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Effect of Obesity on Cardiovascular System: Literature Review

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ABSTRACT

Cardiovascular diseases (CVD) are the leading cause of global morbidity and mortality. Besides imparting a tremendous amount of human suffering, they also inflict huge direct and indirect financial costs on the worldwide society. With the ready availability of affordable therapeutics globally, and the lack of newer innovations, lifestyle interventions are gaining importance to further control this epidemic. Obesity, a lifestyle factor, is consistently and strongly related to a higher risk of CVD incidence and mortality. Therefore, maintenance of optimal weight has become an important goal in the quest for improved CVD health worldwide. This paper reviews the relationship between obesity and cardiovascular diseases.

KEYWORDS: Obesity; Cardiovascular disease; Obesity paradox; BMI; Coronary artery disease

INTRODUCTION

Both excess weight and cardiovascular diseases are globally on the rise. Obesity inflicts a significant harmful effect on cardiovascular diseases. This results in an enormous amount of human suffering, many premature and untimely deaths, and huge financial costs. Attaining and maintaining an optimal body mass index (BMI) is therefore an important goal in reducing this obesity-related plague of CVD morbidity and mortality. This manuscript briefly reviews the global obesity epidemic and its direct and indirect effect on the number one killer in the world – cardiovascular diseases.

THE OBESITY PANDEMIC

Obesity, a growing global health problem [1], has become a dangerous pandemic [2]. According to the World Health Organization (WHO), in 2016, more than half of the world's adult population had an elevated BMI, with 39% being overweight and 13% being obese [3]. According to them, there were more than 1.9 billion adults aged 18 years and older who were overweight in 2016 [4]. Children and adolescents are also experiencing excessive weight gain [5, 6]. WHO reported that in 2016, 41 million children worldwide under the age of 5 were overweight or obese; while over 340 million children and adolescents aged 5–19 were overweight or obese [7]. The collaborative groups of the Global Burden of Disease Study examined data from 68.5 million children and adults between 1980 and 2015 from over 195 countries and territories and found that the prevalence rate of obesity had increased in most countries and had doubled in more than 70 countries [8]. This enormous increase in excess body weight was associated with 4 million deaths, with cardiovascular disease accounting for two-thirds of these deaths [8]. It is expected that by 2030, more than 2.16 billion people will be overweight and 1.12 billion obese in the world [9].

The obesity epidemic has been especially noticeable in the industrialized countries. Obesity in the US has increased from a prevalence of 36.5% in 2011–2014 [10], to a prevalence of 42.4% in

2017-2018 [11]. Severe obesity (body mass index (BMI) ≥ 40 kg/m^2) and morbid obesity, (BMI ≥ 50 kg/m^2) increased 4-fold, and >10-fold, respectively, during the last quarter-century [12]. Obesity is now the second leading cause of preventable premature death in the US, after smoking [13], and may soon become the first [14]. It is expected to negate the gain in US life expectancy which resulted largely from a decline in smoking [15]. In 2014, Europe had an overall obesity prevalence in adults of 15.9% [16]. In Italy, the prevalence of obesity is 20% today and has risen from approximately 7% in the 1970s [17]. Spain is also struggling with excess body weight, with approximately 41% of children aged between 6 and 9 years being overweight/obese in 2015 [18]. Eastern Europe has alarming statistics – 55.5% of Hungarians aged 15 years and older are now overweight or obese [19]. In the Eastern Mediterranean Region, the prevalence of obesity has increased from 15.1% in 1980 to 20.7% in 2015 [20].

