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# Pathophysiology and Management of Dyslipidaemia

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**Abbreviations:** ADA: American Diabetes Association; BAS: Bile Acid Sequestrant; CVD: Cardiovascular Disease; FFA: Free Fatty Acids; GI: Gastrointestinal; HDL-C: High-Density Lipoprotein Cholesterol; HMG-CoA: 3-Hydroxy-3-Methylglutaryl-Coenzyme-A Reductase Inhibitors; IL: Interleukin; LDL-C: Low-Density Lipoprotein Cholesterol; Lp(a): Lipoprotein(a); PCSK9: Proprotein Convertase Subtilisin/Kexin Type 9; ROS: Reactive Oxygen Species; TG: Triglyceride; TNF-α: Tumour Necrosis Factor-α

**ABSTRACT**

Dyslipidaemia is a circumstance described by accelerated total cholesterol, or triglycerides, a low-high-density lipoprotein (HDL) or a combination of these abnormalities. Dyslipidemia is associated with atherosclerosis in the process of causing cardiovascular disease. Cholesterol accumulated due to dyslipidemia is oxidized and accelerates the description of intercellular adhesion molecule-1 and endothelial selectin (E-selectin) for monocyte adhesion, thereupon resulting in monocyte influx and cytokine production. The therapeutic approach and therapeutic objectives depending on the risk of developing atherosclerotic cardiovascular disease, and the criteria are more restricted for those at high risk. It intended to decrease cardiovascular disease risk in the future; thus, management criteria will depend initially on low-density lipoprotein values. Statins prevent the reductase of 3-hydroxy-3-methylglutaryl-coenzyme-A, which is the rate limiting step in the hepatic cholesterol secretion or an enzyme that limits endogenous cholesterol secretion with reduced intracellular cholesterol content and accelerated low-density lipoprotein clearance. Statins remain the 1st line therapy in the treatment of dyslipidemia. American diabetes association recommends that statins should be used, irrespective of baseline lipid levels, in diabetic patients with cardiovascular disease or who are over the age of 40 and have one or further cardiovascular disease risk factor involving family history of cardiovascular disease, hypertension, smoking, dyslipidemia, or albuminuria.

**Keywords:** Dyslipidemia; Pathophysiology; Management

## Introduction

Dyslipidemia can result from an intrinsic, extrinsic, or a combination of genetic predisposition and external factors. Initial dyslipidemias are a heterogeneous group of diseases of genetic, mono, or polygenic etiology, whereas secondary ones sequence from the association of risk factors with external factors or other pathologies. Dyslipidemias can alter the values of Total Cholesterol (TC), TG, Low-Density Lipoprotein (LDL) cholesterol, or High-Density Lipoprotein (HDL) cholesterol and occur from childhood to adolescence alone or in association and persist during adult life [1-3]. Dyslipidemia is more frequent in diabetes mellitus patients because significant enzymes and lipid metabolism pathways are affected [4]. Dyslipidemia is a collection of metabolically interrelated plasma lipid and lipoprotein abnormality including low High-Density Lipoprotein Cholesterol (HDL-C), High Low-Density Lipoprotein Cholesterol (LDL-C), Total Cholesterol (TC) and triglyceride (TG) levels. In DM patients, the most frequent patterns of dyslipidemia were hypertriglyceridemia, declined HDL cholesterol levels, and accelerated levels of LDL particles and it increases the risk of CVD among DM patients [5-7]. People with dyslipidemia are two-times escalated risk of CVD as compared to those with normal lipid levels [8].

## Pathophysiology

Dyslipidemia is associated with atherosclerosis in the procedure of causing cardiovascular disease. Cholesterol accumulated due to dyslipidemia is oxidized and accelerates the description of intercellular adhesion molecule (ICAM)-1 and endothelial selectin (E-selectin) for monocyte adhesion, thereupon sequencing in monocyte influx and cytokine generation. The monocytes differentiate into macrophages and synthesis Monocyte Chemoattractant Protein (MCP)-1 to more promote the influx of monocytes. Furthermore, monocytes synthesis cytokines, such as interleukin (IL)-6, and increases the oxidation of cholesterol through the release of oxidizing substances. Macrophages absorb oxidized cholesterol and become foam cells, which are deposited on the walls of the blood vessels. This procedure sequences in the formation of plaque and causes atherosclerosis. In this manner, dyslipidemia accelerates the risk of atherosclerosis and cardiovascular disease [9-14]. Atherosclerotic lesions are considered to arise from transport and retention of plasma LDL through the endothelial cell layer into the extracellular matrix of the subendothelial space. Once in the artery wall, LDL is chemically revised through oxidation and nonenzymatic glycation, mildly oxidized LDL then recruits monocytes into the artery wall.

