INNOVARE JOURNAL OF LIFE SCIENCE

Vol 12, 2024

ISSN - 2321-550X

Review Article

CLINICAL UTILIZATION OF LIPID PROFILES AND GENETICS OF LIPID METABOLISM

PAWAN KUMAR*

CSIR-Institute of Genomics and Integrative Biology, Delhi University Campus, New Delhi, India.
Email: pawangaba@gmail.com

Received: 23 February 2024, Revised and Accepted: 12 May 2024

ABSTRACT

Lipid testing provides vital information for cardiovascular risk stratification and prevention decision-making. This article overviews evidence-based approaches to screening, risk evaluation, diagnosis of familial hyperlipidemias, and employing emerging pharmacogenetic therapies for managing lipid profile abnormalities.

Keywords: Lipid profile, Genetics, Hyperlipidemias, Familial hyperlipidemias, Apolipoprotein E gene, Proprotein convertase subtilisin/kexin type 9, Apolipoprotein B.

 DOI: http://dx.doi.org/10.22159/ijls.2024v12.50215. Journal homepage: https://innovareacademics.in/journals/index.php/ijls

INTRODUCTION

Clinical lipid profiling, including total cholesterol, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and triglycerides, predicts the likelihood of developing atherosclerotic heart disease and guides recommendations for lifestyle changes, primary prevention, and lipid-lowering therapies [1]. While most circulatory lipid derangements can be managed through dietary adjustments, exercise, and statin medications, up to 20% of patients exhibit inadequate responses or persistently high residual cholesterol levels despite these traditional interventions.

LIPID GUIDELINES

Major guidelines provide screening and treatment recommendations for lipid abnormalities. The 2018 American College of Cardiology/American Heart Association (ACC/AHA) Cholesterol Clinical Practice Guidelines advocate for regular lipid panel testing in all adults aged 40–75 years and monitoring LDL cholesterol for those at increased cardiovascular disease (CVD) risk to inform the need for primary prevention [1]. Target lipid levels differ based on risk factors, with LDL cholesterols <100 mg/dL, <70 mg/dL, and <55 mg/dL advised for low, medium, and high-risk groups, respectively. Non-HDL cholesterols, apolipoprotein B (APOB), and triglycerides offer additional context for patients with obesity or diabetes. Applying this tiered strategy ensures those likeliest to benefit receive appropriate lifestyle counseling and pharmacologics such as statins. Alternate guidelines such as the National Lipid Association recommendations for patient-centered management emphasize clinical judgment in contextualizing lipid results into global risk evaluations and individualized treatment decisions [2]. While consensus lacks on optimal thresholds, lipid testing undoubtedly assists prevention.

RISK EVALUATION

Approaches rather than relying solely on lipid levels, modern cardiovascular risk calculators integrate results with other clinical variables to determine personalized probabilities, subclasses, and quantitative targets. The atherosclerotic CVD (ASCVD) risk estimator from the ACC/AHA utilizes total cholesterol, HDL, age, race, smoking status, diabetes status, hypertension treatment, and sex to estimate 10-year and lifetime risks of developing atherosclerotic complications [3]. This contextualization of lipid markers with coexisting factors facilitates more exact primary prevention by triggering considerations for statins and antihypertensives at higher quantifiable ASCVD risk thresholds. While criticism exists due to the reliance on outdated clinical trial cohorts, ACC/AHA risk scoring represents an improvement from previous percentile categorizations. Ongoing recalibrations against modern, more diverse populations will enhance accuracy [4]. Regardless of the exact calculator, formal risk estimations allow clinicians to tangibly communicate probabilities and offer individually tailored prevention recommendations regarding lipids and lifestyle changes.

FAMILIAL HYPERLIPIDEMIAS

In up to 20% of cases of extreme lipid abnormalities, hereditary factors underlie unusually high LDL cholesterol or triglycerides inadequately responsive to traditional management approaches [5]. Familial hypercholesterolemias (FHs), characterized by total cholesterol levels over 290 mg/dL and LDL cholesterols above 190 mg/dL, frequently stem from autosomal dominant mutations in genes coding LDL receptor proteins, apoB-100, or proprotein convertase subtilisin/kexin type 9 (PCSK9). Cascade screening of first-degree relatives with premature CVD outcomes facilitates early identification for intensive prevention [6]. Familial combined hyperlipidemia exhibits similar phenotypes but demonstrates increased triglycerides simultaneously with LDL accumulations due to polygenic rather than monogenic origins. Recognizing these familial hyperlipidemias prompts referrals to specialist care for advanced therapies. While only constituting a minority subgroup, focusing intensive treatment efforts on those with inherited highest risks with increased lipid derangements enhances prevention and efficiency.

