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Postprandial implications in cardiovascular disease and potential markers to develop new therapies

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ABSTRACT

An unbalanced diet significantly raises the risk of various chronic diseases and cancers, contributing to increased morbidity and mortality globally. Today, the link between metabolic status and cardiovascular disease is well established. Disruptions in glucose and lipid homeostasis, particularly postprandial hyperglycemia and hyperlipidemia are key risk factors for cardiovascular conditions. These postprandial metabolic disturbances promote atherosclerosis and cardiovascular injury, primarily by triggering endothelial dysfunction.

Lifestyle interventions play a pivotal role, and pharmacological treatments aimed at controlling lipid and glucose levels generally lead to improvements in both fasting and postprandial states. However, further research is necessary to establish reference values for biomarkers of postprandial dysmetabolism and to evaluate their clinical relevance. Individuals who exhibit a mismatch between fasting and postprandial levels of glucose and triglycerides, namely, those with normal or mildly elevated fasting levels but exaggerated postprandial responses, may represent a subgroup at heightened and potentially modifiable risk for both microvascular and macrovascular complications. Validating biomarkers of postprandial dysmetabolism could offer valuable clinical tools for improved risk assessment and personalized therapeutic strategies. This review summarises the unique physiology of triglyceride-rich lipoprotein metabolism after meals and the disruptions that can foster cardiovascular complications. Given the scarcity of targeted therapies, it also discusses emerging treatment candidates and their underlying mechanisms.

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Introduction

Western diets that are very rich in calories, combined with over-nutrition and physical inactivity, promote chronic low-grade inflammation that plays a pivotal role in the development of prevalent non-communicable diseases [1]. Is important to understand how this lifestyle activates immune responses for developing strategies to prevent and treat these conditions. Non-communicable diseases account for over 80% of deaths in Western societies, primarily affecting older adults and reducing healthy lifespan. These chronic conditions impose a growing socioeconomic concern, and so far their mechanisms remain poorly understood [1, 2].

The nutrient profile of a meal significantly impacts postprandial metabolism, with high-fat or high-sugar meals inducing a stronger postprandial response [3]. Assessment of the postprandial lipid profile offers a more sensitive and dynamic measure of the lipid metabolic capacity of the patients compared to fasting lipid levels. It reflects the ability of the organism to efficiently clear and process dietary lipids following a meal, thereby serving as an important indicator of general metabolic efficiency and cardiovascular risk. The postprandial state, lasting 6-12 hours, often extends to 16 hours after a meal. This state involves nutrient absorption and is marked by increased blood sugar, lipids, and low-grade systemic inflammation [4]. Postprandial inflammation can lead to endothelial dysfunction, which is a risk factor for heart disease, insulin resistance, obesity, metabolic syndrome and cardiovascular disease [5].

Recent experimental and clinical studies indicate that metabolic syndrome and cardiovascular disease may result from a systemic in-

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flammatory process [6]. This inflammation is marked by elevated levels of acute-phase proteins and pro-inflammatory cytokines, such as C-reactive protein (CRP), tumour necrosis factor-alpha (TNF-α), and interleukins (IL-1, IL-6, and IL-17), along with increased infiltration of immune cells like macrophages and T lymphocytes into insulin-sensitive tissues [7]. Both low-grade systemic inflammation and dyslipidaemia have been recognized as key contributors to atherogenesis and the associated vascular risks [8].

This review aims to summarize the differences in the metabolism of triglyceride-rich lipoproteins in the postprandial phase, as well as the alterations that can disrupt their normal metabolism and the associated complications. Given the current lack of effective therapies to manage these metabolic disturbances, it is important to explore new therapeutic targets. In this review, we have dedicated a section to summarizing several potential therapeutic targets and their mechanisms of action.

Metabolism of the postprandial lipids

Following food uptake, dietary triglycerides (TG) are absorbed in the small intestine and assemble with apolipoprotein B-48 (apoB-48) into chylomicrons by enterocyte (**Figure 1A**). They are secreted into the lymphatic circulation and subsequently enter in the bloodstream. Following their secretion into the circulation, the TG content of chylomicrons is hydrolyzed by lipoprotein lipase (LPL) to chylomicron remnants [9, 10]. These remnants are then cleared by the liver via receptor-mediated endocytosis for further metabolism [10, 11]. The low-density lipoprotein receptor (LDLR) and the LDL receptor–related protein (LRP) are fundamental hepatic receptors that mediate the endocytosis of remnant particles primarily by apolipoprotein E (apoE) binding [12-14]. The VLDL receptor (VLDLR), predominantly expressed in peripheral tissues like muscle and adipose tissue, facilitates the uptake of VLDL particles at these sites. ApoE plays a central role as a ligand, enabling TRL to interact with these receptors for effective clearance from the bloodstream [14].