These monocytes then become transformed into macrophages that increase LDL oxidation. Repeated damage and repair within an atherosclerotic plaque finally lead to a fibrous cap protecting the underlying core of lipids, collagen, calcium, and inflammatory cells such as T lymphocytes. Maintenance of the fibrous plaque is critical to inhibit plaque rupture and subsequent coronary thrombosis [15,16]. Oxidative stress represents one of the basic pathogenetic procedures of atherosclerosis, as the escalated generation of Reactive Oxygen Species (ROS) is closely related to endothelial dysfunction and the promotion of the vascular inflammatory response. Common situations that are also respected as cardiovascular risk factors that predispose to atherosclerosis, such as hypercholesterolemia, hypertension, diabetes, and smoking, are associated with accelerated generation of ROS. Atherosclerosis is also recognized as an inflammatory disorder of the medium and large arteries. Cytokines have a paramount influence on the pathogenesis of this disease as they are included in all stages of atherosclerosis. Tumour necrosis factor-α (TNF-α), interleukin (IL)-1, and IL-6 are pro-atherogenic cytokines generated by macrophages, lymphocytes, natural killer cells, and vascular smooth muscle cells. TNF-α and IL-1 promote the description of cytokines, adhesion molecules, and the migration and mitogenesis of vascular smooth muscle and endothelial cells on the vascular wall during the atherosclerotic procedure [17-20].

### Diagnostic Procedure

Screening can be at fast or postprandial (higher TG in the latter) but must be verified in two fasting samples (12-h minimum fast) if altered, 2–3 weeks apart. The percentage between these two values will be used for diagnostic and therapeutic purposes. The postprandial sample notifies the determination of non-HDL cholesterol by subtracting HDL from the TC. Inflammation secondary to severe infections can cause importantly accelerated TG, for which lipid profile screening should not be performed in 3 weeks after infections. A fasting lipoprotein profile that involves total cholesterol, LDL, HDL, and Triglycerides should be measured [21,22] (Table 1).

**Table 1:** Classification of total LDL, HDL, cholesterol and triglycerides.

| **Total cholesterol** | |
|---|---|
| <200mg/dL | Desirable |
| 200-239mg/dL | Borderline high |
| ≥/240mg/dL | High |
| **LDL cholesterol** | |
| <100mg/dL | Optimal |
| 100-129mg/dL | Near or above optimal |
| 130-159mg/dL | Borderline high |
| 160-189mg/dL | High |
| ≥/ 190md/dL | Very high |
| **HDL cholesterol** | |
| <40mg/dL | Low |
| ≥/60mg/dL | High |
| **Triglycerides** | |
| <150mg/dL | Low |
| 150-199mg/dL | Borderline high |
| 200-299mg/dL | High |
| ≥/500mg/dL | Very high |

### Treatment

The therapeutic approach and therapeutic objectives depending on the risk of developing atherosclerotic CVD, and the criteria are further restricted for those at high risk. It aimed to decrease CVD risk in the future; thus, management procedures will depend initially on LDL values [23].

### Lifestyle Modifications

The management basis is focused on diet and at least 30–60 min of physical activity. Tobacco smoke exposure (passive or active) should be avoided and age-appropriate sleeping habits should be adopted. Restricted total fats, saturated fats, cholesterol intake,

modest accelerate in polyunsaturated fat, accelerated soluble fiber intake and weight reduction (initial goal of 10%) if needed [24-27]. The recommended diet is depending on escalated consumption of fruit, vegetables, and whole grains compared to the average of ingested fat (lipids by 25%–30%; carbohydrates by 55%, and proteins by 15%–20% of the total calories) [28].

## Pharmacological Therapy

Pharmacotherapy should be thought-out comprehending to CVD risk stratification. The decision to commence pharmacological treatment depends on age, severity, and the availability of other individual or familial CVD risk factors [29,30]. The intentions of management are to lower total and LDL cholesterol in order to decrease the risk of first or recurrent events such as myocardial infarction, angina, heart failure, ischemic stroke, or other forms of peripheral arterial disease such as carotid stenosis or abdominal aortic aneurysm [31-33]. Pharmacological management perhaps instituted ad initium in high-risk individuals with LDL of ≥130 mg/dl and age of >10 years. In the case of pharmacological therapy indication, the patient should be referred for hospital consultation [34].

