

Hypertriglyceridemia: From Biochemical Aberration to Cardiometabolic Syndrome - Emerging Pathophysiology, Clinical Challenges, and Novel Therapeutics

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For decades, elevated triglycerides (TGs) were mostly considered a minor lipid aberration compared to LDL cholesterol, often overlooked as a tangential risk factor in cardiovascular disease. However, evolving evidence has dramatically altered this perspective. Low to moderate hypertriglyceridemia confers a persistent, independent risk for atherosclerotic cardiovascular disease (ASCVD), especially among patients with diabetes, metabolic syndrome, and obesity. Elevated triglycerides correlate strongly with insulin resistance and atherogenic dyslipidaemia, a triad recognized as a major driver of premature atherosclerosis. More severe hypertriglyceridemia, defined by fasting TG concentrations above 500 mg/dL, not only magnifies cardiovascular risk but inherently predisposes to acute, potentially fatal pancreatitis. The range of TG elevations thus spans a clinical spectrum—from silent metabolic risk to emergent organ injury. Clinicians face the complex task of stratifying this heterogeneous syndrome, discerning primary genetic forms from secondary causes, and leveraging expanding therapeutic options that now include promising molecular agents like DR10624.

The surge in obesity and type 2 diabetes globally alongside dietary transitions has propelled the prevalence of hypertriglyceridemia to unprecedented levels. Significantly, South Asian populations including those in India demonstrate a particularly high burden due to genetic predisposition interacting with rapid lifestyle changes. This hypertriglyceridemic dyslipidemia manifests with low HDL cholesterol and small dense LDL particles, conferring heightened atherosclerotic risk that traditional LDL-centric treatments inadequately address. Meanwhile, acute complications such as pancreatitis challenge emergency and critical care management, necessitating rapid TG lowering to avert multisystem failure. The clinical paradigm is thus shifting from reactive treatment to anticipatory management, integrating molecular diagnostics, personalized medicine, and genotype-guided therapies.

This comprehensive, 4500-word narrative aims to provide an advanced, holistic review tailored for clinicians and scholars. Each section unpacks the mechanisms influencing plasma triglycerides, genetic drivers, epidemiological trends, clinical implications, and treatment strategies—from lifestyle to cutting-edge therapeutics including apoC-III inhibitors and novel triple agonists. Through case insights and critical reflection on evolving management frameworks, this review empowers practitioners to navigate this dynamic landscape and optimize patient outcomes.

Historical Perspective

The recognition of triglycerides as pivotal in human disease is relatively recent. Early lipidology focused heavily on cholesterol fractions as central drivers of atherosclerosis. However, familial syndromes of massive triglyceride elevation and recurrent pancreatitis were documented in the late 20th century, sparking interest in triglyceride-rich lipoprotein metabolism disorders. Foundational studies involving lipid electrophoresis and enzyme assays helped identify lipoprotein lipase (LPL) deficiency syndromes, revealing their severe clinical phenotypes marked by eruptive xanthomas, hepatosplenomegaly, and catastrophic pancreatitis. Yet, it took the advent of genetic sequencing and proteomics in the 21st century to unravel the complex molecular pathways regulating triglyceride homeostasis and catabolism.

The epidemiological transition with increasing obesity, type 2 diabetes, and westernized diets paralleled a surge in hypertriglyceridemia prevalence worldwide. Public health and clinical trials initially adopted LDL cholesterol as the primary target, theorizing that lowering LDL would sufficiently mitigate cardiovascular risk. However, clinical observations and randomized controlled trials increasingly revealed residual risk linked to triglyceride elevations, especially post-statin therapy. This gap spurred clinical innovation and drug development targeting triglyceride metabolism modifiers such as PPAR agonists, omega-3 fatty acids, and antisense nucleotides targeting apolipoproteins.

In parallel, advanced imaging and biomarkers have confirmed the atherogenic role of triglyceride-rich remnants, solidifying triglycerides' place as a key causal factor in cardiovascular disease and pancreatitis risk. From purely biochemical curiosity to critical clinical phenotype, hypertriglyceridemia is now rightly considered a significant syndrome requiring comprehensive care.

Classification and Diagnostic Framework

Hypertriglyceridemia is clinically classified according to fasting plasma triglyceride concentrations, which dictate risk profiles and therapeutic urgency:

- Mild: 150–199 mg/dL
- Moderate: 200–499 mg/dL
- Severe: 500–1,000 mg/dL
- Very severe: >1,000 mg/dL

These thresholds are critical to clinical decision-making. Even mild elevations confer increased atherosclerotic risk, especially when coupled with other metabolic abnormalities such as low HDL and small dense LDL particles. When TGs rise above 500 mg/dL, the risk of acute pancreatitis rises steeply, prompting urgent intervention. Extremely elevated levels (>1,000 mg/dL) warrant immediate attention to prevent multisystem organ failure.

Hypertriglyceridemia encompasses both primary (genetic) and secondary forms. Primary forms are rare but often severe, resulting from mutations affecting lipoprotein lipase, apolipoproteins C-II and A-V, or regulatory enzymes such as GPIIIBP1. These genetic syndromes frequently manifest in childhood or adolescence and present with recurrent pancreatitis and cutaneous xanthomas. Secondary hypertriglyceridemia is by far more prevalent and results from acquired conditions such as poorly controlled diabetes, metabolic syndrome, obesity, hypothyroidism, nephrotic syndrome, excessive alcohol intake, and medications like corticosteroids or antipsychotics.

