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Review Article

Review on Atherogenic Index of Plasma Lipids and Dyslipidemia

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Abstract



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Dyslipidemia is defined as abnormally levels of lipids in the blood. Different types of lipids and lipoproteins have been identified. Dyslipidemia is a single strong risk factor for the development of cardiovascular events and atherosclerosis is the most common. It has been described as a disease of the economically advanced societies, but recently, it has found its way into the semi-urban societies and among its dwellers, who are at the increasing risk of developing cardiovascular accidents. Hence, early identification and diagnosis of dyslipidemia at its earliest stage among this populace is a worthwhile cardiovascular preventive measure. The study of hyperlipidaemia is of considerable importance, mainly because of the involvement of lipids in cardiovascular diseases. The classification system of hyperlipidaemia is based on which plasma lipoprotein concentrations were increased. Fredrickson classification helped to put lipidology on the clinical map, though it was not a diagnostic classification. It gives little clue as to the aetiology of the disorder. Currently, a more descriptive classification is used for the primary hyperlipidaemia although they can be genetic or secondary factors. This review presents the overview of plasma lipids. This article illustrates the theoretical background and details about dyslipidemias.

Keywords: Dyslipidemia, Atherogenic index, Hyperlipidaemia, Atherosclerosis, Lipoproteins

Introduction

For several decades profound demographic and economic changes that many developing countries have witnessed has created completely new conditions in terms of lifestyle. With urbanization and economic development has emerged a nutritional transition characterized by a shift to a higher caloric content of diet and/or to the reduction of physical activity, and whose consequences are changes in the body composition of the individuals and elevated blood lipid levels.¹

Prospective and retrospective studies have shown that cardiovascular risk factors, namely: Obesity, lipids, unhealthy diet and sedentary lifestyle, have their roots in childhood and tend to track into adulthood.^{2,3} The continuous modernization and technological advancement of the developing world has brought rapid lifestyle changes which result to the consumption of fast-food, caloric dense diets and sedentary lifestyle, which are known to have a major impact in the development of cardiovascular diseases and chronic diseases.⁴

Many investigators have pointed out that excessive intake of dietary saturated fat and especially cholesterol increases the serum cholesterol, thus leading to a high risk in the development of cardiovascular diseases (Silver and Nyerhovwo, 2010).^{1,2,5}

Lipids are organic compounds that are poorly soluble in water but miscible in organic solvents. Lipids have important roles in virtually all aspect of life. Chemically, lipids contain primarily non-polar carbon-hydrogen (C-H) bonds and typically yield fatty acids or complex alcohols after hydrolysis. Some lipids contain sialic, phosphoryl, amino, surfuryl or hydroxyl groups.⁵ The presence of these chemical groups gives lipid molecules an affinity for both water and organic solvents (amphipathic). This allows them to exist at the aqueous inter phase of biological membrane.⁶ Overall, lipids are divided into four major forms based on their chemical structure namely; (a) fatty acids (b) cholesterol (c) triglycerides (d) phospholipids.

Fatty acids with the formulae (RCOOH) are straight chain carbon compounds of varying lengths. They may be saturated, containing no double bond, monosaturated with one double bond or polyunsaturated with more than one double bond. Fatty acids can esterify glycerol to form triglycerides or be non-esterified (NEFAs) or free. Plasma non-esterified fatty acids liberated from adipose tissue by lipase activity are transported to the liver and muscle mainly bound to albumin. The non-esterified fatty acids provide a significant proportion of the energy requirements of the body.⁶

Triglycerides constitute 95% of tissue storage fat and are the predominant form of glyceryl esters found in the plasma. Dietary triglycerides are digested in the duodenum and are absorbed in the proximal ileum. Triglycerides are transported from intestines to various tissues including the liver and adipose tissues as lipoproteins. Following hydrolysis, free fatty acids are taken up, re-esterified and stored as triglycerides. Plasma triglycerides concentration rise after meal, unlike that of cholesterol.⁷

Cholesterol is a steroid alcohol found exclusively in animals and present in virtually all cells and body fluids. It is a precursor of numerous physiological important steroid including bile acids and steroid hormones.⁸ Cholesterol is synthesized by all cells in the body, but particularly by the liver and the intestines. It is esterified to fatty acid to form a cholesteryl ester by two different enzymes. In cells, excess cholesterol is esterified by lecithin cholesterol acyl transferase (LCAT) which helps to reduce the cytotoxicity of excess free cholesterol.

Phospholipids are complex lipids similar in structure triglycerides but containing phosphate and nitrogenous base in place of one of the fatty acids. They fulfill an important structural role in cell membrane and the phosphate group confers solubility on non-polar lipids and cholesterol in lipoproteins.⁶

General function of lipids in the body

It is now known that lipids play a much more important role in the body than previously believed. It was previously known that lipids play the role of storage of energy or forming cell membranes alone. Researchers have found that lipids have a much more diverse and wide spread biological roles in the body in terms of intracellular signalling or local hormonal regulation.⁹ Lipids are synthesized in the body using complex biosynthetic pathways. However, there are some lipids that are considered essential and needed to be supplemented in diets.

Lipids play several roles in the body including acting as chemical messengers, storage and provision of energy etc. The

following are some of the major roles of lipids in the body. Storage and Provision of Energy: Storage lipids are triacylglycerol. These are inert and made up of three fatty acids and glycerol. Fatty acids in non-esterified form are released from triacylglycerol during fasting to provide a source of energy and to form structural components of cells.⁴ Maintenance of Temperature: Layers of subcutaneous fat under the skin also helps in insulation and protection from cold. Maintenance of body temperature is mainly done by brown fat as opposed by white fat.

