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Review Article

AN HUGE UPDATED REVIEW ON DYSLIPIDEMIA ETIOLOGY WITH VARIOUS APPROACHES FOR ITS TREATMENT

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ABSTRACT

Cardiovascular diseases are becoming an increasing problem worldwide and hypercholesterolemia has been correlated for coronary heart diseases. Hyperlipidemia or dyslipidemia is a condition, where the lipids present in blood viz. LDL, VLDL, triglycerides; HDL etc loose their normal levels resulting in imbalance of their levels. Long term increased levels of LDL, VLDL, triglycerides & decreased level of HDL results in hazardous effects such as myocardial infarction, cerebral stroke etc leading cause of mortality. Cardiovascular diseases (CVD_S) carry a major health burden affecting humans. More than 80% of the world population is suffering from heart problems and if not treated earliest can be a major cause of death. Dyslipidemia is a highly predictive risk factor atherosclerosis, coronary artery disease and cerebral vascular diseases and impose a great risk. Epidemiologic, angiographic and postmortem studies have documented a causal relationship between elevated serum cholesterol levels and the genesis of coronary heart disease. This article aims at reviewing the complete overview on dyslipidemia, its impact on the progression of cardiovascular diseases, its various forms, pharmacological interventions involved in its treatment and most recent investigations which are fruitful in the understanding of the disease and helpful to take preventive measures for cardiovascular diseases.

Keywords: Cardiovascular diseases, Dyslipidemias, Atherosclerosis, Coronary artery disease, Cerebral vascular diseases, Pharmacological interventions.

INTRODUCTION

Dyslipidemia is a disorder of lipoprotein metabolism, including lipoprotein overproduction or deficiency. Dyslipidemias may be manifested by elevation of the total cholesterol, the “bad” low-density lipoprotein (LDL) cholesterol and the triglyceride concentrations, and a decrease in the "good" high-density lipoprotein (HDL) cholesterol concentration in the blood. Most dyslipidemias are hyperlipidemias; that is, an elevation of lipids in the blood, often due to diet and lifestyle. The prolonged elevation of insulin levels can lead to dyslipidemia. Increased levels of O-GlcNAc transferase (OGT) are known to cause dyslipidemia.[1]

Hyperlipidemia, hyperlipoproteinemia, or hyperlipidaemia is the condition of abnormally elevated levels of any or all lipids and/or

lipoproteins in the blood.[2] It is the most common form of dyslipidemia (which also includes any decreased lipid levels). Lipids (fat-soluble molecules) are transported in a protein capsule, and the size of that capsule, or lipoprotein, determines its density. Elevated cholesterol in the blood involves abnormalities in the protein particles which transport all fat molecules, including cholesterol, within the water of the bloodstream. This may be related to diet, increased body fat, genetic factors (such as LDL receptor mutations in familial hypercholesterolemia) and the presence of other diseases such as diabetes and an underactive thyroid. The type of hypercholesterolemia depends on which type of particle (such as low-density lipoprotein) is present in excess.[3]

Classifications of Dyslipidemia

Dyslipidemia can be the result of a genetic predisposition, secondary causes, or a combination of both.[1] Cholesterol and triglycerides can produce three forms of dyslipidemia: hypercholesterolemia, hypertriglyceridemia, and a combination of both. In each case, the dyslipidemia is the result of an elevation in either the number or composition of specific lipoproteins, which is an important determinant when selecting the appropriate drug therapy.[4,5]

Etiology

Primary (genetic) causes and secondary (lifestyle and other) causes contribute to dyslipidemias in varying degrees. Also, hyperlipidemia may be idiopathic, that is, without known cause.

Familial (Primary)

Primary causes are single or multiple gene mutations that result in either overproduction or defective clearance of TG and LDL cholesterol, or in underproduction or excessive clearance of HDL.Familial hyperlipidemias are classified according to the Fredrickson classification which is based on the pattern of lipoproteins on electrophoresis or ultracentrifugation.[6]

Acquired (Secondary)[7]

Secondary causes contribute to most cases of dyslipidemia in adults. The most important secondary cause in developed countries is a sedentary lifestyle with excessive dietary intake of saturated fat, cholesterol, and trans fats. Tran's fats are polyunsaturated or monounsaturated fatty acids to which hydrogen atoms have been added; they are commonly used in many processed foods and are as atherogenic as saturated fat. Acquired hyperlipidemias (also called secondary dyslipoproteinemias) may mimic primary forms of hyperlipidemia and can have similar consequences. They may result in increased risk of premature atherosclerosis or, when associated with marked hypertriglyceridemia, may lead to pancreatitis and other complications of the chylomicronemia syndrome.Treatment of the underlying condition, when possible or discontinuation of the offending drugs usually leads to an improvement in the hyperlipidemia. Specific lipid-lowering therapy may be required in certain circumstances.

Unclassified familial forms

Non-classified forms are extremely rare:

- Hyperalphalipoproteinemia
- Polygenic hypercholesterolemia

Classification of Lipoproteins

There are five main classes of lipoproteins:

- Chylomicrons
- Very Low Density Lipoproteins (VLDL)
- Intermediate Density Lipoproteins (IDL)
- Low Density Lipoproteins (LDL)

Lipoproteins are classified by density and size, which are inversely related.

Lipoproteins are large, mostly spherical complexes that transport lipids (primarily triglycerides, cholesteryl esters, and fat- soluble vitamins) through body fluids (plasma, interstitial fluid, and lymph) to and from tissues. Lipoproteins play an essential role in the absorption of dietary cholesterol , long – chain fatty acids and fat soluble vitamins; the transport of triglycerides , cholesterol and fat soluble vitamins from the liver to peripheral tissues and the transport of cholesterol from peripheral tissues to the liver. Lipoproteins contain a core of hydrophobic lipids (triglycerides, cholesteryl

esters) surrounded by hydrophilic lipids (phospholipids, unesterified cholesterol) and proteins that interact with body fluids. Each lipoprotein class comprises a family of particles that vary slightly in density, size, migration during electrophoresis and protein composition.The density of lipoprotein is determined by the amount of lipid and protein per particle.HDL is the smallest and most dense lipoprotein, whereas chylomicrons and VLDL are the larges and least dense lipoprotein particles. Lipoprotein particles range in size from 10 to 1000 nanometers. The largest lipoproteins are about one tenth the size of a red blood cell. The density of lipoproteins increases in proportion to their ratio of proteins to lipids. In general, as the density of a lipoproteins increases, the size of the particles decreases.

Apolipoproteins

Apolipoproteins are proteins that bind to lipids to form lipoproteins, whose main function is to transport lipids. Apolipoproteins are important in maintaining the structural integrity and solubility of lipoproteins and play an important role in lipoprotein receptor recognition and the regulation of certain enzymes in lipoprotein metabolism.

There are six major classes of apolipoproteins: A, B, C, D, E and H. Specific apolipoprotein disorders are rare but there is increasing knowledge and awareness of the importance of apolipoproteins and their relevance to a variety of clinical disorders.

Apolipoprotein A (apo A)

Apo A1

- Apo A1 is the major protein component of high-density lipoprotein (HDL).[9] Deficiency of apo A1 is associated with HDL deficiencies, including Tangier disease and systemic non-neuropathic amyloidosis.
- Apo A1 may have a role in protection against Alzheimer's disease.
- Apo A1 and apo E interact to modify triglyceride levels in coronary heart disease patients.