The obesity burden is also affecting the less developed countries [21-24]. In 2010–2012 the prevalence of overweight and obesity in Chinese adults was 30.1% and 11.9%, respectively [25]. In India, the prevalence of overweight and obesity is increasing rapidly [26-28], and it is estimated that by 2030, 27.8% of all Indians would be overweight, and 5.0% obese [29]. China, India, Pakistan, and Indonesia are now in the top 10 countries with the highest populations of obesity in the world [30]. Obesity has also been increasing at an alarming rate among African countries [31]. Eastern Sudan has a prevalence of 26.8% for overweight and 32.2% for obesity [32]. Uganda has a 17.8% prevalence of overweight [33], while in Ethiopia, overweight/obesity increased significantly from 10.9% in 2000 to 21.4% in 2016 [34]. Africa's child population is expected to become the largest child population among all continents in 2055, reaching 1 billion [35]. Unfortunately, these children are also rapidly becoming obese [36]. According to UNICEF, WHO, and the World Bank, Southern Africa has the highest prevalence of overweight among children under 5 years (14.6%), followed by Central Asia (11.6%) and Northern Africa (11.0%) [37].

Obesity is growing irrespective of the age, population and ethnic groups, and socioeconomic status of the individuals [38]. It is expected to continue rising in the coming decades [39]. The overweight/obesity pandemic and its health-related ramifications have resulted in grave economic consequences, with the world spending billions of dollars on this disorder [40].

ANTHROPOMETRIC MEASUREMENTS FOR BODYWEIGHT

stronomer and mathematician Alphonse Quetelet (Belgian mathematician, astronomer, and statistician) developed the Quetelet Index in 1832, which was subsequently termed the body mass index or BMI (weight (kg/height (m^2)) in 1972 by Ancel Keys (1904-2004) [41]. BMI is nowadays, a widely used measure to define bodyweight.42 BMI is categorized into several groups: < 18.5 kg/m^2 (underweight), 18.5–24.9 kg/m^2 (normal weight), and 25 to 29.9 kg/m^2, (overweight). Obesity is defined as a BMI exceeding 30 kg/m2 and is subclassified into class 1 (30–34.9 kg/m2), class 2 (35–39.9 kg/m2), and class 3 or severe obesity (≥ 40 kg/m2).2 A BMI >50 Kg/m^2 is considered morbid obesity [42]. Asian populations differ from European populations in the percentage of body fat, and health risks [43], and the International Obesity Task Force recommends different BMI categories for them [44]. These are: underweight (<18.5 kg/m^2), normal (between 18.5 and 23 kg/m^2), overweight (between 23 and 25 kg/m^2), obese (between 25 and 30 kg/m^2), and severely obese (≥30 kg/m^2).

OBESITY AND NON-CVD HEALTH IMPLICATIONS

Elevated BMI is associated with several chronic diseases [45]. These include: asthma [46], several cancers (icluding those of the esophagus, colon and rectum, liver, gallbladder and biliary tract, pancreas, breast, uterus, ovary, kidney, thyroid, and blood - leukemia) [47], depression (obese adolescents have a 40% greater risk of being depressed) [48], end-stage renal disease [49], gall bladder disease [50], gout [51], hyperuricemia [52], obstructive sleep apnea [53], osteoarthritis [54,55], nonalcoholic fatty liver disease [56], and poor quality of life [57]. Higher morbidity in obese individuals has also been reported in children and adolescents [58]. Obesity is associated with a rise in disability-adjusted life-years [59] and increased all-cause mortality [60-62]. Obesity is also a strong predictor of CVD risk and greatly influences its clinical course [63].

THE CVD EPIDEMIC

CVDs include high blood pressure (HTN), coronary heart disease (CHD), stroke, heart failure (HF), cardiac arrhythmias, peripheral arterial disease (PAD), deep vein thrombosis (DVT), and atherosclerotic erectile dysfunction (ED) [64,65]. The present global prevalence of hypertension of 26% is projected to rise to 29% by the year 2025 [66]. HTN is an independent predisposing factor for several other CVDs and increases CVD mortality [67]. Coronary artery disease is the most prevalent CVD [68], with a global prevalence of 2%–3% [69]. CHD is the leading cause of death of all diseases, and was responsible for an estimated 8.92 million deaths, globally, in 2015 [70]**.** It is expected that 82% of the future increase in coronary heart disease mortality will occur in developing countries [71]. The primary cause of CHD is atherosclerosis which results from a diseased endothelium, low-grade inflammation, lipid accumulation, and plaque formation within the intima of the vessel wall [72]. This can progress into a flow-limiting stenosis of the large epicardial coronary arteries, resulting in ischemia [73]. Plaque rupture or erosion can provoke superimposed atherothrombosis and subsequent vessel occlusion, leading to a myocardial infarction, and even death [74]. Stroke is prevalent all over the world

