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Review

Remnant Cholesterol: From Pathophysiology to Clinical Implications in Type 1 Diabetes

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Abstract

Remnant cholesterol, contained within triglyceride-rich lipoproteins such as VLDL and IDL, has emerged as an independent risk factor for atherosclerotic cardiovascular disease (ASCVD) in both the general population and individuals with diabetes. Unlike LDL cholesterol, remnant cholesterol has not traditionally been a therapeutic target, despite growing evidence of its role in the pathophysiology of atherosclerosis. These particles exhibit high atherogenic and pro-inflammatory potential, and their metabolism is altered in states of insulin resistance and hepatic dysfunction, both common in diabetes. Epidemiological studies have shown its association with ischemic heart disease, peripheral artery disease, progression of nephropathy, and cardiovascular events in type 2 diabetes. In individuals with type 1 diabetes (T1D), the evidence is more recent but relevant: elevated levels of remnant cholesterol have been linked to persistent hyperglycemia, diabetic nephropathy, diabetic foot, subclinical myocardial dysfunction, and carotid atherosclerosis, even when LDL-C levels are within target range. Moreover, lifestyle factors such as physical activity and a healthy diet are associated with lower levels of remnant cholesterol, suggesting opportunities for non-pharmacological interventions. Despite this, treatments targeting remnant cholesterol have shown limited efficacy in reducing clinical events, and individuals with T1D remain underrepresented in clinical trials. Overall, this review highlights the need to incorporate remnant cholesterol into the assessment of residual cardiovascular risk and into personalized therapeutic strategies, especially for vulnerable populations such as those with T1D.

Keywords: remnant cholesterol; type 1 diabetes; cardiovascular disease

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1. Introduction

Diabetes mellitus, particularly type 1 diabetes, is associated with a significantly increased risk of atherosclerotic cardiovascular disease (ASCVD), even among young individuals and in the absence of traditional cardiovascular risk factors. Despite advancements in the comprehensive management of patients with diabetes, a residual risk of cardiovascular events persists, even when therapeutic targets for low-density lipoprotein cholesterol (LDL-C) are achieved through high-intensity statin therapy. This phenomenon has driven interest in other components of diabetic dyslipidemia that may contribute to this persistent risk, among which remnant cholesterol stands out.

Remnant cholesterol, defined as the cholesterol content carried within triglyceride-rich lipoproteins (TRLs)—such as very-low-density lipoproteins (VLDL), chylomicrons, and

their remnants—has emerged as a potential causal factor in ASCVD [1,2]. In contrast to LDL cholesterol, which is the primary target in most clinical guidelines, remnant cholesterol has not historically been considered a therapeutic goal, partly due to the limited availability of standardized methods for its quantification and the scarcity of studies focused on specific populations such as those with type 1 diabetes.

Recently, observational studies, genetic analyses, and clinical trials have provided robust evidence linking remnant cholesterol to the pathophysiology of atherosclerosis and to major cardiovascular events [2–5], prompting proposals for its inclusion as a complementary risk marker. Building on this background, the present review aims to explore the role of remnant cholesterol—from its pathophysiological mechanisms to its clinical complications—with a particular focus on its relevance in type 1 diabetes. To achieve this objective, we adopted a snowball search strategy, starting from key seminal publications and progressively identifying additional relevant articles through reference lists and citation tracking. This approach was selected to provide a broad and updated overview while maintaining the flexibility characteristic of a narrative review.

2. Pathophysiology of Remnant Cholesterol

2.1. Origin, Metabolism, and Quantification

Remnant cholesterol is defined as the cholesterol content present in all lipoproteins other than LDL and HDL. These include triglyceride-rich lipoproteins (TRLs), which are derived from both the intestine (chylomicrons and their remnants, containing apoB-48) and the liver (VLDL, intermediate-density lipoprotein (IDL), and VLDL remnants, containing apoB-100). These particles play a crucial role in the transport of triglycerides and cholesterol to peripheral tissues, and their metabolism is intricately regulated by insulin as well as various genetic and environmental factors [6].