## 3-Hydroxy-3-Methylglutaryl-Coenzyme-A Reductase Inhibitors (Statins)

Statins prevent the reductase of 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA), which is the rate limiting step in the hepatic cholesterol secretion or an enzyme that limits endogenous cholesterol synthesis with reduced intracellular cholesterol content and accelerated LDL clearance [35,36]. Statins remain the 1stline therapy in the treatment of dyslipidemia. ADA recommends that statins should be used, irrespective of baseline lipid levels, in diabetic patients with CVD or who are over the age of 40 and have one or further CVD risk factor involving family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria. Statin treatment is also recommended for diabetic patients under the age of 40 with multiple CVD risk factors or LDL > 100 mg/dl (82.6mmol/l) despite lifestyle intervention [37]. Statins are most effective at lowering LDL and, to a lesser extent, also lower triglycerides and raise HDL. Furthermore, statins have anti-inflammatory and anti-thrombotic properties and the capability to stabilize atherosclerotic plaques [38]. The most frequently used are rosuvastatin or pravastatin (over 8 years old), and other statins (atorvastatin, simvastatin, or lovastatin) are recommended above 10 years old [39]. Adverse drug reactions: Constipation less than10%; increased serum aminotransferase levels (initially alanine aminotransferase); increased creatine kinase levels; myopathy [40].

## Nicotinic Acid

Nicotinic acid (eg, extended-release niacin, immediate-release niacin) prevents the lipolysis of adipocytes, which sequences in reduced FFA levels, decreased VLDL secretion, and a slight accelerate in HDL generation rate and reduced catabolism of HDL. These alter by niacin subsequently lead to 15%–35% lower TG levels and 10%–25% higher HDL-C concentrations [41-43]. Niacin is recently the frequent potent medicine in increasing HDL cholesterol. Niacin also has moderate effect in lowering LDL-cholesterol, triglycerides and lipoprotein (a) [44]. Adverse drug reactions: Cutaneous flushing; itching (aspirin 325 mg shortly before niacin ingestion); GI intolerance; hyperglycaemia; hhyperuricemia and hepatotoxicity [45,46].

## Bile Acid Sequestrants

Bile acid scavengers (e.g., Cholestyramine resin, colesevelam, colestipol HCl) bind to bile acids, decreasing their absorption, and enhancing their hepatic secretion, thus reducing the cholesterol content of the hepatocytes [47]. Bile Acid Sequestrants (BAS) bind to bile acids in the intestinal lumen, thereupon interrupting the enterohepatic circulation of bile acids. As a sequence, the liver accelerates the generation of bile acids, which leads to reduce in cholesterol pool. BAS lower plasma total and LDL-cholesterol while increasing HDL-cholesterol and apoA1. The cholesterol-lowering effect of BAS perhaps accompanied by accelerates in triglycerides [48-50].

**Adverse Drug Reactions**: Constipation; bloating; epigastric fullness; nausea, and flatulence are most frequently observed and injured absorption of fat soluble vitamins, digoxin, warfarin, thiazides, b-blockers, thyroxine and phenobarbital [51]. The following are recommended for patients receiving BASs accelerate fluid uptake; modify the diet to enhance bulk, and use stool softeners [52].

**Cholesterol Absorption Inhibitors**: Cholesterol absorption inhibitors (e.g., ezetimibe) are a class of hypocholesterolemic medicine that prevents intestinal cholesterol absorption from plant sterols. They can be used from ten years of age as monotherapy or in association with statins, useful in children/adolescents with familial hypercholesterolemia or high-risk factors for immature CVD, who do not reach therapeutic objectives with the optimized statin dose. They do not change TG, vitamin A, and D, fat, or bile acids absorption [53,54]. Ezetimibe decreases the cholesterol content of both fasting and postprandial triglyceride-rich lipoproteins, thereupon lowering the concentrations of atherogenic remnant particles [55].

### Fibrates

Fibrates (eg, Bezafibrate, fenofibrate (micronized/microcoated/nano crystals), gemfibrozil) action is linked to the initiation of transcription of genes included in peroxisomal-oxidation; this procedure is mediated by specific transcription factors called peroxisome proliferator activated receptors (PPARs) [56].

The mechanisms of action of fibrates can be divided into 5 groups:

1) Initiation of lipoprotein lipolysis
2) Initiation of hepatic fatty acid (FA) intake and decrement of hepatic TG generation
3) Escalated removal of LDL particles
4) Decrement in neutral lipid, and
5) Accelerate in HDL generation and stimulation of reverse cholesterol transport [57].

Fibrates are the most potent medicines for lowering triglycerides. They also lower LDL and raise HDL. They are preferentially used in hypertriglyceridemia, but their use in under eighteen years old is not yet confirmed, thus only revealed in children with hypertriglyceridemia of >500 mg/dl or at risk of pancreatitis, who are unresponsive to dietary measure [58]. Adverse drug reactions: Gastrointestinal complaints; rash; dizziness; transient increases in transaminase levels and alkaline phosphatase [59] (Table 2).