VLDL is synthesized in hepatocytes from TG, cholesterol, apoB-100 and microsomal TG transfer protein (MTP). VLDL consists of about 90% lipids and 10% proteins. Within its lipid component, TG account for 70% of the total mass, while the remaining 30% is made up of cholesterol and phospholipids [15]. In circulation VLDL receive ApoCII and ApoE from high-density lipoprotein (HDL), for its maturation into fully functional VLDL . In mature form, VLDL primarily transports endogenous TG from the liver to peripheral tissues [15, 16]. VLDL is considered a pro-atherogenic factor because, in circulation, it is metabolized into IDL and subsequently into LDL, lipoprotein forms that play a central role in the development of atherosclerosis. In particular, the accumulation of LDL, especially small dense LDL particles, is associated with an increased risk of endothelial infiltration, oxidation, and atherosclerotic plaque formation. Thus, by contributing to the generation of these atherogenic particles, VLDL plays a key role in the pathogenesis of cardiovascular disease [9, 11]. The chylomicrons (**Figure 1A**) and VLDL (**Figure 1B**) follow the same metabolic pathway, where LPL hydrolyzes TG into glycerol and fatty acids. The formation and secretion of both TG-rich

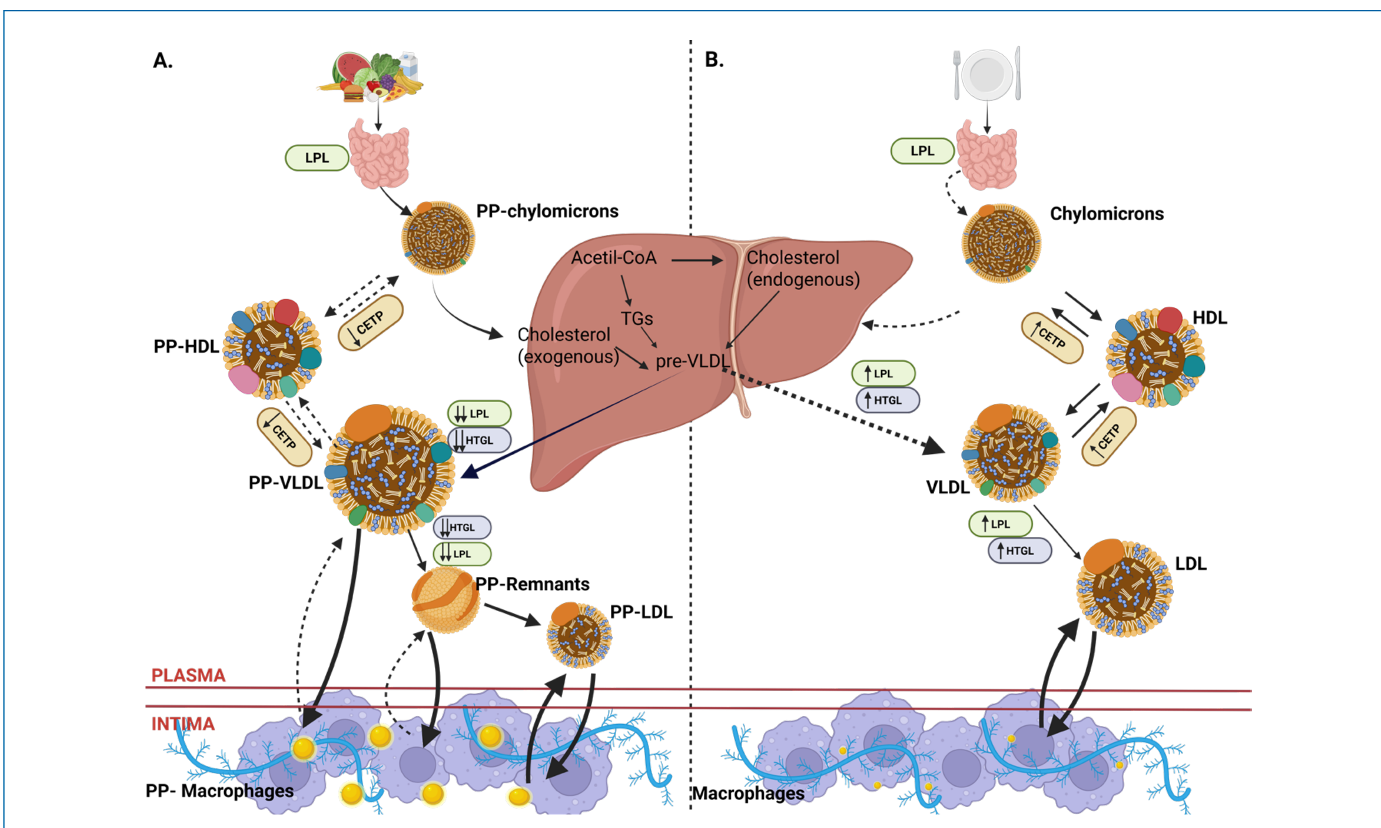

Figure 1 | **Metabolic pathways for TRL metabolism.** Comparative scheme of postprandial (A) and fasting (B) triglyceride-rich lipoprotein and remnant metabolism and its implications. LPL-lipoprotein lipase, HTGL- hepatic (TG) lipase, PP-postprandial, HDL- high density lipoproteins, LDL- low density lipoproteins, VLDL- very low density lipoprotein, CETP- Cholesteryl ester transfer protein. Created in BioRender.

lipoproteins (TRL) require MTP and apoB, without either, the synthesis does not take place [11]. Although chylomicrons and their remnants account for ~80% of the rise in postprandial TG, most particles (~80%) are liver-derived VLDL and their remnants. The concentration and synthesis rate of apoB100 significantly exceed those of apoB48, demonstrating its dominant role in the circulation of atherogenic lipoproteins. Since chylomicrons are preferentially cleared via LPL, the main atherogenic effect may arise from disrupting apoB100 catabolism [17, 18].

