

# Dyslipidemia in Metabolic Syndrome: an Overview of Lipoprotein-Related Disorders

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**Abstract:** The significance of plasma levels of total cholesterol (TC), triglycerides (TG) and each lipoprotein class namely chylomicrons, low density lipoproteins (LDL), very low density lipoproteins (VLDL), and high density lipoproteins (HDL) has been tested time and again for their reliability as diagnostic markers of dyslipidemia. The prevalence of dyslipidemia-related metabolic syndrome is associated with the risk of cardiovascular disease (CVD) and diabetes. This review will focus on the characteristics of major classes of lipoproteins (LPs) and their coexistence with TG and apolipoprotein as estimates of the intensity of metabolic syndrome. It will deal with the suitability of animal models for dyslipidemic studies that match with clinical conditions of diabetes, atherosclerosis and obesity. It also sums up published research and clinical case studies in support of the conceptual paradigm shift from the use of simple lipids to oxidized LDL (OxLDL) and apolipoproteins as diagnostic markers of dyslipidemia. Further, it briefly discusses the use of non-pharmacological approach such as exercise and diet as an effective means of management of dyslipidemia in human as well as subhuman species. Finally, it presents evidence for treatment of dyslipidemia with specific targets, LP and TG as the appropriate therapy only when non-pharmacological means fail to accomplish the standard lipid profile.

**Keywords:** Apoproteins, Atherosclerosis, Diabetes, Chylomicrons, Lipoproteins, Triglycerides, Obesity.

## INTRODUCTION

It is known that dyslipidemia involving abnormal blood lipid levels is an endocrine and metabolic disorder largely of lipoprotein overproduction or deficiency. The condition is associated with a target population world-wide that is at an increased risk of developing cardiovascular diseases (CVDs) and diabetes. Although dyslipidemia is related to genetic predisposition, a high percentage of the population acquires it from multifactorial causes such as obesity, diet and lifestyle habits. The rapid rise in metabolic syndrome (MS) resulting from dyslipidemia leading to major diseases, diabetes type-II (DM2) and coronary artery diseases (CAD) is positively correlated to sedentary lifestyle and obesity. In fact, the cluster of conditions- obesity, dyslipidemia, diabetes and hypertension together is termed "metabolic syndrome". MS is a combination of lifestyle and environmental factors and notably, some populations exhibit greater risk factors for the development of MS. Here we review the role of major players namely lipids in the development of dyslipidemia because of their critical role in development of atherogenic dyslipidemia comprising of hypertriglyceridemia, low levels of high-density lipoprotein (HDL) and predominate levels of low-density lipoprotein (LDL).

Lipids are a diverse group of compounds that are weakly soluble in the aqueous media of the cell. The important lipids are cholesterol, triglyceride and phospholipid. Cholesterol is a precursor of the steroid hormones and of the bile acids necessary for digestion. The liver produces approximately 70% of the cholesterol used by the body, and the other 30% comes from the diet. Cholesterol is synthesized endogenously in the liver through the microsomal enzyme, 3-hydroxy-2-methylglutaryl-COA reductase (this is the rate-limiting enzyme). Although cholesterol and triglycerides have important functions in the body, due to their insolubility they are packed into lipoproteins in order to allow for their transport. The center of a lipoprotein molecule is composed of cholesteryl esters (CE, a compound of cholesterol and a fatty acid), triglycerides (TG, a compound of glycerol and three fatty acids), fatty acids and fat-soluble vitamins like vitamin E. The terms "good" and "bad" cholesterol refer to high density lipoproteins (HDL) and low density lipoproteins (LDL) respectively. The latter is more susceptible to oxidative modification that is referred as oxidized low-density lipoprotein (ox-LDL) and therefore toxic to vascular endothelium.

Fatty acids are usually ingested as triglycerides and the digestion products are absorbed primarily as free fatty acids (FFA) and 2-monoglycerides. However, a small fraction is absorbed as free glycerol and diglycerides. Once these substances cross the intestinal barrier, they are resynthesized into TG and packaged in to chylomicron (CM) or lipoproteins and

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transported through the capillaries of the lymph system, the lacteals and into the blood. The CM binds to the membranes of adipocytes, hepatocytes and skeletal muscle where they are stored and sometimes oxidized for production of energy. In fact, the liver is a major organ for processing CM and liposomes into the various types of lipoproteins that are spherical complex particles made up of hundreds of protein and lipid molecules and vary in size from 10 to 1000 nanometers. In general, as the density of lipoproteins increases, the size of the particles decreases.