[75]. According to WHO, 15 million people worldwide suffer a stroke every year, and kill about 3 million women and 2.5 million men [76]. Stroke is the third most common cause of death globally and results in enormous disabilities in those who survive [77]. HF affected about 40 million people in the world in 2015 [78]. It is estimated that 2% of all adults have heart failure and the rates are increasing [79]. Heart failure severely reduces the quality of life [80]. The mortality can be as high as 10% each year [81]. Cardiac arrhythmias are extremely common [82]. Atrial fibrillation affects about 2% to 3% of the population[83] and puts the affected individuals at a greater risk for embolic stroke [84] and heart failure [85]. SCD is usually due to ventricular arrhythmias and accounts for almost half of all deaths due to CVD [86]. PAD is present in more than 200 million people in the world [87]. It is seen in 7–14 % of the general population [88]. PAD usually involves the legs and is an atherosclerotic disease [89]. and results in about 52,500 deaths annually (2015 data) [90]. Epidemiological studies indicate that ED affects approximately 11% of men over 30 years of age and 37% of the men over 70 years of age [91]. Atherosclerosis of the pelvic and penile vasculature is the major underlying cause [92]. Erectile dysfunction is a strong predictor for other cardiovascular diseases, including coronary artery disease [93]. DVT of the lower extremities is a common venous disease and is associated with significant morbidity and exhibits a high rate of recurrence [94]. Venous thromboembolism is the third most common cause of vascular mortality worldwide, accounting for 5.4 million deaths annually [95].

Combined, these diseases are the leading cause of morbidity and mortality in the world [96]. They cause approximately one-third of all deaths worldwide [97]. They are associated with immense human suffering [98], and are one of the leading causes of disability-adjusted life years (DALYs) [99], and impart a huge financial burden globally [100]. It is expected that CVDs will continue to rise globally in the coming years [101].

ANTHROPOMETRIC MEASUREMENTS FOR CVD

Fat amount and fat distribution is more important for CVD risk and can be missed by BMI measurement alone [102]. Central obesity is associated with a higher CVD risk [103]. In the EUROASPIRE III study, the prevalence rate of central obesity in CVD patients was 53% [104]. Central obesity can be objectively ascertained by several anthropometric measurements [105-107]. These include the waist circumference (WC), waist-hip ratio (WHR), and the weight height ratio (WHtR) [106, 107]. WC should ideally be <102 cm in males and <88 cm in females when measured to the nearest 0.1 cm at the umbilical level in a standing position [105]. In the Asian populations, these numbers are <85 cm for males and, <80 cm for females [108]. Higher values indicate central obesity. Many researchers have also used another anthropometric measurement, WHR (normal is 0.85 or less for women and 0.9 or less for men) for determining central obesity [36]. The WHO advises that a WHR of more than 1.0 increases CVD risk [106]. The WHtR is calculated as WC divided by height. (< 0.5 indicates no central obesity) and ≥ 0.5 is considered to be consistent with central obesity) [107]. Bhatt and group found that central obesity was an indicator of metabolic disorders in 53% of CVD individuals [109]. Rost and group found that another measurement, the body adiposity index (BAI = [(hip circumference (cm)/height (m)1.5) − 18] × 100) and WHtR of males and WC and WHR of females were associated with an increased risk of CVD mortality [110]. It may be therefore prudent to monitor all these measurements, in patients to get a more reliable appraisal of central obesity and CVD risk [111].

OBESITY AND CVD

The EUROASPIRE III study (across all 22 participating countries in Europe) found a 35% prevalence rate of obesity based on BMI in CVD patients [104]. Most of the available studies have used obesity in their research on the connection between excess body weight and CVDs.