Modifications in TRL metabolism and clinical implications

Mutations affecting TRL metabolism can disrupt the synthesis, processing, or clearance of these lipoproteins, leading to altered lipid profiles and increased risk of metabolic and cardiovascular diseases. Such mutations may impair enzymes, receptors, or proteins involved in TRL pathways, resulting in hypertriglyceridemia, pancreatitis, and atherosclerosis. Clinically, these genetic defects can manifest as familial chylomicronemia syndrome, familial combined hyperlipidemia, or other dyslipidemias, necessitating targeted therapeutic approaches to manage elevated triglyceride levels and reduce cardiovascular risk [16].

Familial hyperchylomicronemia syndrome (FCS) is a rare autosomal recessive metabolic disorder primarily caused by mutations in the lipoprotein lipase (LPL) gene. Approximately 80% of FCS cases are due to inherited mutations in both alleles of the LPL gene. The remaining 20% result from mutations in other genes involved in LPL function, including apolipoprotein C-II (APOC2), apolipoprotein A-V (APOA5), glycosylphosphatidylinositol-anchored high-density lipoprotein-binding protein 1 (GPIHBP1), and lipase maturation factor 1 (LMF1). Additional, as yet unidentified, genetic mutations may also contribute to the condition [19]. All of these mutations result in impaired function of the enzyme lipoprotein lipase. Familial hyperchylomicronemia syndrome is a rare and often underdiagnosed condition due to its nonspecific symptoms, making it difficult to determine its exact prevalence. Current estimates suggest it affects between 3,000 and 5,000 individuals worldwide, with a frequency of approximately 1 to 10 cases per million people [20].

Familial combined hyperlipidemia (FCH) is a common and widespread hereditary lipid disorder. It is characterized by a variable expression of elevated plasma cholesterol and triglyceride levels, typically affecting at least two members within the same family [21]. In 1973 Goldstein et al. [22] and Rose et al. [23] were initially described FCH as an autosomal dominant hereditary lipid disorder. However, it was later discovered that FCH precede a multigenic pattern with a complex mode of inheritance [24, 25]. FCH is characterized by elevated serum cholesterol (hypercholesterolemia) and/or triglyceride levels (hypertriglyceridemia). In some cases, it may also present as isolated elevations in apolipoprotein B (apoB), even when the standard lipid profile appears within normal limits [26]. The estimated prevalence of FCH ranges from 0.5% to 4% [27]. The genetic basis of FCH remains incompletely understood. Metabolic abnormalities associated with the condition include increased production of very low-density lipoprotein (VLDL) and delayed clearance of low-density lipoproteins (LDL) and triglyceride-rich lipoproteins [28].

Familial hypobetalipoproteinemia (FHBL) is an autosomal codominant disorder caused by apoB gene mutations that reduce apoB48 and apoB100 secretion. These mutations often lead to truncated proteins from premature stop codons, with over 60 identified variants. Less commonly, FHBL results from PCSK9 loss-of-function mutations. The symptoms can differ between patients; heterozygous formes are mostly asymptomatic or have moderate liver steatosis, while 5-10% may develop severe steatohepatitis that can progress to cirrhosis [29]. Most evidence suggests FHBL may protect against cardiovascular disease, but the realy mechanism is unclear. A meta-analysis of 12 studies with 57.973 subjects showed apoB truncations reduce coronary heart disease risk by 72% [30].

Familial defective apoB100 is an autosomal codominant disorder causing high cholesterol and early atherosclerosis. This results from the substitution of glutamine with arginine at amino acid position 3500 (R3500Q) in the gene for apoB100, reducing its binding to LDL receptors, which decreases LDL clearance and increases plasma LDL levels [31]. The second most frequent mutation in the same position is the substitution of tryptophan for arginine. The R3500Q mutation has been associated with a 60–70 mg/dL increase in serum LDL-C levels [32]. Both mutations (R3500Q and R3500W) of the APOB gene contribute to about 12% of familial hypercholesterolemia (FH) cases. However, mutations in APOB are generally less severe than those in the LDLR, which are the main cause of FH, resulting in moderate increases in serum LDL-C levels [33].

Moreover, overproduction of VLDL-ApoB100 may result from altered gene/protein expression and inflammatory insulin signaling. The ApoB100 rs693 polymorphism is linked to metabolic syndrome, obesity, and elevated TC, LDL-C, TG, and glucose levels [34]. A recent study by Taskinen et al. examined how intestinal triglyceride-rich lipoproteins affect residual cardiovascular risk in overweight/obese diabetic patients on statins. While apoB100 kinetics in VLDL and LDL showed no significant changes, postrandial apoB48 levels were about twice higher, especially in the VLDL1 and VLDL2 density ranges [35].

