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Review Article

Obesity: A Key Causative Factor in Cardiovascular Disease Development

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Abstract

Obesity and cardiovascular diseases have become one of the most pressing public health challenges of the 21st century, garnering widespread attention worldwide. Adipose depot expansion can occur through either an increase in the size of adipocytes (hypertrophy) or the generation of new adipocytes via precursor differentiation during adipogenesis (hyperplasia). Hypertrophy of adipocytes in obesity causes increased hypoxia, triggering fibrosis, inflammation, and necrosis, which contribute to systemic complications, including coronary artery disease, heart failure, and stroke. Furthermore, enlarged adipocytes release pro-inflammatory cytokines like TNF-α and IL-6, driving chronic inflammation that contributes to atherosclerosis, increasing the risk of heart attacks and strokes. We aim to discuss recent insights into the mechanisms by which obesity leads to cardiovascular diseases, which will provide new perspectives for the treatment of obesity and cardiovascular diseases.

Nonstandard abbreviations and acronyms

AGEs: Advanced Glycation End Products; AMP: AMP-Activated Protein Kinase; AMPK: AMP-Activated Protein Kinase; BMI: Body Mass Index; CVD: Cardiovascular Disease; FFAs: Free Fatty Acids; HDL: High-Density Lipoprotein; HFpEF: Heart Failure with Preserved Ejection Fraction; LDL: Low-Density Lipoprotein; LVH: Left Ventricular Hypertrophy; NAFLD: Non-Alcoholic Fatty Liver Disease; oxLDL: oxidized LDL; PPARα: Peroxisome Proliferator-Activated Receptor Alpha; RAAS: Renin-Angiotensin-Aldosterone System; TNF-α: Tumor Necrosis Factor-Alpha; VSMCs: Vascular Smooth Muscle Cells

Introduction

Obesity is a well-established risk factor for cardiovascular diseases (CVD), including atherosclerosis, heart failure, arrhythmias, thromboembolic events, and sudden cardiac death [1-4]. Despite significant advances in understanding the link between obesity and CVD [5], the exact mechanisms driving the onset and progression of these diseases remain incompletely understood. It is clear, however, that obesity induces a range of metabolic and physiological disruptions that contribute to cardiovascular pathogenesis [6]. Key mechanisms involved include insulin resistance, chronic inflammation, and dyslipidemia, all of which play pivotal roles in CVD development [7].

Furthermore, obesity and CVD form a vicious cycle: obesity leads to reduced physical activity, which in turn exacerbates metabolic disturbances, while cardiovascular diseases—through medication side effects, psychological

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stress, and persistent inflammation—can worsen obesity [8-10]. This bidirectional relationship highlights the need for a deeper understanding of the mechanisms linking obesity to cardiovascular and cerebrovascular diseases [11,12]. Such insights are crucial for developing effective treatment strategies that can break this cycle.

This review aims to provide an updated analysis of the pathophysiological mechanisms connecting obesity to cardiovascular and cerebrovascular diseases. By exploring these mechanisms, we hope to offer new perspectives for the prevention and treatment of obesity and its associated cardiovascular complications, ultimately advancing therapeutic approaches that target both conditions concurrently.

Metabolic dysregulation and its role in cardiovascular disease progression in obesity

Obesity is closely associated with a range of metabolic dysfunctions, including insulin resistance, dyslipidemia, and hypertension, which collectively exacerbate cardiovascular risk [13,14]. Insulin resistance, a central feature of obesity, significantly disrupts endothelial function, which is crucial for vascular health [15]. In this condition, reduced cellular sensitivity to insulin impairs glucose uptake, leading to hyperglycemia [16]. Elevated glucose levels promote the formation of Advanced Glycation End products (AGEs), which accumulate in the vasculature and induce oxidative stress [17,18]. This oxidative damage impairs endothelial nitric oxide (NO) production, essential for vascular tone and integrity, resulting in endothelial dysfunction [19,20]. The reduced availability of NO contributes to endothelial cell injury, a pro-thrombotic state, and the dysfunction of vascular smooth muscle cells, ultimately promoting the development of atherosclerosis [21-23]. This cascade of events accelerates arterial plaque formation, leading to vascular narrowing and stiffening, which increases the risk of cardiovascular diseases [24,25].