Obesity deleteriously affects CVDs is several ways:

OBESITY AND HTN

There is a strong relationship between obesity and HTN [112, 113]. Weight gain is associated with an increase in arterial pressure [114] and this relationship appears to be linear [112]. Obesity may result in a 3.5-fold increase in the likelihood of being hypertensive, and obesity may be responsible for 60-70% of HTN in adults [115]. The increasing prevalence of HTN has therefore been linked to the global obesity epidemic [116]. The dramatic increase in body weight in children and adolescents may also explain the increasingly higher prevalence of HTN being noted in this population [117]. Obese children are at a two-fold higher risk of developing HTN compared to normal-weight children [118]. Weight reduction is associated with a significant decrease in arterial pressure in hypertensives [119]. Obesity surgery also reduces arterial blood pressure [120]. Obesity increases renal sodium absorption, impairs natriuresis and these lead to extracellular volume expansion and elevated blood pressures [121].

OBESITY AND CHD

Obesity is an independent risk factor for CHD [122]. Weight gain increases the risk of CHD events and CHD mortality [123]. Coronary artery calcification (CAC) scores are associated with increased CVD events [124] and obesity is a risk factor for CAC, irrespective of metabolic disorders [125]. One recent study indicated that obese patients were twice as likely to have CHD after adjustment for demographics, smoking, physical activity, and alcohol intake [126]. Obesity also results in more complex, raised, and hi-grade atherosclerotic coronary artery lesions [127]. These

plaques demonstrate greater macrophage infiltration and higher plaque instability [128]. Following coronary artery bypass grafting, obese patients show a higher incidence of deep sternal wound infections [129]. Obese patients with CHD, also exhibit higher risks of mortality and unsatisfactory neurological recovery following a cardiogenic arrest recovery [126]. Weight loss in obese CHD patients results in marked improvements in several CHD risk factors, (such as hypertension, C-reactive protein (CRP), lipids, and glucose) [130], a lower incidence of CHD events [131], and reduced CHD mortality [131]. Cardiac rehabilitation is associated with weight loss, and in obese patients, it is associated with significant lowering of CRP levels [132]. Obesity increases several CHD risk-factors, including hypertension, hyperlipidemia, and diabetes mellitus, which contribute to the increased CHD noted in these patients [133]. They also show systemic chronic low-grade inflammation, and this contributes further to CHD related atherosclerosis [134].

OBESITY AND STROKE

Numerous studies have reported an association between an elevated BMI and stroke [135] and this association appears to be linear [135]. Data from the Nurses' Health Study indicate a >2-fold increase in the risk of ischemic stroke and 1.6-fold increase in the risk for total stroke among women with BMI ≥32 kg/m^2 compared with women with BMI <21 kg/m^2 [136]. The Physicians' Health Study showed a significant increase in the risk of total, ischemic, and hemorrhagic stroke with increasing BMI [137]. Men with BMI ≥30 kg/m^2 had a >2-fold risk increase for stroke [137]. In a study of >39,000 healthy women, those with BMI ≥35 kg/m^2 had a 2-fold increase in the risk of total stroke and an almost 3-fold increase in the risk of ischemic stroke compared with women with BMI <20 kg/m^2 [138]. For each 1-U increase in BMI, there is an increase of 4% in the risk of ischemic stroke [135, 137]. This association is linear and affects both men and women, regardless of race [139]. Although the increase in ischemic stroke appears to be well established in obese individuals, the association of the latter with hemorrhagic stroke remains unclear [140]. In a study by Kurth and group, BMI was not a strong risk factor for hemorrhagic stroke [138]. In UK, women with higher BMI demonstrated an increased risk of ischemic stroke but showed a decreased risk of hemorrhagic stroke [141]. The increased risk of stroke results from a higher prevalence of HTN, AF, diabetes mellitus (DM), dyslipidemia, increased inflammation, and a proinflammatory state in obese patients [142, 143].