Also ***epigenetic modifications*** of genes involved in TRL metabolism occur. Epigenetic processes are natural and essential for the normal functioning of organisms. These changes modify gene expression and activity without altering the DNA sequence [36, 37]. Among various epigenetic mechanisms, DNA methylation is one of the most significant. It involves the covalent addition of a methyl group to cytosine-guanine dinucleotides (CpG), a reaction catalyzed by DNA methyltransferases [38]. Since CpG sites are often located in gene regulatory regions, their methylation can significantly influence gene expression [39]. Several studies have investigated the association between DNA methylation at various gene loci and serum TG levels, showing inconsistent results. While some studies found no significant correlation between methylation status and TG concentrations [38, 39], others reported a positive association [36, 40]. There are different epigenetic changes that might affect TG levels; some genes including: ATP Binding Cassette Subfamily G Member 1 (ABCG1), sterol regulatory element-binding protein 1 (SREBP-1) and Carnitine Palmitoyltransferase 1A (CPT1A) have been explored more than others. These genes are required for glucose metabolism and fatty acid and lipid production.

A meta-analysis explored the relationship between DNA methylation at various CpG sites within the these genes and serum TG levels [41]. It found that increased methylation of ABCG1 and SREBP-1, along with decreased methylation of CPT1A, was significantly associated with elevated serum TG levels. These results may help explain the considerable variability in hypertriglyceridemia prevalence observed across different populations. Consequently, investigating these genes may play a crucial role in the prevention of cardio-metabolic risk factors, including total cholesterol and insulin levels, as well as measures of general and abdominal obesity [42-44].

Implication of TRL in cardiovascular diseases

In the postprandial state, chylomicron remnants and VLDL interact with circulating leukocytes and endothelial cells, inducing acute cellular activation characterized by integrin expression, oxidative stress, cytokines release, and complement system activation [45].

Interestingly, although postprandial inflammatory responses may occur multiple times daily following meals, there is limited evidence regarding the specific contributions of nutrients to these processes [46]. It has been demonstrated that elevated TG and glucose levels lead to an increase in neutrophil number, followed by enhanced production of pro-inflammatory cytokines and oxidative stress, which may contribute to endothelial dysfunction [46]. Moreover, TG and glucose have been shown to induce leukocyte activation, both *in vitro* [47, 48] and *in vivo* in hypertriglyceridemic patients [49]. Postprandially, TG and leukocyte number begin to rise after 1–2 hours, indicating the probable initiation of leukocyte activation. Notably, leukocyte activation was observed not only at 6 hours but persisted up to 10 hours postprandially, with no significant differences in activation levels between the 6-hour and 10-hour after oral fat ingestion. The presence of apoB on neutrophils and monocytes supports the binding of TRL to leukocytes [50]. Leukocytes from cardiovascular disease patients showing increased lipid content compared to healthy controls, likely due to the uptake of chylomicrons [51]. Postprandial lipemia has been linked to increased expression of leukocyte activation markers CD11b and CD66b in both healthy patients and those with premature atherosclerosis. CD11b aids early leukocyte-endothelium adhesion, while CD66b is a neutrophil-specific degranulation marker [52]. Elevated levels of these markers have also been observed in fasting leukocytes from patients with cardiovascular disease and diabetes [52].

Additionally, *in vitro* studies have shown that primary human monocytes can internalize remnant lipoproteins [48]. TRL are taken up by macrophages through different receptor- and non-receptor-mediated pathways [14]. Primary human monocytes activated by remnant chylomicron particles exhibited a rapid and sustained production of reactive oxygen species (ROS). Even in the absence of these particles, the monocytes secreted the pro-inflammatory chemokines monocytes chemoattractant protein 1 (MCP-1) and interleukin-8 (IL-8) [48]. Upon treatment with remnant chylomicron particles, IL-8 secretion showed a transient increase and remained detectable even in the presence of pharmacological inhibitors of IL-8 synthesis. Interestingly, monocytes pre-treated with remnant chylomicron particles demonstrated enhanced chemotactic response to MCP-1, an effect that was reversed by the addition of exogenous MCP-1 [48]. Also, neutrophil levels rise after meals in healthy patients, as well as in patients with cardiovascular disease and T2D. This postprandial neutrophil increase is correlated with the synthesis of proinflammatory cytokines and oxidative stress [50].

Some studies have uncovered a novel mechanistic connection between TRL and vascular disease, involving the formation of lipid droplets (LD) within endothelial cells. These LD can suppress nitric oxide production, impairing endothelial-dependent vasodilation

