Two Sides of Triglycerides in Atherogenesis: An Essential Contributor

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Abstract

Background: Atherosclerosis is a complex disease characterized by chronic arterial damage and an inflammatory response, often leading to serious cardiovascular complications. Alterations in lipid metabolism, particularly involving triglycerides, play a pivotal role in atherogenesis. Methods: This review synthesizes current research on triglycerides, examining their multifaceted roles as potential causative agents, biomarkers, or consequences of atherosclerosis. We analyze recent studies that elucidate the relationship between elevated triglyceride levels and cardiovascular risk, focusing on mechanisms and clinical implications. Results: Elevated triglycerides (HTG) are associated with increased risks of atherosclerosis and cardiovascular events. They contribute to endothelial dysfunction by promoting inflammatory responses and facilitating the formation of foam cells, a hallmark of atherosclerotic plaques. Triglyceride-rich lipoproteins (TRLs) can penetrate arterial walls, intensifying inflammation and driving atherogenesis without requiring prior modification, which can make them more atherogenic than low-density lipoproteins (LDL) in specific contexts. Conclusion: Understanding the complex roles of triglycerides is critical for effectively addressing residual cardiovascular risk. Current therapeutic strategies emphasize lipid management but highlight the urgent need for targeted approaches to mitigate the adverse effects of elevated triglycerides. Further research is needed to establish clearer relationships between triglyceride levels and atherosclerosis and to identify effective prognostic markers for early intervention.

Keywords: atherosclerosis; lipids; triglycerides; risk factors; atherogenesis; inflammation; lipid metabolism.

Significance | This review discusses the role of triglycerides in atherogenesis and their potential as biomarkers in cardiovascular disease development.

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Introduction

Atherosclerosis is a leading cause of cardiovascular disease, characterized by the buildup of plaques in arterial walls, leading to various health complications. Recent studies suggest that triglycerides play a significant role in the pathogenesis of atherosclerosis, influencing lipid metabolism and endothelial function. Understanding this relationship is crucial for developing effective prevention and treatment strategies.

This review aims to comprehensively evaluate the existing literature on the association between triglyceride levels and atherosclerosis. To achieve this, we conducted a systematic review of relevant studies published between 2018 and 2024. A comprehensive literature search was performed using PubMed, Scopus, and Web of Science, employing keywords such as "triglycerides,"

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"atherosclerosis," "cardiovascular risk," "lipid metabolism," and "endothelial dysfunction."

Our inclusion criteria encompassed studies focusing on the relationship between triglyceride levels and atherosclerosis, involving human subjects or relevant animal models, and published in peer-reviewed journals. We excluded articles that were not published in English, lacked original data or experimental design, or primarily concentrated on obstructing cardiovascular diseases unrelated to lipid metabolism.

The synthesis of data from the selected studies involved assessing their methodologies, findings, and relevance to the role of triglycerides in atherosclerosis. We categorized the literature based on study types, such as clinical trials and observational studies, to create a comprehensive overview of the current understanding in this field. This integrated approach allows for a critical evaluation of how triglyceride levels influence the development of atherosclerosis and provides insights for future research directions.

2. Atherogenesis

Atherosclerosis is a chronic condition characterized by the progressive accumulation of lipids, immune cells, and fibrous tissue within the arterial wall, leading to various cardiovascular diseases. This complex disease involves multifaceted cellular and molecular mechanisms, highlighting the interplay between lipid metabolism and inflammation. Key players in the atherosclerotic process include monocyte-derived macrophages, smooth muscle cells, dendritic cells, lymphocytes, and platelets, which together orchestrate an inflammatory response to endothelial injury (Libby, 2021).

The pathophysiology of atherosclerosis begins with the retention and modification of lipoproteins in the arterial intima. Low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and their remnants serve as critical sources of lipids that infiltrate the artery wall. When lipoproteins enter the subendothelial intima, they induce the storage of lipids within vascular cells. This lipid accumulation represents an essential initial step in the formation of atherosclerotic lesions (Linton et al., 2000). LDL undergoes various modifications within the intima, making it atherogenic. These modifications enhance its potential to induce intracellular lipid deposition, a critical event in atherogenesis that requires interaction with components of the extracellular matrix.

Once retained in the intima, modified lipoproteins promote complex cellular reactions. Macrophages and smooth muscle cells engage with these modified LDL particles, leading to the formation of foam cells—a hallmark of early atherosclerosis (Summerhill et al., 2019). Notably, this stage is also characterized by a proliferative response in intimal cells, which include increased synthesis of extracellular matrix proteins and a robust pro-inflammatory reaction. Cytokine secretion further exacerbates the inflammatory milieu, and the presentation of modified lipoproteins as autoantigens may stimulate adaptive immune responses.