In the postprandial state, dietary lipids are incorporated into chylomicrons within enterocytes, secreted into the lymphatic system, and then released into the circulation. There, lipoprotein lipase (LPL) hydrolyzes triglycerides, generating free fatty acids and smaller cholesterol-enriched chylomicron remnants. These remnants are normally cleared by hepatic receptors, including the LDL receptor (LDLR) and LDL receptor-related protein 1 (LRP1). When clearance is impaired—due to lipid overload, insulin resistance, or metabolic dysfunction—remnants persist in circulation [7] (Figure 1).

In the fasting state, hepatic VLDL is the predominant source of TRLs. VLDL is also metabolized by LPL into IDL and subsequently LDL. Under conditions of hepatic overproduction or defective lipolysis, VLDL remnants and IDL accumulate, contributing to increased remnant cholesterol levels [7] (Figure 1). This dual origin—intestinal in the non-fasting state and hepatic in the fasting state—illustrates why remnant cholesterol is present irrespective of prandial status and highlights the complexity of its regulation.

Under conditions of normoglycemia and adequate insulin sensitivity, the balance among synthesis, hydrolysis, and clearance of TRLs remains relatively stable. In contrast, in diabetes—particularly when hyperglycemia, insulin resistance, and elevated levels of apoC-III or ANGPTL3 (which inhibit LPL activity) coexist—TRL production is increased, LPL activity is diminished, and hepatic clearance is delayed. Together, these alterations lead to sustained elevation of circulating remnant cholesterol [6].

From a clinical perspective, remnant cholesterol can be estimated indirectly using a standard lipid panel with the following formula:

Total cholesterol − HDL-C − LDL-C [8].

Alternatively, it can be measured directly using more advanced techniques such as nuclear magnetic resonance (NMR) spectroscopy, although these are not yet routinely available in clinical practice.