Inflammatory responses and adipokines

Obesity is characterized by altered adipokine secretion, where adipocytes release a variety of bioactive molecules that play crucial roles in regulating metabolic and inflammatory processes [26,27]. In lean individuals, anti-inflammatory cytokines primarily activate M2 macrophages and inhibit neutrophil-mediated inflammation, thereby promoting an overall anti-inflammatory environment [28]. Adipocytes secrete adiponectin and a range of anti-inflammatory cytokines, including Interleukin-10 (IL-10), Interleukin-4 (IL-4), and Interleukin-13 (IL-13) [27]. Adiponectin enhances endothelial antioxidant capacity, inhibits vascular smooth muscle cell proliferation, and promotes fatty acid oxidation by activating AMP-Activated Protein Kinase (AMPK) and peroxisome Proliferator-Activated Receptor Alpha (PPAR-α), thereby reducing the formation of atherosclerotic plaques [29]. IL-10, IL-4, and IL-13 help alleviate chronic low-grade inflammation by inhibiting macrophage polarization to the pro-inflammatory M1 phenotype and reducing the secretion of other inflammatory mediators, ultimately preserving vascular homeostasis [30]. However, in individuals with obesity, adipocytes secrete excessive amounts of pro-inflammatory cytokines, such as Tumor Necrosis Factor-Alpha (TNF-α), Interleukin-6 (IL-6), resistin, and leptin, which subsequently activate a pro-inflammatory M1 macrophage response [31,32]. TNF-α and IL-6 activate key intracellular signaling pathways, including the NF-κB and JAK/STAT pathways, which upregulate the expression of adhesion molecules (such as ICAM-1 and VCAM-1) on endothelial cells, facilitating the recruitment of inflammatory cells to the vascular walls [33]. Additionally, leptin and resistin contribute by enhancing oxidative stress and further stimulating pro-inflammatory cytokine production, such as IL-1β and TNF-α, in macrophages [34,35]. This creates a positive feedback loop that sustains and amplifies the inflammatory response. As a result, the increased secretion of inflammatory mediators accelerates endothelial dysfunction, promotes lipid accumulation, and fosters the development of atherosclerotic plaques. These adipokines contribute to a state of chronic low-grade inflammation, which has been identified as a key driver of endothelial dysfunction [36]. Chronic inflammation promotes the recruitment of immune cells to sites of vascular injury, further amplifying the inflammatory cascade and facilitating the development of atherosclerosis [37,38] (Figure 1).

In addition to their role in inflammation, elevated adipokine levels disrupt the balance between vasodilators and vasoconstrictors [39]. This imbalance exacerbates vascular dysfunction by impairing the normal regulation of vascular tone. The resultant dysregulation of vascular tone contributes to the development of hypertension and accelerates the progression of atherosclerotic lesions [40,41]. Collectively, these inflammatory and adipokine-mediated alterations in vascular function represent critical mechanisms by which obesity promotes cardiovascular pathology.

In lean individuals, anti-inflammatory cytokines activate M2 macrophages and suppress neutrophil-driven inflammation. In obese individuals, hypertrophic or apoptotic adipocytes in obesity secrete pro-inflammatory molecules, such as leptin, resistin, IL-6, and TNF-α, which trigger an M1 macrophage response.

Altered lipid metabolism and atherosclerosis

Obesity induces significant disruptions in lipid metabolism, primarily through the accumulation of visceral fat, which elevates circulating Free Fatty Acids (FFAs) [42,43]. These FFAs are taken up by various tissues, including the liver, heart, and vasculature, contributing to Non-Alcoholic Fatty Liver Disease (NAFLD) and dyslipidemia, characterized by increased low-density lipoprotein (LDL) cholesterol and decreased High-Density Lipoprotein (HDL) cholesterol [44,45]. The elevated LDL infiltrates the subendothelial space, where it undergoes oxidation to form oxidized LDL (oxLDL). OxLDL is a potent inflammatory mediator that promotes the recruitment of circulating monocytes, which then differentiate into macrophages within the subendothelial space [46]. These macrophages internalize oxLDL, transforming into foam cells and contributing to plaque formation. The accumulation of foam

