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Review Article

HYPERLIPIDEMIA AND ITS TREATMENT: A REVIEW

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ABSTRACT

Hyperlipidemia is a clinical condition characterized by an elevation of lipid profile and/or lipoproteins mainly total cholesterol, triglycerides and low-density lipoproteins along with the diminished level of high-density lipoproteins are recognized to cause hyperlipidemia which is a root cause in the commencement of arteriosclerosis. This elevation of lipoproteins is among the leading threat factors integrated with cardiovascular diseases. Diet has a huge impact on this condition and certain dietary factors and hyperlipidemia are directly correlative. The current attempt has been made to establish an association between recent advancements in the emerging treatment of hyperlipidemia and the manifestation of hyperlipidemia with potential targets to treat hyperlipidemia and also outlined the role of nutraceuticals in treatment of hyperlipidemia.

Keywords: Hyperlipidemia, High-Density Lipoproteins, Low-Density Lipoproteins, Chylomicrons, Cholesterol

1. INTRODUCTION

The hyperlipidemia is traditionally defined as conditions in which the concentration of cholesterol or triglyceride-carrying lipoproteins in plasma exceeds an arbitrary normal limit [1]. It has a remarkable impact on atherosclerosis and considered as one of the main risk factors for cardiovascular diseases [2]. Risk factors include stroke, myocardial infarction, cerebrovascular diseases, coronary heart diseases, heart attack, and the progression of diabetes [3]. Hyperlipidemia also leads to the progression for the development of free radicals in the body which give rise to other pathological diseases. The depletion of anti-oxidants induced by reactive oxygen species is a key factor for the commencement of atherosclerosis and the development of cardiovascular diseases [4]. Hyperlipidemia is a metabolic disorder occurring in serum lipid and lipoproteins profile due to quantitative increase in the net level of low density lipoprotein cholesterol (LDL-C), Very low density lipoproteins (VLDL-C), Total cholesterol (TC), Triglycerides (TAG) with a collateral decrease in the concentrations of high density lipoproteins in the blood circulation [5]. The high-density lipoprotein is a major protective factor that helps in obliterating cholesterol from the arterial wall. The ratio of high-density lipoprotein and total cholesterol is a prevalent way to assess the atherogenicity index; a Ratio of more than 4.5 is atherogenic [6]. Free radicals attack and induce oxidative damage to various biomolecules including proteins, lipids, lipoproteins, and DNA [7, 8]. Some natural anti-oxidants like catalase, superperoxide dismutase, Glutathione peroxidase, Heme-oxygenase act as radical scavengers constitute the repair systems for biomolecules damaged by the attack of free radicals [9]. In many cases, hyperlipidemia is caused by the over-ingestion of a diet rich in cholesterol, alcohol attention is also being paid to treat the patients with hyperlipidemia using strict dietary management and appropriate excerise [10]. The main aim of treatment in patients with hyperlipidemia is to reduce the risk of developing ischemic heart disease or the occurrence of further cardiovascular or cerebrovascular diseases [11]. Hyperlipidemia relates to increased oxidative stress causing significant production of oxygen free radicals, which may lead to oxidative modifications in low-density lipoproteins [12].

2. CLASSIFICATION OF LIPOPROTEINS [13]

- ***Chylomicrons:*** Large particles that carry dietary fat (mainly TG) from the intestine to the liver
- ***Very low density lipoprotein (VLDL)***: Carries endogenous TG synthesized in the liver to the tissues
- ***Low density lipoprotein (LDL)***: Formed from intermediate density lipoprotein (IDL) by hepatic lipase It carries cholesterol from liver to tissues

- ***High density lipoprotein (HDL)***: Carries cholesterol from tissues to liver.

