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Review article:

Lipid profile metabolism, pathophysiology, clinical correlations, and therapeutic strategies in cardiovascular and metabolic diseases

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Abstract:

Lipid abnormalities, encompassing dysregulations in cholesterol, triglycerides, and lipoprotein fractions, have emerged as pivotal modifiable risk factors for cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and other systemic conditions such as nonalcoholic fatty liver disease and chronic kidney disease. This review synthesizes current evidence on the molecular biology of lipid metabolism, including cholesterol biosynthesis and homeostasis, triglyceride synthesis and clearance, and the structure and function of lipoproteins—high-density lipoprotein (HDL) and low-density lipoprotein (LDL), with special emphasis on the atherogenic small dense LDL subfraction. Epidemiological, genetic, and clinical studies linking lipid profiles to disease pathology are critically examined, highlighting the causal and prognostic significance of lipid fractions beyond traditional metrics. The review also discusses advanced lipid markers, their utility in risk stratification, and the emerging concept of HDL dysfunction. Furthermore, correlations between lipid profiles and T2DM, NAFLD, cancer, inflammation, and other diseases are explored. Contemporary lifestyle and pharmacological interventions—ranging from statins, ezetimibe, and PCSK9 inhibitors to novel triglyceride-targeted therapies—are reviewed with respect to efficacy, safety, and guideline recommendations. Advances in precision medicine, including genetic testing and personalized lipid management, are also addressed. The evolving landscape of lipidology underscores the need for comprehensive, multifactorial approaches to lipid abnormalities to optimize patient outcomes and reduce residual cardiovascular and metabolic risk.

Keywords: cholesterol, triglycerides, HDL, LDL, diabetes mellitus, cardiovascular disease.

Introduction

Dyslipidemias or Lipid abnormalities, encompassing dysregulations in cholesterol, triglycerides, and lipoprotein fractions, have emerged as pivotal modifiable risk factors for cardiovascular disease (CVD), type 2 diabetes mellitus (T2DM), and other systemic conditions such as nonalcoholic fatty liver disease and chronic kidney disease. Cardiovascular disease (CVD) burden is partly related to the elevated prevalence of risk factors, including obesity and type 2 diabetes mellitus (T2DM) (1,2).

T2DM is associated with abnormal lipid profiles, including elevated triglyceride and/or low high-

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density lipoprotein cholesterol (HDL-C), a feature that has been referred to as metabolic dyslipidemia (3,4). Whether improvements in the triglyceride–HDL-C phenotype augment CVD risk reduction beyond LDL-C is still a matter of debate (5). Moreover, data on the relationship of metabolic dyslipidemia with incident CVD in overweight or obese individuals with T2DM is scarce (6).

This review provides an evidence-based analysis of lipid metabolism, pathophysiology, clinical correlations, and contemporary therapeutic strategies.

1. Cholesterol: Molecular Biology and Pathophysiology

1.1 Biochemical Structure and Function

Cholesterol is a 27-carbon sterol molecule with distinct hydrophilic, hydrophobic, and rigid domains that enable its amphipathic properties. This unique structure underlies cholesterol's essential roles in cell membrane fluidity regulation, bile acid synthesis, steroid hormone production, and intracellular signaling pathways. Every vertebrate cell possesses the molecular machinery for both cholesterol biosynthesis and metabolism (7).

1.2 Cholesterol Metabolism and Homeostasis

Cholesterol homeostasis involves a dynamic balance between uptake, biosynthesis, transport, distribution, esterification, and elimination. The major cholesterol synthesis pathway—the mevalonate pathway—is tightly regulated at multiple levels, including transcriptional, post-transcriptional, and enzymatic control mechanisms. HMG-CoA reductase (HMGCR) serves as the rate-limiting enzyme, while sterol regulatory element-binding protein 2 (SREBP2) acts as the master transcriptional regulator (8).

Dietary cholesterol contributes significantly to the endogenous cholesterol pool and directly affects serum concentrations, particularly LDL-C levels. Cholesterol elimination occurs primarily through conversion to bile acids via 7α-hydroxylase (CYP7A1), with intermediates in bile acid biosynthesis potentially serving important signaling functions beyond their role as end products (9).

1.3 Pathological Consequences

Because humans cannot efficiently catabolize cholesterol, excessive accumulation leads to atherogenesis through multiple mechanisms, including endothelial dysfunction, foam cell formation, and inflammatory activation. Conversely, severe cholesterol deficiency impairs transport of fat-soluble vitamins (especially vitamins K and E), compromising hemostasis and antioxidant defenses (10).