In the context of atherogenesis, several critical cellular processes unfold. As a response to lipid retention and cellular injury, intimal cells exhibit signs of lipidosis, fibrosis, and inflammation. While some early lesions may regress spontaneously or stabilize, chronic inflammatory responses can lead to detrimental outcomes. Continuous lipid accumulation and inflammation create a vicious cycle that fosters the growth of atherosclerotic plaques, the development of new lesions, and ultimately plaque instability. These factors can precipitate acute clinical events, such as myocardial infarction or stroke (Manduteanu and Simionescu, 2012; Chistiakov et al., 2015).

The conventional approach to managing atherosclerosis centers on intensive lipid level reduction. This strategy emphasizes the pivotal role that circulating lipoproteins—with a particular focus on LDL and triglycerides—play in the initiation and progression of the disease. Current medical guidelines advocate for lowering LDL cholesterol and triglycerides while aiming to increase high-density lipoprotein (HDL) levels (Marques et al., 2018; Ginsberg et al., 2021). HDL is often characterized as "good cholesterol" due to its anti-inflammatory and antioxidant properties and its critical role in reverse cholesterol transport, which helps remove excess cholesterol from peripheral tissues and transport it back to the liver for excretion (Sobenin et al., 2014; Calabresi et al., 2014; van Capelleveen et al., 2013; Jamkhande et al., 2014; Mundi et al., 2018). Understanding the nuanced roles of various lipoproteins, particularly triglycerides, is essential for elucidating their impact on atherosclerosis development. Emerging evidence suggests that not only do triglycerides contribute to atherosclerotic processes, but their levels may also reflect the body's metabolic state, influencing cardiovascular risk independently of LDL cholesterol levels.

Overall, enhancing our understanding of lipid metabolism, including distinctions among various lipoproteins and their contributions to atherogenesis, is crucial for advancing therapeutic strategies aimed at preventing and reversing atherosclerosis.

3. Triglycerides

One of the main functions of triglycerides is energy storage. Triglyceride (TG) and cholesteryl esters (CE) are hydrophobic, which corresponds to the form in which they circulate in the blood. This structure consists of the core of spherical lipoproteins, monolayer phospholipids, free cholesterol cover, and stabilizing apolipoproteins (Feingold, 2000). The primary structural apolipoprotein is Apolipoprotein (apo)B, which exists in two isoforms: liver-derived apoB100 and truncated intestine-derived apoB48. The presence of apoB defines the type of triglyceride-rich lipoprotein (TRL). VLDL is formed in the liver and contains the liver-originated form apoB100 (Behbodikhah et al., 2021). These

particles are metabolized to VLDL remnants, intermediate-density lipoproteins (IDL), and LDL. Chylomicrons, assembled in the intestine, contain apoB48 and are metabolized to remnant particles, but not to IDL or LDL (Feingold, 2000; Behbodikhah et al., 2021).

Lipoprotein lipase (LPL) plays a pivotal role in the metabolism of triglyceride-rich lipoproteins (TRLs). It forms a complex with glycosylphosphatidylinositol high-density lipoprotein protein 1 (GPIHBP1), synthesized by endothelial capillary cells. This binding secures LPL to the endothelial cell surface and initiates lipolysis. During the hydrolysis of TGs by LPL, chylomicron (CM) and VLDL particles are broken down into free fatty acids and glycerol, which are released for cellular uptake and energy production. This process generates lipoprotein remnants, which become enriched with cholesterol esters due to the actions of cholesteryl ester transfer protein (CETP) (Kumari et al., 2021).

Furthermore, microsomal triglyceride transfer protein (MTP) relocates from the cytosol to the endoplasmic reticulum, accompanying nascent APOB as chylomicrons and VLDL are assembled within enterocytes and hepatocytes. Disruption of MTP function through inhibition leads to reduced expression and function of this protein, resulting in decreased biosynthesis and plasma levels of both chylomicrons and VLDL, subsequently lowering plasma LDL and TG levels (Hussain et al., 2011).

