

Diabetic Dyslipidemia Beyond Conventional Lipid Profiles: Molecular Mechanisms, Emerging Biomarkers and Novel Therapeutic Strategies

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ABSTRACT

Diabetic dyslipidemia is a complex metabolic abnormality characterized by hypertriglyceridemia, reduced high-density lipoprotein cholesterol (HDL-C), qualitative abnormalities of low-density lipoprotein (LDL) particles, and accumulation of triglyceride-rich lipoproteins (TRLs) and their remnants. Although LDL cholesterol (LDL-C) remains a major therapeutic target for cardiovascular risk reduction, conventional lipid profiles may not fully capture the heterogeneous lipoprotein abnormalities associated with diabetes. Insulin resistance promotes adipose-tissue lipolysis, increases free fatty acid delivery to the liver, stimulates hepatic very-low-density lipoprotein (VLDL) production, and alters lipoprotein clearance. These processes promote the formation of small dense LDL (sdLDL), cholesterol-depleted HDL, remnant lipoproteins and other atherogenic particles. Increasing evidence indicates that apolipoprotein B (ApoB), remnant cholesterol, sdLDL, lipoprotein(a) [Lp(a)], non-HDL cholesterol and other advanced lipid parameters may provide complementary information regarding residual cardiovascular risk. Therapeutic approaches have consequently expanded from statin-based LDL-C reduction to combination therapy involving ezetimibe, PCSK9 inhibitors, bempedoic acid and selected triglyceride-lowering interventions. Emerging approaches targeting apolipoprotein C-III (ApoC-III), angiopoietin-like protein 3 (ANGPTL3), and other regulators of triglyceride-rich lipoprotein metabolism may further broaden the therapeutic landscape. This review discusses the molecular basis of diabetic dyslipidemia, limitations of conventional lipid assessment, emerging biomarkers and contemporary and investigational therapeutic strategies, emphasising the need for a more comprehensive lipoprotein-centred approach to residual cardiovascular risk in diabetes.

Keywords: Diabetic dyslipidemia; diabetes mellitus; insulin resistance; ApoB; remnant cholesterol; small dense LDL; lipoprotein(a); triglyceride-rich lipoproteins; PCSK9; ANGPTL3.

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1. Introduction

Diabetes mellitus is a major metabolic disorder associated with profound abnormalities in carbohydrate, lipid and protein metabolism. Cardiovascular disease (CVD), particularly atherosclerotic cardiovascular disease (ASCVD), remains a major complication of diabetes. Dyslipidemia contributes substantially to this risk and is therefore an important therapeutic target in the management of diabetes [1,2].

The conventional phenotype of diabetic dyslipidemia is characterized by elevated triglycerides (TG), reduced HDL-C and relatively normal or only moderately increased LDL-C. However, the apparent modest

elevation of LDL-C can be misleading because diabetes is associated with qualitative changes in LDL particles, including an increased proportion of small dense LDL particles. In parallel, VLDL, chylomicron remnants and other triglyceride-rich lipoproteins accumulate in the circulation [3,4].

Historically, clinical assessment has focused predominantly on total cholesterol, LDL-C, HDL-C and TG. These parameters remain fundamental; however, increasing evidence indicates that they do not completely describe the number, composition and atherogenic potential of circulating lipoprotein particles. The 2026 multisociety dyslipidemia guideline

specifically recognizes the importance of atherogenic lipoproteins beyond LDL-C and recommends selective ApoB measurement and at least once-in-a-lifetime Lp(a) assessment for cardiovascular risk evaluation [5].

This changing understanding has shifted the concept of diabetic dyslipidemia from a simple quantitative lipid abnormality to a complex disorder of lipoprotein metabolism. Therefore, evaluation of diabetic dyslipidemia increasingly requires consideration of particle number, particle composition, remnant lipoproteins, inflammation and metabolic dysfunction in addition to conventional lipid concentrations.

2. Molecular Basis of Diabetic Dyslipidemia

Insulin resistance is a central driver of diabetic dyslipidemia. Under physiological conditions, insulin suppresses hormone-sensitive lipase-mediated lipolysis in adipose tissue. In insulin-resistant states, this inhibitory effect is reduced, resulting in increased release of free fatty acids (FFAs) into the circulation. Increased portal delivery of FFAs to the liver provides an abundant substrate for triglyceride synthesis and VLDL assembly [3,6].

The liver incorporates FFAs derived from adipose tissue, dietary remnants and de novo lipogenesis into triglycerides. Increased hepatic triglyceride availability promotes assembly and secretion of VLDL particles containing apolipoprotein B-100. Insulin resistance also reduces intracellular degradation of ApoB and enhances microsomal triglyceride transfer protein-mediated VLDL assembly, thereby increasing hepatic VLDL secretion [3].