OBESITY AND HF

Obesity is a known independent risk factor for HF [144], and this relationship is incremental [145]. Approximately 29–40% of all HF patients (both with reduced and preserved ejection fraction) are overweight and 30–49% are obese.[146] However, >80% of HF patients with preserved ejection fraction are overweight or obese [147]. In the Framingham Heart Study of 5881 patients, there was an increase of HF prevalence of 5% in men and 7% in women for every 1-unit increase in BMI [148]. Morbid obesity is associated with a 5-fold higher risk of incident HF [149]. Severely obese patients with BMI ≥ 40 kg/m^2, have higher rates of pump thrombosis and acute kidney injury following a left ventricular assist device (LVAD) implantation [150]. Obese heart transplant patients have earlier high-grade acute rejection and a higher 5-year mortality when compared to heart transplant patients who were normal weight or overweight [151]. Bariatric surgery-related weight loss in HF patients improves ejection fraction and results in a significant reduction of their New York Heart Association classification [152]. Obesity is associated with HTN, DM, metabolic syndrome, and dyslipidemia, all of which are risk factors for CHD, and can lead to HF [153]. Elevated BMI is known to induce deleterious left ventricular remodeling [154].

OBESITY AND CARDIAC ARRHYTHMIAS

Atrial fibrillation is more common in obese patients [155]. Wanahita et al. reviewed 5 population-based studies (78,602 patients), and found that obese patients had a nearly 50% increased risk of developing AF [156]. In the Women's Health Study, patients who became obese had a 41% increased risk of developing AF compared to those who did not become obese [157]. In both studies the risk of AF escalated with increasing BMI [156, 157]. In the Women's Health Study, there was a 4.7% increase in AF risk with each 1 kg/m2 unit increase in BMI [157]. It is estimated that about 18% of cases of AF could be prevented by achieving an optimal body weight [158]. Sudden cardiac death (SCD) is an unexpected death that occurs within one hour of symptoms onset [159]. Structural heart disease or primary electrical abnormalities of the heart lead to pulseless electrical activity in the heart, ventricular fibrillation, ventricular tachycardia, or asystole, precipitating SCD [160]. SCD was increased in apparently healthy obese patients in the Framingham Heart Study [161, 162]. Annual SCD rates are nearly 40 times higher than in a matched nonobese population [163]. Obesity results in atrial remodeling, with hemodynamic, structural, and electrical derangements of the atria [164], that are similar to the structural and electrical changes that have been identified in patients with structural disease [165-167]. The increased electrical ventricular irritability noted in obese patients may lead to more frequent and complex ventricular dysrhythmias, and this may explain the higher prevalence of sudden cardiac death in this population [168]. Weight loss in overweight animals has been shown to improve electrophysiologic, structural, and histologic cardiac characteristics [169].

OBESITY AND AORTIC STENOSIS

An elevated BMI is positively related to aortic stenosis [170, 171].

In 2014, two studies reported high BMI was associated with an increased risk of aortic valve stenosis [172, 173]. In 2017, Larsson and group showed a dose-response positive relationship between self-reported elevated BMI and risk of aortic valve stenosis [170]. A recent study published in 2020, found a similar relationship [171]. Calcific aortic valve disease in obese patients probably represents an atherosclerotic process, the latter being associated with traditional atherogenic risk factors and pathologically demonstrating lipoprotein deposition, chronic inflammation, and active leaflet calcification [174, 175].

OBESITY AND PAD

High BMI increases the risk of developing PAD [176]. Four out of five people with PAD are overweight or obese [177]. In the Framingham Heart Study (3,313 patients, 53% were women), each 5-point increase in BMI (equivalent to a change from being slightly overweight to being obese) made a person 40% more likely to develop PAD [178]. Obesity is causally associated with PAD after controlling for the potential intermediate factors like hypertension, dyslipidemia, and hyperglycemia [179]. PAD in obese patients is more ominous [180]. It not only increases non-fatal coronary events but also doubles the overall mortality and cardiovascular mortality over ten years if PAD is accompanied by obesity, when compared to the general population [181]. PAD may progress to critical leg ischemia[182] and this increases the risk of hospitalizations and lower extremity amputation [183]. Many researchers have noted a J-shaped association or a U-shaped association of BMI with PAD [184]. Atherosclerotic plaques limiting the blood flow are usually the cause of PAD [185]. Obesity is associated with increased inflammation, which is a major factor in the development of atherosclerosis [186]. Obese patients often have associated DM [187], dyslipidemia [188] and/or hypertension [112], and these also help drive PAD in these patients