Triglycerides (TG) and triglyceride-rich lipoproteins (TRLs) are crucial components of lipid metabolism in the body. TGs serve as a primary form of energy storage, found in adipose tissue and circulating in the bloodstream as part of TRLs. Throughout TRL metabolism, TGs are packaged into chylomicrons and VLDL in the intestine and liver, respectively. These TRLs facilitate the transport of TGs to various tissues for energy utilization or storage. Disruptions in TG and TRL metabolism can lead to dyslipidemia, a significant risk factor for cardiovascular diseases. Understanding the intricacies of TG and TRL metabolism is essential for managing lipid disorders and mitigating associated health risks effectively (Zhang et al., 2022).

Usually, hypertriglyceridemia (HTG) is characterized by a serum TG level exceeding 150 mg/dL. This condition holds pathological significance and is strongly associated with heightened risks of pancreatitis, particularly when TG levels surpass 1000 mg/dL. Furthermore, HTG is correlated with insulin resistance and the accumulation of lipids within internal organs such as the liver, pancreas, and epicardium (Shemesh and Zafrir, 2019).

In the context of HTG, small, dense LDL and smaller, denser HDL particles can develop, exhibiting altered lipid and protein composition and impaired vasculoprotective functions. VLDL particles are assembled in the liver, while chylomicrons are formed in the small intestine. Notably, large TRLs are typically not atherogenic, whereas cholesterol-rich remnants formed by lipoprotein lipase-mediated hydrolysis possess atherogenic properties (Packard et al., 2020).

Numerous longitudinal cohort studies have identified HTG as an independent risk factor for coronary artery disease (CAD) and acute cardiovascular events. Even moderate elevations in triglyceride levels correlate with increased cardiovascular risk. For instance, studies such as the Framingham Offspring Study have consistently shown that triglyceride levels ranging from 100 to 200 mg/dL lead to a rising risk of CVD (Hajar, 2017). The role of HTG in driving atherosclerotic disease is further validated by genome-wide association studies and Mendelian inheritance studies (Hajar, 2017).

Recent research highlights the association between lipoprotein remnants and CAD risk, evidenced across various studies, including the Copenhagen Heart Study, the Jackson Heart Study, the Framingham Study, and cohorts from the PREDIMED trial (Sandesara et al., 2019). In patients already on statin therapy, increased TRL levels correspond with elevated cardiovascular risk, as demonstrated in studies like the MIRACL study and the dalcetrapib OUTCOMES trial. Moreover, the Bezafibrate Prevention Project shows that all-cause mortality increases nearly exponentially as serum triglyceride levels rise in patients with established CAD over prolonged follow-ups (Schwartz et al., 2012).

4. Atherogenic effects of triglyceride-rich lipoproteins and their mechanisms

Recent investigations have revealed that lipoproteins in circulation are predominantly transported through the arterial wall via transcytosis. This transcytotic transport system is limited to lipoproteins with diameters of less than approximately 70 nm, which excludes chylomicrons (CM) and larger very low-density lipoprotein (VLDL) particles (Zhang et al., 2018). Furthermore, the remnants of TRLs can infiltrate the subendothelial space. Unlike low-density lipoproteins (LDL), TRL remnants have a greater cholesterol content per particle due to their larger size. Notably, these particles do not require modification or oxidation to become atherogenic; they can be directly absorbed by macrophages. As previously highlighted, TRL remnants tend to exert a more potent atherogenic effect compared to LDL (Sniderman et al., 2019).

In both human subjects and Watanabe heritable hyperlipidemic rabbits, lipoproteins containing apoB48 and apoB100 have been identified in aortic intima lesions that promote the development of atherosclerosis. The presence of triglyceride-rich residual lipoproteins in human atherosclerotic plaques further substantiates the involvement of TRLs in the development and progression of atherosclerotic lesions. Additionally, elevated levels of circulating triglycerides in a fasting-free state—serving as markers for residual triglyceride-rich particles—are linked to an increased risk of premature cardiovascular disease (CVD) (Peng et al., 2017).

While the mechanisms underlying the atherogenicity of TRLs have garnered increasing attention, they remain insufficiently studied. Recent research compellingly demonstrates that TRLs exhibit a tendency to adhere to the arterial wall, causing damage to the endothelium. They can infiltrate the arterial intima through breaches in the endothelial layer, particularly at sites of atherosclerotic plaques, which enhances the attraction and adhesion of monocytes and ultimately triggers the formation of foam cells—a hallmark of atherosclerosis. Concurrently, TRLs contribute to the development and progression of atherosclerosis by promoting inflammation and modulating the activity of various cytokines (Gimbrone and García-Cardeña, 2016). A schematic representation of the atherogenic effects of TRLs is provided (see Fig. 1).