Membrane Lipid Layer Formation: Linoleic and oleic acids are essential fatty acids. They form arachidonic, eicosapentaenoic and docosahexaenoic acids. These form membrane lipids which are made up of poly unsaturated fatty acids.¹⁰ Polyunsaturated fatty acids are important as constituents of phospholipids where they appear to confer several important properties to the membranes. One of the most important properties are fluidity and flexibility of the membranes.¹¹

Chemical Messengers: All multicellular organisms use chemical messengers to send information between organelles and other cells. Since lipids are small molecules insoluble in water, they are excellent substances for signalling. Molecules further attach to the cell receptors on the cell surface and bring about a change that leads to an action. The signalling lipids in their esterified form can infiltrate membranes and are transported to carry signals to other cells. These may bind to certain proteins and are inactive until they reach to the site of action and encounter the appropriate receptor.¹²

Cholesterol Formation: Much of the cholesterol is located in cell membranes, it also occurs in the blood in free form as plasma lipoproteins. Lipoproteins are complex aggregate of lipids and protein that make travel of lipids in a watery or aqueous solution and enables their transport throughout the body.¹³ The main groups are classified as chylomicrons, very low density lipoproteins (VLDL), low density lipoproteins (LDL) and high density lipoproteins (HDL). Cholesterol maintains the fluidity of membranes by interacting with their complex lipid components, specifically the phospholipids.¹⁴ Cholesterol is also the precursor of bile acids, vitamin D and steroid hormones.

The "fat soluble" Vitamins: The "fat soluble" vitamins (A, D, E and K) are essential nutrients with numerous functions. Acylcarnitines transport and metabolise fatty acids in and out of mitochondria.¹⁵ Polyphenols and their phosphorylated derivative help to transport molecules across membranes. Cardiolipins are subtypes of glycerol phospholipids with four acyl chains and three glycerol groups.¹⁵ They activate enzymes involved with oxidative phosphorylation.

Digestion and absorption of lipids in the body

The digestion of lipids begins in the oral cavity through exposure of lingual lipases which are secreted by glands in the tongue to begin the process of digesting triglycerides. Digestion continues in the stomach through the effect of both lingual and gastric enzymes. The stomach is the major site for the emulsification of dietary fats and fat soluble vitamins with peristalsis as a major contributing factor. Crude emulsions of lipids enter the duodenum as fine lipid droplets and then mix with bile and pancreatic juice to undergo some changes in their chemical and physical form. Emulsification continues in the duodenum along with hydrolysis and micellization in preparation of absorption across the intestinal wall.¹⁶

Bile and pancreatic juice provide pancreatic lipase, bile salts and colipase which functions cooperatively to ensure the efficiency of lipid digestion and absorption. The importance of

bile to the efficiency of this process is indicated by the decrease rate of lipid absorption in humans with bile fistulas.¹⁷

Digestion and Absorption of Triglycerides and Fatty Acids

Triglycerides are digested primarily by pancreatic lipase in the duodenum and are absorbed in the proximal ileum. In the presence of bile acids, they are hydrolyzed to glycerol, monoglycerides and fatty acids in the process called lipolysis.⁸ The triglycerides are rebuilt in the enterocytes from their fragments and packaged together with cholesterol and proteins to form chylomicrons. These are excreted from the cells and collected by the lymph system and transported to the large vessels near the heart before being mixed into the blood. Various tissues can capture the chylomicrons, releasing the triglycerides to be used as a source of energy. Fat and liver cells can synthesize and store triglycerides. When the body requires fatty acids as an energy source, the hormones, glucagon signals the breakdown of the triglycerides by hormone-sensitive lipase to release free fatty acids. As the brain cannot utilize fatty acids as an energy source (unless converted to a ketone), the glycerol component of triglycerides can be converted into glucose, via gluconeogenesis, for brain fuel when it is broken down.¹⁸ Free fatty acids are taken up from the intestinal lumen into the enterocytes and used for the biosynthesis of neutral fat. Once inside the enterocytes, the product of triglycerol hydrolysis must transverse the cytoplasm to reach endoplasmic reticulum where they are used to synthesize complex lipids. Specific binding proteins carry free fatty acids and monoacylglycerols to the intracellular sites where they are used for triglycerides synthesis.

Digestion of Cholesterol

The average western diet contains approximately 300-450 mg of cholesterol per day, which is derived mostly from animal and dietary products, but only 30% to 60% of it is absorbed. Any dietary esterified cholesterol that contains fatty acid attached to the hydroxyl group on the A-ring is rapidly hydrolyzed in the intestines to free cholesterol and fatty acids by cholesterol esterase secreted from the pancreas and small intestines. Before cholesterol is absorbed, it is first solubilized through emulsification by the formation of micelles. The absorption of cholesterol occurs in the middle jejunum and terminal ileum of the small intestines.⁸ In man, increased absorption of cholesterol is followed by increased excretion of cholesterol from the exchangeable pool. Bile salts returning to the liver from the intestines repress the formation of an enzyme catalysing the rate-limiting step in the conversion of cholesterol into bile acids. When bile salts are prevented from returning to the liver, the activity of this enzyme increases and degradation of cholesterol to bile acids is stimulated. Bile acids facilitate the digestion of lipids by acting as emulsifying agents and also aid in the absorption of fat soluble vitamins. Cholesterol is ultimately excreted from the body as bile acids.

