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Modern Management of Dyslipidemia: A Comprehensive Review Study

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Abstract: Dyslipidemia is the metabolic derangement of the lipids in the body, which is often only diagnosed through a blood lipid profile. It is a common pathology affecting the majority of the adult population, with a high disease burden on the healthcare system due to its complications. A better understanding of the latest treatment modalities can aid in providing better care for the patients.
Aim of the study: To establish a better understanding of the symptoms, diagnostic methodology, and management of dyslipidemia.
Materials and methods: This review is a comprehensive search of PUBMED from the year 2021 to 2024.
Conclusion: Dyslipidemia is a silent pathology that requires regular screening and prompt treatment to prevent long-term complications and possible morbidity. Better knowledge about the latest guidelines and treatment modalities can aid physicians in providing optimal care for their patients.
Keywords: Dyslipidemia; Triglycerides; Management; Statins

Introduction

Dyslipidemia is a metabolic condition involving derangement of any or all lipids- such as fats, triglycerides, cholesterol, phospholipids, or lipoproteins in the body- either elevated or reduced from the optimal body range- depending on the individual's age, sex, and other factors.[1] As reported by Pappan et al, depending on the definition and criteria being used, the global prevalence of dyslipidemia in adults is estimated to range from 20% to 80%. It was reported that from 2005 to 2008, nearly 33.5% of the US adult population over the age of 20 had high LDL levels.[2] Dyslipidemia usually does not manifest symptomatically, and often exists along with other risk factors, such as hypertension, diabetes, obesity, and smoking. Thus, it is challenging to directly measure dyslipidemia. [2] In developed countries, hyperlipidemia is the most common form of dyslipidemia. Dyslipidemia serves as a precursor condition that raises the risk for the development of atherosclerotic cardiovascular diseases, such as coronary artery disease, cerebrovascular disease, and peripheral artery disease.[1]

Etiology

Dyslipidemia can be classified as primary and secondary.

Primary dyslipidemia is a hereditary condition stemming from genetic mutations that interfere with the normal pathways of lipid processing in the body.[3] It can be inherited as any genetic pattern: autosomal dominant, autosomal recessive, or X-linked. Primary dyslipidemia encompasses conditions such as familial hypercholesterolemia, familial hypertriglyceridemia, familial combined hyperlipidemia, and familial dysbetalipoproteinemia. Familial hypercholesterolemia has an estimated prevalence that ranges from 1 in 500 to 1 in 250 in most populations.[4] Familial dysbetalipoproteinemia has an estimated prevalence of 1 in 10,000 in the general population, with higher rates among those with obesity or diabetes.[1] Primary dyslipidemia can manifest as functional defects in the synthesis, transport, or degradation of lipoproteins, which are carriers of lipids in blood. It increases the risk of atherosclerosis and cardiovascular disease by causing the accumulation or deficiency of lipoproteins and lipids in the blood.[2]

Table 1: Types Of Primary Dyslipidemias [2]

Primary Dyslipidemia	Genetic Defect	Dysfunction

Familial hypercholesterolemia	mutations in the LDL receptor gene	Leads to impairment of LDL cholesterol uptake from the blood → high LDL cholesterol levels and premature atherosclerosis
Familial hypertriglyceridemia	mutations in the LPL gene or apo C-II gene	Impairs the hydrolysis of triglycerides in chylomicrons and very low-density lipoproteins (VLDL) → high triglyceride levels and pancreatitis
Familial combined hyperlipidemia	overproduction of apo B-containing lipoproteins (VLDL and LDL) by the liver	Leads to high cholesterol and triglyceride levels and insulin resistance
Familial dysbetalipoproteinemia	mutations in the apo E gene	Impairs the clearance of chylomicron and VLDL from the blood→ high cholesterol and triglyceride levels and xanthomas

Secondary dyslipidemia is influenced by lifestyle factors or other medical conditions that alter the lipid levels in the body. These types of dyslipidemias are reversible or modifiable by treating the underlying cause. Risk factors include physical activity, unhealthy nutrition, obesity, diabetes, hypothyroidism, chronic kidney disease, liver disease, alcohol abuse, smoking, and the use of certain drugs.[5] A study reported that in the United States, about 28% of the new cases had one or more potential causes of secondary dyslipidemia, the most prevalent being excessive alcohol intake at 10% and diabetes mellitus 8%.[2]

Table 2: Causes of Secondary Dyslipidemia [2].

