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Review

Obesity as a Predisposing Factor for Atherosclerosis

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Abstract: Obesity stands as a pressing global health concern, associated with a myriad of threats to human well-being and longevity. Within the scope of this review, we zero in on how obesity impacts the onset of atherosclerosis, given its well-established link as a risk factor in its development. The progression of atherosclerosis is notably hastened by obesity, driven by a host of mechanisms including heightened blood pressure, elevated glucose levels, compromised lipid profiles and systemic inflammation. Of particular significance are the intricate cellular and molecular pathways that underpin the genesis of atherosclerosis. To shed light on this complex web, our endeavor has been to gather insights into the distinct roles played by diverse adipokines and lay down a structured framework for understanding their contributions in this context.

Keywords: Atherosclerosis, Obesity, Fat Tissue, CVD, Cardiovascular Disease

Introduction

Obesity

Obesity is a widespread issue, particularly in developed countries. Organizations like WHO and AHA classify obesity using BMI, with specific thresholds for Asians (Weir and Jan, 2024). Contributing factors include poor nutrition and sedentary lifestyles. Globally, around 2 billion adults and over 43 million children under 5 are overweight or obese (Henning, 2021). Obesity causes over 3.4 million deaths annually, with varying impacts on life expectancy (Weir and Jan 2024). It significantly raises the risk of CVD, particularly atherosclerosis and CHD (Powell-Wiley *et al*., 2021). Each 1-point increase in BMI above normal weight corresponds to a 10% increase in risk, while a 10 kg weight gain elevates CAD risk by 12% and raises blood pressure (Powell-Wiley *et al*., 2021). Meta-analyses indicate overweight or obese individuals have higher relative risks of developing atherosclerotic CHD (Huxley *et al*., 2006).

Despite known facts, an "obesity paradox" exists, where moderate obesity may improve survival in atherosclerosis patients (Carbone *et al*., 2019). Debates persist on its genuineness, with research exploring explanations, including the "fat, but fit" hypothesis for obese individuals with good fitness (McAuley and Beavers, 2014; Myasoedova *et al*., 2016). Biases like BMI use, unmeasured factors and bias toward obese patients complicate understanding (Preston and Stokes, 2014). Understanding the links between body composition, aging, fitness and diseases is crucial (Neeland *et al*., 2018).

Obesity, beyond diet and inactivity, can be influenced by genetics, microbiome and environmental factors (Lee and Blumberg, 2019).

Atherosclerosis

Atherosclerosis is a complex process that occurs within the artery walls. It begins with a disruption in the vascular endothelium caused by monocytes, leading to their transformation into macrophages in the subendothelial space (Chistiakov *et al*., 2014). Inflammatory conditions can impair the outflow of cholesterol from these macrophages, resulting in the

accumulation of modified Low-Density Lipoproteins (LDL) and the formation of lipid-rich plaques, which give rise to foam cells (Guerrini and Gennaro, 2019). These macrophages can polarize into either M1 or M2 phenotypes. During the progression of atherosclerosis, monocytes differentiate into M1 macrophages, which play a crucial role in the initiation and advancement of the disease by transforming into cholesterol-laden foam cells (Lin *et al*., 2021a). On the other hand, M2 macrophages are associated with tissue repair and are more prevalent in regressing plaques, displaying a lower atherogenic potential.

Maintaining cholesterol homeostasis within macrophages involves a delicate equilibrium between cholesterol intake, endogenous synthesis, esterification/hydrolysis and efflux (Poznyak *et al*., 2021). Chronic low-grade inflammation related to obesity disrupts this balance, negatively impacting the regulation of cholesterol transport proteins (Chistiakov *et al*., 2015a).

Various cytokines can drive the atherosclerotic process, such as Interferon (IFN)-γ, Tumor Necrosis Factor (TNF)-α and Interleukin (IL)-1β. TNF-α and IL-1β promote inflammation by inducing the expression of cytokines and adhesion molecules and facilitating the migration of Vascular Smooth Muscle Cells (VSMCs) and endothelial cells. IFN-γ contributes to the generation of foam cells (Amin *et al*., 2020).