The outer layer of a lipoprotein is polarized and assists in transporting lipids in the blood. It consists of a hydrophilic layer of apolipoproteins, phospholipids and cholesterol. Apolipoproteins (apo)- apoB, apoC and apoE coat the lipoprotein particles. The apos are recognized by enzymes that can either process or remove lipids from the lipoproteins. For instance, apoC-II activates lipoprotein lipase (LPL) which is efficient in removing TG from CM and very low density lipoprotein (VLDL). The formation of VLDL in the liver is a step-wise lipidation by the apo B. To start the lipidation, the microsomal triglyceride transfer protein (MTTP) in the rough endoplasmic reticulum [1] forms the pri-mordial VLDL [2] and in turn gets converted to triglyceride-poor VLDL by further lipidation [3]. The triglyceride-poor VLDL is secreted from the hepatocytes as VLDL<sub>2</sub> or lipidated to form triglyceride-rich VLDL<sub>1</sub> [4], a process dependent on GTP-binding protein ADP-ribosylation factor 1 (ARF-1) [5]. The final stages of VLDL formation takes place in the golgi complex [6,7] although some data also suggest that the endoplasmic reticulum (ER) is the site of final maturation of VLDL [8].

High density lipoprotein (HDL) is another type of lipoprotein that collects cholesterol, glycerol and FAs from the blood or from the cells if cholesterol is abundant and transports them to the liver unlike VLDL. HDL is a lipoprotein involved in reverse cholesterol

transport and the transfer of cholesteryl esters from atherogenic lipoproteins and peripheral tissues to the liver. This 'reverse transport' mechanism, however, depends on the interactions between HDL, apos and enzyme activity. HDL particles are synthesized and catabolized in the liver as well as the intestine. A circulating enzyme, lecithin-cholesterol acyltransferase facilitates the uptake of free cholesterol from HDL by esterification. The reaction produces a more hydrophobic core and hence increases the density of HDL particle. Another enzyme, cholesteryl ester transfer protein (CETP), mediates the transfer of CE from the HDL core and the circulating lipoproteins such as LDL. Lipoproteins are classified on the basis of their densities as shown in Table 1

Adapted from Skipski [9]. TG, triglycerides; Chol, cholesterol; CE, cholesterol esters; PL, phospholipids; VLDL, very low density lipoproteins; IDL, intermediate low density lipoproteins; LDL, low density lipoproteins; HDL, High density lipoproteins

#### Dyslipidemia is Classified into:

- 1) Primary dyslipidemia: Condition is caused by mutations in a single gene (monogenic) or caused by multiple mutations (polygenic), which may have less effect when present alone. These disorders are characterized by overproduction of lipoproteins and/or reduced clearance from circulation.
- 2) Secondary dyslipidemia: Clinical conditions associated with dyslipidemia with different grades of severity in absence of genetic disorder. These disorders are sub classified into:
  - a) Hypercholesterolemia: Hyperthyroidism, obstructive liver disease, drugs, nephrotic syndrome, use of cyclosporine and thiazides.

**Table 1: Classification of Lipoproteins**

Lipoprotein	Density (g/dL)	Diameter (nm)	Lipid (%)				Protein (%)
			PL	Chol	CE	TG	
Chylomicrons	< 0.95	1000	~8	~1	~3	85-88	1-2
VLDL	~ 0.98	25-90	18-20	8-10	12-15	50-55	5-12
IDL	~ 1.0	40	25-27	8-10	32-35	24-30	10-12
LDL	~ 1.04	26	20-28	8-10	37-48	10-15	20-22
HDL	~ 1.12	6-12.5	26-46	2-10	15-30	3-15	55

- b) Hypertriglyceridemia: Obesity, diabetes mellitus, pregnancy, gastric bypass surgery; stress, sepsis, alcohol, glucocorticoids, use of beta blockers, glycogen storage disease and chronic renal failure
- c) Low HDL: Type-2 diabetes mellitus, rheumatoid arthritis, obesity, cigarette smoking anabolic steroids and use of beta blockers.

