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Mini Review

Hyperlipidemia Background and Progress

Isam Karam[1]*, Ya Jun Yang[2] and Jian Yong Li[2]

[1]Central Laboratory of Veterinary Research, Soba (Animal Resources Research Corporation ARRC) Sudan, [2]Key Lab of New Animal Drug Project of Gansu Province; ; Key Lab of Veterinary Pharmaceutical Development, Ministry of Agriculture; Lanzhou Institute of Husbandry and Pharmaceutical Science of CAAS, China

Abstract

Hyperlipidemia is disorder disease characterize by an excess on blood lipids which include cholesterol, triglyceride, low density lipoprotein and decrease in high density lipoprotein in blood stream. Hyperlipidemia is modifiable risk factor of atherosclerosis and other cardiovascular disease; hyperlipidemia may be primary or secondary type according to the cause of hyperlipidemia either high food intake rich of fat or as result of other disease or metabolic disturbances. Hyperlipidemia may affect different animals, diagnostic by laboratory measure of blood lipid indexes and the treatment of hyperlipidemia depend on reducing lipids on the blood stream.

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***Corresponding author**

Isam Karam, Central Laboratory of Veterinary Research, Soba (Animal Resources Research Corporation ARRC), Sudan, Tel: 00249912624503; Email: isamkarm@yahoo.com

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Introduction

Hyperlipidemia which is a modifiable risk factor for atherosclerosis and related cardiovascular diseases, including coronary heart disease, cerebral stroke, myocardial infarction and renal failure are becoming a major health problem in the world recently [1]. Hyperlipidemia is a heterogeneous group of disorders characterized by an excess of lipids in the blood stream, these lipids include cholesterol, cholesterol esters, phospholipids, and triglycerides.

Jacobson reported that hyperlipidemia refers to elevated levels of lipids and cholesterol in the blood and it is also identified as dyslipidemia [2], to describe the manifestations of different disorders of lipoprotein metabolism. The term hyperlipidemia refers to increased concentrations of lipids (triglycerides, cholesterol, or both) in the blood stream, increased blood concentrations of triglycerides referred to as hypertriglyceridemia, while increased blood concentrations of cholesterol are referred to as hypercholesterolemia [1,3-5]. Another related condition, dyslipidemia indicates disorders of lipoprotein metabolism, including lipoprotein overproduction or deficiency. These disorders may manifest with the elevation of serum total cholesterol, Low-Density Lipoprotein (LDL), triglyceride concentrations, and a decrease in the High Density Lipoprotein (HDL) concentration. The main aim of treatment hyperlipidemia is to reduce the risk of developing ischemic heart disease, cardiovascular and cerebrovascular disease.

The major lipids reported to be present in the plasma are fatty acids, triglycerides, cholesterol, cholesterol esters (compounds), and phospholipids. Lipids are transported in the blood as large lipoproteins. Other lipid soluble substances, present in much smaller amounts but of considerable physiological importance, include steroid hormones and fat-soluble vitamins.

Four main classes of lipids can be recognized from a metabolic stand point. These are free fatty acids, triacylglycerol, phospholipids, and cholesterol and its esters [6]. The principle functions of lipids are to act as energy stores and to serve as important structural component of cells. To fulfill these functions, lipids have to be transported in plasma from one tissue to another, from the intestine or the liver to other tissues such as muscular or adipose tissue, or from the other tissues to the liver [7,8].

There are many groups of lipids three are most important from a clinical perspective: fatty acids, sterols (mainly cholesterol), and acylglycerols (mainly triglycerides) [9,10]. Fatty acids are relatively simple lipids and are also important components of many other lipids [9,10].

Lipids is water insoluble organic compounds, which are essential for many normal functions of living organisms: they are important components of cell membranes, they are used to store energy [11], and they play a significant role as enzyme co-factors, hormones, and intracellular messengers [11]. Because lipids are water-insoluble molecules, they cannot be transported in aqueous solutions, such as plasma. For that reason, lipids are transported in plasma as macromolecular complexes known as lipoproteins [3,5,9-15]. Lipoproteins are spherical structures that consist of a hydrophobic core containing lipids (i.e. triglycerides and/or cholesterol esters), and an amphophilic (i.e. both hydrophobic and hydrophilic) outer layer of phospholipids, free cholesterol and proteins that form a protective envelope surrounding the lipid core [5,9,10,12,15].