Consequently, hepatic overproduction of VLDL1 becomes a major contributor to diabetic hypertriglyceridemia. This mechanism explains why insulin resistance may produce substantial lipid abnormalities even when LDL-C is not markedly elevated.

In addition to increased production, impaired clearance of triglyceride-rich lipoproteins contributes to diabetic hypertriglyceridemia. Lipoprotein lipase (LPL) hydrolyses triglycerides within VLDL and chylomicrons, facilitating the release of fatty acids and subsequent conversion of these particles into smaller remnants. Insulin resistance can impair LPL-mediated clearance and alter hepatic uptake of remnant particles. The resulting accumulation of VLDL, chylomicrons and remnant particles increases the circulating pool of atherogenic lipoproteins [3,7].

Recent research has also highlighted the role of regulatory proteins such as ANGPTL3 and ApoC-III. ANGPTL3 inhibits LPL and endothelial lipase, whereas ApoC-III inhibits LPL-mediated triglyceride hydrolysis and hepatic clearance of triglyceride-rich particles. Both

pathways therefore represent potential therapeutic targets in hypertriglyceridemic states [8,9].

2.1 Insulin resistance and increased free fatty acid flux

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2.2 Impaired clearance of triglyceride-rich lipoproteins

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2.3 Formation of small dense LDL

One of the characteristic qualitative abnormalities in diabetic dyslipidemia is an increase in small dense LDL particles. Excess VLDL and triglyceride-rich lipoproteins promote cholesteryl ester transfer protein (CETP)-mediated exchange of triglycerides and cholesteryl esters between VLDL, LDL and HDL.

LDL particles become enriched in triglycerides and subsequently undergo hydrolysis by hepatic lipase, producing smaller and denser LDL particles. These sdLDL particles are considered particularly atherogenic because they can penetrate the arterial intima more readily and are susceptible to oxidative and glycation-related modifications [3,10].

Importantly, an individual may have an LDL-C concentration that appears acceptable while still carrying an increased number of atherogenic LDL particles. This phenomenon represents an important limitation of relying exclusively on LDL-C in patients with diabetes.

3. Why Conventional Lipid Profiles May Be Insufficient

The standard lipid profile generally consists of total cholesterol, LDL-C, HDL-C and TG. These measurements are essential for clinical management and remain the foundation of lipid assessment. Nevertheless, they provide limited information regarding the number and composition of circulating ApoB-containing particles.

Two patients can have identical LDL-C concentrations

but substantially different numbers of LDL particles. This discordance becomes particularly relevant in insulin resistance, where LDL particles tend to become smaller and more numerous.

Similarly, triglycerides provide an indirect measure of triglyceride-rich lipoprotein metabolism but do not directly quantify the cholesterol content of remnant particles. HDL-C measures the amount of cholesterol carried by HDL but does not necessarily reflect HDL functionality, cholesterol efflux capacity or anti-inflammatory activity.

Recent clinical evidence supports the relevance of residual lipid abnormalities. In the ACCORD cohort, elevated remnant cholesterol was associated with major adverse cardiovascular events (MACE) in patients with type 2 diabetes independently of LDL-C. Each standard-deviation increase in remnant cholesterol was associated with a higher risk of MACE, while visit-to-visit variability in remnant cholesterol was also associated with cardiovascular outcomes [11].

Similarly, a large Korean nationwide cohort of patients with type 2 diabetes demonstrated a positive association between higher remnant cholesterol and subsequent myocardial infarction and ischemic stroke [12]. These findings suggest that assessment of atherogenic lipoproteins beyond LDL-C may improve characterization of residual cardiovascular risk.

4. Emerging Biomarkers in Diabetic Dyslipidemia

ApoB is the structural apolipoprotein present on each atherogenic lipoprotein particle, including VLDL, intermediate-density lipoprotein, LDL and Lp(a). Consequently, ApoB provides an estimate of the total number of circulating atherogenic particles rather than simply their cholesterol content.

ApoB may be particularly informative when TG levels are elevated or when LDL-C and particle number are discordant. The 2026 ACC/AHA multisociety guideline states that ApoB measurement can improve risk assessment and help guide therapy, particularly in individuals with diabetes, elevated TG or low achieved LDL-C [5].