The lipid content and composition of various lipoproteins are represented in Table 2

**Table 2: Composition of Phospholipids of Lipoprotein Classes**

% PL	Phospholipids			
	CM	VLDL	LDL	HDL
PC	57-80	60-74	64-69	70-81
SM	12-26	15-23	25-36	12-14
Lyso PC	4-10	~5	3-4	~3
Other	6-7	6-10	7-10	5-10

Adapted from Skipski [9]. PC, phosphatidyl choline; SM, sphingomyelin; LysoPC, lyso phosphatidyl choline; others, phosphatidyl ethanol amine, phosphatidyl leucine and phosphatidyl inositol

## CARDIOVASCULAR DISEASES AND DYSLIPIDEMIA

Cardiovascular disease (CVD) is the most common cause of death world-wide and hence an understanding of dyslipidemia as a potential risk factor in clinical settings is of utmost importance. One of the major predisposing factors for atherosclerosis is altered lipid profile that is reported in 70% of patients with premature coronary artery disease (CAD). Increased concentration of LDL or decreased levels of HDL are major risk factors of coronary atherosclerosis although TG is independently associated with the disease. Total cholesterol does not accurately predict the risk of CAD, since it represents the sum of all cholesterol carried not only by atherogenic lipoproteins (VLDL, IDL, and LDL) but also antiatherogenic lipoproteins (HDL). Hence, most often treatment depends on LDL cholesterol values which in turn take into consideration LDL heterogeneity. As a matter of fact, small, dense LDL (sdLDL) particles are known to be more atherogenic than large, buoyant LDL particles, and the extent of oxidation of LDL (OxLDL) determines its atherogen-

icity [10, 11]. It is known that plasma OxLDL is a better predictor of coronary heart disease (CHD) and acute coronary syndrome (ACS) based on studies in 115 subjects who had undergone coronary angiography [12]. Further, it is known that apo B may be an even better predictor of CAD compared to just LDL [13]. Besides, LDL contains apolipoproteins (apo B-100) and some other lipoprotein alleles such as apo C-II, apo-C-III, and apo E. Few particles are rich in triglycerides *i.e.*, large VLDL, while others are smaller and contain cholesteryl esters *i.e.* small VLDL and IDL. It is well known that the remnant lipoproteins that contain apo C-III are potentially atherogenic. Clinical studies have shown the differences in LDL particles by size, density, and composition between healthy subjects and CHD patients. One of the best known examples is the Quebec study, wherein male subjects who had an LDL size < 25.6 nm exhibited 2.2-fold increase in the ischaemic heart disease (IHD) when compared to those men whose particle size was >25.6 nm [14]. A study involving multivariate analyses has shown sdLDL particles as predictors of incidence of IHD independent of many other parameters, LDL cholesterol, TG, HDL cholesterol, apo B, and the total cholesterol-HDL ratio. In contrast, records from the Physicians' Health study [15] suggest that sdLDL is not a strong risk factor after comparing the risk factors, small and dense LDL and TG for myocardial infarction (MI). The cases had sdLDL diameter, 25.6±0.9 nm (mean ± SD) compared to 25.9±8 nm in the controls. There were cases with higher TG levels, 168 versus 132 mg/dL. Therefore it has been suggested that the LDL diameter has an inverse correlation with TG and a high direct correlation with HDL-cholesterol. The study also concluded that non-fasting TG levels are strong independent predictors of risk of MI, especially with elevated cholesterol levels. There are a few studies that have held that sdLDL particles are related to their atherogenic properties [16,17]. However, sdLDL particles containing more of CE (phenotype B) are considered to be more atherogenic than buoyant LDL particles (phenotype A).

