PANEVĖŽIO KOLEGIJA ISSN 2029-1280, eISSN 2669-0071. Taikomieji tyrimai studijose ir praktikoje – Applied Research in Studies and Practice, 2023, 19.

OBESITY AS A CARDIOVASCULAR RISK FACTOR

Austėja LIEPONYTĖ[a], Karolis LIČKŪNAS[a], Jurgita LIEPONIENĖ[b]

[a]Lithuanian University of Health Sciences, Lithuania
[b]Panevėžio kolegija/State Higher Education Institution, Lithuania

Abstract. The escalating global prevalence of obesity presents a significant public health challenge, leading to the development and progression of various cardiovascular disorders and escalating mortality rates. Obesity-induced dysregulation of adipocytes, inflammation, and oxidative stress significantly contributes to atherosclerosis and coronary heart diseases, especially in individuals with visceral obesity. Obesity acts as a catalyst for hypertension, mediated by mechanisms involving sympathetic nervous system overactivity, renin-angiotensin-aldosterone system stimulation, and elevated leptin levels, resulting in sodium reabsorption, water retention, and hypertension. Additionally, obesity induces adverse changes in left ventricular parameters, heightening the risk of heart failure, increases the likelihood of atrial fibrillation through various mechanisms and is directly associated with heightened cardiovascular mortality.

Keywords: obesity, overweight, cardiovascular risk, atherosclerosis, coronary heart disease

According to the World Health Organization (WHO), obesity is defined as excess or abnormal fat accumulation that presents a risk to health (World Health Organization, 2021). A body mass index (BMI) over 25 is considered overweight, and over 30 is obese (World Health Organization, 2021) while central obesity is defined as waist circumference > 102 cm and > 88 cm and waist-to-hip ratio ≥ 0.90 and ≥ 0.85 for men and women respectively (Medina-Inojosa et al., 2022). The rising prevalence of obesity has emerged as a profound public health concern, reaching epidemic proportions globally. The WHO estimated that in 2016 more than 1.9 billion adults were overweight (39 % of the population) and over 650 million (13 % of the population) were people with obesity (Cercato & Fonseca, 2019). This escalating phenomenon is accompanied by a concurrent increase in the incidence of cardiovascular diseases (CVDs), which represent the leading cause of global mortality, accounting for approximately 17.5 million deaths annually and constituting roughly 32 % of all global fatalities (Mirzaei et al., 2020). As an intricate and multifaceted entity, obesity is now unequivocally recognized as a potent risk factor for the development and progression of multiple CV pathological disorders leading to the increased risk of CVDs and mortality (Perone et al., 2023). Obesity is linked to numerous diseases of the cardiovascular system, including stroke, venous thromboembolic disease, and pulmonary hypertension, as highlighted by Powell-Wiley et al. (2021). This link is not only limited to the prevalence of these diseases but also extends to the underlying pathophysiological mechanisms that drive them. With an increasing understanding of these mechanisms, novel insights into therapeutic strategies and preventative measures may be revealed, paving the way for more effective management of obesity-related CVDs and ultimately alleviating the burgeoning burden of cardiovascular morbidity and mortality worldwide. Through this endeavor, we aim to contribute to the evolving field of cardiometabolic research and advance our collective knowledge of this pivotal healthcare issue.

The goal of this research is to determine the impact of obesity on the pathophysiology of CVDs, including atherosclerosis, coronary heart disease (CHD), hypertension, heart failure (HF), atrial fibrillation (AF) and cardiovascular (CVD) mortality.

The objectives of the research are:

1. Determine the mechanisms through which obesity is associated with the atherosclerotic process.
2. Identify the role of obesity in the pathogenesis of heart failure.
3. Investigate whether obesity is linked to an increased risk of atrial fibrillation.
4. Establish the associations between obesity and cardiovascular morbidity and mortality worldwide.

Research methods. To perform a comprehensive search on the correlation between obesity/overweight and cardiovascular risk we searched publications in the PubMed, UpToDate and MEDLINE databases and the inclusion and exclusion criteria were applied. The reports relevant to the topic present within the last 10 years and the papers available in the English language alone were selected. Both animal and human studies were referenced. The documents were also searched manually and obtained from Google Scholar. The following search terms (or combination of terms) were used: ‘obesity’, ‘overweight’, ‘cardiovascular risk’, ‘cardiovascular diseases’, ‘cardiovascular risk factor’, ‘atherosclerosis’, ‘coronary heart disease’, ‘hypertension’, ‘heart failure’, ‘atrial fibrillation’, ‘cardiovascular disease mortality’. Alternative searches for cardiovascular disease, coronary heart disease, heart failure and atrial fibrillation were CVD, CHD, HF and AF respectively. Two investigators (A. L. and K. L.) independently performed the literature research. From all the results garnished, the titles and abstracts were analysed for their relevance to the topic and only those that specifically addressed the topic were included in the final reference list.