Non-HDL cholesterol is calculated by subtracting HDL-C from total cholesterol. It represents cholesterol contained in all non-HDL particles, including LDL, VLDL, IDL, chylomicron remnants and other ApoB-containing lipoproteins. Because diabetic dyslipidemia is characterized by increased triglyceride-rich particles, non-HDL-C may provide a more comprehensive representation of atherogenic cholesterol than LDL-C alone [5,13].

Remnant cholesterol refers broadly to cholesterol contained in triglyceride-rich remnant particles, including VLDL and chylomicron remnants. These

particles can enter the arterial wall and contribute to cholesterol deposition, inflammation and atherosclerotic plaque development. Evidence from diabetic cohorts demonstrates that remnant cholesterol is associated with ASCVD outcomes independently of LDL-C [11,12].

sdLDL represents a particularly atherogenic LDL subfraction. In type 2 diabetes, sdLDL levels may increase despite apparently normal LDL-C. A recent review emphasized that sdLDL-C is closely associated with insulin resistance, hypertriglyceridemia and metabolic dysfunction and may provide additional information beyond LDL-C [10]. However, the clinical use of sdLDL testing remains less standardized than conventional lipid measurements.

Lp(a) is an LDL-like lipoprotein containing ApoB-100 covalently linked to apolipoprotein(a). Its concentration is predominantly genetically determined. The 2026 ACC/AHA guideline recommends measuring Lp(a) at least once in adulthood, with ≥ 125 nmol/L (approximately ≥ 50 mg/dL) considered a risk-enhancing level [5]. The 2025 ESC/EAS focused update similarly recommends consideration of Lp(a) as an important cardiovascular risk modifier [14].

5. Inflammation, Oxidative Stress and Lipotoxicity

Diabetic dyslipidemia cannot be considered independently of inflammation and oxidative stress. Hyperglycemia, increased FFAs and dysfunctional adipose tissue can stimulate oxidative stress and inflammatory signaling. These processes contribute to endothelial dysfunction, macrophage activation and progression of atherosclerotic disease.

sdLDL particles are particularly susceptible to oxidative and glycation-related modifications. Modified LDL can be taken up by macrophages through scavenger receptors, promoting foam-cell formation and plaque development [3].

Furthermore, triglyceride-rich remnants may enter the arterial wall and contribute directly to cholesterol accumulation and inflammatory responses. Thus, the cardiovascular consequences of diabetic dyslipidemia may arise not only from the absolute amount of circulating cholesterol but also from particle composition, residence time, susceptibility to modification and interaction with vascular tissues.

The relationship between lipid metabolism and inflammation also provides a rationale for investigating therapeutic strategies that influence both metabolic and inflammatory pathways. Nevertheless, anti-inflammatory therapies should not be considered substitutes for established lipid-lowering treatment, because LDL-containing particles remain a causal factor in atherosclerosis.

6. Current Therapeutic Strategies

Lifestyle modification remains a fundamental component of diabetic dyslipidemia management. Weight reduction where appropriate, regular physical activity, dietary modification, reduction of saturated and trans fats and increased intake of fiber and unsaturated fats can improve lipid parameters and cardiovascular risk [1].

Improvement of glycemic control may also reduce triglyceride concentrations, particularly in patients with poorly controlled diabetes and marked hypertriglyceridemia.

Statins remain the principal pharmacological therapy for ASCVD risk reduction in diabetes. They inhibit HMG-CoA reductase, decrease hepatic cholesterol synthesis and increase hepatic LDL receptor expression, thereby promoting LDL clearance. The 2025 ADA Standards of Care recommend moderate-intensity statin therapy for most adults aged 40–75 years with diabetes without ASCVD, with more intensive therapy considered according to cardiovascular risk [1].

Ezetimibe inhibits intestinal cholesterol absorption through inhibition of NPC1L1. When added to statin therapy, it produces additional LDL-C lowering. The IMPROVE-IT trial demonstrated cardiovascular benefit from adding ezetimibe to statin therapy following acute coronary syndrome [15].

PCSK9 monoclonal antibodies such as evolocumab and alirocumab substantially reduce LDL-C by preventing PCSK9-mediated degradation of hepatic LDL receptors. Cardiovascular outcome trials have demonstrated reductions in cardiovascular events with intensive PCSK9 inhibition [16,17].

Bempedoic acid inhibits ATP-citrate lyase, an enzyme upstream of HMG-CoA reductase in the hepatic cholesterol biosynthetic pathway. The CLEAR Outcomes trial demonstrated a significant reduction in major cardiovascular events in statin-intolerant patients treated with bempedoic acid compared with placebo [18].