**Table 2:** Effects of drug therapy on lipids and lipoproteins.

| Medications | Class | Mechanism of action | Effects on lipids | Effects on lipoproteins |
|---|---|---|---|---|
| Niacin | Nicotinic acid | Decrease LDL and VLDL synthesis | Decrease cholesterol and decrease triglycerides | Decrease LDL, increase HDL and decrease VLDL |
| Cholestyramine resin, colesevelam, colestipol HCl | Bile acid sequestrants | Increase LDL catabolism; decrease cholesterol absorption; | Decrease cholesterol | Decrease LDL and increase VLDL |
| Lovastatin, rosuvastatin, atorvastatin, simvastatin | HMG-CoA or statin | Decrease LDL synthesis and increase LDL catabolism | Decrease cholesterol | Decrease LDL |
| Ezetimibe | Cholesterol absorption inhibitors | Blocks cholesterol absorption across the intestinal border | Decrease cholesterol | Decrease LDL |
| Bezafibrate, fenofibrate, gemfibrozil | Fibrates | Increase VLDL clearance and decrease VLDL synthesis | Decrease triglycerides and decrease cholesterol | Decrease LDL, increase HDL and decrease VLDL |
| Omega-3-fatty acids | Fish oil supplementation | decrease the hepatic synthesis of TG | Decrease TG | Decrease hepatic secretion of VLDL |

### Omega-3-Fatty Acids or Fish Oil Supplementation

Omega-3 fatty acids lower triglycerides but have little effect on LDL and HDL. Additionally to hypotriglyceridemic consequences, omega-3 fatty acids perhaps ameliorate inflammation, attenuate endothelial function and decrease thrombus formation. Omega-3 fatty acids, which reduce the hepatic secretion and accumulation of TG, have been indicated to decrease plasma TG by 25%–30% by effectively decreasing the hepatic synthesis of VLDL [60].

### Proprotein Convertase Subtilisin/Kexin Type 9 (PCSK9 Inhibitor)

PCSK9 inhibitor (eg, Alirocumab; Evolocumab) prevent the lysosomal breakdown of LDL receptors, consequently accelerating their cell surface description. PCSK9 is a protein initially described in liver, intestine and kidney. It binds to LDL receptors and promotes their breakdown, consequently decreasing the removal of LDL from plasma. While gain-of-function mutations of PCSK9 cause hypercholesterolemia, loss-of-function mutations are associated with hypocholesterolemia and decreased risk of CVD [61].

## Combinations

Techniques for combination therapies with statins to reach even lower cholesterol levels have been reviewed. Combinations can be made with ezetimibe, which prevents the intestinal cholesterol absorption by interaction with Niemann-Pick C1 like 1 protein (NPC1L1), which sequences in an additional 20% lowering effect on LDL-C, but without affecting TG or HDL-C concentrations. Statin plus a BAR or niacin plus a BAR provide the highest reduction in total and LDL cholesterol. The concomitant use of fibrates and statins increased adverse muscle effects. Combination therapy of fibrates with statins in patients with diabetes and the characteristic dyslipidemia with high TG and low HDL-C occasionally have beneficial consequences. Thereupon, fenofibrate perhaps used to manage residual dyslipidemia in diabetic patients on top of statin therapy. Regimens aimed to accelerate HDL levels should involve either gemfibrozil or niacin, with statins combined with either of these medicines perhaps sequence in a higher incidence

of hepatotoxicity or myositis. Omega-3 fatty acids have also been indicated to accelerate the transformation of VLDL into IDL, which notifies an additional benefit for combining omega-3 fatty acids with statins by accelerated catabolism of VLDL, IDL and LDL [62,63].

## Conclusion

Dyslipidemia can sequence from an intrinsic, extrinsic, or a combination of genetic predisposition and external factors. Oxidative stress represents one of the basic pathogenetic procedures of atherosclerosis, as the accelerated generation of Reactive Oxygen Species (ROS) is closely related to endothelial dysfunction and the promotion of the vascular inflammatory response. Statins remain the 1stline therapy in the treatment of dyslipidemia. ADA recommends that statins should be used, irrespective of baseline lipid levels, in diabetic patients with CVD or who are over the age of 40 and have one or more CVD risk factor involving family history of CVD, hypertension, smoking, dyslipidemia, or albuminuria. Statin therapy is also recommended for diabetic patients under the age of 40 with multiple CVD risk factors or LDL > 100 mg/dl (82.6mmol/l) despite lifestyle intervention

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## Data Sources

Sources searched include Google Scholar, Research Gate, PubMed, NCBI, NDSS, PMID, PMCID, Scopus database, Scielo and Cochrane database. Search terms included: pathophysiology and management of dyslipidemia.

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## Availability of Data and Materials

The datasets generated during the current study are available with correspondent author.

## Competing Interest

The author has no financial or proprietary interest in any of material discussed in this article.

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