Apo A5

Apo A5 is a probable biochemical and genetic marker of increased triglyceride concentrations and also a risk factor of coronary disease in some populations.[10]

Apolipoprotein B (apo B)

- Apo B is the main apolipoprotein of chylomicrons and low-density lipoproteins (LDLs).[11] High levels appear related to heart disease.
- Apolipoprotein B and the apo B/apo A1 ratios are thought to be a better marker of risk of vascular disease and a better guide to the adequacy of statin treatment than any cholesterol index.[12] Non-fasting Apo B/Apo A1 ratio was superior to any of the cholesterol ratios for estimation of the risk of acute myocardial infarction in all ethnic groups, in both sexes, and at all ages.[13]
- Apo B and the apo B/apo A1 ratio have been shown to be predictive of ischaemic stroke in patients with previous transient ischaemic attack.[14]
- Non-HDL-C and the ratio of total cholesterol to HDL-C were as good as, or better than, apolipoprotein fractions in the prediction of future cardiovascular events.[15]

Abetalipoproteinaemia and hypobetalipo-proteinaemia[16, 17]

Hypobetalipoproteinaemia is a genetic disorder that can be caused by a mutation in the apo B gene; abetalipoproteinaemia is usually caused by a mutation in the microsomal triglyceride transfer protein (MTTP) gene.

Abetalipoproteinaemia

A rare autosomal recessive disorder that interferes with the normal absorption of fat and fat-soluble vitamins. It is caused by a deficiency of apo B48 and apo B100. Heterozygotes have no symptoms and no evidence of reduced plasma lipid levels.

Abetalipoproteinaemia is associated with absent LDL and very low-density lipoprotein (VLDL). Clinical features include fat malabsorption, progressive ataxia (spinocerebellar degeneration), acanthocytic red blood cells and retinitis

pigmentosa. Death usually occurs before the age of 30 years.

Hypobetalipoproteinaemia

Associated with low levels of plasma cholesterol and LDL. Homozygotes present with fat malabsorption and low plasma cholesterol levels at a young age, and develop similar clinical features to abetalipoproteinaemia.

Heterozygotes are usually asymptomatic but have low LDL cholesterol and apo B levels. Secondary hypobetalipoproteinaemia may occur, e.g. with occult malignancy, malnutrition or chronic liver disease. Early diagnosis, high-dose vitamin E and medium-chain fatty acid supplements may slow the progression of the neurological abnormalities.

Apolipoprotein C (Apo C)

Apo C2

- Apo C2 activates lipoprotein lipase in capillaries, liberating fatty acids and monoglycerides from chylomicrons, with the fatty acids then passing into adipocytes or muscle.[18]
- Defective apo C2 production causes hyperlipoproteinaemia type IB, characterised by hypertriglyceridaemia, xanthomas and increased risk of pancreatitis and early atherosclerosis.

Apo C2 deficiency

- Rare autosomal recessive hereditary disorder.
- Apolipoprotein C2 activates lipoprotein lipase and so there is an overlap between lipoprotein lipase deficiency and apolipoprotein C2 deficiency.
- Deficiency of apolipoprotein C2 leads to an accumulation of chylomicrons and triglycerides.
- Xanthomas and hepatosplenomegaly are less common in apo C2 deficiency than in lipoprotein lipase deficiency.
- Diagnosis is by absence of apo C2 on protein electrophoresis.
- Mainstay of treatment is a fat-free diet.

Apo C3

- Apo C3 inhibits lipoprotein lipase and hepatic lipase. Increased apo C3 expression may lead to hypertriglyceridaemia and an atherogenic lipoprotein profile.[19]
- Two susceptibility haplotypes (P2-S2-X1 and P1-S2-X1) have been discovered in apo A1-C3-A4 gene cluster on chromosome 11q23. These confer approximately threefold higher risk of coronary heart disease.
- Serum levels of apo C1 and apo C3 are reduced in patients with stomach cancer and may have a role in the formulation of a diagnostic score for stomach cancer patients.[20]

Apolipoprotein D (Apo D)

- Apo D is a component of HDL in human plasma.[21]
- Apo D is also a biomarker of androgen insensitivity syndrome.

Apolipoprotein E (Apo E)

- Apo E is involved in receptor recognition of intermediate density lipoprotein and chylomicron remnant by the liver. It is essential for the normal catabolism of triglyceride-rich lipoprotein constituents.[22]
- There is thought to be an association between apo E and neurodegenerative conditions such as multiple sclerosis and Alzheimer's disease.[23]
- There is also convincing evidence linking the apo E genotype to risk of cerebral amyloid angiopathy.[24]
- Neonates with brain injuries and/or defects who also have abnormalities in the apo E gene may have an increased risk for cerebral palsy.
- In familial dysbetalipoproteinaemia, increased plasma cholesterol and triglycerides are the consequence of impaired clearance of chylomicron and VLDL remnants because of a defect in apo E.[25]

Apo E2

Apo E2 is associated with hyperlipoproteinaemia type III.

Apo E4

- Apo E4 has been implicated in atherosclerosis, Alzheimer's disease and impaired cognitive function.
- The E4 variant is the largest known genetic risk factor for early-onset Alzheimer's disease in a variety of ethnic groups.[26] Caucasian and Japanese carriers of 2 epsilon 4 alleles have between 10 and 30 times the risk of developing Alzheimer's disease by 75 years of age, as compared with those not carrying any epsilon 4 alleles:
- The genotype most at risk for Alzheimer's disease and at earlier age is apo epsilon 4, 4.
- The 3, 4 genotype is at increased risk, although not to the degree of those homozygous for apo epsilon 4.
- The genotype 3, 3 is considered at normal risk for Alzheimer's disease. People with 2, 4, are also at normal risk.
- The genotype 2, 3 is considered at less risk for Alzheimer's disease.
- Apo E epsilon 4 is also associated with poor outcome after traumatic brain injury and brain haemorrhage.[16]

***Apolipoprotein H (Apo H)*[27]**

- Also called glycoprotein I, beta-2 (B2gp1).
- Apolipoprotein H has been implicated in a variety of physiological processes, including blood coagulation, haemostasis and the production of antiphospholipid antibodies characteristic of antiphospholipid syndrome.

THE PATHWAYS OF LIPID TRANSPORT

There are three main pathways responsible for the generation and transport of lipids within the body. These pathways include the exogenous pathway, the endogenous pathway, and the pathway of reverse cholesterol transport.[28, 29]

Exogenous (Dietary) Lipid Pathway

Following digestion and absorption of dietary fat, TG and cholesterol are packaged to form chylomicrons in the epithelial cells of the intestines. Chylomicrons circulate through the intestinal lymphatic system. In the blood, circulating chylomicrons interact at the capillaries of adipose tissue and muscle cells releasing TG to the adipose tissue to be stored and available for the body's energy needs. The enzyme LPL hydrolyzes the TG and free-fatty acids are released. Some of the components of the chylomicrons are "repackaged" into other lipoproteins, for example, some apolipoproteins are transferred to HDL, and the remaining chylomicron remnant particles are removed from the plasma by way of chylomicron remnant receptors present on the liver. The exogenous pathway transports dietary lipids to the periphery and the liver. The endogenous pathway transports hepatic lipids to the periphery. LPL: lipoprotein lipase, FFA: free fatty acids, VLDL: very low density lipoproteins, IDL: intermediate density Lipoproteins, LDL: low density lipoproteins, LDLR: low density lipoprotein receptor**.**

Endogenous Pathway

The endogenous pathway involves the liver synthesizing lipoproteins. TG and cholesterol ester are generated by the liver and packaged into VLDL particles and then released into the circulation. VLDL is then processed by LPL in tissues to release fatty acids and glycerol. The fatty acids are taken up by muscle cells for energy or by the adipose cells for storage. Once processed by LPL, the VLDL becomes a VLDL remnant. The majority of the VLDL remnants are taken up by the liver via the LDL receptor, and the remaining remnant particles become IDL, a smaller, denser lipoprotein than VLDL. The fate of some of the IDL particles requires them to be reabsorbed by the liver (again by the LDL receptor); however, other IDL particles are hydrolyzed in the liver by hepatic-triglyceride lipase to form LDL, a smaller, denser particle than IDL.