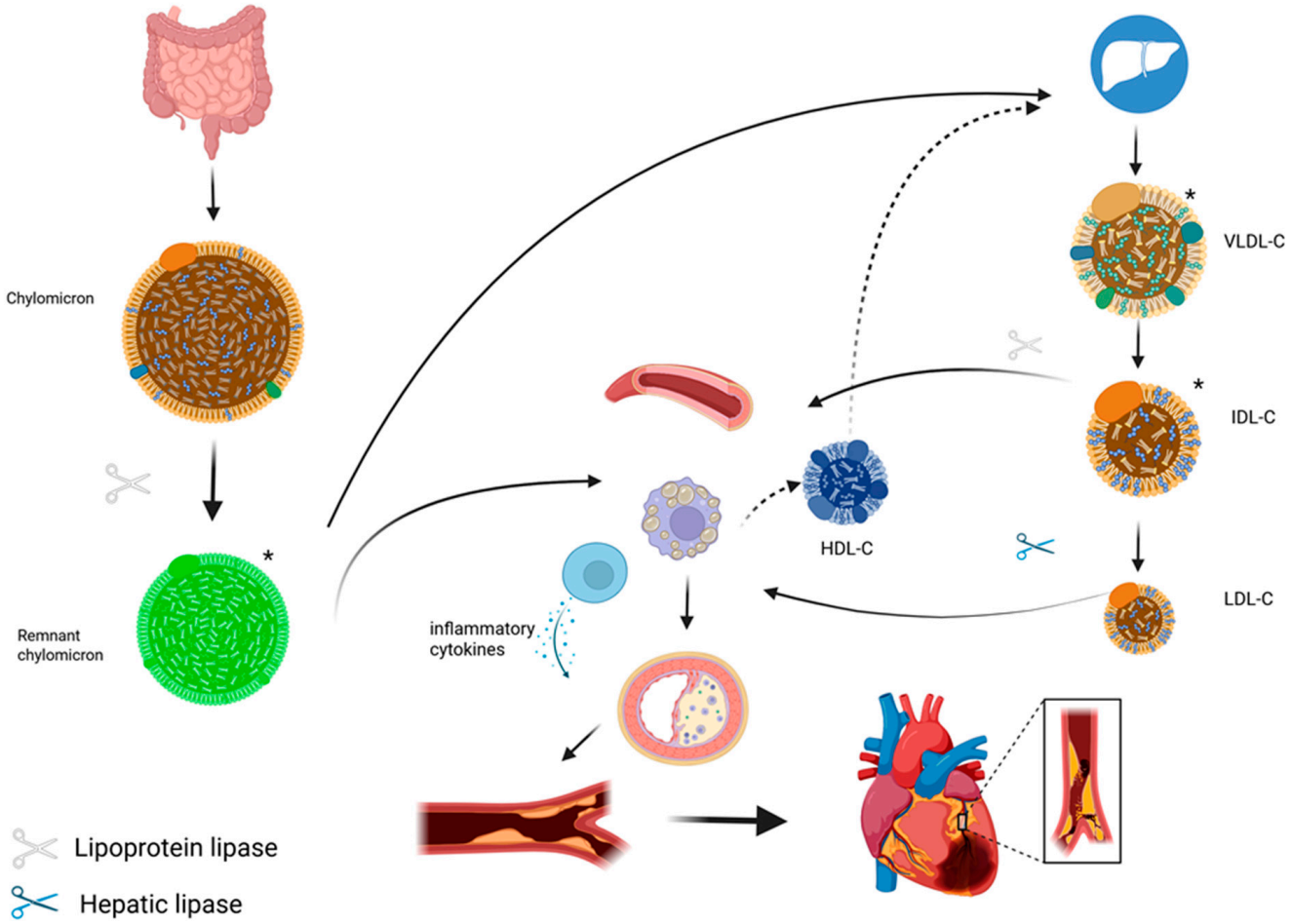


Figure 1. Pathophysiology of Remnant Cholesterol. * Lipoproteins classified as remnant cholesterol. Chylomicrons and very-low-density lipoproteins (VLDL) are hydrolyzed by lipoprotein lipase (LPL), generating remnant lipoproteins—such as remnant chylomicrons and intermediate-density lipoproteins (IDL)—which are enriched in cholesterol. Impaired clearance of these remnants, common in insulin-resistant or dysmetabolic states, promotes their accumulation in circulation. Once retained in the subendothelial space, these particles are readily internalized by macrophages through receptor-mediated and non-receptor–mediated pathways, without the need for prior oxidation. This uptake leads to intracellular cholesterol accumulation and foam cell formation, a key initiating event in atherogenesis. In addition, macrophages exposed to remnant particles release pro-inflammatory cytokines (e.g., IL-1β, IL-6, TNF-α) through activation of the NLRP3 inflammasome, thereby amplifying local vascular inflammation and promoting plaque instability. HDL-C may play a protective role by facilitating reverse cholesterol transport and limiting foam cell formation. Created in © 2025 BioRender.

2.2. Atherogenic and Inflammatory Mechanism

Remnant particles, like LDL, have the capacity to cross the vascular endothelium and become retained within the arterial intima. However, they possess distinct features that make them particularly harmful: they are larger in size, have greater lipid mass per particle (delivering two to four times more cholesterol than a native LDL particle), exhibit lower affinity for hepatic receptors, and have a longer half-life in circulation. These properties enhance their ability to interact with the endothelium and initiate atherogenic processes [6].

Once trapped in the subendothelial space, remnant particles can be directly phagocytosed by macrophages without the need for prior oxidative modification—unlike LDL particles. This leads to the formation of foam cells, representing an early step in the development of atherosclerotic plaques. Additionally, remnant particles can trigger both

local and systemic inflammatory responses. Multiple studies have demonstrated their ability to induce low-grade inflammation [3], mainly through activation of the NLRP3 inflammasome and the release of pro-inflammatory cytokines such as IL-6, TNF-α, and IL-1β [9]. This chronic inflammation contributes to plaque instability and increases the risk of major cardiovascular events [10].

In individuals with type 1 diabetes, particularly those with suboptimal glycemic control, an atherogenic dyslipidemia may develop, characterized not only by elevated remnant cholesterol levels but also by the presence of small, dense LDL particles. These particles are highly atherogenic due to their increased susceptibility to oxidation, enhanced endothelial penetration, and prolonged residence time in plasma [11]. The coexistence of remnant particles and small, dense LDL augments the proatherogenic milieu and may help explain part of the residual cardiovascular risk observed even in young individuals with type 1 diabetes and no other apparent risk factors.