OBESITY AND ED

Obesity is an independent risk factor for ED [189]. Men experience an increased relative risk of 1.5 to 3.0 for ED if their BMI is more than 25 [190]. In the European Male Ageing Study, ED was present in 36.7% of obese men while it affected only 24.8% of healthy weight men [191]. Similar findings were reported by Sarwer et al. who found that 36% of men undergoing bariatric surgery had ED [192]. Non-surgical weight improves erectile function in obese men [193]. Bariatric surgery-related weight loss also helps reverse erectile function [194]. Obesity, and in particular central obesity, reduces testosterone levels and is associated with atherosclerotic ED [195].

OBESITY AND VENOUS DISEASE

DVT of the lower extremities is a common venous disease and is associated with significant morbidity and is plagued with a high rate of recurrence [196, 197]. Venous thromboembolism (VTE) is the third most common cause of vascular mortality worldwide and comprises DVT and pulmonary embolism (PE) In clinical practice, about two-thirds of VTE episodes manifest as DVT and one-third as PE with or without DVT. Immobilization is an important risk factor for DVT.198 Obese individuals are more likely to have protracted hospital immobilization which is conducive for the development of DVT [199]. They are also more likely to be less physically active, and physical activity aimed at the leg musculature, engaging the calf muscle pump, also help reduce post-thrombotic syndrome and venous ulceration [200, 201]. A high BMI, in the INVENT consortium study evaluating 52,632 individuals, was associated with venous thromboembolism (DVT and PE combined) [202]. Obesity is associated with an increased intravascular volume and high-volume lymphatic overload, and this combined with the reduced physical activity seen in obese patients, leads to venous insufficiency, edema, and increased VTE [203].

Obesity is associated with factors such as increased intra-abdominal pressure, chronic low-grade inflammation, increased fibrinogen levels with impaired fibrinolysis, and elevated clotting factor levels. These further contribute to the increased risk for VTE in these individuals [204].

OBESITY AND CVD RISK FACTORS

Obesity is also associated with many CVD risk factors, such as DM [187], dyslipidemia [188], metabolic syndrome [205], obstructive sleep apnea [206], systemic inflammation [207], atherosclerosis [208], depression [209], and end-stage renal failure [210]. These further contribute to the CVD related morbidity and mortality seen in obese patients [211-213].

OBESITY AND CVD MORTALITY

Obesity, is associated with increased CVD mortality [211-213], both in young individuals [214], and adults [215].

CVD BENEFITS OF WEIGHT LOSS

Weight loss is inevitably paralleled by an improvement of other cardiometabolic risk factors [216-218]. Weight loss helps reduce several major cardiovascular events [219]. Bariatric weight loss procedures demonstrate significant CVD risk reduction and mortality reduction, while often eliminating numerous comorbidities and improving the patient's quality of life [220].

OBESITY PARADOX

Despite the clear evidence that obesity results increase the risk of CVD morbidity and mortality, there exists a phenomenon called the 'obesity paradox' The latter has been coined as clinical observations reveals that there is often a better cardiovascular survival in obese patients when compared with normal weight and underweight individuals. The obesity paradox has been noted in HTN [221], CAD [222], AF [223], pulmonary arterial hypertension [224], ST-elevation myocardial infarction [225], and HF [226].

Studies have found that patients demonstrating the obesity paradox have increased lean mass, despite the obesity, and a better cardiorespiratory fitness [227], and these may explain the phenomenon. Other mechanisms may also be involved [228].

CONCLUSION

Elevated BMI is directly associated with increased CVD risk. Central obesity, a stronger predictor of CVD health, maybe missed by BMI measurement alone. Hence WC, WHR, and WHtR should also be used to determine the risk in obese patients. Studies have demonstrated that weight loss, including that following bariatric surgery, improves CVD risk and positively modulates CVD morbidity and mortality.

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