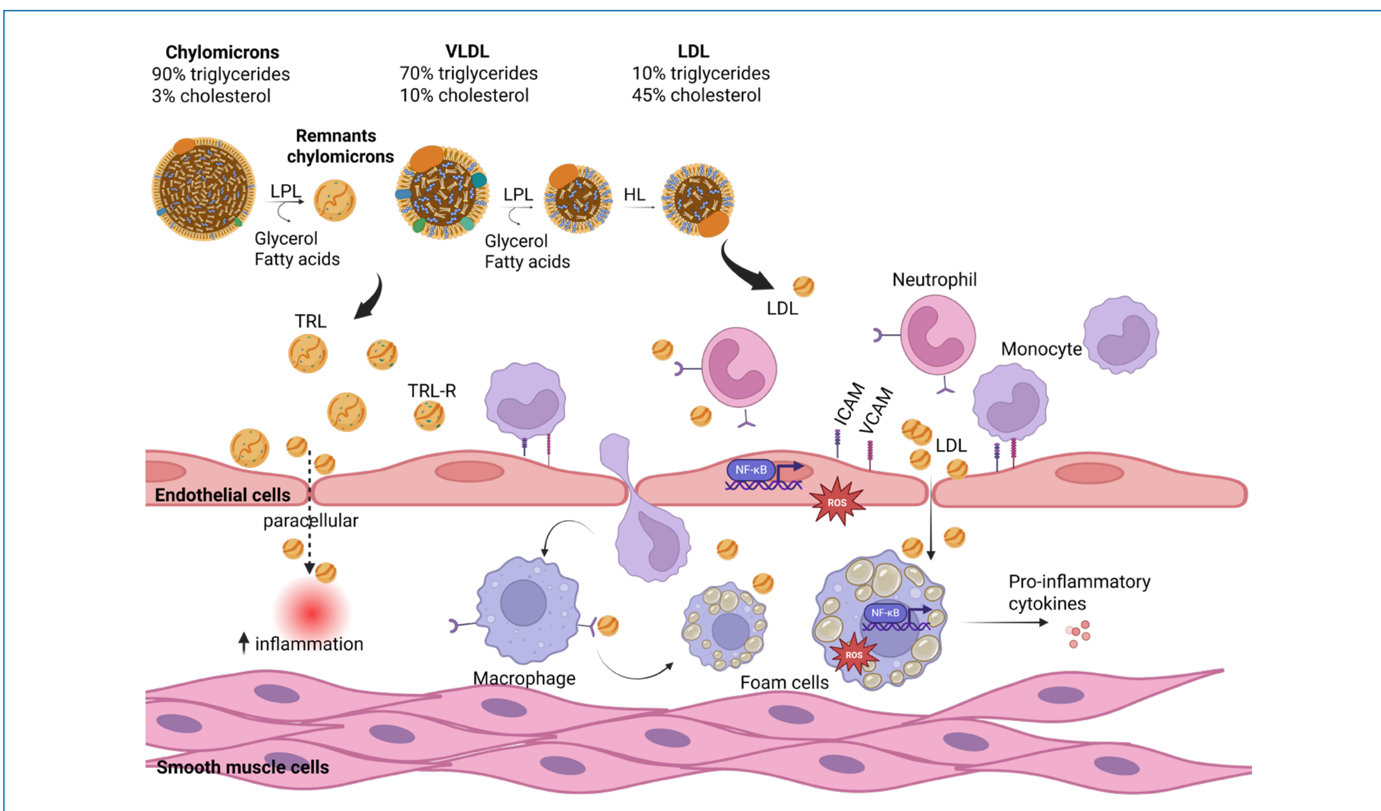

Figure 2 | **Postprandial inflammatory responses and atherosclerosis initiation.**
TRL-tryglycerides-rich lipoproteins, TRL-R-TRL remnants, LPL-lipoprotein lipase, HL- hepatic lipase, ICAM- Intercellular Adhesion Molecule, VCAM- Vascular cell adhesion molecule. Created in BioRender.

and promoting vasoconstriction, which contributes to the development of hypertension [53]. Furthermore, endothelial LD can activate the NF-κB signaling pathway, resulting in increased expression of vascular cell adhesion molecule-1 (VCAM-1). This upregulation enhances leukocyte adhesion to the endothelium, thereby promoting atherogenesis and inflammation within vascular plaques [18, 53].

Transport across the endothelium is highly efficient and does not primarily determine the concentration of atherogenic lipoproteins within the arterial wall. Instead, it is the selective retention of these lipoproteins by the extracellular matrix that governs their accumulation at sites prone to lesion development.*8* This retention occurs through ionic interactions between positively charged amino acid residues in apoB and apoE on the lipoprotein surface and negatively charged proteoglycans secreted by arterial wall cells. Similar to LDL, TRL contain a single apoB molecule per particle, but they also carry multiple apoE molecules, which enhance the binding affinity of TRL remnants for extracellular proteoglycans [17].

Consequently (**Figure 2**), postprandial inflammatory responses may include leukocyte activation through the uptake of TRL, promoting their adhesion to and activation of endothelial cells. This, may enhance the migration of inflammatory cells and lipoproteins into the sub-endothelial space, thereby accelerating the development of atherosclerosis.

Non-traditional postprandial risk factors for atherosclerosis: Telomere shortening and CHIP

Recent study have highlighted the role of telomere shortening and clonal hematopoiesis of indeterminate potential (CHIP) as non-traditional risk factors in cardiovascular disease. Telomere shorting is a hallmark of cellular aging and contributes to genomic instability. It can trigger cell-cycle arrest, senescence, and apoptosis in vascular smooth muscle cells [54], reduce the regenerative capacity of vascular endothelium [55], and can also facilitate necrotic cores formations in atherosclerotic plaques. Telomeres progressively become shorter with age and this process is accelerated by oxidative stress and chronic low-grade inflammation, both involved in the postprandial state stess.

Following an high-fat meals, a transient low grade inflammation state can be triggered, characterized by the increases in circulating TRL, oxidative stress, and inflammatory cytokines. This postprandial inflammatory response contributes to endothelial dysfunction and may amplify and influence telomere attrition in circulating leukocytes and vascular progenitor cells [56]. Repeated episodes of postprandial state stress may result in cumulative damage to telomere integrity and accelerate vascular aging.