Thus, remnant cholesterol serves as a key marker of dyslipidemia and plays a central role in the pathophysiological cascade leading to atherosclerotic cardiovascular disease, particularly in metabolically vulnerable populations such as individuals with type 1 diabetes.

3. Epidemiological Evidence in the General Population and in Type 2 Diabetes

Numerous studies have established a strong association between remnant cholesterol—carried within triglyceride-rich lipoproteins such as VLDL and IDL—and the risk of ASCVD [12–14]. Unlike LDL cholesterol, remnant cholesterol has consistently been identified as an independent risk factor for ASCVD, even in individuals with optimal LDL-C levels. This relationship has been consistently documented in large-scale cohort studies, where elevated remnant cholesterol levels have been linked to an increased incidence of myocardial infarction, stroke, and cardiovascular mortality [1,15].

Among the most robust sources of evidence are the Danish cohort studies, which evaluated both fasting and postprandial remnant cholesterol levels [13]. In these studies, participants consumed a standardized high-fat meal after a 12-h fast, and lipid measurements were taken up to four hours postprandially. This approach allowed researchers to assess the cardiovascular implications of postprandial levels of triglyceride-rich lipoproteins—considered to be more reflective of daily lipid metabolism.

The results revealed a strong association between postprandial remnant cholesterol and ischemic heart disease and cardiovascular events, both in the general population and in individuals with type 2 diabetes [16]. For instance, in a cohort comprising individuals with and without diabetes, elevated remnant cholesterol was associated with greater prevalence and severity of peripheral artery disease, even after adjusting for other conventional lipid parameters [17]. These particles have also been linked to features of increased plaque vulnerability, such as low echogenicity (echolucent plaques), suggesting an active role of remnant cholesterol in carotid plaque instability [18]. In a recent Chinese study including over 13,000 patients undergoing coronary revascularization with diabetes or prediabetes, remnant cholesterol levels were associated with medium-term cardiovascular events and perioperative acute kidney injury [19].

Beyond classical cardiovascular complications, studies in individuals with type 2 diabetes have demonstrated that remnant cholesterol is also associated with the progression of diabetic nephropathy and a higher incidence of cardiovascular events. In a longitudinal study, patients with elevated remnant cholesterol had an increased risk of declining renal function, persistent albuminuria, and major cardiovascular events during follow-up [20].

With regard to subclinical atherosclerosis, recent investigations have explored the relationship between remnant cholesterol and atherosclerotic burden using coronary CT

angiography. One study found that elevated remnant cholesterol was associated with increased plaque volume and extent, even among patients treated with statins and with controlled LDL-C levels [21]. However, whether this increased plaque burden directly translates into a higher rate of clinical cardiovascular events remains to be conclusively established and is the subject of ongoing research. In this context, sex- and gender-related factors appear particularly relevant: premenopausal women generally display lower remnant cholesterol levels than men, largely due to reduced hepatic VLDL-apoB secretion and higher expression of hepatic VLDL receptors, which favor remnant clearance [22]. After menopause, however, remnant cholesterol rises significantly, contributing to a stronger association with coronary heart disease and diabetes in postmenopausal women [23,24]. A summary of the main findings from these key studies is provided in Table 1.

Table 1. Summary of key clinical and epidemiological studies assessing the association between remnant cholesterol and cardiovascular or metabolic outcomes.