The proteins that are part of the lipoproteins are known as apolipoproteins (or apoproteins) and play a significant role in lipid transport and metabolism [5,9,10,14,]. Lipoproteins can contain one or a variety of apolipoproteins, which regulate their metabolic in several physiological functions of lipoproteins such as facilitation of lipid transport, maintenance of structural integrity, and activation of certain enzymes that play key roles in lipid metabolism [5,9,10,14].

Lipoproteins are particles that contain triglycerides, phospholipids and cholesterol and amphipathic proteins called apolipoproteins. Lipoproteins can be differentiated on the basis of their density, but also by the types of lipoproteins it contain. The degree of lipid in a lipoprotein affects its density the lower density of a lipoprotein contains more lipids relative to protein. Plasma lipoproteins differ in their physical and chemical characteristics such as size, density and composition [11].

The four major types of lipoproteins are chylomicrons, Very Low-Density Lipoprotein (VLDL), Low-Density Lipoprotein (LDL), and High-Density Lipoprotein (HDL). Two types of lipoproteins are triglyceride-rich: the chylomicrons and VLDL. Chylomicrons are synthesized by enterocytes from lipids absorbed in the small intestine. VLDL is synthesized in the liver. The function of these lipoproteins is to deliver energy-rich triglycerides to cells in the body [11]. TG is stripped from chylomicrons and VLDL through the action of lipoprotein lipase, an enzyme that is found on the surface of endothelial cells. This enzyme digests the TG to fatty acids and glycerides, which can then diffuse into the cell to be oxidized, or in the case of an adipose cell, to be re-synthesized into TG and stored in the cell. LDL delivers cholesterol to cells in the body. As VLDL particles are stripped of triacylglycerol, they become denser. These particles are remodeled at the liver and transformed into LDL. The function of LDL is to deliver cholesterol to cells, where it is used in membranes, or for the synthesis of steroid hormones [11].

Cells take up cholesterol by receptor-mediated endocytosis. LDL binds to a specific LDL receptor and is internalized in an endocytic vesicle. Receptors are recycled to the cell surface, while hydrolysis in an endolysosome releases cholesterol for use in the cell. HDL is involved in reverse cholesterol transport. Excess cholesterol is eliminated from the body via the liver, which secretes cholesterol in bile or converts it to bile salts. The liver removes LDL and other lipoproteins from the circulation by receptor-mediated endocytosis. Additionally, excess cholesterol from cells is brought back to the liver by HDL in a process known as reverse cholesterol transport [11]. HDL (or really, the HDL precursor) is synthesized and secreted by the liver and small intestine. It travels in the circulation where it gathers cholesterol to form mature HDL, which then returns the cholesterol to the liver via various pathways.

The link between cholesterol and heart disease was recognized through the study of individuals with familial hypercholesterolemia. Individuals with this disorder have several-fold higher levels of circulating LDL due to a defect in the function of their LDL receptors. Without functioning LDL receptors, LDL is not cleared from the circulation. As well, because cholesterol cannot get into cells efficiently, there is no negative feedback suppression of cholesterol synthesis in the liver [11]. A lipid profile typically measures the levels of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides. Dyslipidemia is the term that is used if lipid levels are outside the normal range. High levels of LDL cholesterol (the so-called "bad cholesterol") greatly increase the risk for atherosclerosis because LDL particles contribute to the formation of atherosclerotic plaques. Low HDL levels ("good cholesterol") are an independent risk factor, because reverse cholesterol transport works to prevent plaque formation, or even cause regression of plaques once they have formed. HDL may also have anti-inflammatory properties that help reduce the risk of atherosclerosis. Fasting triglyceride levels are used to estimate the level of VLDL. High levels of triglycerides are also associated with an increased risk for atherosclerosis, although the mechanism is not entirely clear.

Cholesterol is the main sterol in animal tissues, the major source of cholesterol is dietary intake, but it can also be synthesized endogenously by the liver and other tissues. Cholesterol is absorbed from the intestine and transported to the liver by chylomicron remnants. Hepatic cholesterol enters into the circulation as very low density lipoprotein VLDL which is metabolized by lipoprotein lipase enzyme to intermediate lipoprotein LDL and low density lipoprotein LDL which are then removed by liver or peripheral tissues. It plays a fundamental role in central metabolic pathways, such as bile acid metabolism and steroid hormone and vitamin D synthesis [9,10]. In the peripheral tissues cholesterol is converted to steroid hormones or used to form the cell walls and membranes. The quantity of cholesterol transported from the liver to peripheral tissues greatly exceeds its catabolism. So the excess amount of cholesterol is returned back to the liver by high density lipoprotein HDL. High cholesterol diet leading to hyperlipidemia is regarded as an important factor in the development of Ischemic heart disease and the focus so far has been mainly on the systemic and coronary vascular effects of cholesterol. Although only few studies questioned the effect of cholesterol diet on the heart, several structural and functional alterations have been shown, suggesting that the endogenous adaptive mechanisms against myocardial stress are impaired. Thus, it is not surprising that cholesterol is the most "decorated" molecule in history, having contributed to as many as 13 Nobel prizes [16].