4.1 TRLs and Endothelial Dysfunction

Endothelial dysfunction is a precursor to the formation of atherosclerotic lesions, marking one of the initial stages in the pathophysiology of atherosclerosis. A pivotal aspect of this cascade is the potential impact of TRL remnants on endothelial dysfunction, thereby exacerbating atherogenesis. Research has highlighted the connection between flow-mediated and acetylcholine-induced vasodilation and the endothelium's release of nitric oxide (NO), a sensitive indicator of endothelium-dependent vasodilation (Saenz-Medina et al., 2022).

Clinical investigations have substantiated the association between rapid postprandial serum triglyceride elevation, particularly after a high-fat meal, and endothelial dysfunction. This connection has been evaluated through assessments of flow-mediated vasodilation impairment. Additionally, evidence has emerged showcasing the disruptive effect of residual lipoproteins on endothelium-dependent vasomotor function within human coronary arteries (Kim et al., 2012).

Notably, TRL remnants can interact with endothelial cells, leading to increased expression of cell adhesion molecules (CAMs), which promote the recruitment and adhesion of circulating monocytes. In 2016, Lucero et al. explored the impact of circulating TRLs on endothelial function in patients with metabolic syndrome. They found a compelling positive correlation between triglyceride content within TRLs and the inhibition of acetylcholine-mediated vasorelaxation, as depicted through dose-response curves (Lucero et al., 2016). A similar study in Japan involving 4,887 participants assessed the interplay between serum triglyceride levels and endothelial function using brachial artery flow-mediated vasodilation (FMD) (Kajikawa et al., 2016).

Subsequently, it was ascertained that serum triglyceride levels surpassing 98.4 mg/dL exhibited an independent link with the lower quartile of FMD (less than 3.9%), even after accounting for variables like age, gender, and cardiovascular disease risk factors, including HDL-C. This underscores the hypothesis that triglycerides independently predict endothelial dysfunction (Zhong et al., 2018).

Investigations using animal models have led to consistent outcomes. The Matsumoto et al. trial utilized a hereditary postprandial hypertriglyceridemic (PHT) rabbit model, which exhibited significantly elevated serum TG levels after standard feeding. Healthy Japanese white rabbits (JW rabbits) served as controls. The study demonstrated that PHT rabbits showed noticeable intimal thickening in the aorta and impaired endothelial function due to acetylcholine-induced vascular relaxation, likely linked to elevated NO levels (Fan et al., 2015). These results indicate that hypertriglyceridemia can contribute to endothelial dysfunction and the initiation and progression of atherosclerosis (Matsumoto et al., 2014).

Furthermore, TRL remnants can trigger the production of reactive oxygen species (ROS), escalating endothelial permeability and leading to heightened cellular damage, particularly among endothelial cells. These remnants disturb endothelial function through direct and indirect effects on nitric oxide synthase, altering the delicate balance between ROS and NO, which can precipitate endothelial dysfunction and ultimately cardiovascular complications related to hypertriglyceridemia (Mittal et al., 2014).

Moreover, TRLs have been found to inhibit the atheroprotective and anti-inflammatory effects of HDL, significantly correlating with impaired endothelium-dependent coronary vasodilation (Tran-Dinh et al., 2013). The accumulation of TRL remnants fosters a pro-inflammatory environment, further enhancing monocyte and macrophage activation, which play crucial roles in the development of atherosclerotic lesions.

Hypertriglyceridemia's role in atherosclerosis is substantiated by research. Managing plasma triglycerides emerges as a key strategy to mitigate residual cardiovascular disease (CVD) risk, aligning with guideline-recommended LDL cholesterol targets. Anticipated clinical trials will provide further insights (Basu and Bornfeldt, 2020).

4.2. TRLs and foam cells

Activated macrophages, which serve as reservoirs for altered lipoproteins that transform into lipid-laden foam cells, are found in significant numbers within atherosclerotic lesions. Under oxidative stress, triglycerides stored in macrophages are shown to enhance mitochondrial production of reactive oxygen species, further promoting the formation of foam cells (Sanda et al., 2021; Sobenin et al., 2013; Sobenin et al., 2012).

Additionally, in patients with hypertriglyceridemia, low-density lipoprotein (LDL) particles exhibit increased levels of apolipoprotein E (ApoE). This change initiates a conformational

shift in very low-density lipoprotein (VLDL) particles, enhancing their affinity for binding to macrophage scavenger receptors. The remnants of chylomicrons (CM) and intermediate-density lipoprotein (IDL) are small enough to easily penetrate the subendothelial space, where they are readily engulfed by scavenger receptors on macrophages, ultimately leading to the formation of foam cells (Welty, 2013; Sukhorukov et al., 2020).