The increasing prevalence of obesity poses a significant challenge to cardiovascular health, influencing inflammatory processes and pathophysiological mechanisms implicated in atherosclerosis (Csige *et al*., 2018). Obesity frequently correlates with adverse blood lipid profiles, with dyslipidemia serving as a significant risk element for CAD. Among obese individuals, the occurrence of hypertriglyceridemia is substantially higher compared to non-obese counterparts (Shabana *et al*., 2020).

Furthermore, the combination of hypertriglyceridemia with elevated or reduced levels of High-Density Lipoprotein (HDL) cholesterol is more prevalent in individuals who are overweight or obese. Despite efforts to manage LDL cholesterol levels and treat concurrent conditions, there remains a heightened residual risk of Atherosclerotic Cardiovascular Disease (ASCVD) in these populations (Agarwala and Shapiro, 2020; Puchenkova *et al*., 2020). Even with statin therapy or other medications, pathological processes within the arterial walls may persist. Conventional lipid profiles may not effectively capture localized arterial changes, as they primarily reflect systemic cholesterol metabolism in the liver and other systemic influences rather than the specific cellular lipid imbalances within atherosclerotic lesions (Geldenhuys *et al*., 2017).

Relationship between Obesity and Atherosclerosis

There are two types of adipose tissue in the human body: Brown adipose tissue and white adipose tissue. Brown adipose tissue is typically found in small, distinct areas of newborns and plays a role in generating heat through thermogenesis. White adipose tissue predominates in adults and serves as the main fat storage site in the body (Townsend and Tseng, 2012). Traditionally seen as a triglyceride reservoir, recent insights reveal its metabolic activity and interactions with organs (Chait and Den Hartigh, 2020). Excessive calorie intake and sedentary lifestyles lead to subcutaneous adipose tissue accumulation, causing health issues when adipocyte size exceeds 100-120 microns (Henning, 2021; Chistiakov *et al*., 2015b). Adipose tissue is categorized into upper body, abdominal, visceral and lower body fat depots, each impacting health markers differently (Gruzdeva *et al*., 2018).

Visceral adipocytes exhibit higher activity in transferring and releasing free fatty acids compared to subcutaneous adipocytes, secreting more inflammatory adipokines and fewer anti-inflammatory ones and displaying a stronger response to glucocorticoids than subcutaneous adipose tissue. Excessive accumulation of free fatty acids in internal organs like the liver leads to impaired liver metabolism, overproduction of lipoproteins containing apolipoprotein B, increased glucose production, reduced insulin breakdown in the liver and systemic hyperinsulinemia (Jung and Choi, 2014). Excessive adipokine production in visceral fat leads to inflammation and insulin resistance through interactions with cells in the endothelium, fibroblasts and immune cells (De Oliveira Dos Santos *et al*., 2021). Abdominal adipose tissue doesn't protect against atherosclerosis, insulin resistance, or diabetes, with significant accumulation associated with metabolic issues (Balistreri *et al*., 2010; Feijóo-Bandín *et al*., 2020). Visceral obesity causes triglyceride accumulation in the myocardium and localized fat deposits in the heart, linked to coronary issues and mortality rates after myocardial infarction (Talman *et al*., 2014). Research on adipokines' mechanisms in cell cultures and rodents provides insights but may not directly apply to obese patients (Kim *et al*., 2022; Deng and Scherer, 2010). This manuscript focuses on the cardiovascular mechanisms of adipokines, widely accepted by specialists treating obese patients (Landecho *et al*., 2019).

Key adipokines involved in inflammation, notably heightened in visceral obesity, include leptin, resistin, Retinol-Binding Protein 4 (RBP4), Angiopoietin-Like Protein-2 (AngptL-2), IL-6 and MCP-1 (Ouchi *et al*., 2011). These adipokines drive systemic inflammation, endothelial dysfunction, hypercoagulation and insulin resistance, fueling atherosclerosis. Conversely, adiponectin and omentin-1 function as anti-inflammatory and anti-atherogenic adipokines. Figure (1) for graphical summary.