LDL is the main carrier of circulating cholesterol within the body, used by extra-hepatic cells for

cell membrane and steroid hormone synthesis. Much of the LDL particles are taken up by LDL receptors in the liver; the remaining LDL is removed by way of scavenger pathways at the cellular level. As LDL is taken up by receptors, free cholesterol is released and accumulates within the cells. LDL receptor activity and uptake of LDL regulate plasma LDL concentration by several mechanisms, including decreasing the synthesis of hydroxy-3-methyglutaryl coenzyme A (HMG-CoA) reductase (which controls the rate of cholesterol synthesis), suppressing the synthesis of new LDL receptors in the cells, and activating the enzyme, acyl-coenzyme A cholesterol acyltransferase, which esterifies free cholesterol into cholesterol ester, storing cholesterol in the cell.[30]

Reverse Cholesterol Transport

Reverse cholesterol transport refers to the process by which cholesterol is removed from the tissues and returned to the liver.[31] HDL is the key lipoprotein involved in reverse cholesterol transport and the transfer of cholesteryl esters between lipoproteins.[32] The smallest and most dense lipoprotein particle is HDL. HDL is formed through a maturation process whereby precursor particles (nascent HDL) secreted by the liver and intestine proceed through a series of conversions (known as the “HDL cycle”) to attract cholesterol from cell membranes and free cholesterol to the core of the HDL particle. There are subclasses of HDL particles, including HDL_2 and HDL_3. The exact mechanism by which the HDL delivers cholesterol esters to the liver is not well understood, but several mechanisms have been suggested. These include the action of cholesteryl ester transfer protein, which transforms HDL into a TG-rich particle that interacts with hepatic-triglyceride lipase. Cholesterol ester-rich HDL may also be taken up directly by the receptors in the liver. Another mechanism may be that cholesterol esters are delivered directly to the liver for uptake without catabolism of the HDL cholesterol particle.[33,34] In the context of cardiovascular disease risk, it is established that higher levels of HDL are associated with lower levels of heart disease; therefore higher levels of HDL are considered to be protective.[35] In contrast, it is now appreciated that other lipoproteins, including VLDL, IDL, LDL, and the remnant particles rendered in lipid processing, are highly atherogenic. To reflect this, the term "non-HDL cholesterol" has been invoked to describe this increased risk reflected in the lipid profile that may not be otherwise identified by simply examining the LDL alone.[36] Non-HDL cholesterol therefore encompasses a broader indication of cardiovascular disease risk. This parameter is calculated by the equation {non-HDL cholesterol = total cholesterol - HDL}, and is an important consideration in ensuring that patients are treated appropriately to target level.

BIOSYNTHESIS

Synthesis within the body starts with one molecule of acetyl CoA and one molecule of acetoacetyl-CoA, which are hydrated to form 3-hydroxy-3-methylglutaryl CoA (HMG-CoA). This molecule is then reduced to mevalonate by the enzyme HMG-CoA reductase. This step is the regulated, rate-limiting and irreversible step in cholesterol synthesis and is the site of action for the statin drugs (HMG-CoA reductase competitive inhibitors). Mevalonate is then converted to 3-isopentenyl pyrophosphate in three reactions that require ATP. Mevalonate is decarboxylated to isopentenyl pyrophosphate, which is a key metabolite for various biological reactions. Three molecules of isopentenyl pyrophosphate condense to form farnesyl pyrophosphate through the action of geranyl transferase. Two molecules of farnesyl pyrophosphate then condense to form squalene by the action of squalene synthase in the endoplasmic reticulum. Oxidosqualene cyclase then cyclizes squalene to form lanosterol. Finally, lanosterol is then converted to cholesterol.[37]

Regulation of Cholesterol Synthesis

Biosynthesis of cholesterol is directly regulated by the cholesterol levels present, though the homeostatic mechanisms involved are only partly understood. A higher intake from food leads to a net decrease in endogenous production, whereas lower intake from food has the opposite effect.

The main regulatory mechanism is the sensing of intracellular cholesterol in the endoplasmic reticulum by the protein SREBP (sterol regulatory element-binding protein 1 and 2).[35] In the presence of cholesterol, SREBP is bound to two other proteins: SCAP (SREBP-cleavage-activating protein) and Insig1. When cholesterol levels fall, Insig-1 dissociates from the SREBP-SCAP complex, allowing the complex to migrate to the Golgi apparatus, where SREBP is cleaved by S1P and S2P (site-1 and -2 protease), two enzymes that are activated by SCAP when cholesterol levels are low. The cleaved SREBP then migrates to the nucleus and acts as a transcription factor to bind to the sterol regulatory element (SRE), which stimulates the transcription of many genes. Among these are the low-density lipoprotein (LDL) receptor and HMG-CoA reductase. The former scavenges circulating LDL from the bloodstream, whereas HMG-CoA reductase leads to an increase of endogenous production of cholesterol.[36] SREBP pathway regulates expression of many genes that control lipid formation and metabolism and body fuel allocation. Cholesterol synthesis can be turned off when cholesterol levels are high, as well. HMG CoA reductase contains both a cytosolic domain (responsible for its catalytic function) and a membrane domain. The membrane domain functions to sense signals for its degradation. Increasing concentrations of cholesterol (and other sterols) cause a change in this domain's oligomerization state, which makes it more susceptible to destruction by the proteosome. This enzyme's activity can also be reduced by phosphorylation by an AMP-activated protein kinase. Because this kinase is activated by AMP, which is produced when ATP is hydrolyzed, it follows that cholesterol synthesis is halted when ATP levels are low.[37]

Metabolism, Recycling and Excretion

Cholesterol is susceptible to oxidation and easily forms oxygenated derivatives known as oxysterols. Three different mechanisms can form these; autoxidation, secondary oxidation to lipid peroxidation, and cholesterol-metabolizing enzyme oxidation. A great interest in oxysterols arose when they were shown to exert inhibitory actions on cholesterol biosynthesis.[38] This finding became known as the "oxysterol hypothesis". Additional roles for oxysterols in human physiology include their: participation in bile acid biosynthesis, function as transport forms of cholesterol, and regulation of gene transcription.[39] Cholesterol is oxidized by the liver into a variety of bile acids.[40] These, in turn, are conjugated with glycine, taurine, glucuronic acid, or sulfate. A mixture of conjugated and nonconjugated bile acids, along with cholesterol itself, is excreted from the liver into the bile. Approximately 95% of the bile acids are reabsorbed from the intestines, and the remainders are lost in the feces.[41] The excretion and reabsorption of bile acids forms the basis of the enterohepatic circulation, which is essential for the digestion and absorption of dietary fats. Under certain circumstances, when more concentrated, as in the gallbladder, cholesterol crystallises and is the major constituent of most gallstones. Although, lecithin and bilirubin gallstones also occur, but less frequently.[42] Every day, up to 1 g of cholesterol enters the colon. This cholesterol originates from the diet, bile, and desquamated intestinal cells, and can be metabolized by the colonic bacteria. Cholesterol is converted mainly into coprostanol, a nonabsorbable sterol that is excreted in the feces. A cholesterol-reducing bacterium origin has been isolated from human feces.[43]