Furthermore, CM remnants have been shown to promote the progression of atherosclerosis. By infiltrating the subendothelial space, these remnants activate leukocytes, thereby encouraging the formation of foam cells. They also stimulate monocyte activation, which increases the influx of both monocytes and neutrophils following meals (Moore et al., 2013).

4.3. TRLs and inflammation

Several studies consistently indicate that inflammation is a critical risk factor for the initiation and progression of atherosclerosis. The accumulation of triglyceride-rich lipoproteins (TRLs) following meals leads to the retention of remnant particles in the arterial wall, provoking inflammatory responses and oxidative stress. Furthermore, various cell types are involved in inflammation through both direct and indirect mechanisms (Rafieian-Kopaei et al., 2014).

High concentrations of lipolytic products resulting from lipoprotein lipase (LPL)-mediated hydrolysis of TRLs, such as oxidized free fatty acids (FFAs), activate several pro-inflammatory and pro-apoptotic signaling pathways that are pivotal to atherosclerosis pathogenesis. Research has shown that oxidized FFAs induce the production of inflammatory interleukins, contributing to endothelial inflammation. Additionally, TRL remnants enhance the expression of intercellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1), promoting leukocyte migration to sites of inflammation and intensifying the inflammatory response (Goldberg and Bornfeldt, 2013; Chistiakov et al., 2015).

Bleda et al. demonstrated that elevated triglyceride (TG) and VLDL cholesterol levels trigger plaque rupture and arterial inflammation through mechanisms involving the NLRP1 pathway. Activation of NLRP1 by TG and VLDL appears to play a significant role in endothelial inflammation (Bleda and De Haro, 2019).

Moreover, TRLs can influence the levels and particle size of high-density lipoprotein (HDL). Higher TG levels facilitate increased exchange between TG-rich lipoproteins containing apolipoprotein B (ApoB) and cholesteryl ester (CE)-rich HDL via cholesteryl ester transfer protein (CETP). This results in the formation of HDL particles that are rich in TG and poor in CE, which are catabolized more rapidly than larger, CE-rich HDL particles, ultimately reducing HDL cholesterol levels (Franczyk et al., 2021). A recent study also showed that high postprandial triglyceridemia induces a shift towards larger HDL particles, accompanied by cholesterol depletion and enrichment of TG in HDL3 subclasses (Zhao et al., 2021).

The modification of HDL structure is closely linked to its antioxidant capacity, a function that can be altered through HDL remodeling. Current perspectives suggest that different subpopulations of HDL particles, formed by unique protein clusters, carry out specific biological roles. Notably, paraoxonase 1 (PON1), an atheroprotective protein, exhibits enhanced antioxidant, anti-inflammatory, and lipid transfer functions. However, it remains uncertain whether HDL particles enriched with TG and those lacking CE differ in their PON1 content or activity, which may contribute to atherosclerosis development (Thakkar et al., 2021).

Interestingly, one study indicated that PON1 activity does not decrease but actually increases significantly after meals (Meneses et al., 2019; Sobenin et al., 2013; Sobenin et al., 2014). This underscores the urgent need for further investigation into the implications of these structural modifications—including other constituents or proteins such as apolipoprotein A-I, myeloperoxidase, and acetylhydrolase of platelet-activating factor—on HDL's anti-atherogenic functions, particularly in the context of stable postprandial lipemia. Understanding how the mechanism of TG enrichment in HDL subclasses contributes to atherosclerosis is equally crucial. HDL has been observed to transport ApoB-bound sphingosine-1-phosphate (S1P), a lipid mediator with anti-inflammatory properties that supports the generation of inflammatory Th1 cells by inhibiting regulatory T cell differentiation. Consequently, elevated TG levels may alter HDL concentration and size, reducing the presence of large TG-rich HDL and potentially impairing its role in the anti-inflammatory process mediated by regulatory T cells. This transformation could also promote inflammation through pro-inflammatory T cells (Neyla de Lima Albuquerque et al., 2015).

