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Mechanisms of Cardiovascular Disease in Obese Patients

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Abstract

Obesity represents a global health crisis with profound cardiovascular implications. Beyond its role as a risk factor for traditional cardiovascular conditions, obesity directly promotes cardiovascular disease through complex pathophysiological mechanisms. This review examines the multifaceted pathways linking excess adiposity to cardiovascular disease, including adipose tissue dysfunction, chronic inflammation, endothelial dysfunction, and hemodynamic alterations. Understanding these mechanisms is essential for developing targeted therapeutic strategies to reduce the substantial cardiovascular burden associated with obesity.

Keywords: Obesity; Cardiovascular Disease; Hypertension; Dyslipidemia; Adipose Tissue; Inflammation; Insulin Resistance

Abbreviations: PVAT: Perivascular Adipose Tissue; NO: Nitric Oxide; ADMA: Asymmetric Dimethylarginine; OXLDL: Oxidized Low-Density Lipoproteins; HFpEF: Heart Failure with Preserved Ejection Fraction

Introduction

The global obesity epidemic has paralleled a dramatic increase in cardiovascular disease mortality worldwide [1]. Obesity contributes both directly and indirectly to cardiovascular disease development, with effects that extend beyond traditional risk factors such as hypertension, dyslipidemia, and type 2 diabetes [2]. Importantly, adipose tissue distribution-particularly visceral and ectopic fat accumulation-appears more relevant to cardiometabolic risk than total body weight [1]. This review synthesizes current understanding of the mechanistic pathways through which obesity promotes cardiovascular disease.

Adipose Tissue Dysfunction and Adiposopathy

In obesity, adipose tissue undergoes pathological remodeling characterized by adipocyte hypertrophy, inadequate angiogenesis, hypoxia, and immune cell infiltration [3,4]. This state of "adiposopathy" or "sick fat" represents a fundamental shift from healthy adipose tissue function to a dysfunctional endocrine organ that promotes cardiovascular disease [5].

Dysfunctional adipose tissue exhibits impaired adipogenesis in subcutaneous depots, forcing excess lipids into visceral and ectopic sites including the liver, skeletal muscle, pancreas, and myocardium [5,6]. This ectopic lipid deposition leads to lipotoxicity- cellular dysfunction and apoptosis resulting from accumulation of toxic lipid intermediates such as ceramides [7,8]. The consequences include insulin resistance, hepatic steatosis, and direct myocardial injury [8].

Perivascular adipose tissue (PVAT) deserves particular attention in cardiovascular pathophysiology. In healthy states, PVAT exerts vasodilatory and anti-inflammatory effects on adjacent blood vessels [9,10]. However, obesity transforms PVAT into a pro-inflammatory depot that secretes vasoconstrictor mediators, promotes oxidative stress, and contributes directly to endothelial dysfunction and vascular remodeling [9,11].

Inflammation and Adipokine Dysregulation

Obesity induces a chronic low-grade inflammatory state characterized by macrophage infiltration into adipose tissue and elevated circulating pro-inflammatory cytokines [4,12]. This inflammation represents a critical mechanistic link between obesity and cardiovascular disease.

Adipokines- bioactive proteins secreted by adipose tissue- play central roles in cardiovascular pathophysiology [4,13]. Obesity typically increases pro-inflammatory adipokines including leptin, resistin, chemerin, and interleukin-6, while decreasing anti-inflammatory adiponectin [13-15]. Leptin resistance with compensatory hyperleptinemia promotes sympathetic nervous

system activation, contributing to hypertension and cardiac remodeling [7]. Adiponectin deficiency removes important cardioprotective effects including anti-inflammatory, anti-atherogenic, and insulin-sensitizing actions [13,16].

The inflammatory milieu created by dysfunctional adipose tissue extends systemically, promoting oxidative stress, activating inflammatory signaling pathways (NF-κB, JNK, NLRP3 inflammasomes), and creating a prothrombotic state [14,17]. These processes accelerate atherosclerosis development and increase cardiovascular event risk [1,4].