Digestion and transport of lipids

The predominant phospholipid in the lumen of small intestines also contains cholesterol and bile salt. The digestion of phospholipid is carried out primarily by pancreatic phospholipase A2 and other lipases secreted by the pancreas in response to food intake. Free fatty acids are transported in the blood in combination with albumin. Other lipids are transported in the blood in the form of lipoproteins.

Lipoproteins and Apolipoproteins

Lipoproteins are soluble protein complexes that transport lipids in the blood. It is spherical in shape and contains

cholesterol, phospholipids, triglycerides and proteins on their surface. The protein fractions of lipoproteins are beta globulins called apolipoprotein that contains specific proteins. Apolipoproteins have both hydrophobic and hydrophilic charges on their surfaces and function as the interface are soluble protein complexes that transport lipids in the blood. It is spherical in between lipid and water which allow lipid to function in aqueous media.¹⁹ The apolipoproteins helps in the lipid metabolism by inactivating or inhibiting the enzymes and by binding lipoproteins to cell surface receptors. The most significant apolipoproteins are A-I, A-II, B, C-II lipoproteins and C-III.

Classification of Lipoproteins and their Associated Apolipoprotein

Lipoproteins are classified by their buoyant density which inversely reflects their size. The greater the lipid to protein ratio, the larger the size and the lower the density. Lipoproteins can be classified into five main groups. The first three are triglycerides-rich, and because of their large size, they scatter light which can give plasma a turbid appearance (lipaemic) if present in high concentrations.⁶

Chylomicrons are the largest and less dense lipoproteins and transports exogenous lipid from the intestines to all cells. The density of chylomicrons is 0.95 and it contains about 85% of triglycerides. Apo A-I, B, C and E are found in chylomicrons in varying amounts. Very low-density lipoproteins (VLDLs) transports endogenous lipid from the liver to cells. Its electrophoretic mobility is pre-beta (pre-β) and has about 55% of triglycerides. The associated Apo-lipoproteins are B, C and E. Intermediate- density lipoproteins (IDL), which are transient and formed during the conversion of VLDL to low-density lipoprotein (LDL), are not normally present in plasma. Intermediate density lipoproteins are usually seen as broad beta (between beta and pre-beta) in electrophoresis. It has a lipid to protein ratio of 85:15 and the associated apo-lipoprotein is apo B-100.

Lipoprotein Metabolism

Metabolism of lipoproteins can be divided into the (a) exogenous, (b) endogenous (c) intracellular cholesterol transport, and (d) reverse cholesterol transport pathways.

Exogenous Pathway

This pathway deals with lipids and lipoproteins derived from external sources. The role of the exogenous pathway-transport of dietary lipids from the intestines to the liver and peripheral cells is largely mediated by chylomicrons. Nascent chylomicrons, which are 90% triglycerides by mass, are first assembled by the microsomal transfer protein (MTP) in the endoplasmic reticulum of enterocytes by combining triglycerides and other lipids with apo B-48. Chylomicrons are secreted into the lymph and after entering the circulation, acquire from HDL additional apolipoproteins such as apo E and apo C-II. Apo E is a ligand for uptake by the liver, whereas C-II is a potent activator of lipoprotein lipase (LPL), which is attached to the luminal surface of the endothelial cells and rapidly hydrolyses the triglycerides on chylomicrons to free fatty acids. Liberated fatty acids combine with albumin and are taken up by muscle cells as energy source or by adipose cells for energy storage as triglycerides.⁸ As a consequence of lipolysis, chylomicrons are transformed into smaller chylomicrons remnant particles which are rapidly removed by the liver.