OBESITY-INDUCED SYSTEMIC INFLAMMATION, ATHEROSCLEROSIS AND CORONARY HEART DISEASE

The adipocyte dysregulations, present in obese and overweight individuals, appearing as increased levels of pro-inflammatory/atherogenic adipokines and decrease of anti-inflammatory/atheroprotective adipokines, are contributing factors to the imbalance of body homeostasis (Cercato & Fonseca, 2019). Pro-inflammatory adipocytokine expression promotes recruitment and proliferation of pro-inflammatory macrophages and may lead to tissue damage and oxidative stress (Lopez-Jimenez et al., 2022). As a result, the vascular endothelium is left unable to optimally regulate vascular tone, hemostasis, and vascular inflammation, leading to the inception and progression of atherosclerosis (Cercato & Fonseca, 2019; Medina-Inojosa et al., 2022). The objective expression of this process can be observed as increased high carotid intima media thickness (cIMT) - an intermediate outcome in the pathogenesis of atherosclerosis (Turer et al., 2018).

The accumulation of fatty acids gives rise to oxidative stress, which, in turn, precipitates a cascade of consequences, including inflammation, insulin resistance, endothelial cell apoptosis, and the onset of atherosclerosis, (Sobczak et al., 2019). Additionally, the united action of aldosterone, neprilysin, and leptin, in synergy with heightened sympathetic nerve activity, culminates in sodium retention, expansion of plasma volume, hypertension, impaired vascular endothelial function, and ultimately, the development of atherosclerosis. Within the Framingham Health Study, findings reveal that individuals grappling with obesity, particularly those harboring visceral fat accumulation and elevated free fatty acid levels, confront a 50 to 60 percent escalated risk of atherosclerotic cardiovascular disease in comparison to their non-obese counterparts (Henning, 2021).

Both atherosclerotic disease and metabolic dysfunction are specifically associated with upper body and visceral adipose tissues. The accumulation of visceral fat is associated with the excessive storage of triglycerides within the myocardium and the presence of localized fat depots in the epicardium and pericardium, both of which are correlated with the development of coronary stenosis, myocardial infarction, and an increased risk of mortality (Henning, 2021). Data derived from the Copenhagen General Population Study, encompassing more than 70 000 adults with a median follow-up period of 3.6 years, highlights those individuals falling within the overweight or obese BMI categories, but without metabolic syndrome, exhibit a higher risk of myocardial infarction compared to those within the normal BMI range without metabolic syndrome. Specifically, the adjusted hazard ratio (HR) for overweight individuals is 1.26 (95percent CI 1.0-1.61), and it rises to 1.88 (95percent CI 1.3-2.6) for obese individuals (Medina-Inojosa et al., 2022). In a similar vein, a separate study conducted among individuals free of established cardiovascular disease at the study's inception, with consideration for the presence or absence of metabolic abnormalities, has uncovered that obese patients without metabolic abnormalities face an increased risk of coronary heart disease. The multivariate-adjusted hazard ratio (HR) in this context stands at 1.49 (95percent CI 1.45-1.54) when compared to individuals with a normal weight and no metabolic abnormalities (Medina-Inojosa et al., 2022).

So, obesity-induced dysregulation of adipocytes, characterized by inflammation and oxidative stress, significantly contributes to atherosclerosis and coronary heart diseases, particularly in individuals with visceral obesity, highlighting the critical importance of addressing adipocyte dysfunction in preventing obesity related coronary events.

OBESITY AND HYPERTENSION

Obesity is a known causative factor in the development of hypertension (Shariq & McKenzie, 2020). A study by Sabine van Oort et al observed a significantly higher odds ratio of essential hypertension for higher BMI (OR per 1 SD increase, 1.42) (van Oort et al., 2020), while the Swedish Obesity Study observed that at the study's commencement, roughly 50percent of individuals with obesity exhibited hypertension (Medina-Inojosa et al., 2022).