Mild to moderate hypertriglyceridemia (TG levels: 200-800 mg/dL) is associated with low HDL cholesterol, small dense LDL (sd-LDL) particles, and TG-rich atherogenic remnants. sd-LDL is formed through the hepatic lipase modification of VLDL1 and is linked to increased cardiovascular risk in hypertriglyceridemia (Fujii et al., 2020). The atherogenicity of sd-LDL arises from multiple factors, including their small size, which facilitates easy penetration of the arterial wall, and their prolonged presence in the subendothelium due to strong affinity for proteoglycans, promoting lipid accumulation and atherosclerosis (Ivanova et al., 2017). The lower antioxidant content of sd-LDL, such as reduced vitamin E, increases their susceptibility to oxidation. Other mechanisms include potential activation of plasminogen-activator inhibitor-1 and accelerated thromboxane A2 synthesis. Moreover, TRLs and their

remnants can trigger early activation of monocytes and neutrophils, further fostering inflammation (Ding et al., 2022).

Atherosclerosis is influenced by several key cytokines, with apoptosis playing a significant role in vascular damage. Remnants of TRLs induce apoptosis in endothelial cells by increasing levels of pro-apoptotic cytokines, particularly TNF-α and IL-1β. TNF-α has a profound effect on endothelial dysfunction, contributing to inflammation and disrupting nitric oxide production. Elevated TNF-α levels correlate positively with VLDL cholesterol, even in postprandial hypertriglyceridemia (PTH) rabbits. Recent research has linked increased TNF-α levels to heightened expression of JAM-1, which facilitates the progression of atherosclerosis (Amin et al., 2020).

Adipocytes release adipocytokines, including the anti-atherogenic adiponectin and lipolytic leptin. Reduced levels of adiponectin and mRNA in PTH rabbits suggest a connection to atherogenesis (Esfahani et al., 2015).

Finally, TRLs and their remnants promote a procoagulant state by enhancing platelet aggregation and clot formation, which elevates levels of fibrinogen, coagulation factors VII and XII, and plasminogen activator inhibitor-1 (Chapin and Hajjar, 2015).

4.4. Triglycerides and residual risk

In modern cardiology, there is a growing emphasis on identifying the risk of atherosclerotic cardiovascular disease (ASCVD) even in individuals with low low-density lipoprotein cholesterol (LDL-C) levels. Unstable, inflamed plaques that are prone to rupture highlight the need to recognize additional risk factors for vascular inflammation and plaque instability, regardless of the estimated cardiovascular disease (CVD) risk.

The PESA study investigated the impact of hypertriglyceridemia (TG levels >150 mg/dL) on non-coronary atherosclerosis and vascular inflammation. Among participants—primarily young adults with an average age of around 45 years and a low-to-moderate 10-year risk—early signs of atherosclerosis were observed. Individuals with TG levels below 100 mg/dL exhibited subclinical atherosclerosis, and approximately 40% demonstrated increased inflammatory activity. In contrast, TG levels above 150 mg/dL significantly heightened the risk of atherosclerosis and involvement of vascular territories, independent of LDL cholesterol levels. Notably, arterial inflammation and plaque count were correlated with TG levels, with high TGs increasing the risk of arterial inflammation twofold. Additionally, elevated thyroid-stimulating hormone (TSH) levels were associated with systemic disease (Raposeiras-Roubin et al., 2021).

This study underscores the independent role of triglycerides in atherosclerosis and vascular inflammation, marking them as significant risk indicators (Toth et al., 2020). Although the REDUCE-IT trial demonstrated a reduction in cardiovascular events among patients with hypertriglyceridemia (HTG), this outcome was not solely attributable to decreases in triglyceride levels. The ongoing PROMINENT study may provide further insights into the effects of lowering triglyceride levels on ASCVD risk (Pradhan et al., 2020).

5. Targeting triglycerides for therapy of atherosclerosis

However, currently used drugs such as mipomersen (an antisense oligonucleotide inhibitor of apoB translation) and lomitapide (an inhibitor of microsomal triglyceride transfer protein activity) may stimulate non-alcoholic fatty liver disease, alongside their beneficial effects. This limitation indicates that these strategies are not perfect and necessitate further research (Stefanutti et al., 2020; Parham and Goldberg, 2019; Blom et al., 2019).

Another approach involves decreasing the availability of triglycerides (TGs) for very low-density lipoprotein (VLDL) assembly. A reduction in VLDL-TG and apoB secretion by approximately 25–30% can be achieved through high-dose omega-3 fatty acids (3–4 g/day), typically a combination of docosahexaenoic acid (DHA) and eicosapentaenoic acid (EPA). However, the outcomes of EPA supplementation remain controversial (Oscarsson J, Hurt-Camejo, 2017; Nicholls et al., 2020).