Telomeres play an important role in the aging of hematopoietic stem cells (HSC) and in the gradual weakening of the immune system. In rare diseases like dyskeratosis congenita, where the system that protects telomeres does not work properly, bone marrow fails because HSC can no longer renew themselves [57]. But even in people without blood disorders, having short telomeres in white blood cells has been linked to a higher risk of anemia, infections, and heart disease [58, 59]. This may be because short telomeres reduce the ability of HSC to produce new blood cells and endothelial progenitor cells (EPC), which help repair blood vessels.

EPC are important for keeping blood vessels integrity, especially by helping to repair damage. However, their number and function decrease with age and in people with CVD. Studies show that EPC age faster when telomeres become too short or when there is a lot of oxidative stress [60, 61]. Interestingly, some research suggests that statin commonly used for lowering cholesterol level, may help EPC stay younger by protecting their telomeres and boosting telomerase activity [62].

Telomere shortening is also implicated in CHIP, a particular condition characterized by clonal expansion of HSC with some somatic mutations in genes like DNMT3A, TET2, or ASXL1, in patients without hematologic malignancy. CHIP affects over 10% of individuals older than 70 years old and is associated with a two-fold increased risk of coronary artery disease, independent of classical risk factors [63]. The pathogenicity of CHIP appears to be driven by chronic inflammation, mostly mutated clonal myeloid cell in particular macrophages showing an increase of IL-1β and activation of NLRP3 inflammasome, which are common influenced by postprandial state.

However, *in vivo* studies, on mice models support the "telomer-CHIP-atherosclerosis axis". TET2-KO mice develop larger atherosclerotic plaques and show elevated IL-1β expression through NLRP3 activation [56]. In humans, CHIP is associated with increased CRP levels and a pro-inflammatory gene expression profile in monocytes. Mouse models lacking telomerase components like TERC or TERT show a progressive telomere shortening, cardiac dysfunction, impaired cardiomyocyte proliferation and early death, with an increase of expression and activation of p53 [64].

All together, these data support a "telomere–CHIP–atherosclerosis axis" in which telomere attrition and clonal hematopoiesis converge to promote inflammation and vascular aging, particularly under repeated postprandial stress.

Potential postprandial lipid biomarkers

Measuring postprandial secreted markers involved in intestinal lipoprotein metabolism may facilitate the early detection of postprandial dyslipidemia and associated cardiovascular disease risk [65]. Postprandial lipid responses have been studied in research for more then 40 years and could be considered potential tools for the risk of cardiovascular disease. While the ***traditional fasting lipid profile (TG, TC, HDL-C, LDL-C)*** is commonly used to assess cardiovascular diseases risk, evidence does not support its advantage over postprandial measurements. Postprandial lipid testing provides practical benefits, such as a more accurate representation of average daily lipid levels, easier sample collection, and improved patient compliance [66]. Although fasting dyslipidemia is a well-established risk factor for cardiovascular disease, only 47.5% of patients with acute coronary syndrome exhibit abnormal lipid levels in the fasting state. Emerging evidence suggests that postprandial lipid parameters may offer superior predictive value for cardiovascular disease risk compared to traditional fasting measurements [67, 68].

The atherogenic potential of TG and TRL in the postprandial state was first proposed by Zilversmit in 1979 [69] and has been supported by numerous prospective studies. Evidence indicates that *postprandial TG levels* are more strongly associated with cardiovascular events than fasting levels [65]. Remnant lipoproteins, particularly chylomicron remnants, smaller than 70 nm, are small enough to pass the vascular endothelium and accumulate in the subendothelial space [70]. Unlike larger lipoprotein particles, these remnants can pass through endothelial junctions via paracellular transport, a process facilitated by increased endothelial permeability induced by TRL lipolysis products [71]. Once within the arterial wall, remnant lipoproteins (containing up to 40 times more cholesterol than LDL particles [72, 73] are preferentially retained in the intima, contributing substantially to atherosclerotic lesion formation. Additionally, they trigger endothelial inflammation, apoptosis, and the expression of pro-inflammatory and pro-atherogenic proteins such as MCP-1 [74] and PAI-1 [75].

LDL-C has been regarded as standard for assessing atherosclerotic cardiovascular disease risk and evaluating the efficacy of lipid-lowering therapies [16]. However, apoB provides a more broad measure of atherogenic lipoprotein particles, while VLDL, IDL, LDL, and lipoprotein(a) particles contains exactly one apoB molecule. Therefore, *apoB* may provide a more precise assessment of atherosclerotic cardiovascular disease risk, especially in patients who maintain the cardiovascular risk despite receiving optimal lipid-lowering therapy [76]. Reflecting this, current international guidelines now recognize apoB as a feasible alternative to LDL-C measurement, especially in individuals with very low LDL-C levels or those with metabolic syndrome [76]. Furthermore, apoB100 concentrations have shown a positive correlation with both systolic and diastolic blood pressure, and the apoB100/apoAI ratio has demonstrated a stronger association with cardiovascular risk than the traditional LDL/HDL ratio [77].