Causes Of Secondary Dyslipidemia	**Underlying Pathology**	**Result**
Obesity	elevated production of very low-density lipoprotein and reduced liver clearance of chylomicrons	high triglyceride and low high-density lipoprotein cholesterol levels
Diabetes mellitus	insulin resistance and hyperglycemia → impaired triglyceride lipolysis and the uptake of LDL cholesterol	high triglyceride and LDL cholesterol levels and low HDL cholesterol levels
Hypothyroidism	decreased expression of LDL receptors and lipoprotein lipase → impaired the clearance of LDL cholesterol and triglycerides from the blood	high LDL cholesterol and triglyceride levels
Chronic kidney disease	impaired catabolism of apo B-containing lipoproteins and reduced activity of lipoprotein lipase and hepatic lipase → impaired the clearance of triglycerides and cholesterol from the blood	high triglyceride and LDL cholesterol levels and low HDL cholesterol levels
Liver disease	impaired synthesis and secretion of lipoproteins and bile acids → impaired the transport and excretion of cholesterol and triglycerides from the liver	high or low cholesterol and triglyceride levels depending on the type and severity of the liver disease

Alcohol abuse	increased synthesis of VLDL and decreased oxidation of fatty acids by the liver	high triglyceride levels
Smoking	increased oxidative stress and inflammation → impaired the function and synthesis of HDL cholesterol	low HDL cholesterol levels
Use of certain drugs, such as corticosteroids, beta-blockers, oral contraceptives, and antiretroviral agents	affect the metabolism of lipids and lipoproteins by various mechanisms	high or low cholesterol and triglyceride levels depending on the type and dose of the drug

Pathophysiology

Through various biological pathways, dyslipidemia acts as a catalyst for systemic inflammation and oxidative stress, which in turn can precipitate cardiovascular pathologies and broader metabolic impairments.

Table 3: Pathophysiology Of Dyslipidemia [2].

Pathophysiology	**Consequence**
Inflammation	• Retention of LDL and triglyceride-rich lipoprotein → inflammatory response in the blood vessels → atherosclerosis • Activation of inflammatory cells → infiltration and damage the endothelium • Escalation in expression of adhesion molecules → facilitate the attachment and migration of inflammatory cells into the subendothelial space • Modulation in function of endothelial progenitor cells (EPCs) → compromise endothelial integrity and function
Oxidative Stress	• LDL particles undergo oxidative modifications when retained in arterial walls • Oxidized LDL is pro-inflammatory and pro-atherogenic → increased production of reactive oxygen species (ROS), unstable molecules that damage cells and tissues by oxidizing components (lipids, proteins, deoxyribonucleic acid) • Cause decline in the level of antioxidants
Cardiovascular Diseases	• Increased risk of cardiovascular disease by promoting atherosclerosis and its complications • Impairment of nitric oxide production and availability affects cardiovascular function • Induction of endothelial dysfunction → dysfunction in vascular homeostasis

Diagnosis

Dyslipidemia is often asymptomatic; thus, routine lipid screening is the mainstay for diagnosis.[2] Most guidelines recommend screening for males aged more than 20 to 40 years and for females aged more than 20 to 45 years or post-menopausal.[3] Different risk scores, such as Framinghman Risk Score, can be used to determine cardiovascular risk.[8] Dyslipidemia can sometimes manifest as xanthomas, arcus senilis, lipemia retinalis, lower limb ischemia, angina, transient ischemic attacks, and strokes.[2] The assessment of dyslipidemia is done by blood collection and subsequent examination of blood levels for: triglycerides, HDL cholesterol, and LDL cholesterol.[6]

Table 4: Diagnosis For Dyslipidemia [2].

Types Of Cholesterol	**Optimal Levels**	**Clinical Notes**

Total cholesterol	• Desirable: <200 mg/dL • Borderline high: 200 mg/dL to 239 mg/dL • High: ≥240 mg/dL	-
Triglycerides (TG)	• Normal: <150 mg/dL • Borderline high: 150 mg/dL to 199 mg/dL • High: 200 mg/dL to 499 mg/dL • Very high: ≥500 mg/dL	• Levels >1.7mmol/L fasting- indicates dyslipidemia [1] • Measuring TG levels requires fasting for 8-12 hours as non-fasting TG levels can be falsely elevated [6] • TG levels > 10mmol/L – risk factor for acute pancreatitis [7]
High density lipoprotein cholesterol (HDL-C)	• Low: <40 mg/dL (men), <50 mg/dL (women) • High: ≥60 mg/dL	• Low levels indicate dyslipidemia and is a risk factor for complications [1]
Low density lipoprotein cholesterol (LDL-C)	• Optimal: <100 mg/dL • Near optimal/above optimal: 100 mg/dL to 129 mg/dL • Borderline high: 130 mg/dL to 159 mg/dL • High: 160 mg/dL to 189 mg/dL • Very high: ≥190 mg/dL	• High levels increase the risk for cardiovascular disease and indicate dyslipidemia [1]

The differential diagnoses can include: nephrotic syndrome, biliary obstruction, hypothyroidism, pregnancy, and drugs (oral estrogens, glucocorticoids, tamoxifen, thiazides).[2]

Management

Dyslipidemia can be managed using non-pharmacological and pharmacological methods.