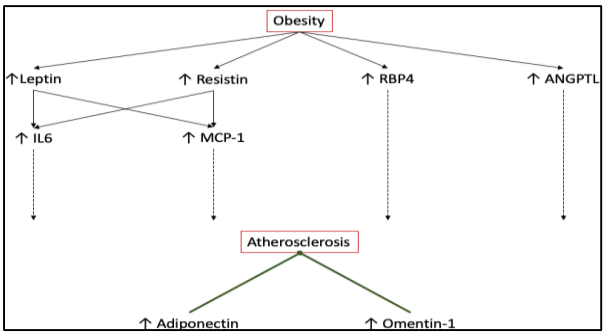

Fig. 1: Atherogenic and atheroprotective action of several molecules elevated in obesity

Leptin

Leptin, known for regulating hunger, sees increased levels of weight gain, notably in visceral obesity (Obradovic *et al*., 2021). Despite resistance to its appetite-suppressing effects, leptin remains potent in triggering inflammation, especially within the vascular network and myocardium.

In obesity, leptin acts as a chemoattractant for immune cells, promoting inflammation by increasing the release of inflammatory molecules (Francisco *et al*., 2018). It enhances adhesion molecule expression, facilitating monocyte recruitment to vascular walls and elevating endothelial permeability, contributing to atheroma formation (Freitas Lima *et al*., 2015). Leptin also triggers reactive oxygen species production, leading to endothelial dysfunction and atherosclerosis (Raman and Khanal, 2021; Sobenin *et al*., 2014a).

Leptin influences lipid metabolism, reducing HDL levels and promoting vascular cell proliferation, migration and aggregation, contributing to vascular stenosis and thrombosis (Gutierrez and Gutierrez, 2021; Singh *et al*., 2010). It also affects the expression of proatherogenic proteins, fostering a prothrombotic state and plaque instability (Poetsch *et al*., 2020).

Elevated plasma leptin levels correlate with acute CV events and increased arterial calcification, emphasizing its role as a therapeutic target in managing obesity-related cardiovascular complications (Chen *et al*., 2018).

Resistin

Resistin, an inflammatory adipokine, binds to receptors in endothelial cells and monocytes, triggering pro-inflammatory pathways (Avtanski *et al*., 2019). Elevated levels are linked to increased inflammatory markers and adhesion molecules (Kany *et al*., 2019). Resistin also induces insulin resistance, promotes lipid accumulation in macrophages and contributes to atherosclerosis (Benomar *et al*., 2013).

Furthermore, resistin influences MCP-1 regulation, promoting monocyte attraction to the subendothelium and exacerbating inflammation (Patel *et al*., 2003). It also counteracts the effects of insulin-sensitizing agents and induces proliferation, migration and atheroma formation in human aortic smooth muscle cells (Jamaluddin *et al*., 2012). High resistin levels (>12.76 ng/mL) are associated with acute myocardial ischemia and myocardial infarction risk, as well as severe atherosclerotic plaque development (Cabrera De León *et al*., 2014; Soldatov *et al*., 2018). Elevated resistin correlates with increased C-reactive protein concentrations and coronary artery calcification, highlighting its role as a biomarker for coronary atherosclerosis (Cabrera De León *et al*., 2014; Soldatov *et al*., 2018).

Retinol Binding Protein 4 (RBP4)

RBP4 is highly expressed in adipocytes, macrophages and the liver, particularly in those with visceral fat accumulation (Rychter *et al*., 2020). Elevated serum RBP4 levels are associated with atherosclerosis risk factors such as dyslipidemia, high BMI, metabolic syndrome and hypertension (Rychter *et al*., 2020). Moreover, RBP4 independently predicts adverse cardiovascular events related to atherosclerosis (Rychter *et al*., 2020).

RBP4 promotes lipolysis in adipose tissue, exacerbating hepatic steatosis and triggering the release of pro-inflammatory cytokines from macrophages (Kilicarslan *et al*., 2020). Elevated RBP4 levels impair glucose transport and induce insulin resistance, contributing to diabetes risk (Kilicarslan *et al*., 2020). Additionally, RBP4 stimulates endothelial cells to produce pro-inflammatory molecules, promoting atherosclerotic plaque formation (Hajjar and Gotto, 2013). Targeting RBP4 shows promise for therapeutic intervention in atherosclerosis (Zhou *et al*., 2018).