2. Triglycerides: Synthesis, Transport, and Metabolic Integration

2.1 Triglyceride Biosynthesis and Regulation

Triglyceride (TG) synthesis occurs through the glycerol phosphate pathway, initiated by glycerol-3-phosphate acyltransferase (GPAT), followed by lysophosphatidic acid acyltransferase (AGPAT), phosphatidic acid phosphatase (PAP), and diacylglycerol acyltransferase (DGAT). The liver serves as the central organ for fatty acid and triglyceride metabolism, with fatty acids derived from hepatocellular uptake and de novo lipogenesis (9).

Under physiological conditions, hepatic TG storage remains minimal despite high metabolic flux. However, in obesity and metabolic dysfunction, altered fatty acid metabolism leads to hepatic triglyceride accumulation and nonalcoholic fatty liver disease (NAFLD) (11).

2.2 Triglyceride-Rich Lipoprotein Metabolism

Triglycerides are transported in triglyceride-rich lipoproteins (TRLs), including chylomicrons (intestinally derived) and very-low-density lipoproteins (VLDL, hepatically derived). The metabolism of TRLs is regulated by several key factors (12):

Lipoprotein Lipase (LPL): The rate-limiting enzyme for TG hydrolysis in capillary beds (12).

Apolipoprotein C-III (ApoC-III): A potent inhibitor of LPL that regulates postprandial TG clearance and has emerged as a therapeutic target for hypertriglyceridemia (13).

Angiopoietin-like proteins (ANGPTL3, ANGPTL4): Endogenous LPL inhibitors that modulate TG partitioning during fasted and fed states(12) .

Accumulation of TRL remnants—partially lipolyzed, cholesterol-enriched particles—contributes significantly to atherogenesis and residual cardiovascular risk beyond LDL-C lowering (12).

2.3. Clinical Significance of Hypertriglyceridemia

Fasting triglycerides >150 mg/dL reflect metabolic dysfunction, insulin resistance, and increased small dense LDL formation. Postprandial hypertriglyceridemia is increasingly recognized as an independent cardiovascular risk factor, with triglycerides serving as markers of atherogenic remnant metabolism(14).

3. High-Density Lipoprotein (HDL): Beyond "Good Cholesterol"

3.1. HDL Structure and Heterogeneity

HDL represents the most abundant yet heterogeneous class of lipoproteins, with particles differing in size (HDL_2 vs HDL_3), protein composition, and functional properties. Proteomics studies have identified nearly 285 different proteins associated with HDL, though approximately 15 apolipoproteins constitute the core structural components (15).

3.2. HDL Metabolism and Function

Reverse Cholesterol Transport (RCT): HDL mediates cholesterol efflux from peripheral tissues to the liver via ATP-binding cassette transporters ABCA1 and ABCG1. This process involves cholesterol esterification by lecithin-cholesterol acyltransferase (LCAT) and subsequent transfer to apoB-containing lipoproteins via cholesteryl ester transfer protein (CETP) (14).

Beyond Cholesterol Transport: HDL exhibits multiple cardioprotective functions, including anti-inflammatory, antioxidant, antithrombotic, and endothelial-protective effects. Recent evidence suggests HDL also modulates glucose metabolism in skeletal muscle, influencing insulin sensitivity (16).

3.3. HDL Dysfunction in Disease States

In metabolic disorders, HDL undergoes compositional and functional changes that impair its protective properties. **HDL dysfunction**—rather than simply low HDL-C levels—is increasingly recognized as clinically relevant. In conditions such as diabetes, chronic kidney disease, and acute coronary syndromes, HDL particles become pro-inflammatory and lose their beneficial functions (17).

Recent clinical trials of HDL-raising agents have failed to demonstrate cardiovascular benefit, reinforcing that HDL function, rather than concentration, determines clinical outcomes (18).

4. Low-Density Lipoprotein (LDL): Atherogenic Mechanisms and Subfractions

4.1. LDL Heterogeneity and Small Dense LDL

LDL particles exhibit significant heterogeneity in size, density, and atherogenic potential. **Small dense LDL (sdLDL)** represents the most atherogenic subfraction due to enhanced arterial wall penetration, prolonged residence time, increased oxidative susceptibility, and reduced LDL receptor affinity (16).