Authors	Population	Exposure	Outcome	Main Findings
Johansen et al., 2025 (Lancet Reg Health Eur) [15]	104,867 adults from Copenhagen General Population Study, no CHD at baseline	Unhealthy lifestyle (smoking, inactivity, poor diet)→elevated remnant cholesterol	MI and CHD incidence	Remnant cholesterol explained 12–21% of excess CHD risk from unhealthy lifestyle, independent of LDL-C
Tian et al., 2024 (ChinaHEART) [14]	3.4 million Chinese adults, prospective nationwide cohort	Baseline remnant cholesterol	CVD and cancer mortality	Higher remnant cholesterol increased CVD mortality (HR ~1.17) but inversely associated with some cancer mortality
Wadström et al., 2023 (Diabetologia) [12]	Contemporary Danish diabetes cohort (107,243 adults)	Remnant cholesterol vs. LDL-C	ASCVD (MI, stroke, PAD, CVD death)	Remnant cholesterol explained ~14–34% of excess ASCVD risk in diabetes, while LDL-C did not explain excess risk
Castañer et al., 2020 (PREDIMED trial) [1]	6901 high-CVD-risk participants, 48% with diabetes	Baseline triglycerides and remnant cholesterol	Major adverse cardiovascular events (MACE)	Remnant cholesterol (HR 1.21 per 10 mg/dL) predicted MACE; LDL-C not predictive when adjusted
Li et al., 2025 (CABG cohort) [19]	13,426 patients with diabetes or prediabetes undergoing CABG	Remnant cholesterol (continuous and categorical)	Perioperative AKI, MACCE, death, MI	Each 1-SD increase in remnant cholesterol raised MACCE risk (HR 1.07), MI (HR 1.11), death (HR 1.07)
Yu et al., 2021 [20]	2282 T2D patients with CKD stage 3–5	Baseline remnant cholesterol	CVD mortality (2 years)	Remnant cholesterol (OR 1.12 per 10 mg/dL) predicted CVD mortality, especially with LDL-C > 100 mg/dL
Lin et al., 2019 (Atherosclerosis) [21]	587 patients undergoing CT coronary angiography	Remnant cholesterol (fasting lipid panel)	Coronary plaque burden (CT-LeSc > 5)	Remnant cholesterol independently predicted higher coronary plaque burden even with optimal LDL-C levels (OR ~3.9)

Table 1. *Cont.*

Authors	Population	Exposure	Outcome	Main Findings
Wadström et al., 2022 (EHJ) [16]	106,937 adults (Copenhagen General Population Study) and 13,974 (City Heart Study)	Calculated remnant cholesterol	Peripheral artery disease, MI, ischemic stroke	Elevated remnant cholesterol strongly associated with PAD (HR 4.9), MI (HR 4.2), stroke (HR 1.8); stronger effect for PAD
Wadström et al., 2024 (Arterioscler Thromb Vasc Biol) [17]	93,461 adults with diabetes in Denmark (statin era)	Baseline remnant cholesterol apoB, and LDL-C	ASCVD (MI, stroke, PAD)	PAD risk was mainly driven by elevated remnants, whereas MI risk was explained by both remnants and LDL.

Abbreviations: AKI, acute kidney injury; ASCVD, atherosclerotic cardiovascular disease; CABG, coronary artery bypass grafting; CHD, coronary heart disease; CKD, chronic kidney disease; CVD, cardiovascular disease; HR, hazard ratio; IDL, intermediate-density lipoprotein; LDL-C, low-density lipoprotein cholesterol; MACCE, major adverse cardiovascular and cerebrovascular events; MACE, major adverse cardiovascular events; MI, myocardial infarction; NMR, nuclear magnetic resonance; OR, odds ratio; PAD, peripheral artery disease; TRL, triglyceride-rich lipoprotein; T1D, type 1 diabetes; T2D, type 2 diabetes; VLDL, very-low-density lipoprotein.

4. Physical Activity and Lifestyle Habits

Regular physical activity is one of the most effective non-pharmacological interventions for improving lipid profiles and reducing cardiovascular risk. Multiple studies have documented its beneficial effects not only on traditional lipid parameters such as triglycerides and HDL-C, but also on triglyceride-rich lipoproteins and remnant cholesterol.

A cross-sectional analysis from the National Health and Nutrition Examination Survey (NHANES), which included 18,396 participants, found a significant association between higher levels of physical activity and a more favorable lipid profile, including an independent inverse association with remnant cholesterol concentrations [25].