Consequently, the principal steps in the absorption of dietary cholesterol are emulsification, hydrolysis of the ester bond by a pancreatic esterase, micellar solubilization, and absorption in the proximal jejunum reduction of cholesterol absorption by inhibiting cholesterol micellization in the intestinal lumen is a new target site of intervention for the treatment of hyperlipidemia. Moreover, it enhances the incorporation of cholesterol into the mixed micelle and aids transport of free cholesterol to the enterocyte. Inhibition of cholesterol esterase is expected to limit the absorption of dietary cholesterol, resulting in delayed cholesterol absorption. In addition, binding bile acids by forming insoluble complexes in the intestine and increasing their fecal excretion have been hypothesized as a possible mechanism of lowering plasma cholesterol level. This consequently reduces the bile acid pool. As a result, greater amount of cholesterol is converted to bile acids to maintain a steady level in the circulation. The continuous ingestion of high amounts of fat seems to be directly related to hyperlipidemia in humans. Consequently, it has been tried to provoke hyperlipidemia in laboratory animals, in order to understand better the relationship between disorders in cholesterol metabolism and atherogenesis and to test possible treatments for the reduction of circulating cholesterol level.

Triglycerides are the most common and efficient form of stored energy in mammal. They can be derived from both dietary sources and endogenous (hepatic) production [9,10]. It is worth noting that free fatty acids are transported bound to albumin and do not require incorporation into lipoproteins for transport [3,5,9,10,13,14]. Plasma lipoproteins differ in their physical and chemical characteristics such as size, density, and composition.

The Risk of Hyperlipidemia

Hyperlipidemia is a condition characterized by increased concentration of lipids (fats) in the bloodstream. Hyperlipidemia is one of the important factors associated with atherosclerosis, others being hypertension, smoking in human, diabetes mellitus, and other factors. Hyperlipidemia, atherosclerosis and related cardiovascular diseases are becoming a major health problem in the world recently even in companion animal clinic [17]. Hyperlipidemia has been thought to be a modifiable risk of cardiovascular disease, a most common cause of mortality worldwide, accounting for almost 17 million deaths annually [18].

Hyperlipidemia is a major risk factor for "Atherosclerosis" leading to heart attack and hypercholesterolemia nevertheless can impart some degree of risk for "Ischemic Heart Disease" (IHD). Atherosclerosis and coronary heart disease are associated with elevated levels of Low Density Lipoprotein (LDL cholesterol) and triacylglycerol with low levels of HDL cholesterol, consequent cardiovascular and cerebrovascular disease. Increased circulating levels of Low Density Lipoprotein (LDL) underlie the development of atherosclerosis. Other complications are coronary heart disease, ischemic cerebrovascular disease, hypertension, obesity and diabetes mellitus (Type -II).

Low Density Lipoprotein (LDL) is pro-atherogenic. Hence high levels of LDL increase "Coronary Heart Disease" (CHD) risk. High density lipoprotein (HDL) is anti-atherogenic. Hence low levels of HDL also increases CHD risk.

Hyperlipidemia elevated LDL and Triglycerides (TG)-associated with increasing risk. Serum levels of HDL inversely related to risk. Hyperlipidemia is a major, modifiable risk factor for atherosclerosis and cardiovascular disease, including coronary heart disease; this is true both of disorders involving hypercholesterolemia and hypertriglyceridemia. Hyperlipidemia is a common risk factor for Cardiovascular Disease CVD, with 53.4 percent of adults in the United States having abnormal cholesterol values and 32 percent having elevated Low-Density Lipoprotein (LDL) cholesterol levels. In the United States the (Am Fam Physician. 2011) mentioned that Cardiovascular Disease (CVD) is the leading cause of mortality accounting for 33.6 percent of all deaths in 2007 [19-21].

Cardiovascular and related illnesses are one of the most common diseases prevalent in many parts of the world. An increased risk of coronary heart diseases primarily associated with a high serum total cholesterol, low density lipoprotein (LDL) concentration and a decrease in High Density Lipoprotein (HDL).