Antibodies targeting apoB100 (anti-apoB100) could be considered a new biomarker for identifying vulnerable atheromatous plaques. Evidence from both animal and human studies indicates that circulating autoantibodies against apoB100 are associated with the stage and severity of cardiovascular disease. These autoantibodies appear to reflect the immune response of the body to atherogenic lipoproteins and have been linked to features of plaque instability, such as inflammation and immune cell infiltration. This relationship suggests that anti-apoB100 could serve not only as markers of overall cardiovascular burden but also as specific indicators of vulnerable atheromatous plaques, those liable to rupture and trigger acute events like myocardial infarction or stroke [16]. In particular, Marchini et al. reported elevated plasma levels of pro-inflammatory anti-apoB IgG in patients with high cardiometabolic risk, including those with arterial hypertension, obesity, and metabolic syndrome. In contrast, levels of anti-apoB IgM, which are considered to have anti-inflammatory properties, were significantly reduced in these patients [16, 78].

The ***oral fat tolerance test (OFTT)***, measure lipid metabolism after a high-fat meal, but is not routinely performed in clinics due to the absence of standardized methods and reference values [79], like the oral glucose tolerance test (OGTT) which is a widely used clinical tool for evaluating glucose intolerance in pre-diabetic or diabetic conditions [80]. Several studies, using the oral glucose tolerance test (OGTT), have demonstrated significant reductions in plasma antioxidant levels and increases in markers of endothelial activation (ICAM, VCAM and E-selectin) and damage [81, 82]. These effects are different based on carbohydrate uptake, the measurement method, and individual metabolic responses [82, 83]. However, not all studies report consistent outcomes; some have shown no significant oxidative or endothelial changes after OGTT in healthy subjects [84, 85]. These difference emphasize the need for standardized methodologies and further investigation into individual susceptibility and the specific properties of different carbohydrate sources [82]. Importantly, studies show that these adverse outcomes can be relieved by the co-administration of antioxidants such as vitamins C and E, glutathione, α-lipoic acid, or statins with antioxidant properties. These interventions did not affect glucose levels, highlight that oxidative stress, not hyperglycemia itself, is the primary link to postprandial endothelial dysfunction. These findings emphasize the critical role of oxidative mechanisms in vascular health and suggest potential therapeutic strategies for protecting endothelial function during periods of acute glucose elevation [82]. In a study using the OFTT, patients with T2D (both normo- and hyperinsulinemic) and healthy individuals received 17 g fat/m^2 body surface area, with blood samples taken at fasting, 2 and 4 hours post-meal [86]. While TG levels were similar across groups, remnant lipoproteins rich in TG and cholesterol were elevated only in hyperinsulinemic T2D patients. This indicates that hyperinsulinemia, rather than T2D itself, may drive postprandial dyslipidemia and associated cardiovascular risk [5].

Postprandial ***glucagon like peptide 1 (GLP-1)*** has been proposed as an early biomarker of metabolic dysfunction in obesity, with some studies showing reduced GLP-1 levels in T2D patients after mixed meals [87, 88], while others report no differences in patients with metabolic syndrome [89]. Overall, findings on GLP-1 changes in obesity and insulin resistance are inconsistent, and further research is needed to explore its relationship with postprandial dyslipidemia [65].

Another recently identified biomarker of systemic inflammation, which has demonstrated strong clinical relevance and is linked to metabolic disorders like diabetes and obesity is *glycoprotein acetylation (GlycA)* [90]. GlycA responses were closely associated with postprandial TG levels, particularly with peak TG concentrations [91]. Visceral fat mass and fasting TG levels have been identified as primary determinants of both fasting and postprandial GlycA concentrations. Notably, visceral adiposity exerts a causal influence on GlycA levels, an effect that is partially mediated by circulating TG. Important, patients showing elevated GlycA responses also demonstrated higher predicted cardiovascular disease risk, highlighting GlycA as a potential marker of cardiometabolic health and systemic inflammation [91]. However, the fact that make GlycA as a promising marker for assessing inflammation in metabolic states is its consistent responsiveness to dietary intake [91], a characteristic not shared by many conventional inflammatory markers, such as CRP [4].

In a study of 30,000 pacients from the Copenhagen General Population Study, higher plasma ***glycerol and β-hydroxybutyrate*** which were considered markers of triglyceride metabolism, were linked to increased risk of cardiovascular, cancer, and other mortality, independent of plasma triglyceride levels and BMI [92]. Patients with the highest plasma glycerol levels (>80 μmol/L) had significantly higher risks of cardiovascular, cancer, and other mortality compared to those in the lowest amount (<52 μmol/L). Similarly, those with the highest plasma β-hydroxybutyrate (>154 μmol/L) had increased risks of cardiovascular, cancer, and other mortality compared with the lowest levels (<91 μmol/L). No significant interaction was found between the two markers across mortality outcomes [92].

From a biochemical perspective, linking plasma glycerol and β-hydroxybutyrate to triglyceride metabolism may seem simplistic. However, since free glycerol mainly comes from triglyceride breakdown and is trapped intracellularly by glycerol kinase (active mostly in the liver), plasma glycerol is widely accepted as a reliable marker of whole-body triglyceride breakdown. In contrast, free fatty acids from triglyceride breakdown are widely used for energy, lipogenesis, or ketogenesis. They can also be produced *de novo* from glucose or fructose in tissues like the liver, muscle, and adipose tissue [93, 94].

Ketone bodies include acetoacetate and β-hydroxybutyrate, with β-hydroxybutyrate being the most stable in plasma and thus the preferred biomarker. Ketogenesis is driven by triglyceride breakdown, not *de novo* synthesis, and since the liver cannot use ketones for energy, all produced ketone bodies are released into the bloodstream. Therefore, β-hydroxybutyrate serves as an indirect indicator of triglyceride breakdown, primarily in adipose tissue [95].

