent decades (1-5).

Obesity clearly has adverse effects on most of the major CVD risk factors, including increasing blood pressure and leading to increased risks of hypertension (HTN), worsening plasma lipids, especially increasing the levels of triglycerides and reducing the cardioprotective levels of high-density lipoprotein cholesterol, and changing the low-density lipoprotein cholesterol into a small, more dense particles that are associated with increased oxidation and atherosclerosis (1,2,4,6). Obesity also worsens blood sugar, which raises the risk of metabolic syndrome and diabetes mellitus, and adipocytes release cytokines that stimulate the liver to procedure inflammatory proteins, thus increasing levels of low-grade systemic inflammation (6). Although my colleagues and I have argued that low levels of physical activity (PA) and exercise may be the fundamental cause of gaining weight and obesity in the first place (7-10), obesity also leads to declining levels of PA and cardiorespiratory fitness (CRF) due to decrements in strength-to-weight ratio (i.e., larger and weaker individuals move less than smaller and stronger (9). Therefore, considering the "heavy" toll that obesity exerts on the CV system (*Figure 1*), not surprisingly, almost all CVD, including HTN, heart failure (HF), coronary heart disease (CHD) and atrial fibrillation are all increased in obesity (1-4,6,11). Additionally, obesity has adverse effects on cardiac structure and function, leading to high amounts of concentric remodeling and concentric and eccentric left ventricular hypertrophy, and increasing the prevalence of systolic, but especially, diastolic left ventricular dysfunction, which increases CVD, especially HF (1-4,6,11,12).

In a recent issue of Clinical Chemistry, Ndumele and colleagues (13) from the Atherosclerosis Risk in Communities (ARIC) study followed over 900 subjects and demonstrated a higher young adulthood to midlife weight, as well as obesity history (lifetime BMI), increased the likelihood of having elevated levels of high-sensitivity cardiac troponin, in turn associated with an increased risk of developing future HF. This is not totally a surprise, considering the very marked effects of obesity to adversely affect CV hemodynamics and increase levels of "cardiac stretch", as well as adversely increase cardiac structural and functional abnormalities (*Figure 1*) (1-4,6). The release of cardiac troponin, which indicates subclinical myocardial damage, as demonstrated in the current manuscript in patients with obesity, and more so longstanding obesity or many years of obesity, adds additional information to the adverse effects of obesity on the CV system and, potentially,

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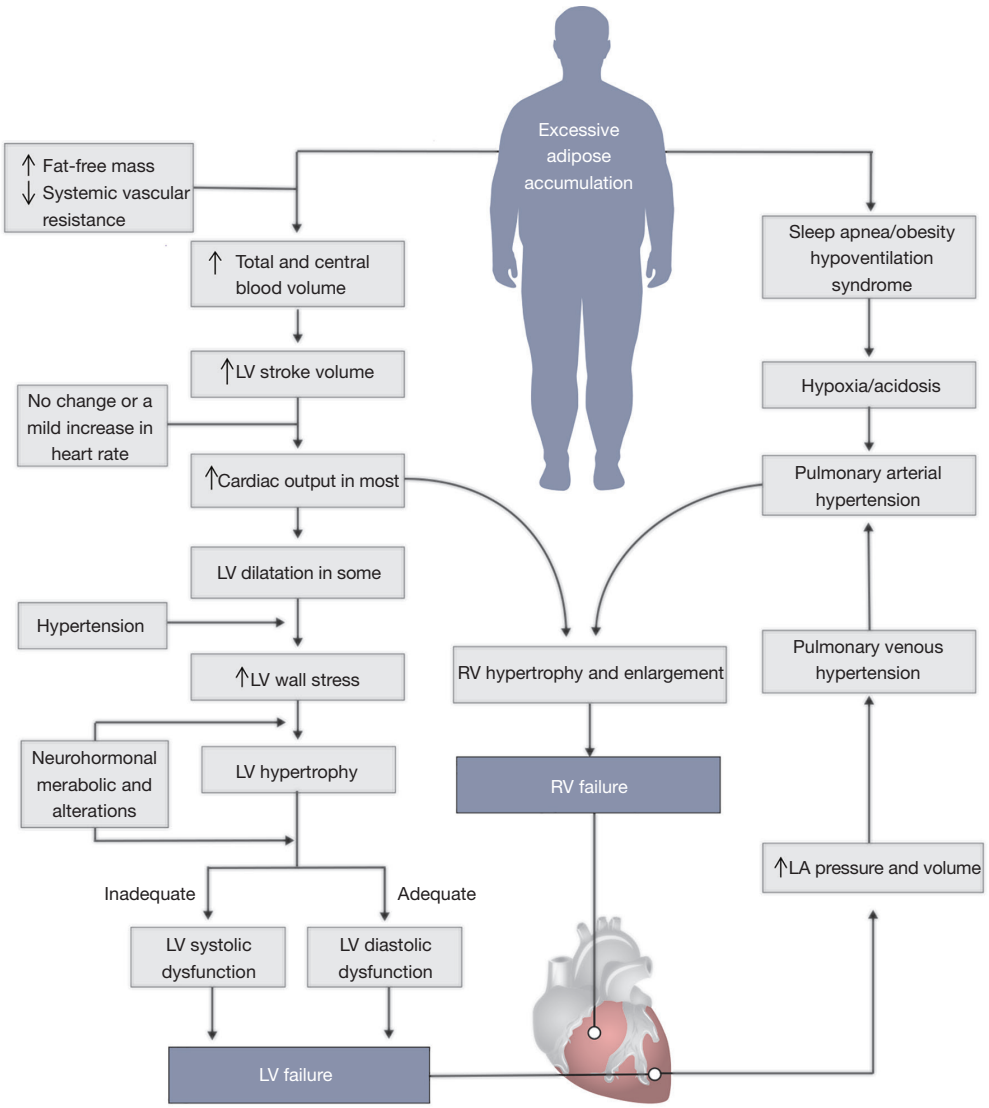