Today; severe hypertriglyceridemia is a known risk factor for pancreatitis in humans [22-25]. An increased risk for pancreatitis from hyperlipidemia has been shown to exist when serum triglyceride concentrations exceed 11.3 mmol/L (1000 mg/dL. Hypercholesterolemia does not constitute a risk factor for pancreatitis in humans [23]. The mechanism by which hypertriglyceridemia induces pancreatitis is not clear, but it has been suggested that serum triglycerides are hydrolyzed by the action of pancreatic lipase, leading to excessive production of free fatty acids, which are toxic to the pancreas [26,27]. However, recent large-scale cohort research in USA and EU countries showed that there is no correlation between CHD incidence and the values of TG and LDL except people with familial hypercholesterolemia [28]. According to the reports, USA Government has abolished the upper limit of intake of cholesterol per day in 2015. Some of other countries made similar notification [29].

Cause and Type of Hyperlipidemia

Dietary intake may not be the major source of cholesterol, of which 80% is synthesized in the body. It may be true that dietary intake affects the amount of total cholesterol somewhat [30], but it can also be synthesized endogenously by the liver and other tissues. Several diseases have been reported to cause hyperlipidemia. Endocrine disease most commonly, canine hyperlipidemia is the result of an endocrine disorder, such as hypothyroidism, diabetes mellitus, or hyperadrenocorticism [5,11,13,14,31-33]. Hyperlipidemia can also be the result of an inherited disease in certain breeds of dogs. Hyperlipidemia in dogs and cats can be physiological (postprandial) or pathological. Pathological hyperlipidemia can result from increased lipoprotein synthesis or mobilization or decreased lipoprotein clearance. It can be primary (genetic or idiopathic) or secondary to other disease processes. Hyperlipidemia Postprandial is physiological and transient, and typically resolves within 7-12 h after a meal, depending on the fat content of the meal [5,13,14,34]. For that reason, any determination of serum lipid concentrations should always follow a fast of at least 12 h. Veterinarians should be familiar with how to recognize and manage this clinical disorder. Protein Losing Nephropathy (PLN) Proteinuria associated with hyperlipidemia, regardless of the cause, is often associated with hyperlipidemia in dogs [11]. The most commonly reported lipid abnormality in dogs with PLN is hypercholesterolemia, which is usually mild or moderate [35-39].

Hyperlipidemia can also result from a single inherited gene defect in lipoprotein metabolic. Genetic defects in lipid metabolism; monogenic familial hypercholesterolemia (homozygous or heterozygous) the defect may due to inactive LDL receptor, familial lipoprotein lipase deficiency the defect may due to inactive lipoprotein lipase; familial combined hyperlipidemia the reason still unknown.

There are two main types of hyperlipidemia:

Primary Hyperlipidemia: This may occur due to high food intake rich of fats and cholesterol or some of genetic defect and heredity factor.

Secondary Hyperlipidemia: This occurs due to some diseases or metabolic disturbances, e.g., diabetes mellitus, hypothyroidism, obstructive liver disease, secondary causes of hyperlipidemia is the most common pathologic form of hyperlipidemia in dogs [11,40]. Several diseases have been reported to cause hyperlipidemia. Endocrine disease more commonly, canine hyperlipidemia is the result of an endocrine disorder, such as hypothyroidism, diabetes mellitus, or hyperadrenocorticism [5,13,14,31-33,41]. Increases in both serum triglyceride and cholesterol concentrations have been reported in dogs with hypothyroidism [11,31,42-45]. In one study,

hypertriglyceridemia and hypercholesterolemia were found in 88% and 78% of dogs with hypothyroidism, respectively [44]. Usually, lipid abnormalities resolve after treatment of hypothyroidism [31]. In dogs with diabetes mellitus, hyperlipidemia is most commonly associated with hypertriglyceridemia but hypercholesterolemia might also be present [5,13,31,41,42,45].Similarly, hypertriglyceridemia usually resolves after successful treatment of diabetes but hypercholesterolemia might persist despite therapy [13,46]. The presence of hyperlipidemia (hypertriglyceridemia and, to a lesser degree, hypercholesterolemia) has long been associated with naturally occurring pancreatitis in dogs [5,13,14,31,32,47-50]. However, it remains uncertain whether hyperlipidemia develops as a result of pancreatitis or can be the cause of pancreatitis in some cases [13,51].

Lipid Metabolism

Lipid metabolism can be divided into two basic pathways: the exogenous pathway, which is associated with the metabolism of exogenous (dietary) lipids Figure 1, and the endogenous pathway, which is associated with the metabolism of endogenously produced lipids [9,10,14].