4.2. Small Dense LDL: Clinical Evidence

Multiple prospective studies demonstrate that sdLDL is an independent cardiovascular risk factor beyond total LDL-C. A meta-analysis of 21 studies (30,628 subjects, 5,693 CHD events) found(19):

- High vs. low sdLDL particle presence: HR 1.36 (95% CI: 1.21-1.52)
- Top vs. bottom quartile sdLDL-C: HR 1.07 (95% CI: 1.01-1.12) (19)

Mechanistic Properties of Small Dense LDL (20):

- Greater arterial entry and retention
- Higher susceptibility to oxidation
- Reduced LDL receptor binding affinity
- Enhanced foam cell formation capacity
- Association with insulin resistance and metabolic syndrome

4.3. Clinical Assessment and Therapeutic Implications

Small dense LDL measurement is not yet routinely available in clinical practice, though the Sampson equation allows estimation from standard lipid parameters. In patients with acute coronary syndromes, sdLDL-C levels >32.6 mg/dL independently predict recurrent cardiovascular events even after optimal statin therapy (21).

5. Correlation of Lipid Profile with Cardiovascular Disease

5.1. Epidemiological Evidence

Extensive meta-analyses demonstrate dose-dependent relationships between lipid parameters and cardiovascular mortality (12):

Total Cholesterol: Each 1 mmol/L (~39 mg/dL) increase confers 27% higher CVD mortality risk (HR 1.27; 95% CI: 1.19-1.36)

LDL-C: Each 1 mmol/L increase is associated with 21% higher risk (HR 1.21; 95% CI: 1.09-1.35)

HDL-C: Each 0.26 mmol/L (~10 mg/dL) increase reduces CVD mortality by 40% (HR 0.60; 95% CI: 0.50-0.72)(12)

5.2. Advanced Lipid Markers and Residual Risk

Beyond traditional lipid parameters, several advanced markers provide additional prognostic information(22):

Non-HDL Cholesterol: Better predictor than LDL-C in patients with triglycerides >200 mg/dL

Apolipoprotein B (ApoB): Represents total atherogenic particle number

Lipoprotein(a): Independent genetic risk factor for cardiovascular events

Triglyceride/HDL-C Ratio: Marker of insulin resistance and metabolic dysfunction

5.3. Genetic Evidence and Causality

Mendelian randomization studies provide compelling evidence for causal relationships between lipid parameters and cardiovascular disease, particularly for LDL-C and triglyceride-rich lipoproteins. Genetic variants affecting cholesterol metabolism demonstrate consistent associations with cardiovascular outcomes, supporting therapeutic interventions targeting these pathways (23).

6. Correlation of Lipid Profile with Diabetes Mellitus

6.1. Diabetic Dyslipidemia Phenotype

Type 2 diabetes mellitus is characterized by a distinct dyslipidemic pattern: (24,25)

- **Hypertriglyceridemia**: Elevated VLDL production due to insulin resistance
- **Low HDL-C**: Enhanced HDL catabolism and reduced synthesis
- **Small Dense LDL**: Increased proportion of atherogenic LDL subfractions
- **Postprandial Lipemia**: Prolonged clearance of triglyceride-rich lipoproteins

6.2. Clinical Evidence

In a cohort study of 367 diabetic patients, LDL-C correlated positively with HbA1c levels ($r > 0$, $p <$

0.05), while only 42.6% of patients on statins achieved LDL-C <100 mg/dL. The correlation between glycemic control and lipid parameters reflects shared pathophysiologic mechanisms involving insulin resistance and hepatic glucose/lipid metabolism (24).

6.3. Mechanistic Links

Insulin Resistance: Central mechanism driving dyslipidemia through:

- Enhanced hepatic VLDL-TG synthesis and secretion
- Impaired LPL-mediated TG clearance
- Altered HDL metabolism and reverse cholesterol transport
- Increased small dense LDL formation

Advanced Glycation End Products (AGEs): Contribute to LDL oxidation and foam cell formation (24).

7. Correlation of Lipid Profile with Other Diseases

7.1. Nonalcoholic Fatty Liver Disease (NAFLD)

NAFLD represents a hepatic manifestation of metabolic syndrome with characteristic dyslipidemia(26):

Lipid Profile in NAFLD:

- Elevated triglycerides (OR 2.6, $p < 0.001$ for NAFLD risk)
- Reduced HDL-C (OR 0.34, $p < 0.001$ for protection)
- Increased TG/HDL-C ratio (OR 3.3, $p < 0.001$)
    - Higher non-HDL cholesterol in patients with hepatic steatosis (26)

Mechanistic Integration: Both hepatic lipid accumulation and insulin resistance contribute through multiple pathways, with lipotoxicity playing a central role in disease progression (27).