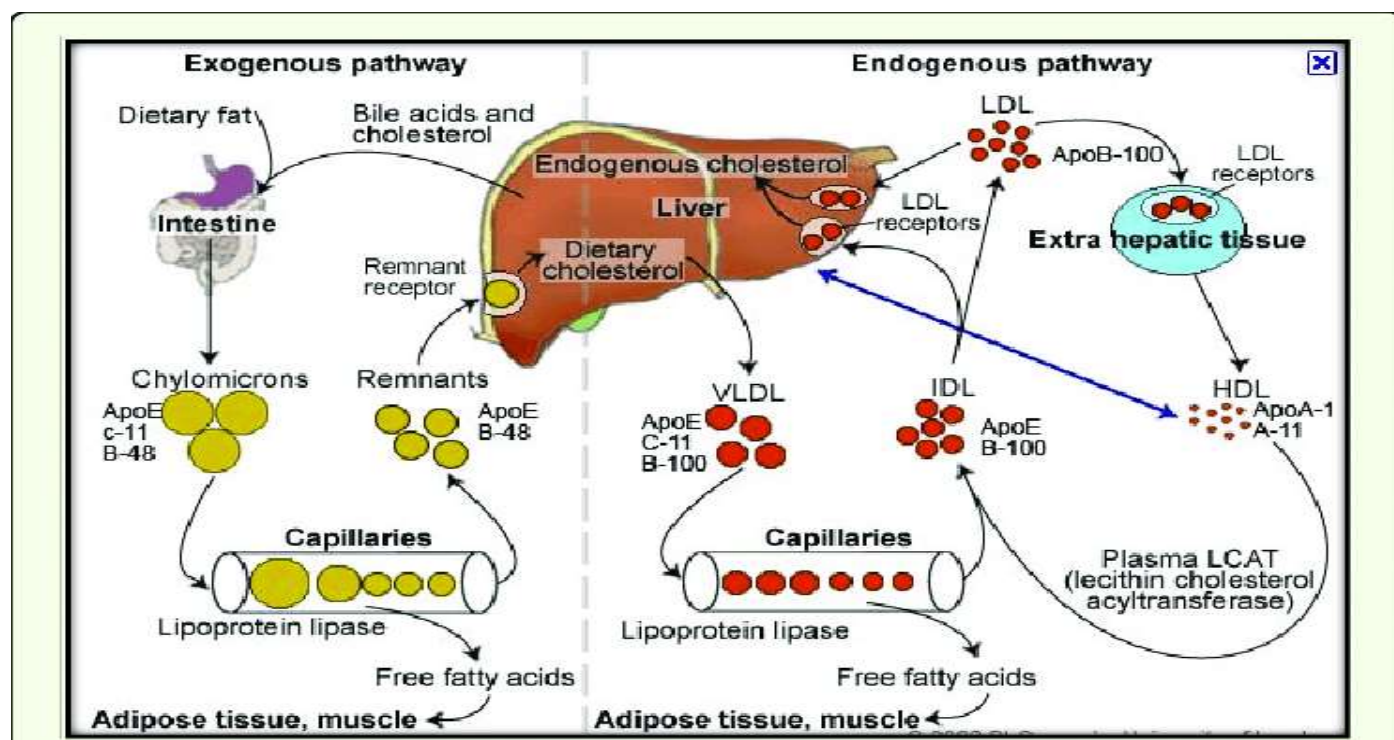


Figure 1: Exogenous and endogenous pathways of lipids, Adopted from Karam *et al.*,²⁰

Endogenous Pathway

The endogenous lipoprotein metabolism involves lipids and lipoproteins produced in the body to synthesize complex lipids in the liver. The function of the endogenous pathway is to transfer hepatic-derived lipids especially triglycerides to peripheral cells for energy metabolism. It is mediated by the apo B-100 containing lipoproteins. Hepatic-derived lipids represent lipids that are synthesized by the liver or dietary lipids by the exogenous pathway. VLDL, which contains approximately 55% of triglycerides by mass and includes one molecule of apo B-100 and some apo E and apo C's, is the principal apo B containing lipoprotein that is secreted by the liver. Like chylomicrons, the apo C-II present on the surface of VLDL also activates LPL on endothelial cells. This leads to hydrolysis of VLDL triglycerides and release of free fatty acids which are taken up by the cells. The progressive lipolysis of triglycerides from the core of VLDL transforms it to IDL and eventually to LDL. The triglyceride on LDL is further depleted by the cholesterol ester transfer protein (CETP), which removes triglycerides from LDL and exchanges it for cholesteryl esters from HDL. Although almost all the cells express the LDL receptor, the majority of LDL is eventually returned to the liver via the LDL receptor which recognizes apo B-100. Cholesterol returned to the liver is reused for the secretion of lipoprotein used in the production of bile salts or extracted directly into the bile.^{8,21}

Intracellular-Cholesterol Transport Pathway

The intracellular-cholesterol transport pathway represents the various homeostatic mechanisms that cells use to maintain their cholesterol balance. Although cholesterol is a necessary and critical component of all cell membranes, excess cholesterol will alter the biophysical properties of membranes and will eventually become toxic to the cell. Besides production from cellular biosynthesis, all cells also receive cholesterol via uptake of extracellular lipoproteins by cell surface receptors, such as the LDL receptor (Figure 2). Most lipoprotein receptors deliver the intact lipoprotein particles to lysosomes, where they are degraded. Any associated

apolipoproteins are degraded to small peptides and amino acids.²² In addition, cholesteryl esters are converted to free cholesterol by lysosomal acid lipase. Because most cells do not catabolize cholesterol further, any cholesterol delivered to the cell is (1) Used for membrane biogenesis, (2) Stored in intracellular lipid drops after re-esterification by ACAT, or (3) Carried from the cell by the reverse-cholesterol transport pathway. In addition, cells have a complex mechanism involving both transcriptional and post transcriptional regulation, so that any excess intracellular cholesterol will inhibit any further cholesterol biosynthesis by down regulating HMG-CoA reductase and several other enzymes in the cholesterol biosynthetic pathway. Excess intracellular cholesterol will also inhibit the expression of the LDL receptor and will induce the synthesis of proteins involved in reverse-cholesterol transport. Hepatocytes are unique in that intracellular cholesterol has several other possible fates. For example, (1) It is repackaged and secreted on lipoproteins, (2) It is converted to bile salts, or (3) directly excreted into the bile. The main mechanism by which statin drugs decrease the incidence of coronary events is by blocking cholesterol biosynthesis, which results in the up regulation of the LDL receptor. The increased concentration of LDL receptors, particularly in the liver, removes pro-atherogenic LDL particles from the circulation, thus accounting for the anti-atherogenic effect of statin type drugs. Macrophages are also unique in that they express high concentrations of oxidized or other modified forms of LDL. Unlike the LDL receptor, these scavenger receptors are not down regulated in response to excess intracellular cholesterol.⁸ This is one of the main reasons that macrophages are prone to accumulate excess cholesterol in intracellular lipid like drops and form what are called foam cells, which play a key role in atherosclerotic plaque development.