Exogenous pathway the first step in dietary lipid metabolism is digestion. Dietary lipids that reach the intestine duodenum then undergo emulsification, then hydrolyzed by the pancreatic and intestinal lipases [11,15]. Hydrolysis products (mainly free fatty acids and monoglycerides) are then transferred to the intestinal epithelial cell, where they diffuse through the epithelial cell membranes into the intestinal mucosal cells [11,15]. In the intestinal mucosal cell, free fatty acids and monoglycerides reassemble to form triglycerides, which then combine with phospholipids, free and esterified cholesterol [9,10,14,15,52]. Chylomicrons are the lipoprotein class responsible for transfer of dietary lipids. After formation in the enterocytes, chylomicrons, which mainly contain triglycerides, are secreted into the lacteals and enter first the lymphatic and later the blood circulation [9,10,14,15,52]. Lipoprotein which is exposed on the chylomicron surface, activates the lipoprotein lipase attached to the capillary beds in adipose and skeletal muscle tissues, which then hydrolyzes triglycerides into free fatty acids and glycerol [9,10,14,15,52]. Free fatty acids enters into the muscle cells (where they are used for energy production) and/or adipocytes (where they are re-esterified into triglycerides for storage). The cholesterol-rich remaining particles (chylomicron remnants), return to HDL and are recognized by specific hepatic receptors that rapidly remove them from the circulation by endocytosis [9,10,14,15,52]. The cholesterol found in chylomicron remnants can be used for lipoprotein (VLDL) and/or bile acid formation, or stored as cholesteryl esters [15,52].

Endogenous pathway while chylomicrons are responsible for transport of dietary lipids, VLDL, LDL and HDL is mainly involved in the metabolism of endogenously produced lipids [15]. Endogenously synthesized triglycerides and cholesterol (and cholesteryl esters). Lipoprotein species VLDL: Very Low-Density Lipoproteins, LDL: Low-Density Lipoproteins, HDL: High Density Lipoproteins. Classification and properties of major human plasma lipoproteins. Lipoproteins Major metabolic function chylomicrons structural, IDL: Intermediate Density Lipoproteins, LDL: Low-Density Lipoproteins, Lp (a): lipoprotein abide with phospholipids to form VLDL [9,10,14,15]. After VLDL molecules reach the vasculature [9,10,14,52]. VLDL activates lipoprotein lipase located in the capillary beds, which in turn leads to hydrolysis of VLDL triglycerides and the production of free fatty acids and glycerol. The VLDL molecules remaining after hydrolysis of VLDL triglycerides (VLDL remnants) are either removed from the circulation by the liver or undergo further transformation by lipoprotein lipase and/or hepatic lipase to form LDL [5,9,10,14,15,52]. LDL which contains mainly cholesteryl esters and phospholipids, circulates in the blood and binds to specific receptors that are widely distributed throughout tissues in order to deliver cholesterol, which can be used for the synthesis of steroid hormones and cell membranes as well as for hepatic metabolism [9,10,15,]. HDLs have a critical role in the reverse cholesterol transport pathway; it is well known that a new attempt to reduce the absorption of free fatty acids is by delaying triglyceride digestion with the inhibition of pancreatic lipase. Pancreatic cholesterol esterase plays a pivotal role in hydrolyzing dietary cholesterol esters. The hydrolysis of cholesterol esters in the lumen of the small intestine is catalyzed by pancreatic cholesterol esterase, which liberates free cholesterol (Figure 1).

Hyperlipidemia in Different Animals

Hyperlipidemia can be the result of an inherited disease in some animals. Hyperlipidemia in dogs and cats can be physiological (postprandial) or pathological. Increased serum triglyceride and/or cholesterol concentrations have been observed in obese dogs [53-55]. The most profound changes were associated with severe chronic obesity [55]. Weight loss in obese dogs leads to significant decreases in both serum triglyceride and cholesterol concentrations [55,56].

In pets, hyperlipidemia most often occurs as a consequence of some other disorder, such as diabetes mellitus (sugar diabetes), hypothyroidism (low levels of circulating thyroid hormones), Cushing's disease (excessively high cortisone levels in the body), certain liver diseases, and protein-losing nephropathy (a disease of the kidneys resulting in protein loss in the urine). However, hyperlipidemia can also occur spontaneously after a meal of high-fat foods, particularly table scraps.