LIPID PROFILE VALUES

Standard fasting blood tests for cholesterol and lipid profiles will include values for total cholesterol, HDL cholesterol (so-called "good" cholesterol), LDL cholesterol (so-called "bad" cholesterol) and triglycerides. Family history and life style, including factors such as blood pressure and whether or not one smokes, affect what would be considered ideal versus non-ideal values for fasting blood lipid profiles. Included here are the values for various lipids that indicate low to high risk for coronary artery disease.[44] Treatment is indicated for all patients with cardiovascular disease (secondary prevention) and for some

without (primary prevention). The National Institutes of Health's National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATPIII) guidelines are the most common reference for deciding which adults should be treated. The guidelines focus primarily on reducing elevated LDL cholesterol levels and secondarily on treating high TGs, low HDL, and metabolic syndrome.[45]

LINK BETWEEN CHOLESTEROL AND CHD

The processes by which lipids and lipoproteins participate in atherosclerotic plaque formation and CHD events continue to be an area of controversy and research. One of the initiating events of atherosclerotic plaque formation appears to be the entrance of lipoproteins LDL and Lp(a) into the subendothelial space with their oxidatively modified free radicals produced by smooth muscle cells, activated macrophages, and endothelial cells. These oxidatively modified lipoproteins enter macrophages through a scavenger receptor pathway, ultimately yielding lipid-rich foam cells. Circulating monocytes are also attracted to smooth muscle and endothelial cells by chemoattractant that is augmented by the oxidatively modified lipoproteins.[46]

As the macrophage scavenger receptor continues to uptake oxidatively modified lipoproteins, foam cells continue to form and progress to the next level of atherogenesis, which is the formation of the fatty streak. At the same time, smooth muscle cells migrate into the subendothelial space and begin proliferating within the intima, contributing to the overall atherogenic process. As the process continues, lesions continue to grow by increased smooth muscle cell proliferation and collagen synthesis. At this point, necrosis of the foam cell and formation of an extracellular lipid core occurs, as long as plasma LDL levels are elevated. The final phase appears to involve an autoimmune inflammatory response that causes T lymphocyte infiltration of the adventitia (the outermost connective tissue covering of a vessel). This inflammatory response appears to complete the process of plaque formation that is the underlying culprit in CHD.[46]

SIGNS AND SYMPTOMS

Although hypercholesterolemia itself is asymptomatic, longstanding elevation of serum cholesterol can lead to atherosclerosis.[47] Over a period of decades, chronically elevated serum cholesterol contributes to formation of atheromatous plaques in the arteries. This leads to progressive stenosis (narrowing) or even completes occlusion (blockage) of the involved arteries. Blood supply to the tissues and organs served by these stenotic or occluded arteries gradually diminishes until organ function becomes impaired. It is at this point that tissue ischemia (restriction in blood supply) may manifest as specific symptoms. For example, temporary ischemia of the brain (commonly referred to as a transient ischemic attack) may manifest as temporary loss of vision, dizziness and impairment of balance, aphasia (difficulty speaking), paresis (weakness) and paresthesia (numbness or tingling), usually on one side of the body. Insufficient blood supply to the heart may manifest as chest pain, and ischemia of the eye may manifest as transient visual loss in one eye. Insufficient blood supply to the legs may manifest as calf pain when walking, while in the intestines it may present as abdominal pain after eating a meal.[48,49] Some types of hypercholesterolemia lead to specific physical findings. For example, familial hypercholesterolemia (Type IIa hyperlipoproteinemia) may be associated with xanthelasma palpebrarum (yellowish patches underneath the skin around the eyelids),[50] arcus senilis (white or gray discoloration of the peripheral cornea),[51] and xanthomata (deposition of yellowish cholesterol-rich material) of the tendons, especially of the fingers.[52,53] Type III hyperlipidemia may be associated with xanthomata of the palms, knees and elbows.[52]

PHARMACOLOGIC INTERVENTIONS

Drug treatment to lower plasma lipoproteins and/or cholesterol is primarily aimed at reducing the risk of athersclerosis and subsequent coronary

artery disease that exists in patients with elevated circulating lipids. Drug therapy usually is considered as an option only if non-pharmacologic interventions (altered diet and exercise) have failed to lower plasma lipids.[54]

Atorvastatin (Lipotor®), Simvastatin (Zocor®), Lovastatin (Mevacor®)

These drugs are fungal HMG-CoA reductase (HMGR) inhibitors and are members of the family of drugs referred to as the statins. The net result of treatment is an increased cellular uptake of LDLs, since the intracellular synthesis of cholesterol is inhibited and cells are therefore dependent on extracellular sources of cholesterol. However, since mevalonate (the product of the HMG-CoA reductase reaction) is required for the synthesis of other important isoprenoid compounds besides cholesterol, long-term treatments carry some risk of toxicity. A component of the natural cholesterol lowering supplement, red yeast rice, is in fact a statin-like compound.

Nicotinic Acid

Nicotinic acid reduces the plasma levels of both VLDLs and LDLs by inhibiting hepatic VLDL secretion, as well as suppressing the flux of FFA release from adipose tissue by inhibiting lipolysis. In addition, nicotinic administration strongly increases the circulating levels of HDLs. Patient compliance with nicotinic acid administration is sometimes compromised because of the unpleasant side-effect of flushing (strong cutaneous vasodilation). Because of its ability to cause large reductions in circulating levels of cholesterol, nicotinic acid is used to treat Type II, III, IV and V hyperlipoproteinemias.

Gemfibrozil (Lopid®), Fenofibrate (TriCor®)

These compounds (called fibrates) are derivatives of fibric acid and although used clinically since the 1930's were only recently discovered to exert some of their lipid-lowering effects via the activation of peroxisome proliferation. Specifically, the fibrates were found to be activators of the peroxisome proliferator-activated receptor-α (PPAR-α) class of proteins that are classified as co-activators. The naturally occurring ligands for PPAR-α are leukotriene B_4 (LTB_4, unsaturated fatty acids and oxidized components of VLDLs and LDLs. The PPARs interact with another receptor family called the retinoid X receptors (RXRs) that bind 9-*cis*-retinoic acid. Activation of PPARs results in modulation of the expression of genes involved in lipid metabolism. In addition the PPARs modulate carbohydrate metabolism and adipose tissue differentiation. Fibrates result in the activation of PPAR-α in liver and muscle. In the liver this leads to increased β-oxidation of fatty acids, thereby decreasing the liver's secretion of triacylglycerol- and cholesterol-rich VLDLs, as well as increased clearance of chylomicron remnants, increased levels of HDLs and increased lipoprotein lipase activity which in turn promotes rapid VLDL turnover.

Cholestyramine or Colestipol (Resins)

These compounds are nonabsorbable resins that bind bile acids which are then not reabsorbed by the liver but excreted. The drop in hepatic reabsorption of bile acids releases a feedback inhibitory mechanism that had been inhibiting bile acid synthesis. As a result, a greater amount of cholesterol is converted to bile acids to maintain a steady level in circulation. Additionally, the synthesis of LDL receptors increases to allow increased cholesterol uptake for bile acid synthesis, and the overall effect is a reduction in plasma cholesterol. This treatment is ineffective in homozygous FH patients, since they are completely deficient in LDL receptors.