Angiopoietin-Like (ANGPTL) Protein

The ANGPTL protein family, including Angptl2, significantly contributes to atherosclerosis development, linking obesity to inflammation and insulin resistance (Kim *et al*., 2018). TNF-α induces Angptl2 expression in adipocytes, leading to vascular endothelial inflammation and atherosclerosis progression (Kwaifa *et al*., 2020; Soldatov *et al*., 2018). Elevated Angptl2 levels correlate with obesity-related factors and negatively impact HDL cholesterol levels (Park *et al*., 2010).

Meanwhile, ANGPTL8 promotes cholesterol absorption and reduces efflux in macrophages, fostering foam cell formation. Loss-of-function mutations in ANGPTL3 decrease cholesterol and triglyceride levels, lowering the risk of atherosclerotic CAD. ANGPTL3 inhibition emerges as a potential therapeutic approach for managing hyperlipidemia and atherosclerosis (Tall *et al*., 2022).

Interleukin-6 (IL-6)

IL-6, pivotal in regulating inflammation and immune responses, exhibits varied effects on insulin sensitivity based on tissue and lifestyle factors (Nara and Watanabe, 2021). While exercise-induced IL-6 from skeletal muscles enhances glucose utilization, excess adipose tissue in sedentary individuals elevates IL-6 levels, fostering inflammation and insulin resistance (Wolsk *et al*., 2010). In obesity, IL-6 exacerbates insulin resistance and promotes lipid uptake by macrophages, contributing to atherosclerotic plaque formation (Ye *et al*., 2018).

Elevated IL-6 levels correlate with an increased risk of coronary artery disease, but targeting IL-6 pharmacologically, alongside IL-1, shows promise in reducing cardiovascular events and coronary revascularization needs in obese individuals (Wainstein *et al*., 2017).

Monocyte Chemoattractant Protein-1 (MCP-1)

MCP-1, produced by various cells including adipocytes and macrophages, increases with obesity, promoting inflammation and atherosclerosis by attracting monocytes/macrophages (Panee, 2012). High MCP-1 levels in atherosclerotic plaques correlate with adverse cardiovascular events (Georgakis *et al*., 2019).

Inhibiting MCP-1 pathways shows promise in reducing atherosclerotic plaque burden and improving plaque stability, suggesting a potential therapeutic strategy for atherosclerosis management (Gonzalez-Quesada and Frangogiannis, 2009).

Adiponectin and Omentum-1: Anti-Inflammatory Adipokines Decreasing Atherosclerosis

Adiponectin

Adiponectin, derived from adipocytes, counteracts inflammation, enhances insulin sensitivity and promotes vasodilation (Jung and Jung, 2021). It impedes TNF-α production, reduces oxidative stress and inhibits foam cell formation (Burhans *et al*., 2019; Sobenin *et al*., 2014b).

Additionally, adiponectin boosts glucose utilization, improves insulin sensitivity and stimulates nitric oxide production (Addabbo *et al*., 2011; Yanai and Yoshida, 2019; Achari and Jain, 2017). It also inhibits growth factor expression, reducing vascular smooth muscle cell proliferation and migration (Miao and Li, 2012; Sobenin *et al*., 2013b).

Low adiponectin levels independently associated with coronary artery disease, while weight loss significantly elevates adiponectin levels, reducing myocardial infarction risk (Izadi *et al*., 2013; Sobenin *et al*., 2012; Foula *et al*., 2020).

Omentin-1

Omentin-1, an adipokine known for its anti-inflammatory properties, is predominantly produced by stromal vascular cells in visceral fat tissue (Escoté *et al*., 2017). It exhibits an inverse relationship with BMI and fasting insulin levels, indicating its potential role in metabolic health. Moreover, omentin-1 positively correlates with insulin sensitivity, adiponectin levels, HDL levels and vascular endothelial function.