Measuring glycerol and β-hydroxybutyrate may slightly under- or overestimate whole-body triglyceride breakdown. Some TG are only partially metabolized or used locally in tissues, while ketones can also come from amino acids, and glycerol may enter circulation via the gut or from lipoprotein metabolism [96]. Most lipases in adipose tissue, the gut, and blood vessels mainly produce 2-monoacylglycerol, not glycerol, due to their bond preferences [97]. Glycerol production is minimal in the gut and slow in the vasculature. In contrast, adipocytes fully break down triglycerides into glycerol and free fatty acids, mak-

Table 2 | Postprandial Markers and Cardiovascular Risk.

Markers	Clinical involvement	Ref.
Fasting lipid profile (TG, TC, HDL-C, LDL-C)	– Traditional CVD risk assessment tool; – Limited predictive value compared to postprandial lipids; – ~47.5% of ACS patients shows abnormal lipid levels in the fasting state.	[66, 67]
Postprandial TG	Stronger correlation with cardiovascular events than fasting TG.	[65, 69]
Remnant lipoproteins	– Rich in cholesterol; – <70 nm, can cross endothelium and enter subendothelial space; – Activate MCP-1 and PAI-1 expression; – Promote inflammation, apoptosis, and lesion formation.	[70-75]
ApoB	One molecule per particle VLDL, IDL, LDL, Lp(a).	[16, 76]
ApoB100/apoAI ratio	– Correlates with CVD risk better than LDL/HDL ratio; – Strong predictor of cardiovascular events.	[77]
Anti-apoB100 antibodies (IgG/IgM)	Reflect immune response to plaque instability and atheroma vulnerability.	[16, 78]
OFTT (Oral Fat Tolerance Test)	– Measures lipid metabolism after fat meal; – Not standardized; – Not widely used in clinics like OGTT.	[79]
GLP-1	– Potential early biomarker of metabolic dysfunction; – Is reduced in T2D; – Findings inconsistent.	[65, 87-89]
Glycoprotein acetylation (GlycA)	– Responds to dietary intake and correlates with TG peaks and visceral fat; – Promising marker for metabolic inflammation and cardiometabolic risk.	[4, 90, 91]
Plasma glycerol and β-hydroxybutyrate	– Increased risk of cardiovascular, cancer, and other mortality, independent of plasma TG levels and BMI; – Reliable markers of whole-body TG breakdown.	[92-95] [96]

ing them the main source of plasma glycerol and ketogenesis substrates; both reasonable markers of triglyceride metabolism [92].

In **Table 2** are summarized the postprandial potential markers and their clinical implication in cardiovascular development.

Current therapeutic agents for postprandial lipids

Targeting postprandial lipids with specialized therapies could enhances the control and the reduction of cardiovascular complications.

The FDA recently approved **angiopoietin-like 3 protein (ANGPTL3) inhibitors**, a new class of lipid-lowering drugs. By increase LPL and endothelial lipase activity, these agents improve VLDL remnant clearance and lower LDL-C levels despite of LDLR function. They are mainly used for homozygous familial hypercholesterolemia and mixed dyslipidemia. ***Evinacumab*** and ***vupanorsen*** are the first drugs in this class [98]. Evinacumab, a monoclonal antibody targeting ANGPTL3, lowers LDL-C by enhancing clearance of apoB lipoproteins, reducing LDL-C by 25%, ApoB by 31%, and non-HDL-C by 46% at 20 mg/kg monthly. Over 18 months, reductions reached 45.5% for LDL-C, 38.8% for ApoB, 48.4% for non-HDL-C, and 57.2% for triglycerides, with no major side effects. In contrast, vupanorsen, an antisense oligonucleotide targeting ANGPTL3 mRNA, shows modest lipid-lowering effects in T2D patients, reducing LDL-C by 18%, ApoB by 12%, and non-HDL-C by 9% compared to placebo [99].

Conclusion

The link between metabolic imbalance and cardiovascular disease is now well established, with postprandial hyperglycemia and hyperlipidemia emerging as key contributors to vascular dysfunction. These postprandial disturbances initiate a cascade of effects that induce atherosclerosis and cardiovascular modifications, primarily through endothelial dysfunction. Excess nutrient intake leads to low-grade systemic inflammation which plays a central role in this process, driven by pro-inflammatory cytokines and inflammasome activation, further amplifying endothelial injury and oxidative stress, immune cells implications that accelerate the progression of cardiovascular disease.

Throughout the years, a series of changes in the metabolism of triglyceride-rich lipoproteins and their clinical implications have been described. In recent years, both epigenetic factors and non-traditional postprandial risk factors such as telomere shortening and CHIP have also been identified, targets that should be further explored.

In this review, we highlighted the changes that occur following food intake and how these alterations impact lipoprotein metabolism, which together with inflammation contribute to the development of cardiovascular diseases. Additionally, we provided an overview of certain molecules that may serve as potential early biomarkers for the onset of cardiovascular diseases and their complications. Further research is needed to fully understand the complex interplay between postprandial inflammation, atherosclerosis, and cardiovascular disease. Identifying the specific mechanisms and developing targeted therapies to reduce postprandial inflammation could be crucial in preventing and treating cardiovascular disease.

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