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Review Article

Overview of Dyslipidaemia in Adults

Mohammad Shoaib Hamrah[1*], Mohammad Hassan Hamrah[2,5], Mohammad Hussain Hamrah[3,5], Toba Dahi[4], Ahmad Edris Hamrah[5] & Mohammad Hashem Hamrah[5]

[1]*Center for Rural Health, School of Health Sciences, University of Tasmania, Australia*

[2]*Faculty of Stomatology, Kunduz University, Kunduz, Afghanistan*

[3]*Arya University Faculty of Medicine, Mazar-i-Sharif, Afghanistan*

[4]*Faculty of Dentistry, AbantIzzet Baysal University, Bolu, Turkey*

[5]*Dr.Mohammad Hashem Hamrah's Curative Clinic*

[*]**Correspondence to:** Dr. Mohammad Shoaib Hamrah, Center for Rural Health, School of Health Sciences, University of Tasmania, Australia.

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Abstract

Dyslipidaemia is a risk factor for atherosclerotic cardiovascular disease (ASCVD) including coronary artery disease (CAD), stroke, and peripheral artery disease. Control of lipid levels is the most effective intervention in both primary and secondary prevention of ASCVD. The combination of therapeutic lifestyle modification and pharmacologic treatment can be used for the management of patients with dyslipidaemia. This article explains the recent changes in guidelines for screening and management of dyslipidaemia among adult.

Introduction

Cardiovascular disease (CVD) is the leading cause of mortality worldwide [1]. CVD is responsible for 32% (17.3 million) of all deaths (54 million) annually, 47.4% (8.2 million) of CAD, and 37.6% (6.5million) stroke [2]. The causes of CVD are both modifiable and non-modifiable risk factors. The modifiable risk factors such as hypertension, unhealthy diet, Dyslipidaemia, tobacco use, and physical inactivity. In the recent decades lifestyle changes and control of modifiable risk factors had great potential benefits [3].

ASCVD including CAD, stroke, and peripheral artery disease is the leading cause of mortality worldwide [4]. Control of lipid levels is the most effective intervention in CVD prevention. According to an epidemiological study, dyslipidaemia play a major role in the development of CVD [5]. Dyslipidaemia is treated by pharmacologic and life style changes [6].

Pathophysiology of Atherosclerosis

Dyslipidaemia is noted a main predisposing factors in the development of atherosclerosis. The rise in LDL-C levels can both directly and indirectly contribute to atherogenesis. The rise in plasma LDL-C levels causes changes in permeability of arterial endothelial cells that allows the migration of apoB-containing lipoproteins [LDL-C, very low-density lipoprotein (VLDL), and apo E remnants] inside the arterial wall. Then, lipoproteins are modified (oxidation, glycation, enzymatic), which, along with other atherogenic factors, promotes activation of endothelial cells, which resulted in monocyte transmigration into the sub-endothelial space. They differentiate mononuclear phagocytes that ingest the accumulated normal and modified lipoproteins, which transforms them into the cholesterol-laden foam cells. The migration of circulating monocytes into the subendothelial space occurs in the initial stage in the process of atherosclerotic plaque formation activated through a regulated multistage process and mediated by chemoattractant, cell adhesion molecules and their receptors. Endothelial cells contribute to inflammation via immune cells recruitment including dendritic cells, mast cells, regulatory T (T-reg) cells, and T helper 1 (Th-1) cells [7-9].

Classification

Hyperlipidaemias may be classified as either familial (also called primary) and acquired (also called secondary).

Primary hyperlipidaemia: When resulting from a genetic defect, it may be monogenic: a single gene defect or polygenic: multiple gene defects.

Secondary hyperlipidaemia: When resulting from another underlying disorder that leads to changes in plasma lipid and lipoprotein metabolism [10]. Hyperlipidaemia refers to increased levels of lipid in the blood, including cholesterol and triglyceride. However, dyslipidaemia refers to abnormal level of lipid in the blood whether higher or lower levels of lipid in the blood.