Reverse-Cholesterol Transport Pathway

The function of the reverse cholesterol pathway is to remove excess cellular cholesterol from peripheral cells and return it to the liver for excretion. This process is largely mediated by HDL. Because most peripheral cells do not catabolize

cholesterol and do not secrete cholesterol on lipoprotein, cholesterol under certain circumstances will accumulate and become toxic to cells. HDL aids cells in their cholesterol homeostasis by removing it from cells by several different mechanisms.²³ Cholesterol is actively pumped out of cells by the ABCA1 transporter onto lipid-poor apo A-I, which binds to cells. This process results in the formation of disc-shaped nascent HDL, which is made in the liver and intestine. Discoidal HDL also interacts with ABCA-1 in peripheral cells, such as the macrophages, and removes additional cholesterol. LCAT, which esterifies cholesterol on HDL, plays a key role in reverse-cholesterol transport because cholesteryl esters are much more hydrophobic than cholesterol and remain trapped in the core of HDL until they are removed by the liver. The esterification of cholesterol on HDL converts the disc-shaped nascent HDL to spherical HDL. Spherical HDL, the main form

of HDL in the circulation, also acts as an extracellular acceptor for cholesterol that may be removed from cells by the ABCA1 transporter or by a passive-diffusion mechanism. In the next stage of the reverse-cholesterol transport pathway, the liver selectively removes cholesteryl esters from the lipid-rich spherical HDL and lets the lipid-depleted HDL return to the circulation for additional rounds of cholesterol removal from peripheral cells. CETP also plays an important role in this pathway because a significant fraction of cholesterol that is removed from cells by HDL is transferred as cholesteryl esters onto LDL by CETP and is eventually removed from the circulation by hepatic LDL receptors. Besides promoting the efflux of excess cellular cholesterol, HDL also has antioxidant, anti-inflammatory, and anti-clotting properties, which are not as well understood but are also likely beneficial in reducing atherosclerosis.²²

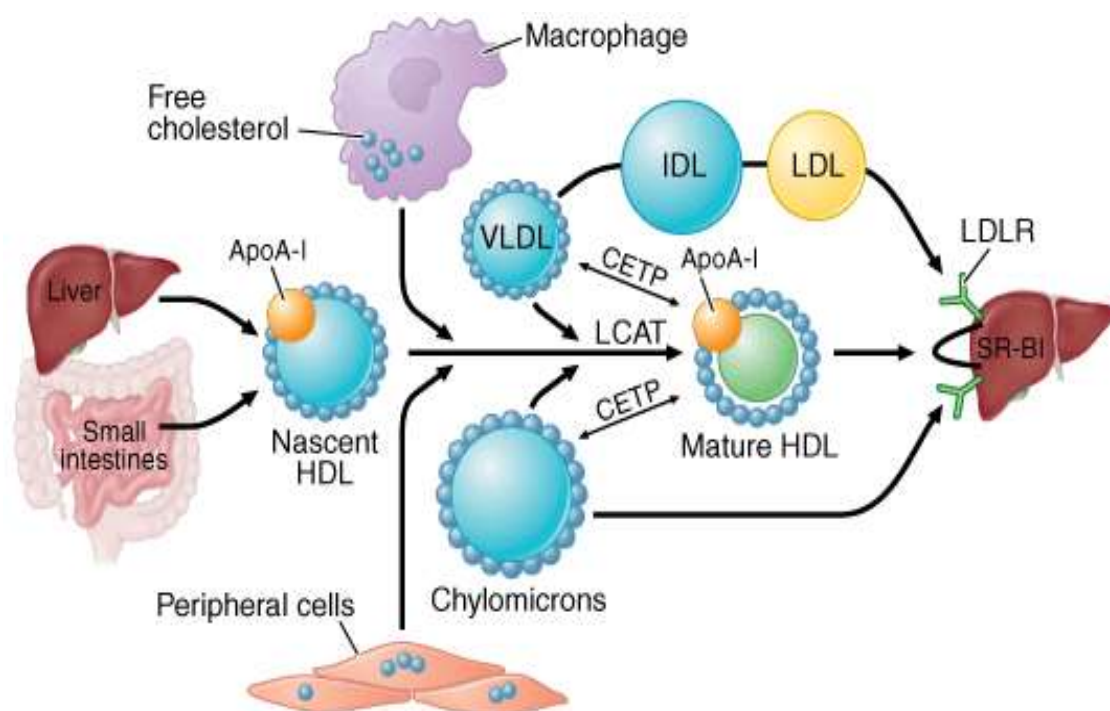


Figure 2: Reverse cholesterol pathway. This pathway transports excess cholesterol from the periphery back to the liver for excretion in the bile. The liver and the intestine produce nascent HDLs. Free cholesterol is acquired from macrophages and other peripheral cells and esterified by LCAT, forming mature HDLs. HDL cholesterol can be selectively taken up by the liver via SR-BI (scavenger receptor class BI). Alternatively, HDL cholesterol ester can be transferred by CETP from HDLs to VLDLs and chylomicrons, which can then be taken up by the liver. LCAT, lecithin-cholesterol acyltransferase; CETP, cholesteryl ester transfer protein; VLDL, very low-density lipoprotein; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; HDL, high-density lipoprotein; LDLR, low-density lipoprotein receptor.