The mechanisms involved include sympathetic nervous system (SNS) overactivity, stimulation of the renin-angiotensin-aldosterone system (RAAS), alterations in adipose-derived cytokines such as leptin, insulin resistance, and structural and functional renal changes. SNS activation in obesity is triggered by abnormal adipokine secretion, RAAS stimulation, insulin resistance, and baroreceptor dysfunction. Furthermore, obesity often coexists with obstructive sleep apnea (OSA), leading to chronic intermittent hypoxia and activation of carotid body chemoreceptors, which reflexively upregulate SNS activity (Shariq & McKenzie, 2020).

Individuals with obesity commonly exhibit higher levels of plasma renin activity, angiotensinogen, angiotensin-converting enzyme (ACE), and aldosterone relative to their lean counterparts. The activation of the Renin-Angiotensin-Aldosterone System (RAAS), coupled with concurrent structural and functional alterations in the renal system, encompassing physical compression of the kidneys, lead to increased renal sodium reabsorption and water retention. These combined effects culminate in intravascular volume expansion, a pivotal precipitating factor in the genesis of hypertension (Shariq & McKenzie, 2020).

Obesity is further linked to elevated blood pressure, a result of elevated leptin levels. Leptin plays a role in regulating nitric oxide production and stimulating the sympathetic system, ultimately leading to sodium retention, systemic vasoconstriction, and an increase in blood pressure (Cercato & Fonseca, 2019).

In conclusion, obesity serves as a well-established catalyst for hypertension, underpinned by mechanisms encompassing sympathetic nervous system overactivity, stimulation of the renin-angiotensin-aldosterone system, and

elevated levels of leptin. These intricate pathways converge to intensify sodium reabsorption, water retention, and ultimately, hypertension in individuals with obesity.

OBESITY AND HEART FAILURE

Being overweight or obese is associated with blood volume overload and higher cardiac output, contributing to adverse structural and functional changes in the left ventricular parameters such as a high end-diastolic volume and increased left ventricular filling pressure. Increased intravascular volume and neuro-humoral mechanisms lead to left ventricular diastolic dysfunction and left ventricular hypertrophy (LVH), which predispose an enhanced incidence of HF (Medina-Inojosa et al., 2022) (Lopez-Jimenez et al., 2022).

Based on the findings of a prospective investigation that examined the association between higher BMI and the occurrence of heart failure, coronary heart disease and stroke, it was revealed that obesity amplifies the risk of developing HF by nearly fourfold (Ndumele et al., 2016). A study conducted as part of the Nord-Trøndelag health examination in Norway yielded similar outcomes. The research indicated that when adjusting for age and sex, the hazard ratio (HR) for heart failure in obese individuals – both metabolically healthy and metabolically unhealthy – was 1.6 and 1.7 for men and women, respectively, when compared to metabolically healthy participants with a normal weight (BMI <25 kg/m^2) (Mørkedal et al., 2014).

Moreover, an analysis stemming from the Framingham Heart Study, involving 5,881 participants with no prior history of HF, over a follow-up period averaging 14 years, displayed a twofold increase in the risk of HF in subjects with obesity as opposed to those without obesity (Bastien et al., 2014). Upon adjusting for established risk factors such as hypertension, CHD, diabetes, and left ventricular hypertrophy (LVH), it was observed that for every 1 kg/m^2 increment in BMI, there is a 5 percent amplification in risk observed among men, and a 7 percent escalation among women (Medina-Inojosa et al., 2022).

To sum up, overweight and obesity induce elevated blood volume and cardiac output, leading to detrimental alterations in left ventricular parameters, including increased end-diastolic volume and filling pressure. These changes, associated with left ventricular diastolic dysfunction and hypertrophy, substantially enhance the risk of heart failure.

OBESITY AND ATRIAL FIBRILLATION

Atrial fibrillation is another condition that has a significantly higher chance of development in obese individuals than those with a normal BMI (Spragg, 2023).

The primary mechanism responsible for this development may be associated with left atrial enlargement, common in obese individuals. This often leads to increased left atrial pressure and volume causing a shortened effective refractory period in the left atrium, proximal and distal pulmonary veins as well as diastolic dysfunction. Pericardial fat and inflammation are thought to contribute as well (Spragg, 2023).

As a result, studies have shown about a 5 percent risk increase of AF for every surplus unit of BMI even after adjustment for inflammatory markers (Spragg, 2023) (US Preventive Services Task Force et al., 2020). After the assessment of dynamic risk, it was concluded that adjusted short-term increase in the risk of AF development can be associated with both overweight (HR 1.22) and obesity (HR 1.65). Compared to normal weight patients, a short-term increase in BMI >25 kg/m^2 was attributable to a total of 18.3percent of AF cases while becoming obese during the first 60 months showed a 41percent adjusted risk increase of AF development ($p = 0.02$) in contrast to individuals who maintained a BMI below 30 kg/m2 (US Preventive Services Task Force et al., 2020).