In the past two decades it has been established that oxidative stress-dependent oxidation of LDL particles leads to atherosclerosis and that OxLDL serves as an additive to the global score of atherosclerosis based on age, gender, HDL-cholesterol, total cholesterol, and other conditions such as diabetes mellitus, smoking and hypertension [18-20]. For example, sdLDL and oxidative stress have been reported as cooperative factors in atherogenesis leading to CVD in dyslipidemic Japanese male and female patients aged above 60

years [21]. There are also reasons to believe that sdLDL is a strong risk factor for CAD since sdLDL particles can enter the arterial wall more easily and bind to arterial proteoglycans [22] and are subjected to oxidative modifications leading to macrophage uptake [23].

Studies on TG-rich lipoproteins have discovered that hypertriglyceridemia is an independent risk factor for the development of CVD [24]. The size of lipoproteins actually determines their ability to enter the arterial intima through the endothelial barrier. For instance, sdLDLs of 20 to 60 Svedberg flotation units,  $S_f$  and IDLs of  $S_f$  12 to 20 enter the intima unlike the chylomicrons and large VLDLs which are about 60 to 400  $S_f$ . Results from the Monitored Atherosclerosis Regression Study (MARS) have provided evidence for a positive correlation between the progression of CADs and TG-rich lipoprotein remnants [25]. A substudy of the Cholesterol and Recurrent Events (CARE) in patients with MI and on pravastatin, showed average LDL concentrations at 115 to 174 mg/dL and baseline concentrations of VLDL lipids, and apo E in VLDL+LDL and in HDL. These patients when compared to those who had earlier MI and patients who did not have any cardiovascular event during the 5 years of follow-up has shown that plasma VLDL and apo C-III in VLDL and LDL, are more reliable and specific markers of CHD risk than plasma TG [26].

### DYSLIPIDEMIA AND ADIPOSITY

Fat distribution in the body has an important role on metabolic and cardiovascular risk factors. It is known that increased abdominal fat is a potent risk factor for CAD, diabetes type II (DM2), hypertension and stroke. The National Cholesterol and Education Program (NCEP) has included obesity, waist circumference, >102 cm in men and > 88 cm in women, as a component of common cluster that contributes to MS. The abdominal fat referred as visceral fat is related to hyperinsulinism, insulin resistance, raised plasma FFAs, hypertension, thrombosis, hypertriglyceridemia, sdLDL particles, and concomitant reduction in HDL. However, elevated LDL cholesterol is not considered as a marker of dyslipidemia. Elevated apo B indicative of increased number of sdLDL (VLDL and LDL) is recognized as a more reliable indicator of dyslipidemia. Obesity leads to over secretion of TG-rich VLDL particles and an increased FFA uptake in the liver which stimulates the secretion of apo-B-containing particles and hence hypertriglyceridemia [27]. In the presence of elevated TGs, LDL particles become

enriched in TGs at the expense of core cholesteryl esters. The hepatic lipases act to hydrolyze these TG-rich LDL leading to sdLDL particles, a well established risk factor for MI.

### FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL)

This type of hyperlipidemia is a genetic disorder and is associated with 1.7 to 10-fold elevated risk of CAD [28]. Studies on patients with MI have shown 11% prevalence of FCHL without premature CAD and 10-14% prevalence of FCHL in patients with premature CAD [29]. In FCHL patients, there is excess generation of apo B in lipoproteins, VLDL, IDL and LDL with reduction of HDL production. This disorder is expressed after the third decade and is usually thought of in terms of central adiposity. It is also associated with increased insulin resistance, abdominal obesity and hypertension, all of which are characteristic of metabolic syndrome [30-32].

### DYSLIPIDEMIA AND DIABETES

It is known that the incidence of several types of CVDs happen in patients with either type 1 (DM 1) or type 2 (DM 2). Development of dyslipidemia is known to signal the onset of diabetes which is essentially the occurrence of high TGs and LDL levels with low levels of HDL. In DM2, LDL is converted to smaller, more atherogenic sdLDL which in contrast to DM1, is not rectified with glycemic regulation [33]. It is now established with certainty that the onset of diabetic dyslipidemia is related to insulin effects on hepatic apoprotein synthesis, regulation of LpL, CETP action, and insulin influence on muscle and adipose tissue. DM2 patients are known to be at high risk of CAD and hence treated aggressively for lipid lowering therapies [34, 35].