GENETIC DETERMINANTS

Beyond FHs, common single nucleotide polymorphisms (SNPs) distributed widely within populations also influence lipid regulation. Large-scale genome-wide association studies quantify the impacts of single nucleotide variants [7]. Apolipoprotein E (ApoE) and LDL receptor (LDLR) polymorphisms alter LDL clearance rates, with certain alleles increasing circulating cholesterol. SNPs in APOA1/C3/A4/A5 genes all demonstrate significant associations with plasma triglycerides [8]. Moreover, previously identified variants explain only 15% of heritability, indicating substantial undiscovered genetic contributors. Next-generation sequencing promises more comprehensive genetic risk profiling by extending beyond SNP analyses to identify rare causal mutations. Already targeted gene panels can detect individuals with heightened genetic burdens averaging 5–10 lipid-altering alleles that collectively shift risk distributions. Moving

forward, delineating multifaceted genetic architecture promises increased predictive power and personalized prevention opportunities.

Genetic factors influencing lipid metabolism

SNPs, variations in a single nucleotide within a DNA sequence, have been identified as key players in lipid metabolism. Genes such as ApoE, which encodes apolipoprotein E, and PCSK9, involved in LDL receptor degradation, harbor SNPs that impact lipid levels and cardiovascular risk.

ApoE gene

The ApoE gene, located on chromosome 19, encodes a protein crucial for lipoprotein metabolism. Specific SNPs in the ApoE gene, such as the ε2, ε3, and ε4 alleles, are associated with varying levels of plasma cholesterol and triglycerides. The ε4 allele, for instance, is linked to an increased risk of cardiovascular diseases and Alzheimer's disease [9].

PCSK9 gene

PCSK9 is a key player in LDL cholesterol regulation. SNPs in the PCSK9 gene can affect the function of the encoded protein, leading to altered LDL receptor activity and, consequently, impacting LDL cholesterol levels. Certain PCSK9 variants are associated with FH and increased cardiovascular risk [10].

Lipoprotein lipase (LPL) gene

LPL is an enzyme crucial for triglyceride hydrolysis. SNPs in the LPL gene have been linked to variations in triglyceride levels. Specific variants may result in reduced LPL activity, leading to impaired triglyceride clearance and an increased risk of hypertriglyceridemia [11].

Cholesteryl ester transfer protein (CETP) gene

The CETP gene encodes a protein involved in the transfer of cholesteryl esters between lipoproteins. Certain SNPs in the CETP gene are associated with altered HDL cholesterol levels. Variants that increase CETP activity may lead to decreased HDL cholesterol concentrations, contributing to an increased risk of cardiovascular diseases [12].

HMGCR gene

The HMGCR gene encodes 3-hydroxy-3-methylglutaryl-coenzyme A reductase, a key enzyme in cholesterol synthesis. Variants in this gene influence cholesterol levels and are the target of statin medications used to lower cholesterol [13].

SORT1 gene

SORT1 is involved in intracellular trafficking of lipoproteins and is associated with LDL cholesterol levels. Variants in this gene have been linked to variations in LDL cholesterol and cardiovascular risk [14].

TRIB1 gene

The TRIB1 gene is associated with lipid metabolism and has been linked to both LDL and HDL cholesterol levels. Variants in TRIB1 are implicated in cardiovascular risk [15].

ABCA1 gene (chromosome 9)

ABCA1 codes for a transporter protein involved in the formation of HDL particles. Variants in ABCA1 are associated with changes in HDL cholesterol levels, and other lipid-related phenotypes [16].

FH

FH is a hereditary disorder characterized by elevated cholesterol levels and an increased risk of premature cardiovascular disease. Mutations in genes such as LDLR, APOB, and PCSK9 are known to cause FH, highlighting the direct link between genetic factors and lipid metabolism disorders [17]

LDLR gene

LDLR: Mutations in the LDLR gene are the most common cause of FH. The LDLR gene provides instructions for making the LDL receptor, responsible for removing LDL cholesterol from the bloodstream.

APOB gene

APOB: Mutations in the APOB gene can also lead to FH. APOB is a component of LDL cholesterol, and alterations can result in impaired LDL receptor binding.

PCSK9 gene

PCSK9: Variants in PCSK9 can cause FH by increasing the degradation of LDL receptors, reducing their effectiveness.

INHERITANCE PATTERN

FH follows an autosomal dominant pattern, meaning that an individual only needs to inherit one copy of the mutated gene from either parent to develop the disorder. Individuals with FH have a 50% chance of passing the condition to each of their children.

EMERGING THERAPIES

Capitalizing upon exponentially expanding genetic insight, novel RNA therapies now provide specialized treatment avenues for managing the subset of FHs and statin non-responders. Small interfering RNAs targeting PCSK9 production build upon the successes of PCSK9 monoclonal antibodies to lower LDL cholesterols previously unresponsive to other modalities [18]. Inclisiran leverages RNA interference through twice-yearly injectable treatments that suppress hepatic PCSK9 synthesis, maintaining LDL reductions for 6 months per dose [19]. Moreover, base editing of liver cells' LDL receptors enables durable corrections of FH mutations. Parallel vaccine development trains the immune system to recognize and degrade circulating PCSK9 proteins with lasting effects after a short immunization series. Such innovations epitomize the translational potential of genetics-guided drug design.