Recent studies have also unveiled that alterations in one's lifestyle, incorporating weight reduction, can mitigate the recurrence and severity of atrial fibrillation (Lopez-Jimenez et al., 2022). Data from the “REVERSE-AF” trial have demonstrated that a 3percent to 9percent reduction in weight, achieved through guidance from healthcare professionals and lifestyle management, leads to the transformation from persistent AF to paroxysmal AF or no AF in roughly 49percent of the individuals involved. Clinical outcomes become even more notable with substantial weight reduction, as individuals achieving a reduction of 10percent or more in body weight exhibit an 88percent reversal from persistent AF to paroxysmal AF or no AF (Lopez-Jimenez et al., 2022). Moreover, it should be noted that bariatric surgery has been associated with a diminished incidence of new-onset AF as well as the reversal of existing AF (Lopez-Jimenez et al., 2022).

In summary, obesity significantly elevates the risk of atrial fibrillation (AF) through mechanisms such as left atrial enlargement, pressure changes and pericardial fat. A higher BMI is directly associated with AF risk, even after adjusting for additional factors, although lifestyle modifications, including weight loss, offer a promising approach to reducing AF severity and recurrence.

OBESITY AND CARDIOVASCULAR DISEASE MORTALITY

Elevated body weight represents a substantial risk factor not only to morbidity, but also to mortality, contributing to approximately 4.0 million fatalities on a global scale in 2015. Nearly 70 percent of the mortality attributed to elevated BMI is ascribed to cardiovascular disease, and more than 60 percent of these fatalities are concentrated within the obese population (GBD 2015 Obesity Collaborators et al., 2017).

Obesity's impact on life expectancy varies, with class III obesity (BMI ≥ 40 kg/m^2) resulting in an average reduction of approximately 10 years, and class I obesity (BMI 30–34.9 kg/m^2) decreasing it by about 3 years compared to individuals with a normal weight. A BMI exceeding 25 kg/m^2 shows a robust positive correlation with a heightened risk of CVD mortality, particularly affecting coronary heart disease and ischemic stroke. Mendelian randomization studies consistently establish a causal link between lifelong higher BMI, especially when accompanied by a high percentage of body fat, and an increased risk of CVD mortality, aortic valve stenosis, and various other cardiovascular diseases (Lopez-Jimenez et al., 2022).

The impact of abdominal obesity on CVD mortality was studied in a cohort of 44,636 women participating in the Nurses' Health Study. The relative risk significantly increased from the lowest to the highest waist circumference quintiles (1.00, 1.04, 1.04, 1.28, and 1.99 respectively), even after accounting for BMI and other confounding variables over 16 years of follow-up. Notably, this association remained significant even among women with a normal weight (BMI 18.5 to < 25 kg/m^2) (Medina-Inojosa et al., 2022).

Furthermore, individuals with elevated BMI or central obesity are at an increased likelihood of experiencing prolonged QT intervals, a factor that has been suggested as a potential mechanism for sudden cardiac death (SCD) in individuals with obesity. This risk factor compounds the already elevated risk of CVD mortality (Medina-Inojosa et al., 2022).

In summary, obesity significantly amplifies cardiovascular morbidity and mortality risks globally. Higher body mass index, especially in obesity, reduces life expectancy and is causally linked to increased cardiovascular mortality. Abdominal obesity independently heightens cardiovascular mortality risk, emphasizing the urgent need for targeted interventions to mitigate these adverse outcomes.

CONCLUSIONS

Obesity triggers systemic inflammation and oxidative stress, promoting the atherosclerotic process and escalating the occurrence of coronary heart events in individuals with obesity.

Obesity contributes to elevated total blood volume through diverse mechanisms, resulting in hypertension and eventually causing structural and functional alterations in the left ventricle, manifesting as heart failure.

Higher BMI is independently linked to increased atrial firbillation risk, even after accounting for other factors, highlighting the significance of lifestyle changes such as weight loss.

Obesity significantly heightens global cardiovascular morbidity and mortality risks, reducing life expectancy, particularly in cases of high body mass index and abdominal obesity, which are causally linked to increased cardiovascular mortality.

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