In terms of its mechanisms of action, omentin-1 activates various pathways such as AMPK and PI3K while inhibiting NADPH oxidase, leading to enhanced insulin sensitivity and reduced inflammation (Henning, 2021; Noor *et al*., 2020). It also plays a crucial role in endothelial cell function by suppressing TNF-alpha-induced inflammation and promoting vasodilation. Additionally, omentin-1 has been shown to mitigate arterial atheroma formation and inflammation, contributing to vascular protection.

On the other hand, the accumulation of saturated fatty acids due to obesity contributes to the development of atherosclerosis (Manna and Jain, 2015). These fatty acids induce oxidative stress, triggering inflammatory responses, endothelial dysfunction and atherosclerosis. Moreover, excess free fatty acids directly impact vascular endothelial cells, leading to inflammation, thrombosis and atherosclerosis.

In clinical studies, obese individuals with heightened free fatty acid levels exhibit an increased risk of developing Atherosclerotic Cardiovascular Disease (ASCVD) (Korakas *et al*., 2018). Conversely, adherence to a Mediterranean diet rich in monounsaturated fatty acids or chronic statin therapy has been associated with decreased levels of inflammatory markers and reduced risk of atherosclerotic vascular disease.

Adipose Immune Cells in Chronic Inflammation and Atherosclerosis

Adipose tissue houses a diverse array of immune cells, encompassing both innate and adaptive components (Huh *et al*., 2014). In a healthy state, a balance is maintained by anti-inflammatory cells like M2 macrophages, CD4Th2 cells, regulatory T cells (Tregs) and eosinophils, which release cytokines dampening inflammation (Liu and Nikolajczyk, 2019).

However, obesity disrupts this balance (Kiernan and MacIver, 2021). Pro-inflammatory cells such as M1 macrophages, Th1 cells, CD8 T cells and mast cells increase, while anti-inflammatory cells decrease. This shift results in the secretion of pro-inflammatory cytokines, fueling insulin resistance and endothelial dysfunction. Neutrophils and mast cells play pivotal roles in perpetuating inflammation in obese adipose tissue.

Activation of CD4Th1 cells leads to monocyte polarization into M1 macrophages and the release of pro-inflammatory cytokines like IFN-γ, TNF-α and IL-1β (Lee and Lee, 2014). Neutrophils exacerbate inflammation by infiltrating adipose tissue and promoting the recruitment of M1-type macrophages. Mast cells, activated by T cells, release inflammatory mediators, further intensifying the inflammatory response. Consequently, chronic inflammation, insulin resistance and atherosclerosis are prominent consequences of obesity due to the dysregulated immune environment in adipose tissue.

Perspectives

Our review sheds light on the pressing necessity for inventive therapeutic solutions and investigative approaches to confronting the intricate relationship between obesity and atherosclerosis. Delving into the intricate web of dysfunctions in adipose tissue and the progression of atherosclerosis, emerging avenues stand out as potential game-changers for mitigating cardiovascular risks in individuals with obesity.

One avenue of promise lies in targeting adipokines, key molecules implicated in inflammation and lipid metabolism regulation. Precision interventions to modulate the expression or function of adipokines like leptin, resistin and adiponectin could potentially disrupt the pro-inflammatory cascade associated with obesity-driven atherosclerosis.

In addition, anti-inflammatory therapies present a compelling strategy to combat the chronic low-grade inflammation prevalent in obesity. By deploying agents that temper cytokine activity and immune responses, we may alleviate the inflammatory burden within adipose tissue and arterial walls, potentially slowing atherosclerotic advancement.

Moreover, interventions focused on enhancing metabolic health, such as improving insulin sensitivity and lipid regulation, hold promise for curbing atherosclerotic cardiovascular risks in obese individuals. By honing in on metabolic pathways intricately linked to adipose tissue dysfunction, novel therapeutic avenues could be uncovered.

A paradigm shift towards personalized medicine, tailoring interventions based on an individual's unique adipose tissue distribution, adipokine profile, genetic makeup and metabolic status, could revolutionize the landscape of managing obesity-related atherosclerosis. Customized treatments that address the specific molecular drivers of atherosclerosis have the potential to yield more targeted and efficacious outcomes.