Figure 1 This diagram shows the central hemodynamic alterations that result from excessive adipose accumulation in severely obese patients and their subsequent effects on cardiac morphology and ventricular function. Left ventricular (LV) hypertrophy in severe obesity may be eccentric or concentric. Factors influencing LV remodeling and geometry include severity and duration of obesity, duration and severity of adverse LV loading conditions (particularly HTN), and, possibly, neurohormonal and metabolic abnormalities such as increased sympathetic nervous system tone, activation of the renin-angiotensin-aldosterone system, insulin resistance with hyperinsulinemia, leptin resistance with hyperleptinemia, adiponectin deficiency, lipotoxicity, and lipoapoptosis. These alterations may contribute to the development of LV failure. LV failure, facilitated by pulmonary arterial HTN from sleep apnea/obesity hypoventilation, may subsequently lead to right ventricular (RV) failure. CVD, cardiovascular disease; LA, left atrial. Reproduced with permission from Lavie *et al.* (4).

on increasing CVD risk, especially HF.

Two other high-profile recent reports have also focused on the impacts of obesity to increase most CVD (14,15). Khan and colleagues (14) recently in JAMA Cardiology assessed the lifetime risks of CVD and subtypes of CVD across 10 large US populations with 3.2 million person years of follow-up and demonstrated that obesity was associated with shorter longevity and significantly increased risk of CVD morbidity and mortality compared with normal BMI. Overweight individuals, despite having similar longevity

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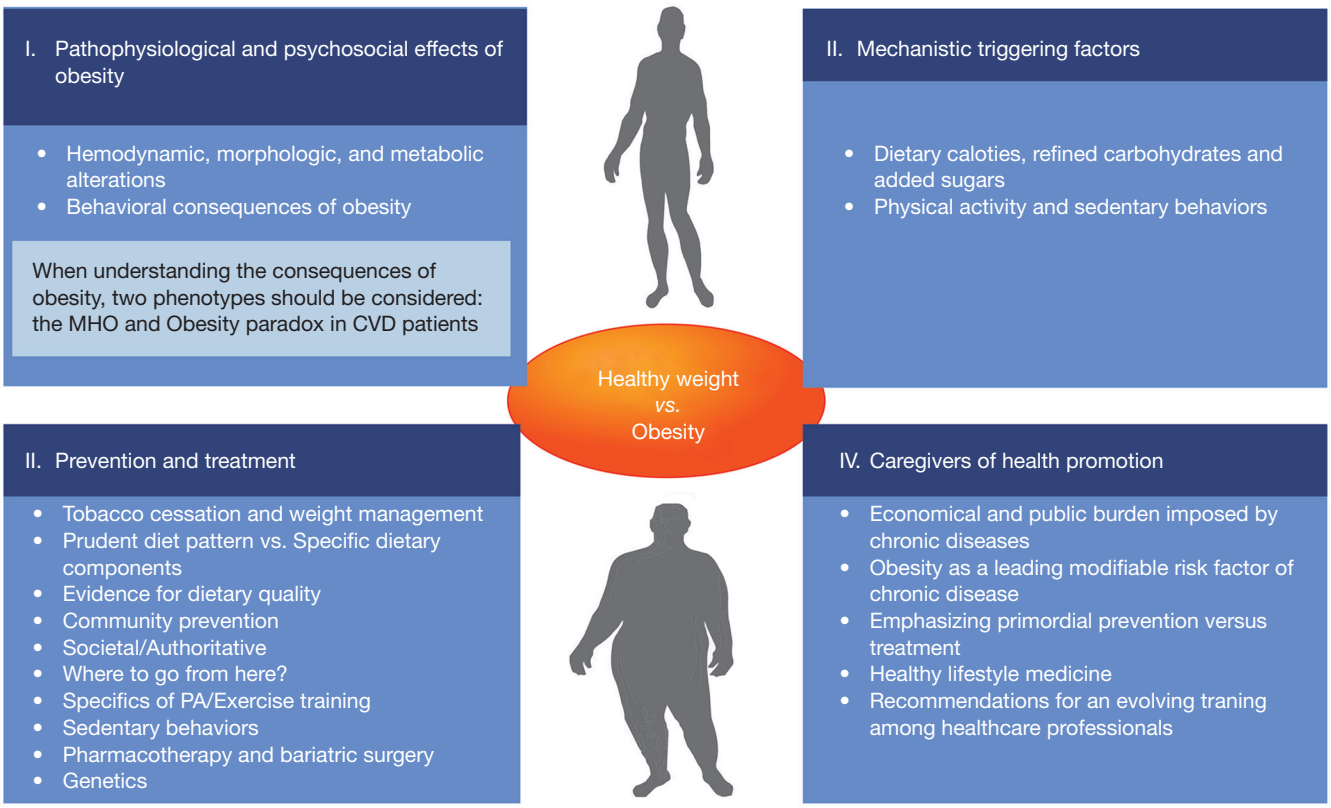