After eating a meal, the nutrients in an animal's body pass into the small intestine, from which chylomicrons, micro particles of liquid fat, are absorbed 30-60 minutes later. Chylomicrons are in the classes

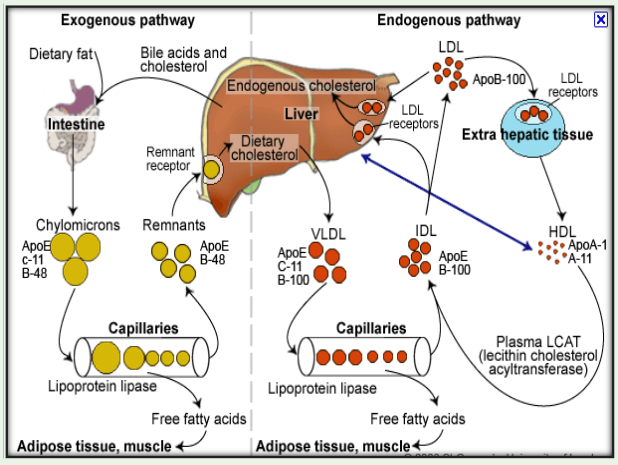

Figure 1: The lipid metabolism can be divided into two basic pathways: the exogenous pathway and endogenous pathway.

of lipids, which includes both triglycerides and cholesterol, and which are formed during the digestion of fats from food.

Normally, the absorption of chylomicrons increases serum triglycerides for 3-10 hours, but some animals will have high cholesterol and high triglyceride levels for more than twelve hours after a meal - one of the main indications of hyperlipidemia.

In Equine Poor feed quality or decrease in feed intake, particularly during a period of high-energy requirement (e g, pregnancy, systemic disease), may result in hyperlipidemia syndrome [17]. Hyperlipidemia is seen most commonly in ponies, miniature horses, and donkeys, and less frequently in standard-size adult horses.

A number of studies have shown that the feeding of fat supplements to ruminant's raises the cholesterol concentration in the serum but not in the tissues or milk in non-ruminants, including primates and man, hypercholesterolemia may be increased by dietary manipulations such as feeding excessive cholesterol or fats with a high saturated fatty acid content. The serum cholesterol concentration does not rise uniformly and hyper-responsiveness has been variously attributed to excessive absorption of cholesterol, e.g [57]. In some species of monkey, to diminished re-excretion of cholesterol or bile acids, or to the failure of absorbed cholesterol to exert appropriate feedback inhibition on cholesterol synthesis. As ruminants normally derive all of their cholesterol from endogenous biosynthesis [57], it is reasonable to suppose that the fat-induced hypercholesterolemia in ruminants is due to either an increased synthesis of cholesterol and/or a decreased fecal excretion of cholesterol or bile acids.

A great number of animal models, such pigeons, chickens, swine, cats, dogs, non-human primates, mice, rabbits and rats, have been tested for hyperlipidemia [58,59]. Consequently, it has been tried to provoke hyperlipidemia in laboratory animals, in order to understand better the relationship between disorders in cholesterol metabolism and atherogenesis and to test possible treatments for the reduction of circulating cholesterol level.

For inducing hypercholesterolemia in rats triglycerides-rich diets containing cholesterol, with or without cholic acid have been used [60]; the level of cholesterol varies substantially as well.

Diagnosis 0f Hyperlipidemia

Diagnosis of hyperlipidemia it depend on laboratory measures for hyperlipidemia indexes, which include Triglycerides TG, Total Cholesterol TC, Low Density Lipoprotein LDL and High Density Lipoprotein HDL, hyperlipidemia can be characterized by increasing in TG, TC, LDL and decreasing in HDL, any determination of serum lipid concentrations should always follow a fast of at least 12 h. Methods for quantification and characterization of lipids in blood Routine quantitative assessment of total cholesterol and triglyceride concentrations in serum or plasma is usually achieved by use of spectrophotometric or enzymatic methods [61]. Other methods (e.g., lipoprotein electrophoresis, ultracentrifugation) have also been used but have limited use in the routine clinical evaluation of hyperlipidemic dogs [13,61]. Interference with laboratory measurements it is important to note that lipemia can often interfere with the determination of several analytes, depending on the methodology and analyzer used. Analytic the determination of which has been reported to be affected by lipemia (i.e., falsely increased or decreased) include, but are not limited to, bilirubin, liver enzymes, amylase, lipase, electrolytes, protein, albumin, and glucose [61], in dogs compared to humans [5]. Persistent fasting hyperlipidemia is always considered abnormal and can be either secondary to other diseases or drug administration or primary.