Looking ahead, investigative efforts should aim to unravel the mechanistic underpinnings connecting obesity and atherosclerosis at the molecular level. Leveraging advanced technologies like single-cell sequencing, omics approaches and state-of-the-art imaging techniques can deepen our understanding of the intricate interplay between adipose tissue biology and atherosclerotic plaque composition. Longitudinal studies tracking changes in adipose tissue dynamics and plaque characteristics over time may unveil novel biomarkers and therapeutic targets for precision medicine interventions.

In harnessing the collective wisdom garnered from the study of obesity-related atherosclerosis, we are poised to forge new paths in therapeutic innovation and investigative inquiry that could potentially redefine the management of cardiovascular disease in individuals grappling with obesity. Collaboration across disciplines and a holistic approach will be crucial in advancing our comprehension and clinical management of these intertwined health challenges.

Biases and Limitations

The reviewed literature on obesity and atherosclerosis provides a detailed analysis of their interconnectedness. However, certain biases may influence the interpretation of the presented findings.

One notable bias lies in the reliance on Body Mass Index (BMI) as the primary measure of obesity, which could oversimplify the diverse nature of adipose tissue distribution and individual metabolic health. This oversimplification might overlook nuances in body composition and metabolic differences among individuals, particularly in diverse populations.

Furthermore, there could be a bias in the selection of studies, favoring those that support the association between obesity and atherosclerosis. This bias may omit studies with contradicting findings, potentially skewing the overall understanding of their relationship.

Publication bias is another concern, where studies with statistically significant results are more likely to be published, leading to incomplete and potentially skewed representations of the literature. The complex interplay of factors contributing to obesity and atherosclerosis, such as genetics, environment and lifestyle, may not be adequately addressed, potentially impacting the validity of conclusions drawn.

Moreover, the generalizability of findings to diverse populations may be limited, as the literature primarily focuses on industrialized countries, neglecting the nuances of obesity-related health outcomes globally. Extrapolating findings from rodent studies to humans may introduce biases due to biological differences between the two species.

The emphasis on adipokines as key players in the obesity-atherosclerosis link may overlook alternative explanations, such as microbiome composition, circadian rhythms, or environmental factors. Considering these factors in future research is essential for a more comprehensive understanding of the intricate relationship between obesity and atherosclerosis.

Conclusion

In conclusion, the intricate relationship between obesity and atherosclerosis underscores the critical need for comprehensive strategies to address these intertwined health issues. Obesity, characterized by excessive accumulation of adipose tissue, serves as a major risk factor for the development and progression of atherosclerosis, a chronic inflammatory condition that underlies various cardiovascular diseases. The impact of obesity on atherosclerosis is multifaceted, involving a complex interplay of metabolic dysregulation, chronic low-grade inflammation, altered lipid metabolism and endothelial dysfunction.

Studies consistently show that as Body Mass Index (BMI) increases, so does the risk of atherosclerotic cardiovascular events, such as coronary artery disease and stroke. The adipose tissue itself functions as an endocrine organ, secreting various bioactive molecules called adipokines, including leptin, resistin and adiponectin, which modulate inflammation and lipid metabolism. This adipose tissue-mediated inflammatory milieu contributes significantly to the initiation and progression of atherosclerotic plaques in obese individuals.

Moreover, recent research has highlighted the heterogeneity in adipose tissue distribution and composition, with visceral adiposity being particularly detrimental in promoting a pro-inflammatory state conducive to atherosclerosis. Understanding the molecular mechanisms by which adipose tissue influences atherosclerosis holds promise for the development of targeted therapeutic interventions that may help mitigate the cardiovascular risks associated with obesity.

Moving forward, further investigations into the specific roles of adipokines, immune cells and metabolic pathways in obesity-related atherosclerosis are warranted. By elucidating these intricate interactions, researchers can identify novel therapeutic targets and interventions aimed at reducing the burden of cardiovascular disease in individuals with obesity. Embracing a holistic approach that integrates lifestyle modifications, pharmacological interventions and possibly novel biologics targeting adipose tissue signaling pathways may hold the key to achieving better cardiovascular outcomes in this high-risk population.

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Ethics

This article is original and contains unpublished material. The corresponding author confirms that all of the other authors have read and approved the manuscript and that no ethical issues are involved.

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