Non-Pharmacological Management

Non-pharmacological lifestyle modifications are recommended for all individuals with dyslipidemia. Dietary changes are recommended to aim at reducing blood lipid levels along with weight reduction if needed, in accordance with the treatment plan devised by the physicians with the involvement of a dietician. The diets should be regularly revised. As a method of primary prevention- a 3-month dietary trial is recommended before considering medication, while secondary prevention and in high-risk individuals, medication should be used in conjunction with diet. Recommended diets are the DASH diet, Mediterranean diet, low glycemic index diet, the Portfolio diet, and the vegetarian diet. [8]

Other non-pharmacological methods include physical activity, weight management, and smoking cessation. Physical activity is a way of lifestyle modification. For adults, the American Heart Association (AHA) recommends at least 150 minutes of moderate-intensity aerobic exercise, 75 minutes of vigorous-intensity aerobic exercise per week, or a combination of both. Dyslipidemia patients who are overweight or obese should aim for gradual and sustained weight loss of 5% to 10% over a period of 6 to 12 months in consultation with the physician, by caloric intake reduction and physical activity. Lipid profile can be adversely deranged by smoking, thus cessation aids in improving lipid profile and reducing CVD risk.[2]

Pharmacological Management

Pharmacological treatment is recommended based on Framinghan Risk Scores. The recommendation for high-risk individuals is statin therapy along with non-pharmacological intervention. Depending on individual patient factors such as age, cholesterol levels, and risk factors, statin therapy should be started with those at immediate risk.[8] Pharmacological therapy helps in reducing LDL-C levels more quickly compared to lifestyle modifications. Add-on drug therapy is advisable if one drug fails to lower LDL-C levels.[9]

Table 7: Pharmacological Therapy For Dyslipidemia [10].

DRUG	CLINICAL NOTES
HMG-CoA reductase inhibitors (statins)	• First line treatment [2] • Inhibit 3-hydroxy-3methylglutaryl-coenzyme A reductase [2] • reduce LDL-C levels with plaque reduction in coronary atherosclerosis [9] • side effects include myalgia, rhabdomyolysis, hepatic dysfunction, renal impairment secondary to rhabdomyolysis [9] • Ezetimibe is recommended for patients unable to the side effects [9]
Ezetimibe	• Recommended as secondary treatment alongside statin therapy [9] • enhances the efficacy of statin therapy for individuals at high risk of cardiovascular events, decreasing the incidence of non-fatal heart attacks and strokes [10] • mechanism of action is inhibition of the NPC1L1 protein-inhibiting cholesterol absorption [9][2]
Bile acid sequestrants	• Reduce bile acid reabsorption, therefore increasing clearance of LDL [2] • adverse effects include constipation, reflux esophagitis, and nausea [10] • reduction of LDL-C by 15-30% and elevation of HDL-C by 3-5% [10]
Fibrates	• Primarily affect triglyceride levels [10] • decrease the complications with high triglyceride levels like pancreatitis [10] • compared omega-3-fatty acids, reduce triglycerides by 50% [10] • side effects: elevated liver enzymes and creatine phosphokinase, myopathy, cholelithiasis, and venous thrombosis [10]
Niacin	• Elevates HDL and reduces VLDL, decreasing LDL levels [2] • side effects are significant but aspirin can reduce side effects [2]
PCSK9 Inhibitors	• These are monoclonal antibodies that bind PCSK9 and decrease LDL levels [2] • ODYSSEY OUTCOME trial and FOURIER trial demonstrated a reduction in cardiovascular morbidity [10]
Bempedoic acid	• Acts on the cholesterol synthesis pathway- causing upstream of statins at ATP citrate lyase [11] • CLEAR wisdom and CLEAR harmony trials demonstrated its efficacy in LDL-C reduction [10]

Conclusion

Dyslipidemia is a silent pathology that requires regular screening and prompt treatment to prevent long-term complications and possible morbidity. Better knowledge about the latest guidelines and treatment modalities can aid physicians in providing optimal care for their patients.

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