Ezetimibe

This drug is sold under the trade names Zetia® or Ezetrol® and is also combined with the statin drug simvastatin and sold as Vytorin® or Inegy®. Ezetimibe functions to reduce intestinal absorption of cholesterol, thus effecting a reduction in circulating cholesterol. The drug functions by inhibiting the intestinal brush border transporter involved in absorption of cholesterol. This transporter is known as Niemann-Pick type C1-like 1 (NPC1L1). NPC1L1 is also highly expressed in human liver. The hepatic function of NPC1L1 is presumed to limit excessive biliary

cholesterol loss. NPC1L1-dependent sterol uptake is regulated by cellular cholesterol content. In addition to the cholesterol lowering effects that result from inhibition of NPC1L1, its inhibition has been shown to have beneficial effects on components of the metabolic syndrome, such as obesity, insulin resistance, and fatty liver, in addition to atherosclerosis.

CONCLUSION

The information provided by AHA (American Heart Assosiation) indicates that cardiovascular diseases kill many people every year and the number is approximetely equal to other death reasons such as cancer, ALDS, children death and incidents.Therefore prediction of CHDs is of most importance in cure and preventionof the disease. This paper reviews the overall understanding of the progression of dyslipidemias, its relation to cardiovascular diseases and its pharmacologial interventions for its treatment**.** Early detection of dyslipidemia may avoid the further complications of coronary heart disease and after detection it should be properly treated with the available therapies that can prevent the further complications in the patients. Further conclusion was drawn that frequent estimation of the cholesterol level can avoid the further complications by changing the life style and food habits as discussed.

Table 1: Various classes of dyslipidemias

Name	Lipoprotein(s) In Excess	Possible Cause (s) For Elevated Levels	Clinical Significance	Treatment Options
Hypercholesterolemia				
Polygenic	LDL	1)Nutritional 2)Genetic (less active LDL receptors)	Decreased LDL clearance from circulation	HMG-Co A reductase inhibitors, bile acid sesquestrants , nicotinic acid.
Familial	LDL	3) Genetic Homozygous Heterozygous (defective gene for the LDL receptor)	Decreased LDL clearance from circulation	Homozygous (probucol) heterozygous (HMG-CoA reductase inhibitors ,bile acid sequestrants or combination of both)
Hypertriglyceridemia				
Diet induced	VLDL	Excessive consumption caloric Alcohol	Increased VLDL Secretion From Liver	Diet modification, nicotinic acid, fibric acids.
Primary hypertriglyceridemia	VLDL	Often associated with other medical problems obesity , diabetes	Increased production of triglycerides and VLDL particles (decreased HDL particles , increased small LDL particles) → artherogenic	Weight loss, diet modification, tight control of blood glucose levels, HMG-CoA reductase inhibitors, nicotinic acid, and fibric acid.
Secondary	VLDL	Often secondary to	Increased production	Weight loss, tight

hypertriglyceridemia		other medical problems obesity, diabetes, nephrotic syndrome.	of triglycerides and VLDL particles	control of blood glucose levels, HMG-CoA reductase inhibitors, nicotinic acid, fibric acid, bile acid sequestrants.
Mixed hyperlipidemias				
Familial combined hyperlipidemia	VLDL and LDL	Genetic (overproduction of apolipoprotein B - 100)	Increased production of VLDL particles → elevated triglyceride levels.	HMG-CoA reductase inhibitors, nicotinic acid, fibric acid derivatives.
Lipoprotein lipase deficiency	Chylomicron and VLDL	Genetic (deficiency of lipoprotein lipase enzyme)	Reduced ability of delipidize triglyceride molecules from VLDL and chylomicron particles	HMG-CoA reductase inhibitors, fibric acid derivatives, niacin.

Table 2: Causes of dyslipidemia

Dyslipidemia – Primary Causes	
Elevated LDL Cholesterol	Low HDL Cholesterol
LDL receptor deficiency	Apo a-1 deficiency
Familial homozygous hyperlipidemia	Apo a-1 mutations
	LCAT deficiency (partial or complete)
	Tangiers disease
	Familial hypoalpaliproteinemia
Dyslipidemia –Secondary Causes	
Elevated LDL Cholesterol	Low HDL Cholesterol
Obesity	Metabolic syndrome
High fat intake	Diabetes mellitus
Hyperthyroidism	Obesity or weight gain
Diabetes mellitus	Physical inactivity
Nephrotic syndrome	Tobacco use
Anabolic steroids	Beta blocker therapy
Progestins	Low fat or high polysaturated fat diets
Obstructive hepatobiliary disease	Anabolic steroids
	Progestrins
	Thiazide diuretics

Table 3: Different lipoproteins, their density, lipid and protein proportion, and the predominant kind of lipid

Lipoprotein	Density	Protein (% total weight)	Lipids (% total weight)	Predominant Lipid (% of total weight)
Chylomicrons	<1.006	2	98	Triacylglycerol (85 %)
VLDL	0.950-1.006	10	90	Triacylglycerol (50%)
IDL	1.006-1.019	12	88	About 40 % Cholesterol (30 % esterified and 10 % free)
LDL	1.019-1.063	25	75	About 50 % Cholesterol (40 % esterified + 10% free)
HDL	1.063-1.210	55	45	Phospholipids (35 %)

Table 4: Frederickson classification of lipid disorders

Type	Elevated particles	Associated clinical disorders	Serum TC	Serum TG	Defects
I	Chylomicrons	Lipoprotein lipase deficiency, apolipoprotein C-II deficiency	→	↓↓	Decreased lipoprotein lipase (LPL), Altered ApoC2, LPL inhibitor in blood
IIa	LDL	Familial hypercholesterolemia, polygenic hypercholesterolemia, nephrosis, hypothyroidism, familial combined hyperlipidemia	↑↑	→	LDL receptor deficiency
IIb	LDL, VLDL	Familial combined hyperlipidemia	↑↑	↑	Decreased LDL receptor and increased ApoB
III	IDL	Dysbetalipoproteinemia	↑	↑	Defect in Apo E 2 synthesis
IV	VLDL	Familial hypertriglyceridemia, familial combined hyperlipidemia, sporadic hypertriglyceridemia, diabetes	→↑	↑↑	Increased VLDL production and Decreased elimination
V	Chylomicrons, VLDL	Diabetes	↑	↑↑	Increased VLDL production and Decreased LPL

IDL = intermediate-density lipoproteins; LDL = low-density lipoproteins; TC = total cholesterol; TG = triglycerides; VLDL = very low-density lipoproteins;

↑ = Increased; ↑↑ = Greatly Increased; → = Normal; →↑ = Normal or Increased

Table 5: Apolipoprotein classifications

Apoprotein - MW (Da)	Lipoprotein Association	Function and Comments
apoA-I - 29,016	Chylomicrons, HDL	Major protein of HDL, binds ABCA1 on macrophages, critical anti-oxidant protein of HDL, activates lecithin:cholesterol acyltransferase, LCAT
apoA-II - 17,400	Chylomicrons, HDL	Primarily in HDL, enhances hepatic lipase activity
apoA-IV - 46,000	Chylomicrons and HDL	Present in triacylglycerol rich lipoproteins; Synthesized in small intestine, synthesis activated by PYY, acts in central nervous system to inhibit food intake
apoB-48 - 241,000	Chylomicrons	Exclusively found in chylomicrons, derived from apoB-100 gene by RNA editing in intestinal epithelium; lacks the LDL receptor-binding domain of apoB-100
apoB-100 - 513,000	VLDL, IDL and LDL	Major protein of LDL, binds to LDL receptor; one of the longest known proteins in humans
apoC-I - 7,600	Chylomicrons, VLDL, IDL and HDL	May also activate LCAT
apoC-II - 8, 916	Chylomicrons, VLDL, IDL and HDL	Activates lipoprotein lipase
apoC-III - 8,750	Chylomicrons, VLDL, IDL and HDL	Inhibits lipoprotein lipase, interferes with hepatic uptake and catabolism of apoB-containing lipoproteins, appears to enhance the catabolism of HDL particles, enhances monocyte adhesion to vascular endothelial cells, activates inflammatory signaling pathways
apoD, 33,000	HDL	Closely associated with LCAT
cholesterol ester transfer protein, CETP	HDL	Plasma glycoprotein secreted primarily from the liver and is associated with cholesteryl ester transfer from HDLs to LDLs and VLDLs in exchange for triglycerides
apoE - 34,000 (at least 3 alleles [E_2, E_3, E_4] each of which have multiple isoforms)	Chylomicron remnants, VLDL, IDL and HDL	Binds to LDL receptor, $apoE_{\varepsilon\text{-}4}$ allele amplification associated with late-onset Alzheimer's disease
apoH - 50,000 (also known as β-2-	Chylomicrons	Triacylglycerol metabolism