Dyslipidaemia develops as a result of an underlying disorder including diabetes, nephrotic syndrome, chronic alcoholism, hypothyroidism and with use of drugs like corticosteroids, beta blockers and oral contraceptives. Secondary hyperlipidaemia together with significant hypertriglyceridemia can cause pancreatitis [11]. There are five main classes of lipoproteins including chylomicron, VLDL, intermediate density lipoprotein, LDL, and HDL. Thus, all these forms carry cholesterol and triglyceride to varying degrees for example LDL carrying the majority of cholesterol and VLDL carrying the majority of triglyceride. The VLDL is about one-fifth of the triglyceride level. Higher levels increase the risk of CVD. However, increased levels of HDL-C are associated with lower risk of CVD. The lipid screening includes a measurement of total cholesterol, LDL-C, HDL-C and triglyceride. Non-HDL-C is calculated by subtracting HDL-C from total cholesterol. Non-HDL-C is a good predictor of cardiovascular risk. Table 1 shows the ATP III Classification of LDL-C, total, HDL-C, and triglyceride (mg/dL). Basic metabolic panel, creatinine, and thyroid and liver function tests should be performed in order to exclude any secondary causes of hyperlipidaemia [12] Fasting lipid profile is not routinely recommended recently [13,14]

Table 1: *Classification of LDL-C, Total, HDL-C Cholesterol and Triglycerides (mg/dL)*

LDL-C Cholesterol	
<100	Optimal
100-129	Near optimal/above optimal
130-159	Borderline high
160-189	High
>/=190	Very high
Total Cholesterol	
<200	Desirable
200-239	Borderline high
>/=240	High
HDL-C Cholesterol	
<40	Low
>/=60	High
Triglycerides	
<150	Optimal
150-199	Borderline high
200-499	High
>500	Very high

Clinical Findings

Generally, patients with dyslipidaemia are a symptomatic. They are usually detected during routine laboratory testing or patients are at the danger stage of a stroke or CAD. Familial hyperlipidaemia or patients with hypercholesteremia can develop xanthomas which are deposits of cholesterol may form under the skin, especially under the eyes. Patients with severe hypertriglyceridemia may present with acute pancreatitis [15].

Diagnosis

The US Preventive Services Task Force recommends the following:

• Lipid screening is needed every 5 years for adults over 20 years old.

• Lipid screening is needed to start at age of 35 among men without risk factors for CAD and at age of 20-35 among men with risk factors i.e. men with DM, a family history of CAD among close relative (age<50 among a close man relative or age <60 among a close relative women). A family history of hypercholesteremia. Multiple CAD risk factors (eg, smoking, hypertension).

• Those at the risks of CAD are needed to treat based on the results of their lipid profiles.

• Lipid screening is needed among older people who have not been screened.

Treatment

Non-pharmacologic Treatment

Total cholesterol and LDL-C levels generally increase among both males and females. Higher cholesterol and LDL-C levels have been linked to ASCVD including CAD, stroke, and peripheral artery disease. There is an increase the prevalence of obesity, diabetes, and metabolic syndrome, which increased CAD risk occur. Therefore, weight loss, regular exercise, and a healthy diet should be emphasized to reduce CAD risk. Dietary factors that influence lipid levels include modification of nutritional components, consumption of specific foods, use of food additives and supplements, and major dietary approaches.

The following is a summary of the American Heart Association guidelines for patients with dyslipidaemia include caloric restriction, reducing intake of saturated and trans fat; increasing intake of polyunsaturated and monounsaturated fats; total fat should not comprise more than 30% of caloric daily intake, and total cholesterol intake should be less than 300 mg/day. The Modified Mediterranean diet is another successful dietary intervention, such as fruits and vegetables, whole grains, legumes and nuts fish and olive oil [16,17].

Pharmacologic Treatment

HMG-CoA Reductase Inhibitors (statins)

Statins are the most commonly prescribed lipid-lowering agents used to treat dyslipidaemia. Statins inhibit the enzyme HMG-CoA reductase, which play a main role in the production of cholesterol in liver. The intrahepatic cholesterol levels decrease, hepatic LDL-C receptor expression is induced and increased uptake of LDL-C and decreased hepatic synthesis of VLDL and LDL-C through these mechanism results in an increase LDL-C receptor expression. Moreover, statin therapy has been shown to increase the level of plasma HDL-C levels. The most common side effects of statins including myalgia, myositis, reversible

transaminitis, and rarely rhabdomyolysis. The statins currently include simvastatin, atorvastatin, pravastatin, rosuvastatin, fluvastatin, and lovastatin [18].