An additional strategy is to reduce the cholesteryl ester enrichment of remnants. Since the transfer of cholesteryl esters from high-density lipoprotein (HDL) to triglyceride-rich lipoproteins (TRLs) is essential in remnant lipoprotein formation, inhibiting cholesteryl ester transfer protein (CETP) may be beneficial. Significant decreases in the cholesterol-to-TG ratio in VLDL have been observed in studies involving evacetrapib or anacetrapib (Lincoff et al., 2017). However, CETP inhibitors have generally proven ineffective in preventing cardiovascular disease. Current research on obicetrapib indicates its potential therapeutic benefits (Kastelein et al., 2024).

Another method to lower plasma TG levels in patients is the stimulation of lipolysis. Fibrates are commonly used for this purpose, as they enhance lipoprotein lipase (LPL) activity and reduce the synthesis of apoCIII, thereby increasing the clearance efficiency of VLDL. The effectiveness of stimulating lipolysis to decrease remnant concentrations depends on the efficiency of hepatic uptake pathways. Both apoCIII and ANGPTL3 are known inhibitors of LPL, and targeting these factors may yield benefits, as supported by several studies (Ueda et al., 2020; Ahmad et al., 2019; Gaudet et al., 2020; Witztum et al., 2019).

Additionally, improving the clearance of remnants is another viable strategy. Statin therapy can upregulate LDL receptors, promoting remnant catabolism and reducing the levels of remnant particles. Moreover, statins enhance the clearance of chylomicron remnants

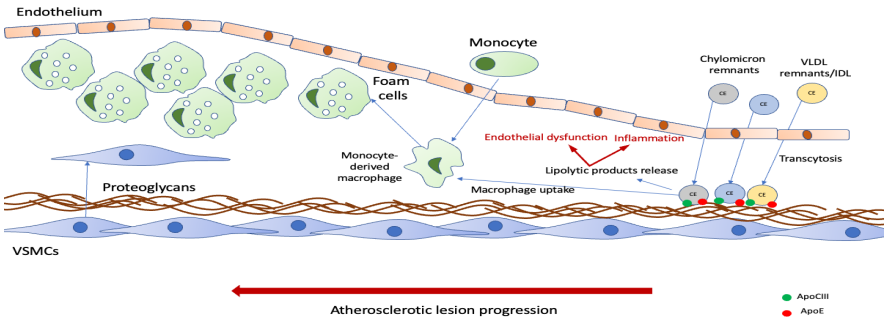

Figure 1. Role of TRLs and remnants in atherogenesis. Chylomicron remnants, VLDL, and IDL particles enter the artery wall through transcytosis. These particles can adhere to proteoglycans of extracellular matrix via located on the surface (apo) CIII and apoE. Degradation of these particles releases bioactive lipids, contributing to endothelial dysfunction and inflammation. Monocytes and monocyte-derived macrophages are recruited from the circulation, internalize the arterial wall. Uptake of cholesterol-enriched lipoproteins by macrophages result in their transformation into foam cells.

and lower lipemia after fat-rich meals (Chait et al., 2020). PCSK9 inhibitors have also been shown to enhance LDL receptor activity and increase the clearance rate of IDL in healthy subjects, although their effectiveness is generally lower than that of statins (Taskinen et al., 2021).

Peroxisome proliferator-activated receptors (PPARs), which are integral nuclear receptors, play a crucial role in modulating genes associated with lipid metabolism, inflammation, and vascular functions. By leveraging the diverse effects of PPAR activation—such as reducing inflammation, improving lipid profiles, and enhancing insulin sensitivity—researchers are discovering novel strategies to combat atherosclerosis.

Clinical investigations into PPAR agonists, including fibrates and thiazolidinediones, have demonstrated their capacity to mitigate atherosclerosis through regulation of lipid metabolism and attenuation of vascular inflammation. Moreover, the development of dual or pan-PPAR agonists, which target multiple PPAR isoforms simultaneously, shows promise for achieving synergistic effects with enhanced therapeutic outcomes.

As ongoing research deepens our understanding of the distinct roles played by various PPAR isoforms in atherosclerosis, the potential for tailored and innovative treatments continues to expand. By integrating cutting-edge science with clinical trials, the landscape of atherosclerosis therapy is poised for significant advancements that could transform cardiovascular care (Miao et al., 2023).

