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EFFECT OF OBESITY ON CARDIOVASCULAR DISEASES

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Abstract:

Obesity is a major health problem globally. It is directly linked with with an increased cardiovascular risk and obesity and also brings up other medical conditions (hypertension, diabetes, insulin resistance, and sleep apnoea syndrome). Obesity has major role in atherosclerosis and coronary artery disease. It leads to structural and functional changes of the heart, which directly or indirectly causes heart failure. The change in myocardial structure enhances the possible chance of atrial fibrillation and sudden cardiac death. However, obesity also has a protective effect on the clinical outcome of underlying cardiovascular disease, the phenomenon called obesity paradox. In this review, we attempt to summarize the relationship between obesity and cardiovascular diseases and outline the underlying mechanisms.

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INTRODUCTION:

Obesity has been a health problem of growing significance all over the world; its prevalence is increasing in both developed and developing countries [1]. According to WHO numeric conclude that 39% of population above 18 years of age are overweight and of these, 13% are obese. Many studies have demonstrated a relationship between obesity and cardiovascular diseases (stable coronary disease, acute myocardial infarction, heart failure, cardiac arrhythmias, and sudden cardiac death). The association between obesity and hypertension, diabetes mellitus, dyslipidaemias, and sleep apnoea syndrome has also been shown to increase the incidence of cardiovascular disorders [2]. Body mass index (BMI) is used for measuring the extent of obesity; however, it gives no information on fat distribution, which is of high significance in cardiovascular risk [3]. So that, novel clinical quantification (e.g., abdominal circumference and the calculation of waist/hip ratio) have been introduced with the aim of characterizing central or abdominal obesity. In the case of men abdominal circumference above 102 cm and in the case of women above 88 cm are eligible as central obesity and involves increased cardiovascular risk [4]. Ratio above 0.9 of waist/hip in the case of men and above 0.85 in the case of women specifies central obesity [5]. In the previous three decades, many details of the pathophysiological processes of obesity and atherosclerosis have been revealed. Previously, both diseases had been regarded as lipid storage disorders with triglyceride accumulation in the fat tissue and cholesterol esters in atherosclerotic plaques. Nowadays, both obesity and atherosclerosis are considered chronic inflammatory conditions, in which the activation of both nonspecific and adaptive immune processes is assigned a significant role [6, 7]. The pathogenesis of obesity and atherosclerosis has several common factors. In both cases, lipids, oxidized LDL particles, and free fatty acids activate the inflammatory process and trigger the disease. Inflammation is responsible for all the steps towards atherosclerosis, from early endothelial dysfunction to the atherosclerotic plaques causing complications, and is related to obesity, insulin resistance, and type 2 diabetes. Moreover, the increased level of C-reactive protein is associated with an increased risk of myocardial infarction, peripheral vascular disease, and diabetes mellitus [8]. Interestingly, a clinical study performed on obese women confirmed that body weight reduction achieved through lifestyle changes reduces the level of inflammatory biomarkers and insulin resistance. In the course of the process, adiponectin, an anti-inflammatory and insulin sensitizing adipocytokine, is released [9]. Obesity and Coronary Artery Disease

Obesity is closely interconnected to coronary atherosclerosis. A study performed on young patients showed that atherosclerosis begins several decades before manifested coronary artery disease. Patients with higher BMI values are more often and advanced in their atherosclerotic vascular lesions as compared to subjects with normal body weight [10]. According to longitudinal studies, at least two decades of obesity is likely to be an independent risk factor of coronary artery disease [11]. A 10 kg rise in body weight increases the risk of coronary artery disease by 12% and at the same time, systolic blood pressure rises by 3 mmHg and diastolic by 2.3 mmHg as a consequence [12] (Figure 1). Furthermore, in the case of non-ST segment elevation myocardial infarction (NSTEMI) affecting young people, excess weight can be considered the most important risk factor, ahead of smoking. The higher the BMI, the sooner NSTEMI develops [13]. The same relationship can also be observed in the case of ST elevation myocardial infarction (STEMI). Based on the data available, obesity is an independent risk factor of STEMI developing at a young age but at the same time excess weight can also be related to other vascular events. An increase in BMI by one unit causes a 4% rise in the risk of ischemic and a 6% rise in haemorrhagic strokes [14]. Obesity and Heart Failure The frequency of heart failure is increasing; it is one of the major causes of death globally with a prevalence of approximately 3% in developed countries. A close correlation can be observed between heart failure and obesity. According to data from the Framingham Heart Study, the rise of BMI by 1 kg/m2 increases the risk of heart failure by 5% in the case of men and 7% in the case of women [15]. Studies on heart failure show that 32%–49% of patients suffering from heart failure are obese and 31%–40% are overweight. In the case of obese and overweight patients, heart failure develops 10 years earlier than in the case of subjects with a normal BMI. The duration of morbid obesity is closely correlated to the development of heart failure: after 20 years of obesity, the prevalence of heart failure grows by 70% and after 30 years, the prevalence rises by 90% [16]. The significance of obesity is indicated by the fact that the Framingham Heart Study emphasized the pathogenic role of obesity for the development of heart failure in 11% of males and 14% of females [17]. Both structural and functional changes of the heart observed in obesity alone come up with worsening in myocardial function, which is also known as “obesity cardiomyopathy” . There could be many direct or indirect mechanism that leads to heart failure. Excess weight leads to haemodynamic changes. A rise in both cardiac output and blood pressure has been observed; an increase in