### ANIMAL MODELS OF DYSLIPIDEMIA

Animal models have been utilized to understand dyslipidemia in humans especially for antiatherogenic drug target delivery and as validation model for dyslipidemia. Among the models of dyslipidemia abnormal lipid profiles and atherosclerosis have been studied extensively and a number of wild-type, naturally defective, and genetically modified animal species such as rabbits, mice, pigeons, dogs, pigs and monkeys have been characterized [36,37]. In humans, the fractional esterification rate in apolipoprotein B-depleted plasma FER(HDL) has been demonstrated to correlate with the quality of LDL particles. Plasma lipid

profiles and FER(HDL) values have been characterized in some species namely, cat, pigs, rabbits and guinea pigs and wide variations with a positive correlation are seen with FER(HDL) and TG, but not with HDL [38].

Genetic hyperlipidemic disorders in *Watanabe* rabbits and in transgenic mice and in primate, *Macaca nigra* are useful models for studying interactions between diabetes and AS (atherosclerosis) [39]. Plasma lipoproteins and FA compositions have been studied and reported for five mouse strains, six other non-primate species, and four non-human primate (NHP) species [40]. Such studies on animal models of dyslipidemia are of prime importance since the success rate of drug development has not gone beyond statins and the major cause for this has been the limitations of the efficacy of treatments in the clinics [41]. Recognizing the importance of statins in alleviating plasma LDL for treatment of dyslipidemia in humans, studies by Yin *et al* [40] on simvastatin treatment in several species of animals have demonstrated that non-human primates (NHPs), followed by dogs are the animal models that are the closest match to human dyslipidemia. For practical and routine purposes, data obtained by Strack *et al*. [42] have shown hamster and dog as useful models for target validation in dyslipidemia. For the subset of dyslipidemic population with high TG levels, the closest matches are hamster

and *db/db* mouse for use in drug validation. Animal [43] and tissue culture [44] studies too have suggested that fatty acids modulate apoB secretion in the liver.

It is possible to study dyslipidemia in animals by streptozotocin or alloxan treatment [45, 46], or by maintaining the animals on a high fat diet [47] or by intralipid administration [48]. Animal models of disease therefore permit us to study the initiation and progression of pre-clinical stages of dyslipidemia and relevant information can be obtained for treatment and prevention since these models mimic human disease closely.

The use of animal models in lipid metabolomics has been summarized in Table 3

### THERAPEUTIC INTERVENTIONS FOR TREATMENT OF DYSLIPIDEMIA

Although at present drug treatment has been an effective therapy for overcoming dyslipidemia, concern for safety has driven many clinicians and researchers to prefer non-pharmacological therapies [49-52]. This part of the chapter briefly examines the cholesterol lowering efficacy of the NCEP and the recommendations of the Adult Treatment Panel III (ATP-III) about certain therapies in place of drug therapy. Another approach relates to the modification in

**Table 3: Animal Models of Dyslipidemia**

S. No	Animal Models	Studies	References
1	Rats and mice	Metabolic syndrome, dyslipidemia and atherosclerosis	[70]
2	Mice, rat, hamster, rabbit dog and monkey	Relationship between plasma HDL level and CETP activity	[71]
3	Rabbits	CETP inhibition and reduction of atherosclerosis	[72]
4	Rabbits	Pharmacological modification of CETP in atherogenic dyslipidemia	[73]
5	CF rats	Hyperlipidemic model in small animals through high fat diet obesity, hyperlipidemia, dyslipidemia and insulin intolerance	[74]
6	Hamster, rat, db/db mouse, dogs, rabbit, ZDF rat, humans	Plasma lipoproteins, lipid fractions and fatty acid composition	[75]
7	Humans, rats, swine, rabbits monkeys, swine, dogs, hamsters dogs, hamsters	Effect of n-3 fatty acids on triglyceride levels is seen in rats and swine but rarely seen in mice, rabbits, monkeys, dogs, and hamsters	[40]
8	<i>Psammomys</i> (rodent model of obesity) type 2 diabetes	Lipid component and other characteristics of metabolic syndrome	[76]
9	WHHL rabbits	Use of transgenic rabbits to study human atherosclerosis	[77]
10	WHHL rabbits	Endothelial lipase and HDL metabolism	[78]
11	Obese SHR rats	Metabolic syndrome, non-insulin dependent	[79]
12	Yucatan swine	Diabetic dyslipidemia and LDL	[80]