In another prospective study involving over 100,000 adults from the Copenhagen General Population Study, followed for a median of 9.2 years, researchers evaluated whether remnant cholesterol could explain part of the excess cardiovascular risk associated with unhealthy lifestyle behaviors [15]. Smoking, physical inactivity, and poor dietary adherence were all associated with higher remnant cholesterol levels. Mediation analyses showed that remnant cholesterol accounted for 12% to 21% of the excess risk of myocardial infarction and coronary heart disease attributable to these behaviors.

Evidence supports that higher levels of physical activity are associated with lower triglyceride concentrations and higher HDL-C levels, whereas physical inactivity or insufficient exercise is linked to an increased likelihood of atherogenic dyslipidemia (elevated triglycerides and low HDL-C) [26,27]. Beyond these quantitative changes, physical activity also improves the functional quality of HDL particles. Both acute and chronic aerobic exercise have been shown to increase plasma HDL-C levels in a dose-dependent manner. In this regard, high-quality meta-analyses have confirmed that total exercise volume (i.e., total duration and frequency) has a greater impact on HDL-C elevation than exercise intensity [28–30]. Additionally, exercise has been shown to enhance cholesterol efflux capacity from macrophages to HDL—a key atheroprotective mechanism [31].

With respect to hepatic lipid metabolism, physical activity appears to exert a relevant modulatory effect. Experimental studies have shown that exercise reduces hepatic lipid accumulation, which may translate into decreased hepatic VLDL production [32,33]. This effect is further enhanced by increased free fatty acid oxidation, driven both by adipose tissue lipolysis and the hydrolysis of VLDL triglycerides. As a result, TRL turnover is accelerated, which may contribute to lower circulating remnant cholesterol levels.

Taken together, these findings suggest that regular physical activity not only improves the conventional lipid profile but may also exert a beneficial effect on the metabolism and clearance of remnant particles. This may modulate a highly atherogenic lipid axis of particular relevance in individuals with diabetes. These benefits would add to the well-established anti-inflammatory effects of exercise and its role in reducing overall cardiovascular risk.

5. Clinical Trials

Several clinical trials have evaluated therapies aimed at reducing triglyceride and remnant cholesterol levels, with mixed results regarding their impact on cardiovascular disease. It is worth noting that individuals with type 1 diabetes are often underrepresented or even excluded from these studies, limiting the generalizability of their findings. Fibrates, such as fenofibrate (ACCORD trial) and pemafibrate (PROMINENT trial), have demonstrated significant efficacy in lowering triglycerides and remnant cholesterol. However, these effects did not translate into a significant reduction in major cardiovascular events. In the ACCORD trial, combining simvastatin with fenofibrate did not offer additional benefit compared to simvastatin alone, except in a subgroup with atherogenic dyslipidemia. Similarly, the PROMINENT trial, which evaluated pemafibrate in individuals with type 2 diabetes, was terminated early for futility, despite achieving a 44% reduction in remnant cholesterol. This outcome was likely due to a concomitant increase in LDL cholesterol and apoB levels, which may have offset any potential benefit [34,35].

Another therapeutic strategy has involved supplementation with omega-3 polyunsaturated fatty acids. The REDUCE-IT trial, which used icosapent ethyl (a purified EPA formulation), demonstrated a 25% relative risk reduction in cardiovascular events, with beneficial effects observed in individuals both with and without type 2 diabetes [36]. In contrast, the STRENGTH trial, which used a combination of EPA and DHA, did not show cardiovascular benefit and was halted for lack of efficacy [37]. These discrepancies may be explained by mechanisms beyond lipid modification, such as the anti-inflammatory effects of EPA observed in REDUCE-IT (e.g., significant reduction in C-reactive protein), which were not seen with other formulations. Overall, these findings underscore that merely lowering triglycerides or remnant cholesterol does not automatically translate into clinical benefit, and it is essential to consider the broader impact on apoB and the total number of atherogenic particles [6,10].

Currently, the conventional therapeutic arsenal for lowering remnant cholesterol includes fibrates, PCSK9 inhibitors, statins, and omega-3 fatty acids [38]. These strategies largely act by increasing LDL receptor expression or modulating hepatic production of triglyceride-rich lipoproteins [6].