7.2. Chronic Kidney Disease (CKD)

CKD profoundly alters lipid metabolism through multiple mechanisms (28):

Impaired Lipoprotein Clearance: Reduced LPL activity and altered receptor function

- **HDL Dysfunction**: Loss of anti-inflammatory and antioxidant properties
- **Uremic Toxins**: Direct effects on lipid metabolism and HDL functionality
- **Chronic Inflammation**: Alters lipoprotein composition and function

7.3 Cancer and Cholesterol Metabolism

Emerging evidence links cholesterol metabolism to cancer biology (8):

- **Tumor Cell Reprogramming**: Altered cholesterol synthesis and uptake pathways
- **Membrane Effects**: Cholesterol influences membrane fluidity and signaling
- **Steroid Hormone Synthesis**: Cholesterol-derived hormones affect cancer progression
- **Therapeutic Implications**: Cholesterol-lowering drugs may have anti-cancer effects

7.4 Inflammatory and Infectious Diseases

Sepsis and Critical Illness: Hypocholesterolemia predicts worse outcomes, reflecting the severity of systemic inflammation and impaired lipoprotein-mediated immune modulation (29).

COVID-19: Prolonged disturbances in cholesterol metabolism pathways persist during recovery, with severity correlating with metabolic dysfunction (30,31).

Thalassemia Major: Ferritin has a role as an acute-phase reactant and inflammatory marker(32). Ferritin levels inversely correlate with HDL-C ($r = -0.45$, $p < 0.01$), suggesting HDL-C as a potential noninvasive marker of iron overload (33).

7.5 Sleep and Circadian Disorders

Sleep restriction induces changes in cholesterol metabolism pathways and inflammatory responses. Prolonged sleep deprivation decreases expression of cholesterol transporters and increases inflammatory pathway activation, leading to potentially higher cardiometabolic risk (34).

8. Treatment of Elevated Lipid Profile

8.1. Lifestyle Interventions

Dietary Modifications:

- Mediterranean diet: Reduces total cholesterol by 0.46 mg/dL (95% CI: -0.55, -0.38, p = 0.001) in NAFLD patients (35)
- Increased meal frequency: Modest reductions in LDL-C and total cholesterol (low-quality evidence) (36)
- Plant sterols: 2-3g daily reduces LDL-C by 6-15%(35)

Physical Activity: Regular aerobic exercise increases HDL-C levels and shifts HDL subpopulations toward larger, more protective particles (37).

8.2. Statin Therapy: Foundation of Lipid Management

8.2.1. Mechanism and Efficacy

Statins inhibit HMG-CoA reductase, reducing hepatic cholesterol synthesis and upregulating LDL receptors. **High-intensity statins** (atorvastatin 40-80 mg, rosuvastatin 20-40 mg) reduce LDL-C by ≥50% and cardiovascular events by ~25% per mmol/L LDL-C reduction (38).

8.2.2. Clinical Guidelines and Implementation

Current guidelines emphasize **early intensive statin therapy** in acute coronary syndromes, with targets of LDL-C <55 mg/dL (1.4 mmol/L) and >50% reduction from baseline. However, real-world data show suboptimal target achievement, with only 17.8% of post-ACS patients reaching guideline-recommended levels (39).

8.3. Combination Lipid-Lowering Therapy

8.3.1. Ezetimibe

Ezetimibe inhibits intestinal cholesterol absorption via Niemann-Pick C1-Like 1 (NPC1L1) transporter blockade. When combined with statins, ezetimibe provides an additional 15-20% LDL-C reduction and further cardiovascular benefit (40).

Clinical Evidence: Meta-analysis of 11 studies (106,358 patients) demonstrated that combination statin-ezetimibe therapy vs. statin monotherapy reduces:

- All-cause mortality: OR 0.75 (95% CI: 0.62-0.92, p = 0.01)
- Cardiovascular mortality: OR 0.75 (95% CI: 0.66-0.84, p < 0.001)
- Major adverse cardiovascular events: OR 0.72 (95% CI: 0.63-0.82, p < 0.001) (40)

8.3.2. PCSK9 Inhibitors

PCSK9 inhibitors (evolocumab, alirocumab) enhance LDL receptor recycling, achieving 50-60% additional LDL-C reduction beyond statin therapy. These monoclonal antibodies demonstrate cardiovascular benefit in high-risk patients, though cost-effectiveness remains a consideration(41).

Inclisiran: siRNA-based PCSK9 inhibitor with twice-yearly dosing shows promise for improving adherence(41).

8.3.3. Novel Therapeutic Targets

Bempedoic Acid: ATP citrate lyase inhibitor providing ~20% LDL-C reduction with demonstrated cardiovascular benefit in secondary prevention (42).

ANGPTL3 Inhibitors: Target triglyceride-rich lipoprotein metabolism for residual risk reduction(41).

CETP Inhibitors: Under investigation for HDL modification, though clinical outcomes remain unclear (41).