Disorders of Lipid and Lipoprotein Metabolism

Chylomicron Syndrome

Deficient lipoprotein lipase activity due to mutation in the LPL gene is a rare autosomal recessive disorder characterized by notably hyperchylomicronemia, with triglyceride concentrations reaching as high as 10,000 mg/dL (113 mmol/L). LPL is critical for the hydrolysis of triglycerides on chylomicrons and their subsequent conversion to chylomicron remnants. It is possible for the concentration of VLDL cholesterol also to be increased, but the concentrations of HDL cholesterol and LDL cholesterol are low (type I pattern). This disorder is often first diagnosed in childhood, usually after recurrent episodes of severe abdominal pain and repeated attacks of pancreatitis. Eruptive xanthomas and lipemia retinalis are usually present when plasma triglyceride

concentrations exceed 2000 and 4000 mg/dL (22.6 to 45.2 mmol/L), respectively. The concentration of triglycerides often shows great fluctuations in response to diet and other factors that are not well understood. Individuals with this disorder are not predisposed to atherosclerotic disease. The diagnosis is made by the determination of LPL activity in plasma collected after the injection of heparin into patients to release the LPL that is bound to heparin sulfates and other glycosaminoglycans on the surface of endothelial cells. Deficient or defective apo C-II, the main activator of LPL, also results in an impairment of chylomicron catabolism, although it is usually less severe than with LPL gene mutations. The diagnosis is made by demonstrating low LPL activity in post heparin plasma that is restored after the addition of apo C-II to the LPL assay mixture. Apo C-II deficiency is also inherited in an autosomal recessive mode, but it occurs at an even lower

frequency than LPL mutations. This disorder is also called chylomicron syndrome.^{6,8}

Familial Combined Hyperlipidemia

Familial combined hyperlipidemia (FCHL) is the most common familial form of hyperlipidemia. Its genetic defect, however, is unknown. It accounts for as much as 10% to 15% of individuals with premature CHD. Families with FCHL often have increased plasma concentrations of total and LDL cholesterol (type IIa), or triglyceride (type IV), or both (type IIb). The lipoprotein patterns also vary in an individual over time. In all cases, apo B-100 concentrations are increased because of over- production. LDL in these patients tends to be small and dense because of a decreased lipid to protein ratio. LDL cholesterol is usually only modestly increased to about 190 mg/dL (2.14 mmol/L), which is lower than what is typically observed in heterozygous familial hypercholesterolemia (FH) (350 mg/ dL; 3.95 mmol/L). Triglycerides are usually between 200 and 400 mg/dL (2.26 and 4.52 mmol/L), but may be significantly higher. The concentration of HDL cholesterol is often mildly depressed, particularly in patients with hypertriglyceridemia. In this order, the lipid levels typically become abnormal after age 30 but sometimes at a younger age, especially in people who are overweight or have metabolic syndrome. The diagnosis of familial cholesterol hyperlipidemia is suspected if there is a family history of hyperlipidaemia, particularly if family members show different lipoprotein phenotypes.^{8,24}

Hyperapolipoproteinemia

Hyperapobetalipoproteinemia is characterized by increased apo B-100 concentrations with normal or only moderately increased LDL cholesterol. The ratio of LDL cholesterol to apo B-100 is usually 1.2. Total cholesterol and triglyceride concentrations may be normal but are usually increased, and HDL cholesterol and apo A-I concentrations are decreased. This disorder is apparently caused by an overproduction of VLDL and apo B-100 in the liver. The exact mode of inheritance and prevalence of the disorder remain unclear. Features common to hyperapobetalipoproteinemia have also been reported to occur with FCHL, suggesting metabolic and genetic associations between the two disorders.²²

Familial Hypertriglyceridemia

Familial hypertriglyceridemia (FHTG) is characterized by a moderate increase in serum triglycerides and HDL cholesterol is often decreased. Overproduction of large VLDL particles with abnormally high triglyceride content is thought to be responsible for this disorder, but the exact genetic defect is unknown. The cholesterol content of VLDL is also increased, but the concentration of plasma LDL cholesterol is within the reference range and there is a delayed conversion of VLDL to LDL. This disorder is an inherited autosomal dominant disease which develops after puberty and is rare in childhood. There may be an increased risk of cardiovascular disease. Acute pancreatitis may also occur, and is more likely when the concentration of plasma triglycerides is more than 10 mmol/L.²⁵

Dysbetalipoproteinemia

Dysbetalipoproteinemia, also termed type III hyperlipoproteinemia is caused by a defect in the removal of lipoprotein remnants from both chylomicrons and VLDL. Apo E present on the surface of lipoprotein remnant particles interacts with specific hepatic receptors and facilitates the removal of these particles. Apo E exists in three common polymorphisms or variants, designated E2, E3, and E4. Some individuals with dysbetalipoproteinemia are homozygous for the apo E2 isoform, which does not efficiently bind to hepatic

remnant receptors, thus leading to the accumulation of remnant particles. Although rare, genetic mutations in the apo E gene also have been associated with the disorder. The remnant particles that accumulate are enriched in cholesterol, have a density less than 1.006 g/mL, and are commonly referred to as Pre-VLDL or floating Pre-lipoprotein, based on their electrophoretic migration pattern.⁶ Both LDL and HDL cholesterol are lower than normal in these individuals. Dysbetalipoproteinemia has a late onset and rarely manifests itself in childhood. The most distinctive clinical feature of dysbetalipoproteinemia is the presence of palmar xanthomas, yellow fat deposits in the creases of the palms. Tuberous and tuberoeruptive xanthomata also occur on the elbow and knees, but are not unique to this syndrome.²⁵ Premature atherosclerosis commonly develops, particularly in the lower extremities. Thus the occurrence of the defective alleles is necessary but not sufficient to produce the disorder. The expression or penetrance of the disease is apparently modulated by genetic, hormonal, and/or environmental factors, such as diabetes, hypothyroidism, obesity, and diet.⁸