Treatment of Hyperlipidemia

Therapeutic strategies for hyperlipidemia treatment depend on reduce blood lipids, there are many chemical drugs that lower cholesterol level in the body; commonly known as lipid-lowering drugs. Such as statins, fibrates, ezetimibe and nicotinic acid, but most of them are expensive and have undesirable effect [62]. The main aim of treatment in patient with hyperlipidemia is to reduce the risk of developing ischemic heart disease, cardiovascular and cerebrovascular disease (Figure 2). However, to fight these problems of hyperlipidemia, to treat hyperlipidemia in human, extensive interventions have been performed including diet control, exercise and administration of hypolipidaemic drugs [63]. One of the most important strategies in the prevention and treatment of hyperlipidemia includes delaying fat digestion and absorption through gastrointestinal mechanisms such as the inhibition of pancreatic lipase, pancreatic cholesterol esterase activities as well as the inhibition of cholesterol micellization, and bile acid binding. However, the complex mechanisms by which these molecules act are only beginning to be appreciated. Evidences suggest that lipid lowering modes of therapy also reduce inflammation, which may reduce the risk of cardiovascular events; even for individuals with LDL-Clevels in the normal range (< 130 mg/dL) based on the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III) guidelines. Several drugs are used to decrease LDL cholesterol such as "-statins" (HMG-CoA reductase inhibitor), bile acid sequestrates, nicotinic acid and gemfibrozil.

The most important drugs for the treatment of dyslipidemia are by far, one group of drugs (statins) lowers cholesterol by interfering with the cholesterol biosynthetic pathway. Most of the drugs (statins) available today are inhibitors of 3-hydroxy3 methyl gluataryl coenzyme -A reductase, which is involved in cholesterol biosynthesis in the liver. The most effective and widely used drugs for the treatment of hyperlipidemia are the "-statins". Their primary site of action is in the liver where they inhibit HMG- CoA reductase; the metabolic pathway that produces cholesterol and isoprenoids. Statins have been

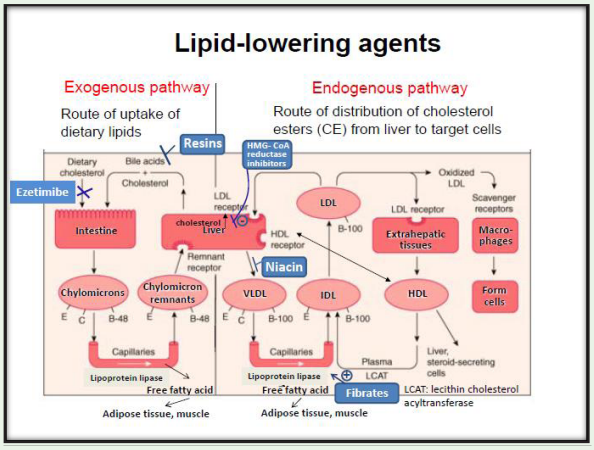

Figure 2: The lipid lowering drugs acting on hyperlipidemia. Such as: statins, fibrates, ezetimibe, resins and niacin.

shown in multiple clinical trials to reduce cardiovascular events and mortality. Statins have been shown to effectively lower LDL levels and reduce both mortality and morbidity associated with coronary heart disease by 30%. However, as noted Steinberg and colleagues [64]; this still leaves a significant percent TGe of individuals for whom statin therapy will not prevent the occurrence of adverse events. Statins have the most convincing data for primary prevention, especially for higher risk patients. Therefore, risk stratification is essential. Statin therapy is also recommended for secondary prevention in all patients with known cardiovascular disease or the risk equivalent. High-dose statins should be initiated in patients with acute coronary syndrome [65].

Pharmacologic treatment of hyperlipidemia in conjunction with therapeutic lifestyle changes for human can be used for both primary and secondary prevention of cardiovascular disease. There is good evidence for using statins in the secondary prevention of stroke and peripheral arterial disease [66].

Hyperlipidemia is a common cause for CVD, with elevated Low-Density Lipoprotein (LDL) cholesterol levels. National Institute for Health and Clinical Excellence (NICE) guidelines recommend offering a fixed-dose statin based on CHD risk stratification, and recommend against checking cholesterol levels after a patient starts statin therapy. For secondary prevention, NICE recommends a treat-to-target therapy that is less aggressive than that recommended by the Adult Treatment Panel (ATP) III. The ATP III recommendations are based on the assumption that achieving the mean LDL cholesterol level observed in clinical trials will produce similar results in practice, but no clinical trial has assessed a treat to target strategy. However, based on statins medical use, importance, and popularity, Elevated serum lipids have been shown to be a major risk factor for the development of coronary heart disease and atherosclerosis [67].