8.4. Triglyceride-Targeted Therapy

8.4.1. Fibrates

Fibrates activate peroxisome proliferator-activated receptor-α (PPAR-α), reducing triglycerides by 25-50% and modestly increasing HDL-C. **Fenofibrate** shows particular benefit in diabetic patients with hypertriglyceridemia.

8.4.2. Omega-3 Fatty Acids

High-dose omega-3 fatty acids (icosapent ethyl 4g daily) reduce cardiovascular events in patients with elevated triglycerides despite statin therapy. The REDUCE-IT trial demonstrated 25% reduction in major cardiovascular events with EPA supplementation (43).

8.4.3. Emerging Triglyceride Therapies

ApoC-III Inhibitors: Volanesorsen and other antisense oligonucleotides targeting apoC-III show dramatic triglyceride reductions in severe hypertriglyceridemia (13).

GLP-1 Receptor Agonists: Beyond glycemic effects, these agents favorably impact small dense LDL and triglyceride-rich lipoproteins (44).

8.5. Personalized and Precision Medicine Approaches

8.5.1. Genetic Testing

Familial Hypercholesterolemia: Genetic screening identifies patients requiring intensive early intervention (41).

Pharmacogenomics: CYP2C19 and SLCO1B1 variants affect statin metabolism and myopathy risk(42).

Polygenic Risk Scores: Integration of multiple genetic variants enhances cardiovascular risk prediction beyond traditional factors (45).

8.5.2 Advanced Lipid Testing

Lipoprotein Particle Analysis: NMR spectroscopy and ion mobility provide detailed particle size and number information (46).

Apolipoprotein B: Better than LDL-C for risk assessment in metabolic syndrome patients (47).

Lipoprotein(a): Genetic risk factor requiring specific therapeutic approaches (48).

8.6 Treatment Guidelines and Clinical Implementation

8.6.1. Risk-Based Treatment Paradigms

Modern guidelines emphasize **risk-based treatment** rather than lipid level thresholds alone. Risk calculators integrate multiple factors to guide intensity of lipid-lowering therapy (49):

Primary Prevention: 10-year ASCVD risk >7.5-10% generally warrants statin initiation (50).

Secondary Prevention: All patients with established ASCVD receive high-intensity statin therapy unless contraindicated (51).

Very High-Risk Categories: Include recent ACS, diabetes with target organ damage, and familial hypercholesterolemia (52).

8.6.2. Monitoring and Follow-up

Lipid Testing: Baseline assessment followed by 4-8 week evaluation after therapy initiation or modification (53).

Safety Monitoring: Hepatic transaminases (baseline and as clinically indicated) and assessment for muscle symptoms (50).

Adherence Support: Critical for long-term success, with single-pill combinations improving compliance.

8.7. Future Therapeutic Directions

8.7.1. RNA-Based Therapeutics

siRNA Technology: Expanding beyond PCSK9 to target multiple lipid metabolism pathways (41).

Antisense Oligonucleotides: Targeting apoC-III, apoB, and other key regulatory proteins (13).

8.7.2. Metabolic Pathway Modulation

AMPK Activation: Central regulator of glucose and lipid metabolism with therapeutic potential.

Bile Acid Sequestrants: New-generation agents with improved tolerability profiles (41).

Microbiome Modulation: Emerging evidence for gut microbiota influence on lipid metabolism(54).

Summary and Clinical Implications

This comprehensive systematic review demonstrates that lipid profile assessment extends far beyond simple cholesterol and triglyceride measurement. The evidence supports several key clinical principles:

1. **Multi-target Approach**: Optimal cardiovascular risk reduction requires addressing LDL-C, non-HDL-C, triglycerides, and HDL functionality rather than focusing on isolated parameters.
2. **Early Intensive Therapy**: Combination lipid-lowering therapy initiated early in high-risk patients provides superior outcomes compared to sequential approaches.
3. **Personalized Medicine**: Integration of genetic factors, advanced lipid testing, and individual risk factors enables precision approaches to dyslipidemia management.
4. **Beyond Cardiovascular Disease**: Lipid abnormalities contribute to NAFLD, diabetes, kidney disease, and other systemic conditions, requiring comprehensive management strategies.
5. **Therapeutic Innovation**: Novel agents targeting triglyceride-rich lipoproteins, PCSK9, and other pathways expand treatment options for residual risk reduction.

The evolving understanding of lipid metabolism, coupled with advances in therapeutic options, positions comprehensive lipid management as a cornerstone of modern preventive medicine. Future research should focus on optimizing combination therapies, developing more accessible advanced lipid testing, and implementing precision medicine approaches to maximize individual patient benefit while minimizing treatment burden and cost.

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