CF, Carworth Farms; CETP, Cholesteryl ester transfer protein; db/db mouse, diabetic dyslipidemia; HDL, high density lipoprotein; LDL, low density lipoprotein; WHHL, Watanabe Heritable Hyperlipidemic rabbits; SHR, spontaneously hypertensive rats; ZDF, Zucker diabetic fatty rats.

lifestyle which is termed Therapeutic Lifestyle Changes (TLC). This involves one or more of the following:

- a) Reducing total fat intake to 25-35% daily energy low saturated fat diet combined with exercise
- b) Lowering saturated fat intake to 7% daily energy
- c) Reducing cholesterol intake to 200 mg/day
- d) Using nutritional supplementation such as fish oil, bran, and oats combined with exercise

The combination therapies are most effective since exercise and diet can elicit complementary effects on the lipid profile. Diet therapies, with some exceptions, are effective in lowering total TC and LDL concentrations, while exercise interventions increase HDL and decrease TG levels. The synergistic effects of exercise and supplements in lowering LDL, TG and improving HDL have been well demonstrated as a function of age in laboratory rats [53, 54]. Specific interventions, which comprise low saturated fat diets combined with exercise lower TC, LDL-C, and TG concentrations by 7–18, 7–15, and 4 –18 %, respectively, while increasing HDL-C levels by 5–14 %. However, when nutritional supplements are combined with exercise, TC, LDL-C, and TG concentrations decrease by 8–26, 8 –30, and 12–39%, respectively, while increasing HDL-C levels by 2–8% [55]. These findings suggest that combination lifestyle therapies are an efficacious, preliminary means of improving cholesterol levels in those diagnosed with dyslipidemia, and should be implemented in place of drug therapy.

Several publications report on the efficiency of aerobic exercises to improve the lipid profile. The relationship between physical exercise and dyslipidemia control is yet to be clarified. A Meta analysis assessing around 51 studies have indicated no direct relationship between the intensity of exercise and improvement in the lipid profile, *i.e.*, there is no dose response relationship [56]. Other studies have shown that the benefits of physical exercise are primarily on the control of body adiposity and subsequent obesity prevention, which would result in a better lipid profile [57, 58]. In addition, studies on the effects of the amount and intensity of exercise on lipoproteins have shown that the amount of exercise, and not the intensity, promotes beneficial effects on plasma levels of lipoproteins [59, 60]. Hence, the beneficial effect of exercise on a variety of lipid and lipoprotein variables is seen most clearly with the high

amount of high-intensity exercise. These studies corroborate the findings which show that the maintenance of physical activity throughout life (childhood, adolescence and adulthood) promotes the prevention of dyslipidemia and associated diseases.

## DISCUSSION

The progressive escalation of metabolic syndrome has created many health concerns. Lowering LDL cholesterol has been an essential priority in the management of dyslipidemia in patients with type 2 diabetes, more so, in those with or without at risk for CVD. The occurrence of metabolic syndrome is related with an increased incidence of coronary heart disease (CHD) and myocardial infarction in males and females as well. Dyslipidemia is a part of metabolic syndrome since both these terms encompass hypertriglyceridemia (serum triglycerides  $\geq 150$  mg/dl) and a low HDL cholesterol ( $<40$  mg/dl for men and  $<50$  mg/dl for women or HDL-C  $<35$  mg/dl for men and  $<40$  mg/dl for women by WHO). It is now recognized that the abnormalities of lipoprotein metabolism, namely, elevated TG, VLDL and LDL levels, occur together than individually. Clinical studies report that many patients with CVDs are not properly treated for their dyslipidemia disorder, 'Atherogenic Lipid Triad' that is characterized by high serum TG level, low serum HDL level, and high LDL level. All of these can exacerbate increased incidence of diabetes [61]. More importantly, increased insulin resistance results in deficiency of lipoprotein lipase, an enzyme responsible for low clearance of fasting and postprandial triglyceride-rich lipoproteins (TRLs), and decreased production of HDL. All these are major contributors to the CVDs in subjects with type 2 diabetes [62]. If the LDL/HDL ratio is  $>5$ , then increased TG levels is known to confer an additional risk of CHD as analyzed from studies of the Helsinki Heart Study [63]. It is now certain that the base risk prediction of CADs and treatment approaches must be on a complete lipid profile and not by cholesterol or LDL determination. In order to explain the involvement of LDL cholesterol in CHDs, it is pertinent to understand the endothelial events. LDL entry through the endothelium modifies it by stimulating macrophages chemoattractant protein-1 (MCP-1) in order to recruit monocytes and scavenge receptors that take up to form foam cells. The foam cells synthesize growth factors and adherence proteins. HDL is also known to inhibit ox-LDL synthesis, the cytokine-induced expression of adhesion proteins and MCP-1. HDL is also anti-thrombotic and anti-apoptotic. Interestingly, it has been noted and well accepted that a 1% increase