BMI of 5 kg/m2 involved a 5 mmHg rise in systolic blood pressure [18]. On one hand, it is related to the activation of the renin-angiotensinaldosterone system and on the other hand, to the increased activity of the sympathetic nervous system. Obesity increases both the aldosterone level and the mineralocorticoid receptor expression, which promote interstitial cardiac fibrosis, platelet aggregation, and endothelial dysfunction. The above mechanisms explain the results of EMPHASISHF trial: eplerenone therapy was more beneficial for treatment of heart failure with reduced ejection fraction in patients with abdominal obesity [19]. Increased blood volume facilitates venous backflow, which enhances ventricular preload causing increased ventricular wall tension and ultimately leading to ventricular dilatation. Abdominal obesity is associated with subclinical left ventricular dysfunction [20]. Hypertension increases left ventricular afterload, which raises the danger of structural and electrical myocardial remodelling. This process ultimately leads to left ventricular hypertrophy and to diastolic and later to systolic ventricular dysfunction [21]. Inflammatory cytokines (TNF-α, IL-1, IL-6, IL-8, etc.), whose production is increased in obesity, also play an important role in the development of heart failure . The inflammatory mediators and acute-phase proteins in circulation cause myocardial fibrosis, which increases myocardial stiffness and may thereby lead to diastolic and later to systolic heart failure [22]. Through their effect on metabolism, tissue structure, and the extracellular matrix, leptin and adiponectin contribute directly to the myocardial transformation. The integrity of skeletal muscle mass is crucial for retaining the physical activity. Diet-induced obesity has been shown to promote muscle atrophy and catabolism. This process plays an important role in the progression of CVD in obese patients [23]. Moreover, obesity has been shown to increase the chances of heart failure not only by itself but also through the associated medical comorbidities. The frequently appearing insulin resistance reduces the contractility of the myocardium, while it enhances the activity of the renin-angiotensin-aldosterone system, which can result in hypertrophy and apoptosis of cardiac myocytes and to myocardial fibrosis [24]. Alterations in lipid metabolism enhance atherosclerosis and thereby the risk of ischemic cardiomyopathy.

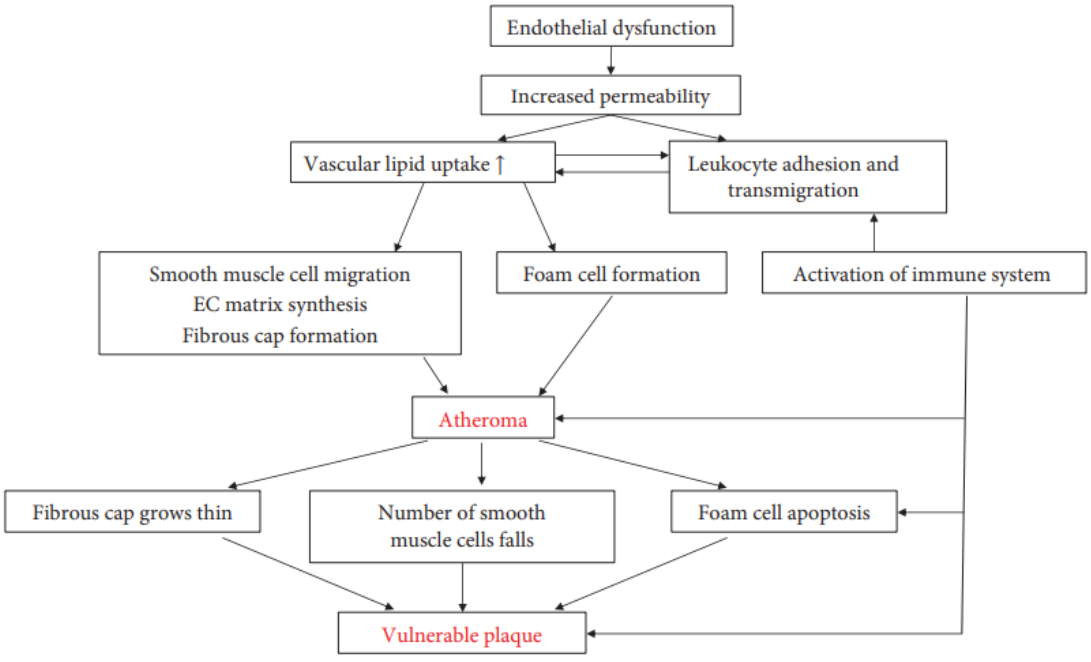

FIGURE 1: The pathomechanism of coronary artery disease in obesity.