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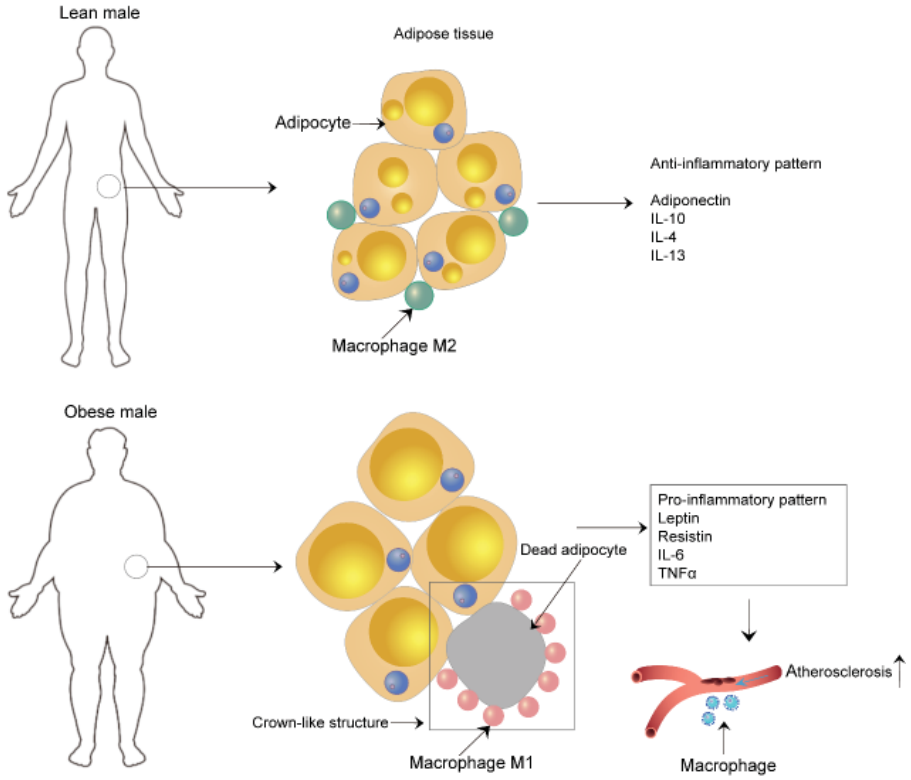

Figure 1: Adipokine Imbalance and Chronic Inflammation in Obesity (Image: Created by the authors).

cells triggers a sustained inflammatory response, which attracts additional immune cells, establishing a self-perpetuating cycle of inflammation and lipid deposition [47]. Concurrently, vascular smooth muscle cells (VSMCs) migrate to the site of the plaque, proliferate, and may transdifferentiate into foam cells, further exacerbating plaque expansion [48]. This process not only accelerates the progression of atherosclerotic lesions but also enhances plaque instability, setting the stage for potential rupture and subsequent thrombotic events [49,50]. Simultaneously, increased FFAs impair endothelial function and exacerbate lipid accumulation, further advancing plaque progression. Fat accumulation in the vascular wall increases oxidative stress, destabilizing plaques and heightening the risk of rupture [51].

Plaque rupture exposes thrombogenic material to the bloodstream, triggering platelet aggregation and thrombus formation, which significantly raises the risk of myocardial infarction and stroke. Therefore, obesity-induced alterations in lipid metabolism—through effects on LDL, FFAs, and oxidative stress—play a central role in atherosclerosis and its cardiovascular complications [52].

Mechanical stress and cardiac remodeling

Obesity imposes mechanical stress on the heart due to increased adipose tissue volume, which demands higher blood flow and elevates cardiac output [53]. Over time, this results in Left Ventricular Hypertrophy (LVH), where the left ventricle enlarges and thickens in response to the added workload. LVH can progress to Heart Failure with Preserved Ejection Fraction (HFpEF), a condition frequently observed in obese individuals [54]. Additionally, increased abdominal visceral fat contributes to systemic hypertension by compressing the kidneys and activating the Renin-Angiotensin-Aldosterone System (RAAS), a key blood pressure regulator [55]. This hypertension further raises the risk of cerebrovascular events, such as stroke [56]. Thus, the mechanical overload and associated hemodynamic changes from obesity contribute to both heart failure and stroke, creating a vicious cycle that exacerbates cardiovascular morbidity.

Discussion

In summary, obesity (especially hypertrophic obesity) significantly contributes to the development and progression of cardiovascular and cerebrovascular diseases through a series of interconnected mechanisms. Metabolic dysregulation, including insulin resistance, dyslipidemia, and hypertension, plays a central role in promoting endothelial dysfunction and accelerating atherosclerosis. Chronic inflammation driven by altered adipokine secretion exacerbates vascular damage, while increased oxidative stress and lipid accumulation further contribute to the formation of atherosclerotic plaques. Additionally, mechanical stress induced by excess adipose tissue results in cardiac remodeling, increasing the risk of heart failure and stroke. These interconnected pathways underscore the critical role of obesity in cardiovascular pathology (Figure 2).

When energy intake far exceeds expenditure, the excess energy is stored in fat, leading to either adipocyte hyperplasia (healthy obesity) or hypertrophy (unhealthy obesity). Hypertrophic adipocytes secrete adipokines, including TNF-α