glycoprotein I)		
apo(a) - at least 19 different alleles; protein ranges in size from 300,000 - 800,000	LDL	Disulfide bonded to apoB-100, forms a complex with LDL identified as lipoprotein(a), Lp(a); strongly resembles plasminogen; may deliver cholesterol to sites of vascular injury, high risk association with premature coronary artery disease and stroke

Table 6: Lipid profile - normal values

Test	Normal Values	
Serum Cholesterol	American Heart Association recommendation	Normal upto 200 mgs/dl
	Borderline	Upto 239 mgs/dl
	Elevated if > 240 mgs/ dl. on repeated values	
Serum Triglycerides	<180 mgs/dl. normal. Values vary depending on diet, alcohol, metabolic state, exercise etc. Elevation of values to be considered only if repeated values are high.	
HDL Cholesterol	30-60 mgs/dl	
LDL Cholesterol	100-190 mgs/dl	Borderline
	>190 mgs/dl	Risk
	Formula for calculating LDL Cholesterol is INVALID if TGL> 400 mgs/dl	
Total/HDL ratio	<4	Normal
	4-6	Low Risk
	> 6	High Risk

Table 7: National Cholesterol Education Program Adult Treatment Panel III Approach to Dyslipidemias

Measure fasting lipoproteins (in mg/dL)	
TC (mmol/L)	
< 200 (< 5.17)	Desirable
200–239 (5.17–6.18)	Borderline high
≥ 240 (≥ 6.20)	High
LDL cholesterol (With LDL cholesterol the lower the better)	
< 100 (< 2.58)	Optimal
100–129 (2.58–3.33)	Near optimal/above optimal
130–159 (3.36–4.11)	Borderline high
160–189 (4.13–4.88)	High
≥ 190 (≥ 4.91)	Very high

HDL cholesterol (With HDL cholesterol the higher the better.)	
< 40 (< 1.03)	Low
≥ 60 (≥ 1.55)	High
TG (With triglycerides the lower the better)	
< 150 (< 1.695)	Desirable
150–199 (1.695–2.249)	Borderline high
200–499 (2.26–5.639)	High
≥ 500 (≥ 5.65)	Very high

Table 8: Major drugs used for the treatment of hyperlipidemia[55]

Drug	Major Indications	Starting Dose	Maximal Dose	Mechanism
1.HMG-CoA reductase inhibitors (statins)	Elevated LDL			↓ Cholesterol Synthesis ↓ Hepatic LDL Receptor ↓ VLDL Production
Lovastatin		20 mg daily	80 mg daily	
Parvastatin		40 mg qhs	80 mg qhs	
Simvastatin		20 mg qhs	80 mg qhs	
Fluvastatin		20 mg qhs	80 mg qhs	
Atorvastatin		10 mg qhs	80 mg qhs	
Rosuvastatin		10 mg qhs	40 mg qhs	
2.Bile acid sequestrants	Elevated LDL			↑ Bile Acid Excretion ↑ LDL Receptors
Cholestyramine		4 g daily	32 g daily	
Colestipol		5 g daily	40 g daily	
Colesevelam		3750 mg daily	4375 mg daily	
3.Nicotinic acid	Elevated LDL,Low HDL, elevated TG			↓ VLDL Hepatic Synthesis
Immediate release		100 mg tid	2 g tid	
Sustained release		250 mg bid	1.5 g bid	
Extended release		500 mg qhs	2 g qhs	
4.Fibric Acid Derivatives	Elevated TG,elevated			↑ LPL ↓ VLDL Synthesis
Gemfilbrozil		600 mg bid		

Fenofibrate	remnants	160 mg qd		
5.Fish Oils	Severely elevated TG	3 g daily	12 g daily	↓ Chylomicrons and VLDL Production
6.Cholesterol Absorption Inhibitors	Elevated LDL	10 mg daily	10 mg daily	↓ Intestinal Cholesterol Absorption
Ezetimibe				

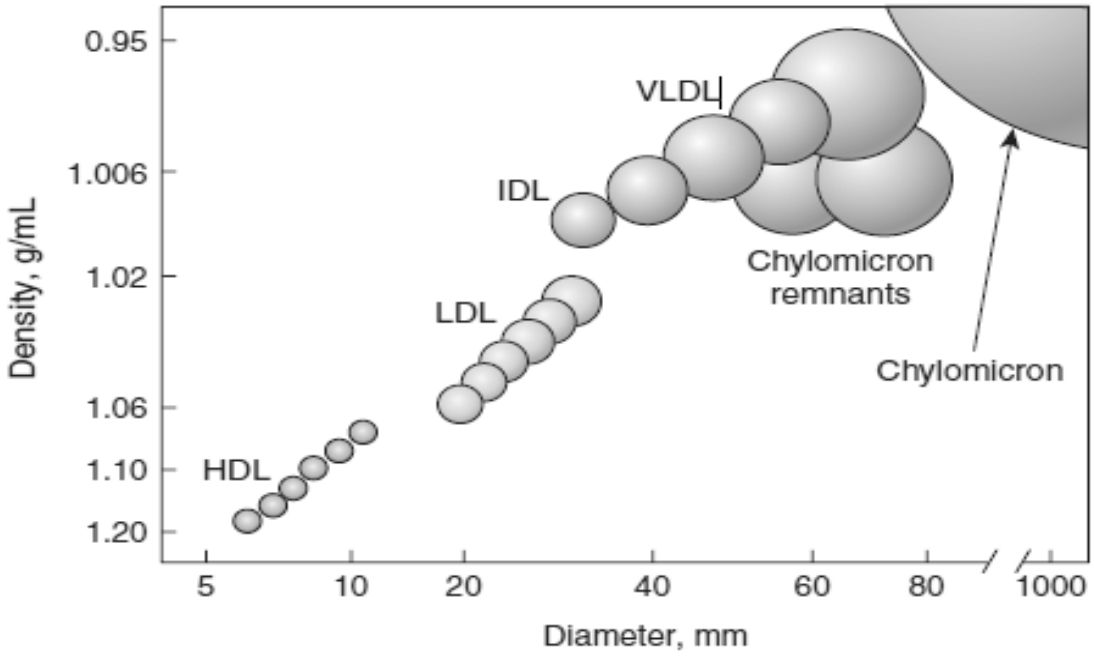

Figure 1: The density and size distribution of the major classes of lipoprotein particles