Figure 2 A schematic for the management of obesity to optimize long-term prevention and treatment. Reproduced with permission from Lavie *et al.* (4).

compared with normal BMI subjects, had significantly increased risk of developing premature CVD, resulting in greater proportion of life lived with CVD.

Likewise, Iliodromiti and colleagues (15) in a recent study in European Heart Journal assessed nearly 30,000 Europeans without CVD and determined that increased adiposity, determined by BMI, but even more so with higher % body fat and waist circumference (WC), had a detrimental association with CVD health in middle-aged men and women.

Although both of these studies by Khan *et al.* (14) and Iliodromiti *et al.* (15) made suggestions that there was no "obesity paradox", we have emphasized that despite the impact of obesity to increase CVD, there is still substantial evidence of an obesity paradox, meaning that among patients with established CVD, the overweight and at least mildly obese seem to have a better prognosis than do their leaner counterparts with the same CVD (1-4,6,16,17). In fact, our research has emphasized the importance of CRF to improve prognosis across the lifespan, and among the patients with CVD and preserved CRF, the prognosis is generally quite favorable (18-20). Importantly, only among those with low CRF is an obesity paradox present when defining obesity using BMI in HF (21) and for BMI, % body fat and WC for CHD (22), with the heavier patients with low CRF having a better prognosis than do the leaner CVD patients with low CRF (21,22).

There has also been substantial attention directed at metabolically healthy obesity (MHO), suggesting the patients with MHO often become unhealthy over time and have an increased risk of CVD (23-25). Although clearly remaining lean and metabolically healthy throughout the lifespan would be ideal, substantial evidence also suggests that having a preserved CRF also impacts the MHO, with the patient with MHO and high CRF having a very favorable long-term prognosis (23-26).

Nevertheless, one of us (CJ Lavie) has recently led a JACC Promotion Series on healthy weight and prevention of obesity (*Figure 2*) (4). Certainly, greater efforts are needed at primordial prevention of obesity in the first place, as well

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as preventing overweight and obese from gaining more weight during their life time. A multimodality approach is needed to accomplish these goals, with long-term efforts to reduce caloric intake, and increase PA, exercise, and levels of CRF in primary and secondary prevention of obesity (4). Likewise, overweight and obese who maintain high levels of CRF usually have a favorable cardiac prognosis despite their weight (1-4,6,18), and despite still presenting an increased risk for HF (1-4). We, therefore, emphasize the role of prevention regarding personal, educational/environmental, and societal/authoritative factors, as well as efforts to provide guidance for caregivers of health promotion, regarding healthy weight and prevention of obesity.

In the study from ARIC by Ndumele and colleagues (13), they did not include an assessment of CRF, which likely would have affected their results. Nevertheless, these results provide further support for preventing obesity in the first place (primordial prevention) and reducing the lifetime BMI for the primary and secondary prevention of CVD (4,13). Clearly, increasing PA, exercise training and levels of CRF throughout the lifespan would go a long way to accomplish these goals (1-4,6,18-20,23-26). In fact, these ARIC investigators had previously shown that high PA significantly attenuated the risk of subclinical myocardial damage, being highest in obese/low PA and lowest in non-obese/ recommended PA (27), further supporting the importance of PA and weight management in the prevention of CVD, especially HF.

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