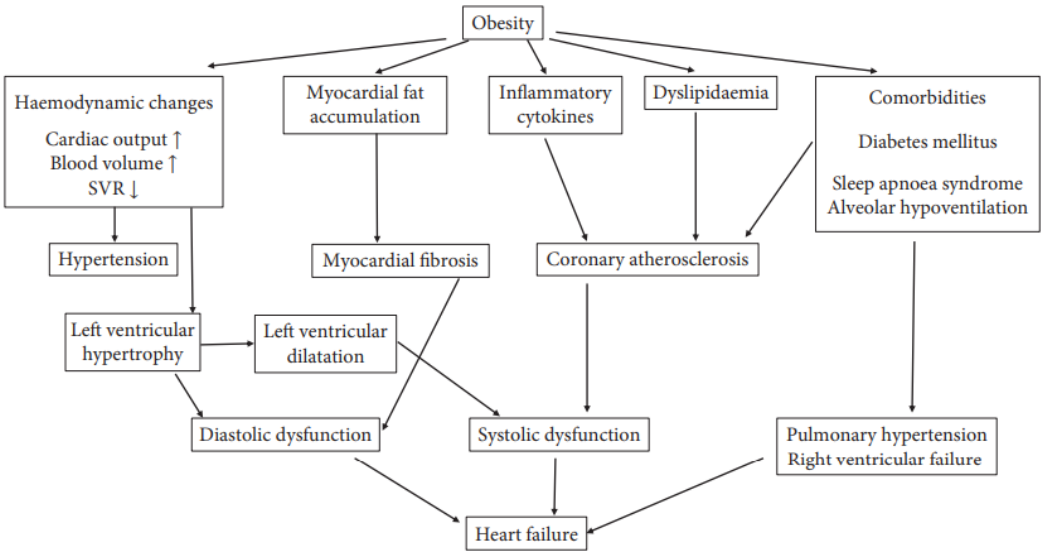

FIGURE 2: The pathomechanism of heart failure in obesity.

Major independent risk for coronary artery disease is Obesity Myocardial lipid accumulation and enhanced fibrosis can also play a pathogenic role in the genesis of various cardiac arrhythmias, which may contribute to the development of heart failure [25] (Figure 2). Hippocrates concluded in the 4th century already that "sudden death is more common in those who are naturally fat than in the lean.

Among the cardiac arrhythmias, atrial fibrillation has the highest clinical significance. Its incidence and prevalence is increasing worldwide, affecting 1–2% of the adult population. Atrial fibrillation is responsible for about one third of the hospitalizations due to arrhythmias; it significantly increases morbidity, mortality, and health care expenditure. Over 6 million Europeans suffer from this type of arrhythmia, and this number is estimated to double in the next fifty years [26]. The occurrence of atrial fibrillation shows a correlation with age; its frequency among people aged 40–50 is under 0.5%, while it rises to 5–10% by the age of 80 years. Various studies have proven the relationship between obesity and atrial fibrillation. Obese patients have a 1.52 times higher risk for the development of atrial fibrillation compared to the normal weight population [27]. A 1-unit rise in BMI increases the frequency of newly developed atrial fibrillation by 4%. At the same time, in patients with atrial fibrillation, there is an increased risk for sudden cardiac death, stroke, thromboembolic complications, and heart failure. Moreover, atrial fibrillation lengthens hospitalization and worsens quality of life and physical capacity [28]

Left atrial dilation and dysfunction are known consequences of obesity. A 5 mm increase in left atrial cross diameter has been shown to raise the chances of paroxysmal atrial fibrillation 1.39 times [29]. Furthermore, recent studies have confirmed the correlation between increased epicardial fat tissue and atrial fibrillation. Through its paracrine effect, epicardial fat contributes to the development of atrial interstitial fibrosis. The increased epicardial fat, the infiltration of myocardium with adipocytes, and fibrosis together result in a heterogeneous atrial pulse conduction, e.g., anisotropy, which contributes to endo- and epicardial electrical dissociation [30-31]. All these processes facilitate the development of atrial reentry, which serves as the electrophysiological background of atrial fibrillation. Increased adipocyte necrosis triggers macrophage, neutrophil, and lymphocyte infiltration as well as the accumulation of proinflammatory cytokines [32]. It has also been proven that atrial fibrillation in obese patients shortens the refractory period of the atrial and pulmonary vein myocardial cells. Enhanced adiposity triggers alterations in the ECG, too: higher amplitude P waves with lengthened duration, longer PR time, and P wave terminal force. Remarkably, similar changes were registered in cases of congestive heart failure, hypertension, and myocardial infarction. However, the pathogenic role of complex signalisation pathways (TGF, cTGF, and endothelial system) in atrial fibrosis is not yet precisely elucidated [33].

Excess weight and obesity are associated with an increased risk of cardiovascular diseases. This is a

consequence on the one hand of obesity itself and on the other hand of associated medical conditions (hypertension, diabetes, insulin resistance, and sleep apnoea syndrome). In case of already established cardiovascular diseases, the mortality of overweight and obese patients is often lower than that of people with a normal body weight, which is known as "obesity paradox." The exact mechanism of the latter is not clear yet. Considering the increased cardiovascular risk, the regular cardiology screening, and control of still symptom-free obese patients is important for the early diagnosis and treatment of subclinical medical conditions.

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