Pemafibrate, a selective PPARα modulator, shows promise in treating atherosclerosis in patients with hypertriglyceridemia and low HDL cholesterol levels (Yamashita et al., 2020). In the PROMINENT study, pemafibrate effectively reduced triglycerides, VLDL cholesterol, remnant cholesterol, and apoC-III levels but did not demonstrate a significant difference in cardiovascular events compared to placebo. Despite some adverse effects, pemafibrate offers advantages over traditional fibrates like fenofibrate, including stronger PPARα activation and a lower incidence of adverse events. Research suggests that pemafibrate has potential in managing atherogenic dyslipidemia and warrants further exploration for preventing cardiovascular events and managing atherosclerosis (Kim et al., 2022; Yamashita et al., 2023).

6. Results and Discussion

Our review highlights the intricate relationship between elevated triglycerides (HTG) and the risk of atherosclerosis and cardiovascular events. A comprehensive synthesis of current literature indicates that HTG significantly contributes to endothelial dysfunction and inflammatory responses that promote atherogenesis. Numerous studies have demonstrated that elevated triglyceride levels lead to impaired endothelial function. In particular, postprandial elevations in triglycerides correlate with a decrease in flow-mediated vasodilation (FMD), a critical measure of endothelial health. Participants with triglyceride levels exceeding 150 mg/dL consistently exhibit reduced FMD, establishing hypertriglyceridemia as an independent predictor of endothelial dysfunction.

The role of triglyceride-rich lipoproteins (TRLs) and their remnants is pivotal in this process, as these particles penetrate the endothelial barrier, exacerbating inflammation. TRL remnants not only promote the formation of foam cells—a hallmark of early atherosclerosis—but also enhance the expression of adhesion molecules on endothelial cells, thereby facilitating the recruitment of monocytes. Findings from animal models further corroborate that TRL remnants directly contribute to intimal thickening and the progression of atherosclerotic lesions.

Moreover, elevated triglycerides initiate an inflammatory cascade characterized by increased production of reactive oxygen species (ROS) and pro-inflammatory cytokines, further intensifying endothelial injury and perpetuating dyslipidemia. This creates a vicious cycle that fosters the development of atherosclerosis. Specifically, oxidized free fatty acids, derived from TRL hydrolysis, have been demonstrated to activate pathways that contribute to endothelial dysfunction and subsequent atherogenic processes.

The clinical implications of these findings are considerable. Elevated TRL levels are consistently associated with increased cardiovascular risk across various studies, including the Framingham Offspring Study and the PREDIMED trial. Such evidence suggests that triglyceride levels should be integrated into cardiovascular risk assessment protocols, especially for patients who still face residual risk despite proper management of low-density lipoprotein cholesterol (LDL-C).

Overall, the findings elucidate the multifaceted roles of triglycerides in the pathogenesis of atherosclerosis, underscoring the importance of understanding these roles to develop targeted interventions for cardiovascular disease prevention. The direct impact of TRL remnants on endothelial function is particularly significant. As these remnants infiltrate the arterial wall, they induce dysfunction by increasing ROS production, disrupting nitric oxide synthesis, and enhancing monocyte adhesion. Addressing TRL remnants could therefore represent a valuable therapeutic strategy to restore endothelial function and reduce the risk of atherosclerosis.

Additionally, the transformation of macrophages into foam cells, facilitated by the uptake of TRL remnants, signifies a critical aspect of early atherosclerosis. The presence of these lipid-laden macrophages in arterial plaques highlights the necessity of targeting the lipid composition of circulating lipoproteins. Interventions aimed at lowering both triglyceride and TRL levels may play a crucial role in mitigating foam cell formation and stabilizing plaques.

Furthermore, the review emphasizes the inflammatory nature of atherogenesis associated with hypertriglyceridemia. Chronic inflammation, driven by disturbances in lipid metabolism, accelerates the progression of atherosclerosis while complicating cardiovascular disease management. Recognizing triglycerides as a pro-inflammatory factor opens new therapeutic avenues that incorporate anti-inflammatory strategies alongside established lipid-lowering agents.

In light of these insights, it becomes evident that current interventions primarily focus on lowering LDL cholesterol, yet the evidence supports a more comprehensive approach that includes triglyceride management. Emerging therapies, such as PPAR agonists and CETP inhibitors, may prove beneficial in addressing triglyceride levels and their atherogenic effects. Ongoing clinical trials will be instrumental in determining the efficacy of these interventions in reducing cardiovascular events linked to hypertriglyceridemia.

Author contributions

Original draft preparation was conducted by A.V.P. The manuscript was reviewed and edited by V.N.S., T.V.K., T.I.K., I.A.S., D.F.B., and A.N.O. All authors have read and approved the final version of the manuscript for publication.

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Competing financial interests

The authors have no conflict of interest.

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