A thorough laboratory evaluation begins with fasting lipid profiles, complemented by glucose, thyroid function, renal screening, and targeted genetic testing in severe or refractory cases. Physical examination for characteristic xanthomas, lipemia retinalis, and hepatomegaly provides important

diagnostic clues. Longitudinal monitoring accounts for fluctuations driven by dietary intake, metabolic status, and therapy adherence.

Epidemiology: Hidden Epidemic

Hypertriglyceridemia is widely prevalent yet underdiagnosed until complications arise. In the U.S., approximately 30% of adults have triglyceride levels exceeding 150 mg/dL, with 1–2% exceeding the critical 500 mg/dL threshold. Globally, prevalence is rising, mirroring trends in obesity, diabetes, and sedentary lifestyles. South Asia, notably India, reports some of the highest hypertriglyceridemia rates worldwide, reflecting interactions between genetic predisposition and rapid urbanization.

The coexistence of atherogenic dyslipidemia—high TGs, low HDL cholesterol, and small dense LDL particles—forms a metabolic triad strongly linked to insulin resistance, endothelial dysfunction, and accelerated atherosclerosis. This phenotype drives premature cardiovascular morbidity and challenges conventional risk-reduction strategies focused solely on LDL cholesterol. Consequently, hypertriglyceridemia increasingly commands clinical attention as a modifiable risk factor for global cardiometabolic disease burdens.

Molecular Pathophysiology: What Drives Triglycerides Up?

Fundamentally, elevated plasma triglycerides result from an imbalance among production, clearance, and hydrolysis of triglyceride-rich lipoproteins (TRLs), mainly chylomicrons and very-low-density lipoproteins (VLDL). Increased hepatic VLDL production is a hallmark of insulin resistance states and excessive caloric intake, often exacerbated by the dysregulated adipose tissue lipolysis releasing free fatty acids.

Concurrently, impaired catabolism of TRLs happens predominantly through deficiency or dysfunction of lipoprotein lipase (LPL), the essential enzyme anchoring triglyceride hydrolysis at the endothelial surface of capillaries. Genetic mutations or acquired inhibitors such as apoC-III and angiopoietin-like proteins negatively regulate LPL activity, delaying TRL clearance and promoting remnant accumulation.

Hormonal regulation is pivotal: insulin suppresses hepatic VLDL production and stimulates LPL activity; insulin resistance hampers these controls, causing further TG elevation. Moreover, inflammatory cytokines and medical therapies disrupt apolipoprotein expression and lipoprotein receptor function, further tipping balance toward hypertriglyceridemia.

Clinical Consequences: More Than a Number

Cardiovascular Disease

TGs and remnant lipoproteins directly contribute to atherosclerosis via endothelial dysfunction, inflammatory activation, and foam cell formation. Despite statin therapy reducing LDL cholesterol, a significant residual cardiovascular risk remains attributable to elevated triglycerides, especially in populations with metabolic syndrome or diabetes. Reducing this "residual risk" is a contemporary therapeutic priority, underscored by clinical trial data demonstrating benefit from TG-lowering agents in selected patients.

Acute Pancreatitis

Severe hypertriglyceridemia (>1,000 mg/dL) triggers acute pancreatitis by lipoprotein lipase-mediated release of free fatty acids within pancreatic capillaries. These fatty acids induce local cytotoxicity, microvascular thrombosis, ischemia, and amplified inflammation. Pancreatitis severity correlates with

TG concentration and other factors like alcohol. Prompt reduction of TG levels is lifesaving, requiring aggressive medical and sometimes plasmapheresis interventions.

Conclusion:

The contemporary view of hypertriglyceridemia has transformed from a neglected lipid metric to a pivotal clinical syndrome encompassing cardiometabolic risk and acute organ injury. The evidence is compelling that triglycerides—and their remnant particles—play a causal role in atherosclerosis and cardiovascular events, independent of LDL cholesterol. This knowledge has redefined treatment goals, emphasizing not only LDL lowering but also aggressive management of elevated triglycerides to reduce residual cardiovascular risk, particularly in patients with diabetes and metabolic syndrome.

Simultaneously, clinicians must remain vigilant about the extreme consequences of very high triglyceride levels, notably the danger of acute pancreatitis. Advances in the understanding of pathophysiology, including the interplay of free fatty acids, inflammation, and endothelial injury, have improved acute management strategies and outcomes.

The management landscape is rapidly evolving with the arrival of targeted therapeutics that modulate triglyceride metabolism at the molecular level. ApoC-III inhibitors, ANGPTL3 antagonists, and especially novel triple agonists like DR10624 hold promise for unprecedented triglyceride reduction and multi-domain metabolic benefits—including glucose control, weight reduction, and improved hepatic steatosis. The clinical trials demonstrating dramatic triglyceride lowering and improved biomarkers herald a new era in the personalized treatment of HTG.

However, challenges remain in translating these advances into widespread impact. The diagnostic complexity of distinguishing primary from secondary forms, the importance of holistic lifestyle interventions, management of comorbidities, and accessibility of expensive novel drugs require coordinated multidisciplinary approaches. Furthermore, patient education, close monitoring, and addressing social determinants are crucial to optimize adherence and clinical outcomes.

Looking forward, genetic insights and precision medicine promise to further tailor therapies and refine risk stratification. Combined with continuing advances in drug development and meaningful public health initiatives, these innovations offer hope to reduce the burden of hypertriglyceridemia and its devastating cardiovascular and pancreatic complications.

In essence, hypertriglyceridemia now stands as a clinical syndrome of great significance—one that demands nuanced understanding, integrative care, and incorporation of cutting-edge therapies. As research translates into practice, patients and clinicians alike can anticipate strides toward mitigating atherogenic risk and preventing catastrophic acute events, ultimately improving long-term cardiometabolic health.

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