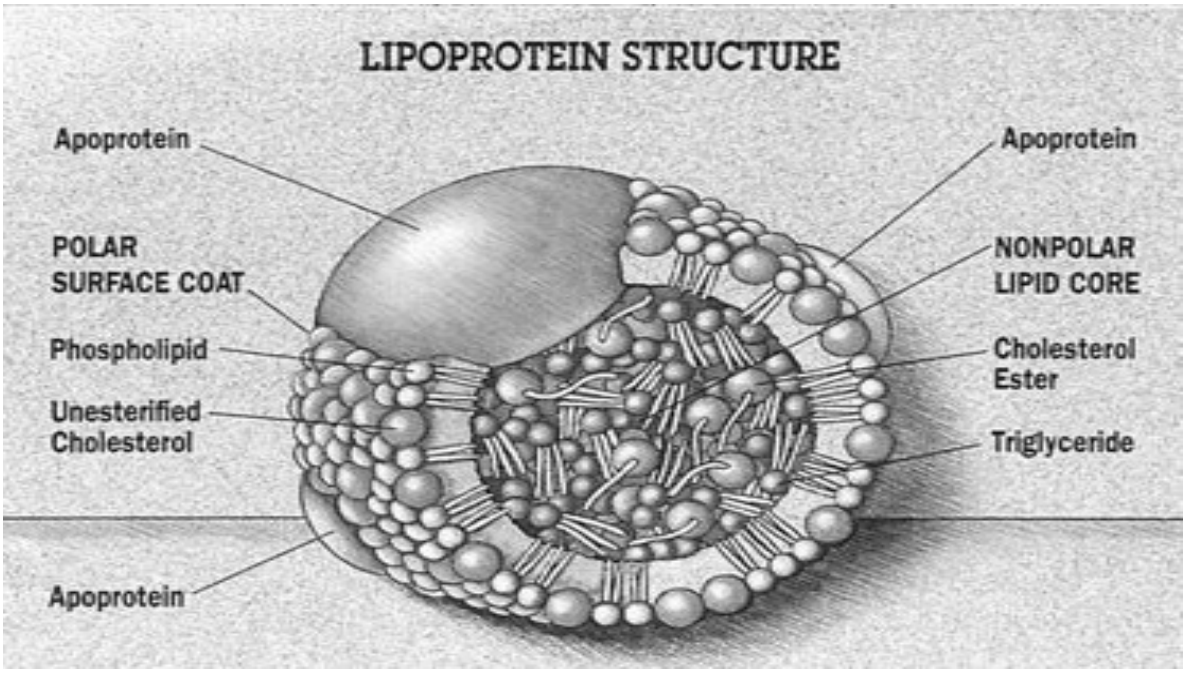

Figure 2: Lipoprotein structure

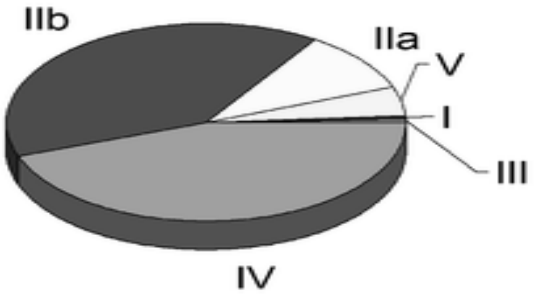

Figure 3: Relative prevalence of familial forms of hyperlipoproteinemia[7]

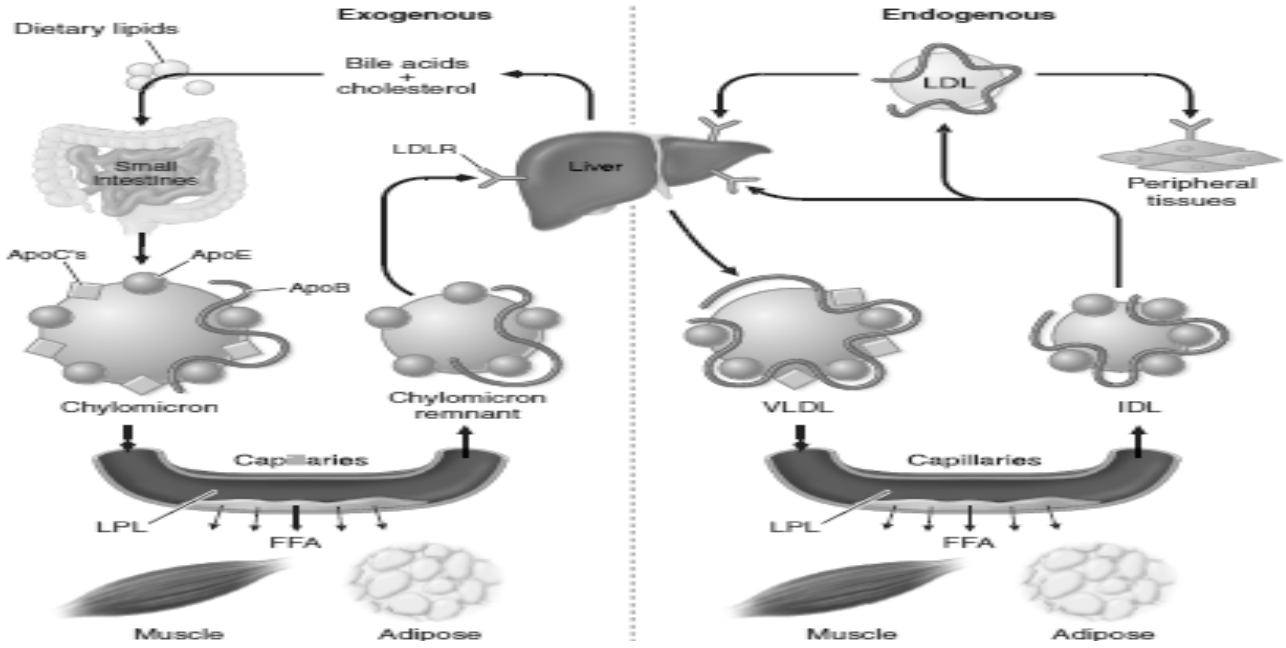

Figure 4: The exogenous and endogenous lipoprotein metabolic pathways

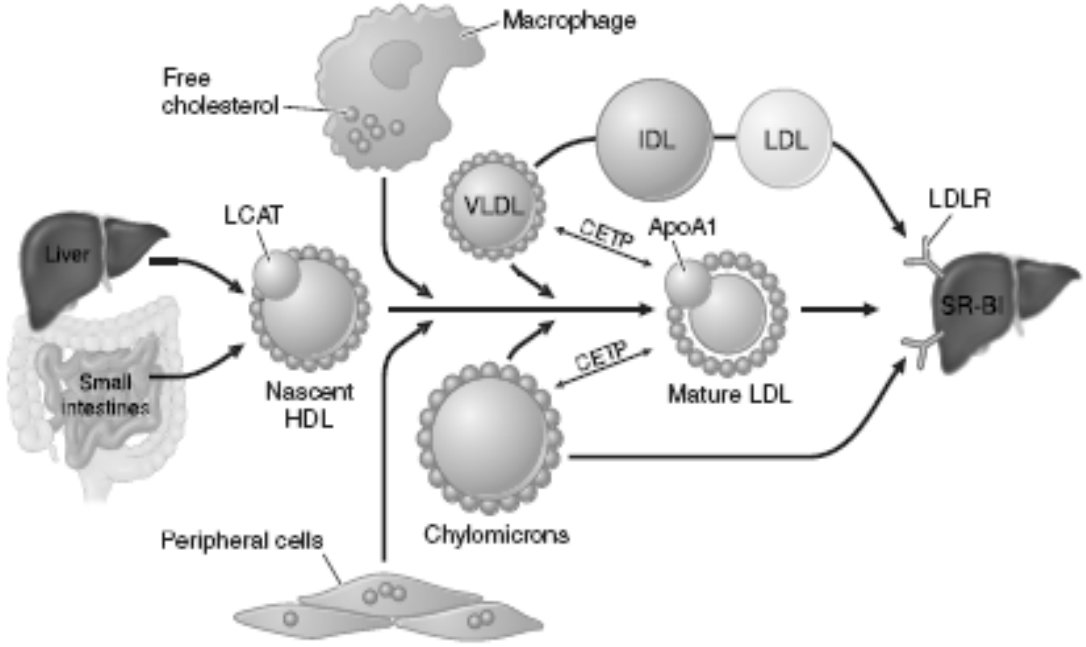

Figure 5: HDL metabolism and reverse cholesterol transport

LCAT, lecithin-cholesterol acyltransferase; CETP, cholesteryl ester transfer protein; VLDL, very low density lipoproteins; IDL, intermediate-density lipoproteins; LDL, low-density lipoproteins; HDL, high-density lipoproteins; LDLR, low-density lipoprotein receptor; TG, triglycerides; SR-B1, scavenger receptor class B1.