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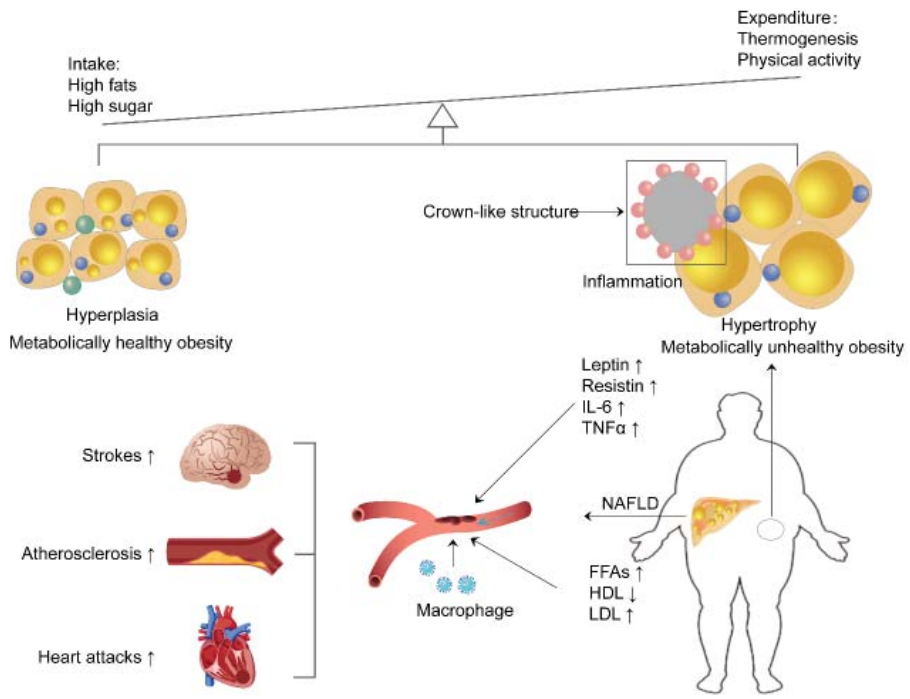

Figure 2: Obesity as a Pivotal Contributing Factor in the Pathogenesis of Cardiovascular Diseases (Image: Created by the authors).

and IL-6, which induce chronic inflammation. Meanwhile, the decrease in HDL and the increase in LDL and free fatty acids contribute to the development of fatty liver. Together, these factors promote atherosclerosis, stroke, heart disease, and other related conditions.

Obesity is a well-established risk factor for CVD. However, emerging research has introduced the "obesity paradox," which suggests that individuals with obesity and pre-existing CVD may have better survival outcomes compared to their lean counterparts [57]. This paradox may be explained by factors such as higher muscle mass, better physical fitness, and the potential benefits of interventions like weight loss or increased physical activity. These findings imply that while obesity remains a significant risk factor for CVD in the general population, its impact may be less detrimental in individuals with established CVD, depending on factors like fitness, muscle mass, and metabolic health. Nevertheless, the obesity paradox does not negate the overwhelming evidence linking obesity to increased CVD risk in the broader population [32]. Further research is needed to elucidate the mechanisms underlying this paradox and its clinical implications. Future studies should explore how interventions can mitigate the effects of obesity on cardiovascular health and whether personalized treatment strategies, considering metabolic and genetic profiles, can optimize outcomes.

Research on obesity-induced CVD faces several key challenges. The complex interplay between genetic, environmental, and lifestyle factors remains insufficiently understood, and the precise molecular mechanisms linking inflammation and lipid metabolism to CVD are yet to be fully elucidated. Moreover, the heterogeneous nature of obesity—shaped by individual metabolic profiles, genetic predispositions, and comorbidities—complicates the development of universal therapeutic strategies. Current animal models and clinical studies often fail to accurately replicate human conditions or account for the multifactorial aspects of obesity. Future research should prioritize personalized approaches that integrate genetic and metabolic factors, enabling a deeper understanding of individual responses to obesity-related CVD. This could help identify more effective, targeted interventions for prevention and treatment, advancing the field toward precision medicine in cardiovascular care. Looking ahead, a more comprehensive understanding of the mechanisms underlying obesity-induced CVD could facilitate the development of more targeted prevention and treatment strategies. The first priority should be weight management, including reducing the intake of high-calorie foods and increasing physical activity. Furthermore, critical pathways warranting attention include inflammation, lipid metabolism, and insulin resistance, with particular emphasis on the roles of pro-inflammatory cytokines, oxidative stress, and adipokines in driving endothelial dysfunction and atherosclerosis. Targeting specific molecular mediators such as TNF-α, IL-6, and NF-κB may help mitigate the inflammatory burden associated with obesity. In addition, therapies aimed at improving lipid metabolism, particularly those targeting dysregulated HDL and LDL cholesterol, hold considerable promise. Personalized cardiovascular care, tailored to individual dietary habits, metabolic profiles, and genetic factors, is vital for optimizing treatment and enabling more precise interventions. As the global prevalence of obesity continues to rise, addressing these underlying mechanisms will be crucial in alleviating the long-term burden of CVD and improving patient outcomes.

Author contributions

S. W. had the idea for this article and drafted the manuscript.

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