In parallel, novel therapies targeting key regulatory proteins in lipid metabolism are under development, using RNA interference technologies, antisense oligonucleotides (ASOs), monoclonal antibodies, and gene-editing platforms. These therapies are aimed at apoC3, ANGPTL3, ANGPTL4, and apoB, with the goal of dramatically reducing remnant cholesterol levels while offering less frequent dosing and greater hepatic specificity [39]. One notable example is volanesorsen, an antisense oligonucleotide targeting apoC-III, which reduces plasma triglycerides by more than 80%. Although approved for the treatment of familial chylomicronemia syndrome, its use in multifactorial dyslipidemias has been limited by adverse effects such as severe thrombocytopenia [40].

Advanced-stage candidates include AKCEA-APOCIII-LRx (with liver-selective action and lower hematologic risk), evinacumab (a monoclonal antibody against ANGPTL3), and vupanorsen (an ASO targeting ANGPTL3). These agents have shown substantial reductions in triglycerides (>70–80%) and remnant cholesterol, along with additional decreases in LDL cholesterol, non-HDL cholesterol, and apoB [39]. These emerging therapies represent a

promising strategy for intensive modulation of the atherogenic lipid axis, particularly in patients with high residual cardiovascular risk, although they currently lack phase III trials assessing cardiovascular outcomes.

6. Evidence in Type 1 Diabetes

Cardiovascular disease remains the leading cause of mortality in individuals with type 1 diabetes [41,42]. While hyperglycemia is a key determinant of micro- and macrovascular complications, intensive glycemic control does not fully eliminate cardiovascular risk. Even among individuals with well-controlled glycemia, the risk of myocardial infarction, heart failure, and cardiovascular mortality remains elevated compared to the general population [42–44]. In this context, the concept of "residual cardiovascular risk" has gained relevance, highlighting the potential role of remnant lipoproteins regardless of LDL-C levels [8,45]. Although evidence regarding the impact of remnant cholesterol in type 1 diabetes is limited, emerging studies are beginning to highlight its relevance.

As discussed previously, remnant cholesterol, primarily contained within triglyceride-rich lipoproteins such as VLDL and IDL, is highly atherogenic. These particles readily penetrate the arterial intima, are taken up by macrophages to form foam cells, and trigger inflammatory responses through the release of free fatty acids and monoacylglycerols [46–48]. Various studies have suggested that disturbances in the metabolism of these particles contribute to cholesterol deposition in arteries and have proposed remnant cholesterol as a predictor of diabetic retinopathy and nephropathy in individuals with type 1 diabetes [49].

A prospective five-year study found that baseline remnant cholesterol was independently associated with the progression of nephropathy (defined as increased albuminuria or decreased eGFR) and cardiovascular mortality, reinforcing its role as a prognostic marker beyond glycemic control [50]. Similarly, data from the FINN-Diane study, one of the largest cohorts of individuals with type 1 diabetes, emphasized the impact of non-LDL lipids and triglycerides on cardiovascular risk, suggesting that non-traditional lipid factors should be integrated into risk stratification to bridge the gap between known risk factors and cardiovascular events in this population [51].

In a Spanish cohort of over 300 individuals with type 1 diabetes using glucose monitoring sensors, higher levels of remnant cholesterol were significantly associated with greater hyperglycemia and reduced time in range, suggesting a link between atherogenic dyslipidemia and poor glycemic control [52]. A strong association with diabetic nephropathy was also observed, whereas no such relationship was found with diabetic retinopathy—suggesting the possibility of a bidirectional relationship between remnant cholesterol and triglyceride-rich lipoproteins with diabetic nephropathy. In a matched case–control study of a high-risk type 1 diabetes cohort, elevated remnant cholesterol and triglyceride levels were associated with a higher risk of diabetic foot, with a gradient of increasing risk according to lipid levels, even after adjustment for HbA1c, diabetes duration, and lipid-lowering therapy [53].