The treatment of hypertriglyceridemia in diabetes requires differentiation between prevention of pancreatitis and reduction of ASCVD risk. The REDUCE-IT trial demonstrated that icosapent ethyl significantly reduced cardiovascular events in statin-treated patients with elevated TG levels and established cardiovascular disease or diabetes plus additional risk factors [19]. In contrast, the ACCORD Lipid trial did not demonstrate a significant reduction in the primary cardiovascular outcome with routine addition of fenofibrate to simvastatin in the overall population with type 2 diabetes [20].

7. Emerging Therapeutic Targets

ApoC-III is an important regulator of triglyceride-rich lipoprotein metabolism. It inhibits LPL-mediated triglyceride hydrolysis and hepatic clearance of triglyceride-rich particles. Emerging antisense oligonucleotide and small-interfering RNA approaches targeting ApoC-III include volanesorsen, olezarsen and plozasiran. Recent evidence demonstrates substantial reductions in TG and ApoC-III with these approaches, although the extent to which these treatments reduce ASCVD events in broad diabetic populations remains under investigation [8,21].

ANGPTL3 regulates lipid metabolism partly through inhibition of LPL and endothelial lipase. Increased ANGPTL3 activity can contribute to accumulation of triglyceride-rich lipoproteins. Recent work has identified ANGPTL3 as a potential target for diabetic dyslipidemia. Inhibition of ANGPTL3 has been associated with reductions in triglyceride-rich lipoproteins and other lipid parameters [9]. The ARCHES-2 trial evaluated zodasiran, an RNA interference therapeutic targeting ANGPTL3, in patients with mixed hyperlipidemia and demonstrated substantial lipid-lowering effects [22].

RNA-based therapies are increasingly being investigated for lipid disorders. Antisense oligonucleotides and siRNA molecules can selectively suppress hepatic production of specific proteins involved in lipid metabolism. This approach offers the possibility of prolonged biological effects with less frequent dosing than conventional oral medications. ApoC-III, ANGPTL3 and Lp(a) are among the pathways receiving considerable research attention. However, these therapies remain at different stages of clinical development, and their long-term efficacy, safety, cost-effectiveness and cardiovascular outcome benefits require continued evaluation.

8. Future Perspective: Toward Precision Assessment of Diabetic Dyslipidemia

The future management of diabetic dyslipidemia is likely to move from a conventional concentration-based model toward a particle- and pathway-based model.

A potential future assessment could integrate LDL-C, non-HDL-C, triglycerides, ApoB, remnant cholesterol, sdLDL, Lp(a), glycemic status, insulin resistance, inflammatory markers and metabolic and hepatic status.

Such an approach may allow identification of different lipid phenotypes within the broad category of diabetic dyslipidemia. One patient may have predominantly LDL-related risk, whereas another may have relatively controlled LDL-C but persistent hypertriglyceridemia, elevated remnant cholesterol and increased ApoB.

The concept of residual risk is therefore particularly important. Even after effective LDL-C reduction,

patients with diabetes may continue to have elevated triglyceride-rich lipoproteins, remnant particles, sdLDL and inflammatory/metabolic abnormalities. The development of therapies directed toward ApoC-III, ANGPTL3 and Lp(a) provides an opportunity to address some of these previously under-recognized pathways.

Nevertheless, emerging biomarkers should complement rather than automatically replace conventional lipid testing. Standardization, accessibility, cost, assay reproducibility and evidence linking biomarker-guided treatment to improved clinical outcomes remain important considerations.

9. Conclusion

Diabetic dyslipidemia is a multifaceted disorder extending beyond elevated triglycerides, reduced HDL-C and conventional LDL-C measurements. Insulin resistance promotes adipose-tissue lipolysis, hepatic VLDL overproduction and impaired triglyceride-rich lipoprotein clearance, ultimately contributing to remnant accumulation and formation of small dense LDL particles.

The increasing recognition of ApoB-containing particles, remnant cholesterol, sdLDL and Lp(a) provides a broader understanding of residual cardiovascular risk in diabetes. Current therapeutic management remains centered on lifestyle modification and statin-based LDL-C reduction, with ezetimibe, PCSK9 inhibitors, bempedoic acid and selected triglyceride-lowering therapies providing additional options.

Emerging approaches targeting ApoC-III and ANGPTL3 illustrate a transition toward mechanism-specific lipid therapy. Future research should determine which biomarkers provide the greatest incremental predictive value and, importantly, whether biomarker-guided interventions translate into improved cardiovascular outcomes.

A comprehensive approach integrating conventional lipid measurements with particle-based biomarkers, metabolic status and emerging molecular targets may ultimately provide a more precise framework for the management of diabetic dyslipidemia.

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