CONCLUSION

In total, lipid profile screening and interpretation remain essential for individualizing cardiovascular risk assessments and prevention plans. Simultaneously, recognition of familial hyperlipidemias prompts more aggressive efforts to mitigate genetic predispositions early. Finally, harnessing the powers of gene sequencing and editing culminates in RNA therapies and vaccines providing last-line options where traditional recommendations fall short. Only by integrating genetic insights across each of these clinical domains can the field achieve genuine precision and personalization for maximizing benefit while minimizing harm in the management of lipid abnormalities.

REFERENCES

1. Grundy SM, Stone NJ, Bailey AL, Beam C, Birtcher KK, Blumenthal RS, *et al.* 2018 AHA/ACC/AACVPR/AAPA/ABC/ACPM/ADA/AGS/APhA/ASPC/NLA/PCNA guideline on the management of blood cholesterol: A report of the American college of cardiology/American Heart association task force on clinical practice guidelines. Circulation 2019;139:e1082-43.
2. Jacobson TA, Maki KC, Orringer CE, Jones PH, Kris-Etherton P, Sikand G, *et al*. National lipid association recommendations for patient-centered management of dyslipidemia: Part 2. J Clin Lipidol 2015;9:S1-122.e1.
3. Arnett DK, Blumenthal RS, Albert MA, Buroker AB, Goldberger ZD, Hahn EJ, *et al*. 2019 ACC/AHA guideline on the primary prevention of cardiovascular disease: A report of the American college of cardiology/American heart association task force on clinical practice guidelines. Circulation 2019;140:e596-646.
4. Emerging Risk Factors Collaboration, Angelantonio ED, Gao P, Pennells L, Kaptoge S, Caslake M, *et al*. Lipid-related markers and cardiovascular disease prediction. JAMA 2012;307:2499-506.
5. Abul-Husn NS, Manickam K, Jones LK, Wright EA, Hartzel DN, Gonzaga-Jauregui C, *et al*. Genetic identification of familial hypercholesterolemia within a single U.S. health care system. Science 2016;354:aaf7000.
6. Knowles JW, Rader DJ, Khoury MJ. Cascade screening for familial hypercholesterolemia and the use of genetic testing. JAMA 2017;318:381-2.

7. Dron JS, Wang J, McIntyre AD, Cao H, Hegele RA. The polygenic nature of mild-to-moderate hypertriglyceridemia. J Clin Lipidol 2020;14:28-34.e2.
8. Qi L, Liu S, Rifai N, Hunter D, Hu FB. Associations of the apolipoprotein A1/C3/A4/A5 gene cluster with triglyceride and HDL cholesterol levels in women with type 2 diabetes. Atherosclerosis 2007;192:204-10.
9. El-Lebedy D, Raslan HM, Mohammed AM. Apolipoprotein E gene polymorphism and risk of type 2 diabetes and cardiovascular disease. Cardiovasc Diabetol 2016;15:12. Erratum in: Cardiovasc Diabetol 2016;15:35.
10. Doi T, Hori M, Harada-Shiba M, Kataoka Y, Onozuka D, Nishimura K, *et al.* Patients with LDLR and PCSK9 gene variants experienced higher incidence of cardiovascular outcomes in heterozygous familial hypercholesterolemia. J Am Heart Assoc 2021;10:e018263.
11. Dron JS, Hegele RA. Genetics of hypertriglyceridemia. Front Endocrinol (Lausanne) 2020;11:455.
12. Gudnason V, Kakko S, Nicaud V, Savolainen MJ, Kesäniemi YA, Tahvanainen E, *et al.* Cholesteryl ester transfer protein gene effect on CETP activity and plasma high-density lipoprotein in European populations. The EARS Group. Eur J Clin Invest 1999;29:116-28.
13. Das KC, Hossain MU, Moniruzzaman M, Salimullah M, Akhteruzzaman S. High-risk polymorphisms associated with the molecular function of human HMGCR gene infer the inhibition of cholesterol biosynthesis. Biomed Res Int 2022;2022:4558867.
14. Gustafsen C, Kjolby M, Nyegaard M, Mattheisen M, Lundhede J, Buttenschøn H, *et al.* The hypercholesterolemia-risk gene SORT1 facilitates PCSK9 secretion. Cell Metab 2014;19:310-8.
15. Quiroz-Figueroa K, Vitali C, Conlon DM, Millar JS, Tobias JW, Bauer RC, *et al.* TRIB1 regulates LDL metabolism through CEBPα-mediated effects on the LDL receptor in hepatocytes. J Clin Invest 2021;131:10.1172/JCI146775.
16. Chen L, Zhao ZW, Zeng PH, Zhou YJ, Yin WJ. Molecular mechanisms for ABCA1-mediated cholesterol efflux. Cell Cycle 2022;21:1121-39.
17. Vrablik M, Tichý L, Freiberger T, Blaha V, Satny M, Hubacek JA. Genetics of familial hypercholesterolemia: New insights. Front Genet 2020;11:574474.
18. Rikhi R, Shapiro MD. Proprotein convertase subtilisin/kexin Type 9 inhibition: The big step forward in lipid control. Eur Cardiol 2023;18:e45.
19. Nishikido T. Clinical potential of inclisiran for patients with a high risk of atherosclerotic cardiovascular disease. Cardiovasc Diabetol 2023;22:20.