in HDL-cholesterol will result in 1% alleviation in coronary disease events, and even more interesting is the fact that it is irrespective of the LDL-cholesterol level [64].

Considering, the pharmacotherapeutic aspects, using statin monotherapy has proved to be unsuccessful towards achieving the required lipid levels as reported by the ACCORD (The Action to Control Cardiovascular Risk in Diabetes) study. A concomitant outcome of this study on atherogenic dyslipidemia is that fibrates in combination with statins are efficient risk reducers of cardiovascular events [65]. Currently, dyslipidaemia has a high worldwide prevalence, and many patients are turning to alternatives to pharmacotherapy to manage their lipid levels. However, lifestyle modification is considered of utmost priority in all patients to reduce cardiovascular risk and can be initiated before pharmacotherapy in primary prevention of CVD.

One other approach for lowering LDL is through many functional foods and natural health products such as soy protein, green tea, plant sterols, probiotic yogurt, marine-derived omega-3 fatty acids and red yeast for potential lipid-lowering properties [66] although not to the same extent as statins. We shall discuss one such functional food *i.e.* probiotics. Probiotics are "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" as defined by the Expert Panel commissioned in 2001 by the Food and Agriculture Organization of the United Nations, and supported by the World Health Organization [67]. Importantly, probiotics have also been studied for their cholesterol-lowering effects in animal and human studies. A study by Xiao *et al.* [68] has shown that *Bifidobacterium longum* BL1 decreases serum TC, LDL-cholesterol, and TG, and increases HDL-cholesterol in humans. A recent study by Kim *et al.* [69] on experimentally-induced hypercholesterolemia in rats with a combined treatment with probiotic mixtures (PM), two strains belonging to the species *Lactobacillus (L. reuteri and L. plantarum)* and *Bifidobacterium (B. longum, B. lactis, and B. breve)* for eight weeks signifies lowering of TC, LDL and TG but with increases in HDL. PM reduced expressions of cholesterol synthesis-related proteins such as sterol regulatory element-binding protein 1 (SREBP1), fatty acid synthase (FAS), and acetyl-CoA carboxylase (ACC) in the liver were the underlying mechanisms for these modifications.

Additional research is, however, warranted in the use of functional foods, which should incorporate large,

high-quality randomized controlled trials with long follow-up periods to investigate associations with cardiovascular end points inclusive of LDL cholesterol.

## CONCLUSION

To sum up, dyslipidemia represents abnormal levels of lipids transported by lipoproteins in the blood. Hyperliproteinemia/hyperlipidemia refers to abnormal levels of total cholesterol, LDL-the bad-cholesterol, or triglycerides as well as too low HDL-the good cholesterol. This review has attempted to provide a comprehensive report on the importance of the lipid profile, the cause-effect relation between coronary artery diseases and diabetes, the synergistic effects of physical activity and dietary manipulations as non-pharmacological means of regulating lipids. However, additional studies are indeed required to account for the increase in lipoproteins with normal aging, which increases the risk of the mentioned diseases. Overall, the world-wide prevalence of the dyslipidemia-related pathological conditions makes it essential that accurate lipid profiling is crucial in order to classify individuals who are at risk of dyslipidemia-related diseases.

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