Cholesterol Absorption Inhibitors

Ezetimibe is cholesterol absorption inhibitor that selectivity inhibits the absorption of biliary and dietary cholesterol from the small intestine. Ezetimibe decreases total cholesterol in the liver, and increases the hepatic LDL-C receptor expression, which results in a reduction of the LDL-C. Ezetimibe block the Niemann-Pick C1-like 1(NPC1L1) protein on the gastrointestinal tract epithelial cells and in hepatocytes. Combination of ezetimibe and statins have a synergetic effect, and liver function needs to be monitored when ezetimibe used with statins.

Fibric Acid Derivatives (Fibrates)

Fibrate therapy leads to decrease in serum triglycerides and an increase in serum HDL-C.

Fibrates activate peroxisome proliferator-activated receptors (PPAR), especially PPARα, which leads to an increase hepatic lipase and lipoprotein lipase activity and the clearance of VLDL is increased. The most common side effects of fibrates include cholelithiasis, myalgia, and elevated transaminase levels. Combination therapy with statins is effective at lowering LDL-C cholesterol, triglycerides. However, fibrates can decrease statin elimination. As a result, statin and fibrates together increase the risk of myositis and rhabdomyolysis. The commonly used fibrates include: gemifibrozil, fenofibrate, benzafibrate, ciprofibrate, clofibrate.

Bile Acid Sequestrants (BAS)

The BAS is a group of drugs used to bind certain component of bile the in the gastrointestinal tract.

They interrupt the enterohepatic circulation of bile acids by binding bile acid and preventing reabsorption and enterohepatic circulation, and the increased expression of the LDL-C receptor results in a decrease in total body and intra hepatic cholesterol. The LDL-C receptor bind LDL-C from plasma and therefore results in a decreased plasma level of LDL-C. Combination of BAS and statins have a synergetic effect. BAS leads to an increased VLDL levels. Thereby, this group of drugs is advised for patients with relatively normal triglyceride levels. BAS is not systematically absorbed. The side effects of BAS include bloating and constipation. The commonly used BAS includes cholestyramine, colesevelam, colestipol.

Nicotinic Acid (niacin)

Nicotinic acid decreases the synthesis of triglyceride and VLDL and increase increased HDL-C.

some of the more common side effects of niacin can include elevated transaminase, hyperglycaemia, gastritis, and flushing. Liver enzyme monitoring with niacin use recommended. Niacin-induced hepatitis is a potential side effect with low-dose time-release niacin. The combination of statins and niacin at usual dose not increase the risk of hepatotoxicity and have a synergetic effect [19].

Omga-3 Fatty Acids (fish oils)

Omega-3 polyunsaturated fatty acid reduces plasma triglycerides which include the long-chain alpha-linolenic acid (ALA), eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA). According to the Food and Drug Administration, EPA and DHA do not exceed 3 g/day with no more than 2 g/day from dietary supplementation [20]. Potential mechanisms of triglyceride reduction are unknown. The American Heart Association recommends EPA and DHA patients with coronary heart disease and hypertriglyceridemia [21].

New Treatment Approaches

Recently, a number of new approaches to the treatment of have been developed among them are the proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors. These drugs are very effective at reducing LDL-C and risk of coronary heart disease [22]. PCSK9 should only be used in certain cases such as patients with hypercholesteremia who cannot be treated by other lipid lowering drugs because LDL-C levels are so high or they are statin-intolerant patients or patients with clinical atherosclerotic cardiovascular disease who require additional lowering of LDL-C [23].

Treatment of Familial Hyperlipidaemia

The treatment of familial hyperlipidaemia includes 1.non-pharmacologic i.e. changes in lifestyle and diet regulation.

2. Pharmacologic therapy such as statins, BAS. 3. Invasive procedures including lifelong lipid apheresis, and, liver transplantation [24].