Additional evidence points to an association between triglyceride-rich lipoproteins—particularly VLDL—and subclinical macrovascular disease. In a cross-sectional study of 189 adults with type 1 diabetes at high cardiovascular risk but without established disease, the association between advanced lipoprotein profiling (measured by 1H-NMR) and carotid plaque presence was assessed [54]. Thirty-five percent of participants had subclinical atherosclerosis. These individuals were older, had longer diabetes duration, higher prevalence of hypertension, and a lipid profile characterized by fewer LDL and HDL particles but more VLDL particles. After adjustment for multiple confounders, including conventional lipids, a lower number and cholesterol content of HDL particles was inversely associated with plaque presence, whereas a higher proportion of LDL and non-HDL

particles per unit of total cholesterol was positively associated [54]. Furthermore, a recent Spanish study found that TRLs were independently associated with subclinical myocardial dysfunction, as assessed by tissue Doppler echocardiography, even after adjusting for conventional risk factors [55]. This supports a potential direct role for remnant cholesterol in the pathogenesis of diabetic cardiomyopathy via mechanisms involving lipotoxicity and cardiac lipid accumulation.

Despite these findings, individuals with T1D remain markedly underrepresented in lipid-lowering clinical trials, limiting the ability to derive evidence-based therapeutic strategies specific to this population. Consequently, some studies have focused on the role of lifestyle interventions. In an observational study by Leroux et al. [56], the impact of healthy lifestyle behaviors on the cardiometabolic profile of adults with type 1 diabetes was assessed. The cohort included 115 participants in whom physical activity (measured by accelerometry), diet quality (Canadian Healthy Eating Index), and smoking status were objectively assessed. Only 11% of participants met all three healthy lifestyle criteria, whereas 23% met none. A greater number of healthy lifestyle behaviors was associated with lower levels of adiposity, systolic blood pressure, total cholesterol, non-HDL cholesterol, and triglycerides, with a linear trend of improvement. There was also a trend toward reduced insulin resistance and lower HbA1c levels, although some associations did not reach statistical significance after multivariable adjustment.

In addition to lifestyle measures, pharmacological approaches—particularly statin therapy—have been consistently associated with lower cardiovascular risk in T1D. Large real-world cohorts consistently associate statin therapy with lower cardiovascular risk. In a nationwide Korean cohort of 11,009 adults with T1D, statin use (modeled as a time-varying exposure) was linked to a 24% lower hazard of the composite of myocardial infarction or stroke (adjusted HR 0.76, 95% CI 0.66–0.88) [57]. Likewise, in the Swedish National Diabetes Register, lipid-lowering therapy—predominantly statins—was associated with a 22–44% reduction in cardiovascular disease and cardiovascular mortality in primary prevention; moreover, high adherence after initiation reduced nonfatal CVD, whereas early discontinuation increased risk [58]. By contrast, in adolescents with T1D, the AdDIT program reported lipid improvements but no short-term benefit on carotid intima-media thickness, underscoring the paucity of T1D-specific randomized outcome data [59]. Reflecting these data and the high baseline risk, contemporary guidelines recommend moderate- to high-intensity statins for most adults with T1D according to age and risk profiles [60].

Collectively, current evidence indicates that remnant cholesterol is a plausible contributor to the residual cardiovascular risk in T1D, with potential involvement in both micro- and macrovascular complications. Incorporating remnant cholesterol into risk stratification models and exploring targeted interventions—pharmacological or lifestyle-based—may represent an important step toward reducing the disproportionate cardiovascular burden in this population. Future studies specifically designed in T1D cohorts are urgently needed to determine whether lowering remnant cholesterol can translate into meaningful reductions in cardiovascular events.

7. Conclusions

Remnant cholesterol and triglyceride-rich lipoproteins have emerged as relevant cardiovascular risk factors in both the general population and in individuals with diabetes. However, key challenges remain, including clarifying their role in primary prevention, determining their specific impact on cardiovascular disease in type 1 diabetes, and identifying therapeutic strategies capable of reducing clinical events through their modulation. Current evidence suggests that incorporating remnant cholesterol as a marker and potential therapeutic target could represent a meaningful step forward in addressing residual

cardiovascular risk—particularly in high-risk metabolic populations such as those living with type 1 diabetes.

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