Familial Hypercholesterolemia

Familial Hypercholesterolemia FH is caused by defects in the expression and/or function of the LDL receptor, which binds and removes LDL from the circulation. LDL thus accumulates in the plasma, resulting in its increased deposition in the skin, tendons, and in arteries where it causes atherosclerosis.²² Apo B-100, the main protein in LDL is increased in proportion to LDL cholesterol. Triglyceride concentration is either normal or only slightly increased, and HDL cholesterol concentration is slightly decreased. Type V hyperlipoproteinemia is characterized by an increase in both chylomicrons and VLDL. Although its exact cause is unknown, it appears to be associated with an increased production and/or decreased removal of VLDL. The activity of LPL in these individuals is either normal or low, and the plasma concentration of apo C-II is normal. Clinical presentations include (1) eruptive xanthomas, (2) lipemia retinalis, (3) pancreatitis, and (4) abnormal glucose tolerance.⁸ Premature atherosclerotic complications are not as commonly seen as in FH. This heterogeneous syndrome appears to be inherited in an autosomal dominant mode. majority of these patients have gene defects in the LDL receptor itself. Hypercholesterolemia is often present at birth and persists throughout life. Also, xanthomas appear toward the end of the second decade, and clinical manifestations of atherosclerotic disease appear often during the fourth decade.⁶

Familial Defective Apolipoprotein B-100

Familial Defective Apolipoprotein B-1 Familial defective apo B-100 is the result of mutations in apo B-100, which reduces its affinity for the LDL receptor. Apolipoprotein B is the ligand upon the LDL particle for the LDL receptor. LDL cholesterol is increased but triglycerides and HDL cholesterol are usually normal. Like FH, these individuals also have an increased incidence of CHD. Clinical differentiation between this disorder and heterozygous FH is sometimes difficult, but the management of both disorders is similar.²⁴

Hypoalphalipoproteinemia

Hypoalphalipoproteinemia or low HDL cholesterol is caused by several genetic defects and is often associated with an increased incidence of CHD because of the beneficial role of HDL in preventing atherosclerosis. Mutations or deletions of the apo A-I gene are a rare cause of hypoalphalipoproteinemia. LCAT deficiency is also associated with low HDL. These patients often have cloudy corneas as a result of infiltration of lipid, and glomerulosclerosis because of the production of an abnormal lipoprotein particle that becomes trapped in the

glomerulus. Tangier disease is a rare autosomal recessive disorder that is also associated with a notable reduction of HDL. Like FH, the elucidation of the genetic defect in Tangier disease has added greatly to our knowledge of lipoprotein metabolism and the reverse-cholesterol transport pathway in particular. The major clinical signs of Tangier disease are (1) hyperplastic orange tonsils, (2) splenomegaly, and (3) peripheral neuropathy. Other possible signs include hepatomegaly and corneal opacities. There is an increased deposition of cholesteryl esters in various tissues of the body, particularly macrophages, which form foam cells. Tangier disease is due to mutations in the ABCA1 transporter, which mediates the first step of the reverse-cholesterol transport pathway, the efflux of cholesterol from cells of apo A-I with phospholipids and cholesterol. Without this process, apo A-I is quickly catabolized via renal and hepatic clearance because of its small size. ABCA1 promotes the lipidation of apo A-I in both the liver and intestine and is responsible for the biogenesis of most of the circulating HDL. The efflux of excess cholesterol from macrophages is also largely dependent upon the activity of ABCA1, and without it they will rapidly accumulate cholesteryl esters and form foam cells.^{8,25}

Atherosclerosis

Atherosclerosis is the hardening and thickening of large and medium-sized muscular arteries primarily due to involvement of tunica intima and is characterized by fibro fatty plaques or atheromas. The term atherosclerosis is derived from athero (meaning porridge) referring to the soft lipid-rich material in the centre of atheromas, and sclerosis (scarring) referring to connective tissue in the plaques. Atherosclerosis is the most common and the most important of coronary artery disease. Though any large and medium sized artery may be involved in atherosclerosis, the most commonly affected are the aorta, the coronaries and the cerebral arterial systems.

Pathogenesis of Atherosclerosis

The method of atherogenesis is not fully understood, however there are a number of current models that suggest that stress corrupt the vascular integrity allowing the abnormal accumulation of lipids, cells and extracellular matrix within the arterial wall.²⁶ Due to its very slow progression, it is not surprising that atherosclerosis goes undetected and remains asymptomatic until the atheroma obstructs the blood flow within the artery; hence atherosclerosis is often referred to as the “silent killer”.^{27,28}

The response-to-injury hypothesis of atherosclerosis suggests that even before development of the fatty streak, damage to the endothelium lining the blood vessel sets the stage for lesion development. The endothelium is a continuous layer of cells that separates blood from the vessel wall. As an active, dynamic tissue, endothelium controls many important functions such as maintenance of blood circulation and fluidity as well as regulation of vascular tone, coagulation and inflammatory responses (Gonzalez and Selwyn, 2003).²⁹

Common Risk Factors of Atherosclerosis

Atherosclerosis is a complex disease that does not occur for a single reason. Epidemiological studies have identified factors that influence both the susceptibility to atherosclerosis and its progression and outcome. Disease mediators that influence the clinical outcome of atherosclerosis are termed “risk factors”.²⁷ Risk factors may be divided into those that can be modified and those that cannot. Non-modifiable risk factors include age, male sex, certain genetic mutations and a positive family history of early-onset atherosclerosis. The modifiable risk factors for atherosclerosis include smoking, overweight and obesity, lack of exercise, psychological stress, low social

status, poor diet, high blood pressure, high LDL, low HDL, high triglycerides, high levels of a lipoprotein called Lp (a) and the presence of diabetes mellitus.