The U.K. National Practice Guidelines U.S., U.K., and Canadian guidelines are available to help physicians manage hyperlipidemia. These guidelines agree that therapeutic lifestyle changes are the mainstay of hyperlipidemia management, and that LDL cholesterol should be the primary target of therapy. Treatment of hyperlipidemia improves outcomes for patients with known Coronary Heart Disease (CHD) or the risk equivalent, and for high-risk patients (i.e., those with a 10-year CHD risk of greater than 20 percent) without known CHD or the risk equivalent. In the past 20 years, major strides have been made in the understanding and treatment of hypercholesterolemia and other dyslipidemias. Since its inception in 1985, the National Cholesterol Education Program (NCEP) in USA has battled to reduce the prevalence of high blood cholesterol through educational campaigns and science-based practice guidelines, however cholesterol levels are still under treated. The U.S. National Cholesterol Education Program, Adult Treatment Panel (ATP) III guidelines advocate for a treat to target approach and are more aggressive than other guidelines [68].

Omega-3 fatty acids may be a good alternative after myocardial infarction for patients who cannot tolerate statins. Fibrates and niacin have not been shown to reduce all-cause mortality in secondary prevention, but may be useful adjuncts when statins alone cannot adequately control lipid levels. Other cholesterol-lowering medications used for primary or secondary prevention of cardiovascular disease have not been shown to consistently improve patient-oriented outcomes.

On the other hand, fibrates decrease fatty acid and triglyceride levels by stimulating the peroxisomalβ-oxidation pathway. Apart from these drugs, ezetimibe, which selectively inhibits intestinal cholesterol absorption, cholestyramine, colestipol, and colesevelam, which sequester bile acids, torcetrapib, which inhibits cholesterol ester transfer protein, avasimibe, which inhibits acyl-CoA: cholesterol acyltransferase, implitapide, which inhibits microsomal triglyceride transfer protein, and niacin, which modifies lipoproteins, providing clinicians with several therapeutic options for lipid lowering. To retard or prevent the formation of atherosclerosis come hyperlipidemias on one of the present therapeutic challenges. Elevated plasma cholesterol levels have long been established as risk factors for CHD, and lowering cholesterol levels, particularly low – density lipoprotein cholesterol (LDL-C) has been the focus of the prevention of CHD and it's squealed for almost 25 years.

The pharmacological, dietary and herbal treatment of Coronary Heart Disease (CHD) is based on the hypothesis that reduced cholesterol biosynthesis will lead to lower blood levels of cholesterol. Lowering lipids and cholesterol levels by a drug or dietary interventions could reduce the risk of Coronary Heart Disease. Current interest in natural products has stimulated the search for new cholesterol-lowering agents from these sources. Several synthetic hypocholesteromic agents such as statins, fibrates, resins and nicotinic acid are capable of efficiently reducing plasma Total Cholesterol (TC) levels, but LDL does not undergo any significant alteration. Also, synthetic hypolipidemic agents have one or more side effects and are unable to increase HDL levels. Karam reported that Aspirin Eugenol Ester (AEE) which is novel drug compound between aspirin and eugenol had anti-hyperlipidemia effect on blood lipids indexes in rats which induced hyperlipidemia with feeding high fat diet the drug significantly decrease TG, TC, LDL and increase HDL [17].

Many herbal medicinal products were reported to have a potential to reduce lipid and cholesterol in body and to enhance the safety profile by elevating HDL levels and inhibiting lipid oxidation, such as Berberine which had regulation effect on hyperlipidemia indexes [69-72]. The major portion of the global population in developing countries still relies on botanical drugs to meet its health needs [71]. The attention paid by health authorities to the use of herbal medicines has increased considerably, because herbal medicines they are often only medicine available in less developed areas and because they are becoming a popular alternative treatment in more developed areas [69].

There is an obvious need for more efficacious and alternative treatment options. Many Chinese herbal medicines contain polysaccharides which can exert a wide range of pharmacological effects, including lipid lowering drugs [73]. In modern practice, there are many drugs which are in use as hypolipidemic agent but the therapy is not cost-effective and as such these drugs do not fulfill the WHO guidelines of essential drugs. Herbal treatment of hyperlipidemia has no side effects and relatively cheap and locally available.

So there are increasing interest in alternative/herbal medicine for the prevention and treatment of hypercholesterolemia. Currently

available hyperlipidemic drugs have been associated with a number of side effects. Many of the medicinal plants widely used to reduce plasma cholesterol and to reduce the risk of atherosclerosis-related diseases. Therefore it is a need of the day to search other materials from natural sources that are less toxic, less expensive, which can provide better safety and efficacy on a long term usage. Natural products from plants area rich source used for centuries to cure various ailments (Figure 2).

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