Endothelial Dysfunction and Atherosclerosis

Endothelial dysfunction represents a critical early step in atherosclerosis development and is consistently observed in obesity [1,11,18]. The primary mechanism involves reduced nitric oxide (NO) bioavailability resulting from multiple converging pathways [11,18,19].

Obesity-induced inflammation increases reactive oxygen species production, particularly through NADPH oxidase activation, which rapidly degrades NO [17,19]. Elevated levels of asymmetric dimethylarginine (ADMA), an endogenous nitric oxide synthase inhibitor, further impair NO production [18]. Additionally, oxidized low-density lipoproteins (oxLDL)-increased in obesity due to enhanced LDL oxidation-directly damage endothelial cells and promote foam cell formation [1].

Visceral adiposity accelerates atherosclerosis through multiple mechanisms beyond traditional risk factors [1]. Inflammation promotes LDL oxidation and increases expression of adhesion molecules (VCAM-1, ICAM-1), facilitating monocyte recruitment and transformation into macrophage foam cells [17]. The insulin-resistant state characteristic of obesity produces atherogenic dyslipidemia with elevated triglycerides, low HDL cholesterol, and small dense LDL particles [1]. Importantly, obesity associates with atherosclerotic lesions even after accounting for traditional cardiovascular risk factors, indicating direct pathogenic effects [1].

Insulin Resistance as a Central Integrator

Insulin resistance occupies a pivotal position linking adipose tissue dysfunction to cardiovascular disease [20]. Abnormal adiposity triggers insulin resistance through multiple mechanisms including elevated free fatty acids, inflammatory cytokines, ectopic lipid deposition, and adipokine dysregulation [8,20].

Insulin resistance manifests through impaired substrate oxidation, oxidative stress, inflammation, endothelial dysfunction, and a prothrombotic state [20]. These abnormalities cluster as metabolic syndrome, which substantially increases cardiovascular disease risk [20]. The progression from insulin resistance to metabolic syndrome to overt cardiovascular disease represents a continuum driven by obesity-related metabolic derangements [20].

Hemodynamic and Structural Cardiac Changes

Obesity produces profound hemodynamic alterations that directly impact cardiac structure and function [1,7]. Excess adipose tissue increases total blood volume and cardiac output while paradoxically reducing systemic vascular resistance [1]. This volume overload increases preload and left ventricular wall stress [7].

Simultaneously, obesity activates the renin-angiotensin-aldosterone system and sympathetic nervous system, promoting hypertension and increasing afterload [1,7]. These combined hemodynamic stresses lead to left ventricular hypertrophy, which may be eccentric (from volume overload) or concentric (from pressure overload) [7,21].

Obesity also promotes direct myocardial changes including myocardial fat accumulation (steatosis), fibrosis, and cardiomyocyte apoptosis [1,7]. These cellular alterations contribute to left ventricular diastolic dysfunction, a hallmark of obesity-related heart failure with preserved ejection fraction (HFpEF) [1]. Patients with obesity demonstrate greater concentric remodeling, increased epicardial fat, pericardial restraint, and right ventricular dysfunction compared to lean individuals [1].

The duration and severity of obesity determine the extent of cardiac remodeling [7,21]. Prolonged obesity from early adulthood produces more severe structural and functional abnormalities, emphasizing the importance of early intervention [22].

Conclusion

Cardiovascular disease in obesity results from complex, interconnected pathophysiological mechanisms rather than a single pathway. Adipose tissue dysfunction initiates a cascade involving chronic inflammation, adipokine dysregulation, insulin resistance, endothelial dysfunction, and hemodynamic alterations that collectively promote atherosclerosis, hypertension, and heart failure. Importantly, adipose tissue quality and distribution-particularly visceral and ectopic fat-appear more critical than total adiposity in determining cardiovascular risk. These mechanistic insights highlight the importance of preventing and treating obesity to reduce cardiovascular disease burden and suggest potential therapeutic targets beyond traditional risk factor modification.

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