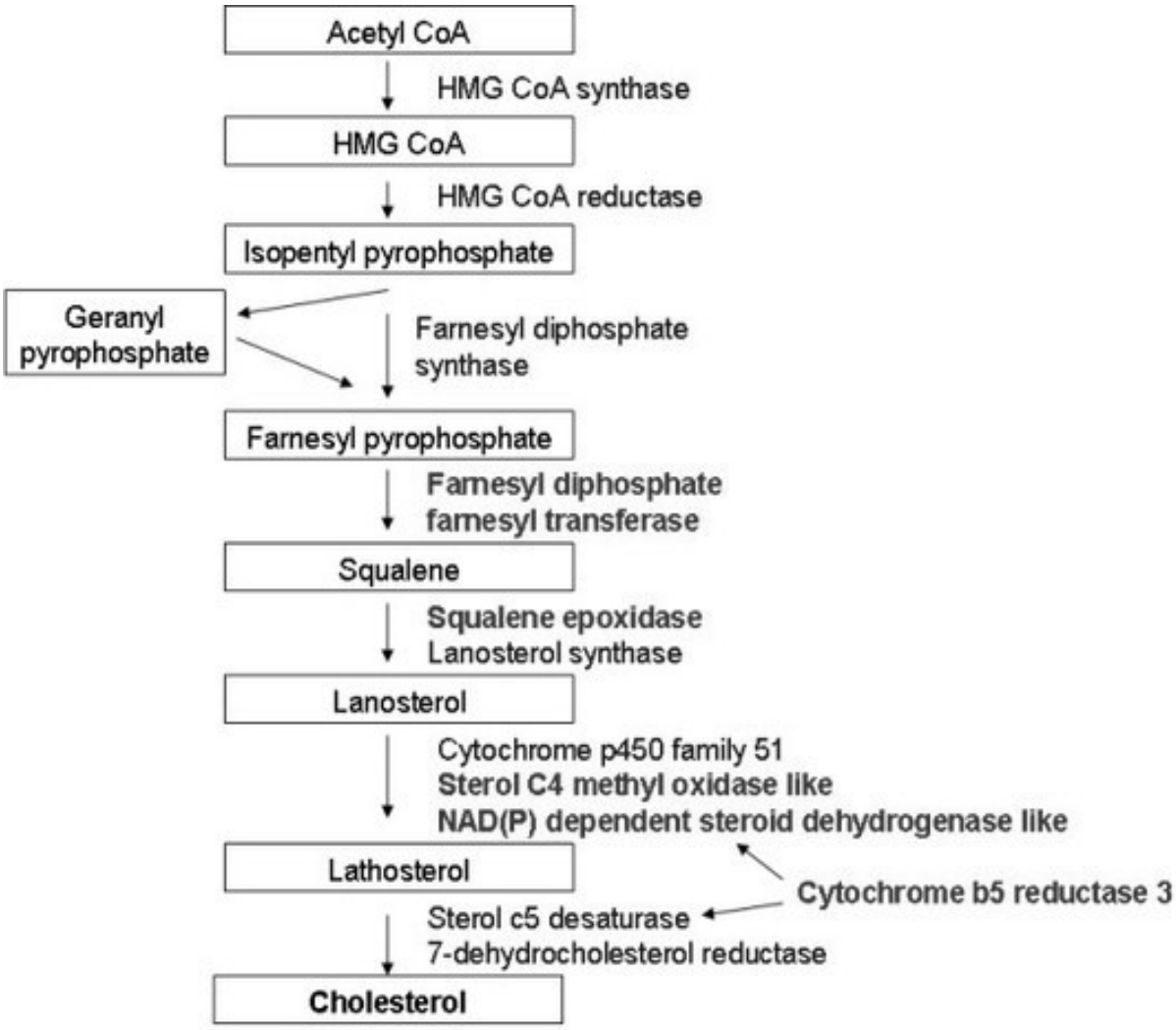

Figure 6: Biosynthesis of cholesterol

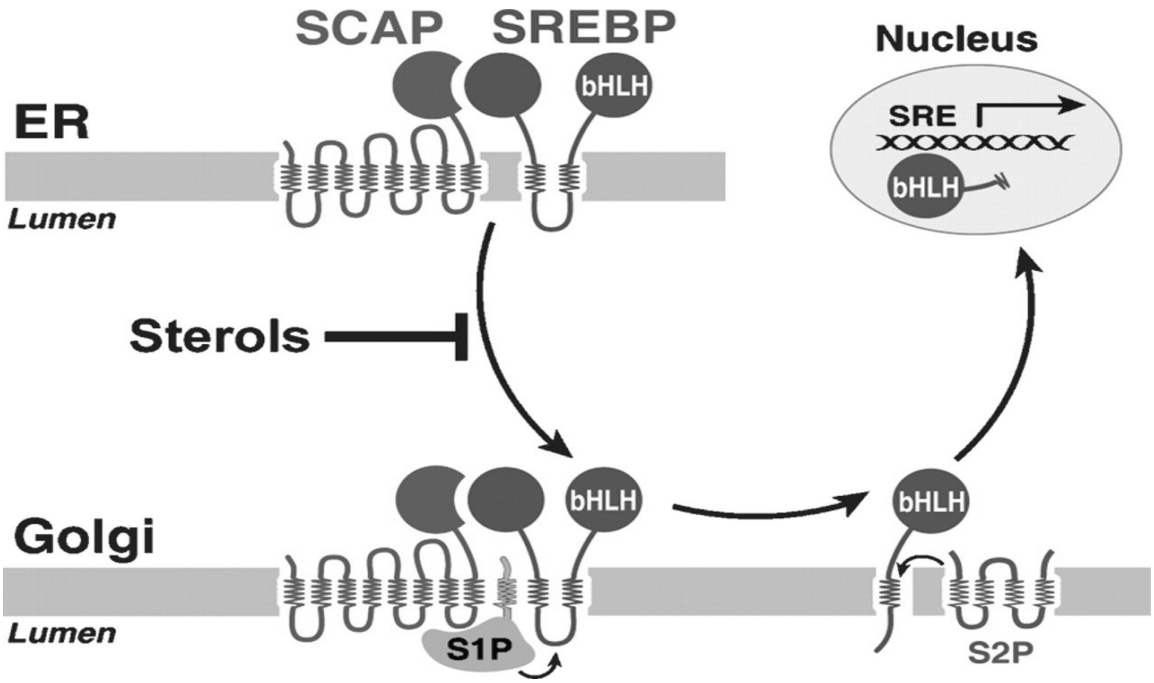

Figure 7: SREBP pathway (sterol regulatory element-binding protein)

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