Table 2: *First-line antihypertensive drugs*

Drug names and classes	Dose	Indications	Comments and Side Effects
Thiazide-type diuretics			
Chlorthalidone	12.5-25 mg once daily	First-line therapy or add-on as second or third agent	Hyponatremia (more likely in older women), hypokalemia, orthostatic hypotension,
Hydrochlorothiazide	2.5-50 mg once daily		
Indapamide	1.25-2.5 mg once daily		
ACE inhibitors			
Benazepril	5-80 mg/day, in one or two doses		
Fosinopril	10-80 mg/day, in one or two doses		
Lisinopril	5-40 mg once daily		

Moexipril	7.5-30 mg/day, in one or two doses	First-line therapy or add-on as second or third agent; CKD with albuminuria; congestive heart failure; after myocardial infarction, alternative for patients with chronic cough or ACE-inhibitors-associated cough	Do not use in combination with ARB or direct renin inhibitor; hyperkalemia; may cause serum creatinine elevation in patients with CKD or bilateral renal-artery stenosis; angioedema is infrequent but is 2 to 4 times as common among blacks as among whites; contraindicated in pregnancy. Increased risk of hyperkalemia especially in patients with CKD or in those potassium supplement or potassium sparing drugs
Perindopril	4-16 mg/day, in one or two doses		
Quinapril	10-80 mg/day, in one or two doses		
Ramipril	2.5-20 mg/day, in one or two doses		
Trandolapril	2-8 mg/day, in one or two doses		
ARBs			
Azilsartan	40-80 mg once daily	First-line therapy or add-on as second or third agent; CKD with albuminuria; congestive heart failure; after myocardial infarction; alternative for patients with chronic cough or ACE-inhibitor– associated or cough	Do not use in combination with ACE inhibitor or direct renin inhibitor; hyperkalemia; may cause serum creatinine elevation in patients with CKD bilateral renal-artery stenosis; contraindicated in pregnancy. Do not use if history of angioedema with ARBs patients. Patients with history of angioedema with an ACE inhibitors can receive an ARB beginning 6 weeks after ACE inhibitors discontinued
Candesartan	8-32 mg/day, in one or two doses		
Eprosartan	600 mg/day, in one or two doses		
Irbesartan	150-300 mg once daily		
Losartan	25-100 mg/day, in one or two doses		
Olmesartan	20-40 mg once daily		
Telmisartan	20-80 mg once daily		
Valsartan	80-320 mg once daily		
Calcium-channel blockers			
Dihydropyridine type			
Amlodipine	2.5–10 mg once daily	First-line therapy or add-on as second or third agent; no effect on serum creatinine level; minimal effect on cardiac output	Edema of the legs and feet; may worsen proteinuria; may worsen left ventricular outflow tract obstruction associated with dose-related pedal edema, which is mote in women than men. Avoid use in patients with HFrEF Amlodipine or Felodipine may be used if required
Felodipine	2.5–10 mg once daily		
Isradipine	5–10 mg/day, in two doses		
Nicardipine ER	5–20 mg once daily		
Nifedipine ER	30-120 mg/day, in one or two doses		
Nisoldipine ER	17-34 mg once daily		
Nisoldipine ER	20-60 mg once daily		

Nondihydropyridine type			
Diltiazem SR	180-360 mg/day, in two doses	Tachycardia, left ventricular outflow tract obstruction, hyper dynamic cardiac function migraine prophylaxis	Constipation; heart block if used in combination with, beta-blocker. Do not use in patients with HFrEF
Diltiazem ER	120-480 mg once daily		
Verapamil SR	120-480 mg/day, in one or two doses		
Verapamil delayed-onset ER	100-480 mg once daily		

ACE denotes angiotensin-converting enzyme, ARB angiotensin-receptor blocker, CKD chronic kidney disease, ER extended release, and SR sustained release, HPrEF heart failure with reduced ejection fraction

Conclusion

Dyslipidaemia is a risk factor for cardiovascular and vascular events. Control of lipid levels is the most effective intervention in both primary and secondary prevention of cardiovascular events.

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Conflict of Interest

None

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