Risk factors specific to women include pregnancy and complications of pregnancy gestational diabetes, preeclampsia, third trimester bleeding, preterm birth and birth of an infant small for gestational age. During early pregnancy there is an increase in body fat accumulation, associated with both hyperphagia and increased lipogenesis. The increased lipid production during pregnancy is necessary as an energy store to fulfil maternal and foetal metabolic needs while maternal hypertriglyceridemia, especially towards late gestation, has an important role as a source of triglycerides for milk formation just before parturition. During late pregnancy there is an accelerated breakdown of fat deposits, that plays a key role in foetal development. Moreover, using placental transferred fatty acids the foetus benefits from two other products: glycerol and ketone bodies. Although maternal glucose is quantitatively the main substrate crossing the placenta, glycerol is the preferential substrate for maternal gluconeogenesis.³¹ Additionally, enhanced ketogenesis under fasting conditions and the easy transfer of ketones to the foetus allow maternal ketone bodies to reach the foetus, where they can be used as fuels for oxidative metabolism as well as lipogenic substrates. Although maternal cholesterol is an important source of cholesterol for the foetus during early gestation, its importance becomes minimal during late pregnancy, due to the high capacity of fetal tissues to synthesize cholesterol. Maternal hypertriglyceridemia is a characteristic feature during pregnancy and corresponds to an accumulation of triglycerides not only in very low-density lipoprotein (VLDL-C) but also in low (LDL-C) and high-density lipoprotein (HDL-C). Although triglycerides do not cross the placental barrier, the presence of lipoprotein receptors in the placenta, together with lipoprotein lipase, phospholipoproteins A2 and intracellular lipase activities, allows the release to the foetus of polyunsaturated fatty acids transported as triglycerides in maternal plasma lipoproteins.³²

Clinical Features and Complications of Atherosclerosis

Many of the clinical features of atherosclerosis are due to the formation of a thrombus at the site of an atherosclerotic plaque. When this occurs in the heart, the result is a myocardial infarction, which is commonly known in the US as a ‘coronary’ and in Britain and its former colonies as a ‘heart attack’. If the process occurs in the brain, the result is a stroke. More rarely, blockage of an artery supplying a lower limb, a kidney or part of the gut may occur, resulting in death (necrosis) of these tissues also. A feature of atherosclerosis occurring particularly in the arteries of the neck is that many small emboli may be formed over that shoot into the brain causing temporary blockage of small brain arteries. This may lead to multiple small strokes (transient ischaemic attacks) that recover in a short space of time. Such transient ischaemic attacks require urgent attention, as they are often the harbingers of full-blown stroke. Finally, it has become clear in recent years that many cases of dementia in the elderly are not due to Alzheimer’s disease, but due to diffuse atherosclerosis of the arteries of the brain, sometimes accompanied by multiple transient ischaemic attacks.³¹ This is termed vascular dementia. Previously, it was thought that such clotting occurs mainly at the site of advanced disease. However, more recent research has shown that smaller atherosclerotic plaques termed ‘culprit lesions’ are more often associated with thrombotic events. These culprit lesions are metabolically active and are characterized by a soft lipid core covered by a fibrous cap. In most cases, the event leading to thrombosis

appears to be a tear of the fibrous cap in a process called plaque rupture. This exposes the circulating blood to the interior of the atherosclerotic lesion, which triggers the clotting cascade in the blood. In some cases, it appears that thrombosis may occur even without rupture when there is a break in the layer of cells lining the artery at the location of an atherosclerotic plaque. Such a break in this layer of cells is termed superficial erosion.³² Other important clinical features of atherosclerosis relate to the ability of some plaques to reduce flow in the affected artery so that the oxygen supply of the downstream tissue is precarious. An oxygen supply that is adequate under resting circumstances may no longer be sufficient when tissue demand rises as, for example, during exercise. This lack of oxygen causes pain in the affected tissue. If this occurs in the heart, the result is angina pectoris, if it occurs in the legs it results in a condition known as intermittent claudication. A further important complication of atherosclerosis concerns the aorta, which is the main artery leading from the heart. Atherosclerosis of the aorta may weaken the wall of this vessel to such an extent that it bulges out.³⁰ This is called an aortic aneurysm. An aortic aneurysm may bleed, causing pain. Alternatively, and catastrophically, it may burst, leading to massive internal bleeding and sudden death.

Atherogenic Index of Plasma (AIP) Evaluation

The atherogenic index is calculated as the logarithm of ratio of triglycerides to HDL (Dobiasova, 2004).

AIP= AIP values of -0.3 to 0.1 is associated with low risk of cardiovascular disease, values between 0.11-0.24 is associated with intermediate risk and > 0.24 values is associated with increased risk.

Castelli index I and II evaluation

The Castelli index I was calculated with the formula.³³

CR-I-Values greater than 3.5 in males and >3.0 in females is associated with cardiovascular diseases.

The Castelli index II was calculated with the formula.³³

CR-II- Values greater than 3.3 is associated with cardiovascular disease in both males and females.

Atherogenic coefficient evaluation

Atherogenic coefficient is the ratio of total cholesterol (TC) minus high density lipoprotein (HDL) to high density lipoprotein (HDL).³³

AC= Values greater than 3.0 is associated with cardiovascular disease in both males and females.

Conclusion

The prevalence of hyperlipidemia, a major cause for coronary heart disease is very high. The relation between hyperlipidemia and occurrence of cardiovascular diseases has been already established. Various studies have reported the treatment of hyperlipidemic patients with antioxidants, fibrates, bile acid binding resins, etc. Though many Ayurvedic formulations and herbal remedies are available to treat hyperlipidemia, the problem of enhanced cholesterol levels in the blood is still prevailing and is being a cause for many coronary disorders.

Competing Interests Statement

The authors declare no conflicts of interest.

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