Table 1: Risk Factors for Hyperlipidemia [14]

Exogenous	Corticosteroids, anabolic steroids, isotretinoin, thiazide diuretics anticonvulsants, beta blockers, estrogen, anti-retrovirals, Alcohol, obesity, ketogenic diets
Endocrine	Hypothyrodism, Cushing syndrome, Hypopituitarism, Diabetes mellitus, Lipodystrophy
Storage diseases	Glycogen storage diseases, Gaucher disease, Cystine storage, Tay-Sachs disease, Neumann-Pick disease, Acute intermittent porphyria
Gastrointestinal	Cholestasis, Hepatitis, Cirrhosis, Pancreatitis
Renal	Nephrotic syndrome, Renal failure, Hemolytic uremic syndrome, Anorexia nervosa
other factors	Malnutrition, Anorexia nervosa, Idiopathic hypercalcemia, Progeria, Systemic lupus erythematous

3. CLASSIFICATION OF LIPOPROTEINS [15, 16]

LDL Cholesterol - <100 Optimal, 100-129 Near optimal/above optimal, 130-159 - Borderline high, 160-189 – High, ≥ 190 - Very High.

Total Cholesterol <200-Desirable, 200-239- Boderline high, ≥240 – High.

HDL Cholesterol <40 – Low, ≥60 – High.

Triglycerides<150 Normal, 150-199 Boderline high, 200-499High, ≥500 Very High.

4. DIABETIC DYSLIPIDEMIA [17]

This concept states that increases in glucose concentration due to defects in insulin action lead to a remarkable increased net amount of lipoproteins in blood circulation. The Diabetic Dyslipidemia has been used to narrate the pathophysiology surrounding the effects of insulin resistance on abnormal lipid levels. Glucose intolerance develops due to the subsequent increase in lipids, which adds to the advancement of atherosclerosis and cardiovascular diseases. Even the marginal increase in lipoproteins levels in diabetic patients are correlated with a substantial increase in cardiovascular diseases, Hyperlipidemia affects diabetic patients to a greater extent than a non-diabetic patient or a general population. Very few studies to date have studied the direct relationship between changing levels of insulin resistance and dyslipidemias in a clinical setting.

5. MANAGEMENTS OF HYPERLIPIDEMIA [18]

The major treatment used for hyperlipidemia divided into three parts as given below. The main aim of the therapy is to reduce the level of LDL cholesterol levels

- ***Dietary control (Non-Pharmacological therapy):*** This part emphasizes to control the intake of food rich in saturated fat and cholesterol. Focus on supplementation of a diet rich in omega-3-fatty acid that helps to lower triglycerides also includes fiber-rich foods, fruits, and vegetables
- ***Lifestyle change:*** This part includes emphasizing on physical activities like daily exercises, since regular exercises will lead to an improvement in controlling lipoprotein concentration in blood circulation i.e., daily walking will reduce triglyceride level by an average of 10 mg/dL and elevation within HDL level by 5 mg/dL.

6. MEDICAL TREATMENTS

6.1. HMG-COA reductase inhibitors (statins) (first-line treatment for elevated LDL levels)

Drugs:Atorvastatin, Lovastatin, Simvastatin, Pravastatin, Rosuvastatin, Fluvastatin [19].

Statins inhibit the major enzyme required for the biosynthesis of cholesterol, the rate-limiting step in de novo cholesterol biosynthesis. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductases, interrupting the conversion of HMG-CoA to mevalonate, this, in turn, diminish synthesis of LDL. This triggers the catabolism of Low-Density Lipoproteins negotiated through LDL receptors appear to be the pivotal mechanisms for antihyperlipidemic effects [20] Constipation occurs in fewer than 10% of patients taking statins. Further, elevation in serum aminotransferase levels), creatine kinase levels, myopathy, and rarely rhabdomyolysis also occur [21].

6.2. Bile acid resins (Cholestyramine, Colestipol)

The bile acid sequestrants are class of ion exchange resins, they exchange the ion with that of bile acids [15] that bind to certain constituents of bile in the gastrointestinal tract. Namely taurocholic acid glycocholic acid and taurochenodeoxycholic acid glycochenodeoxycholic acid are bile salts. They interrupt the enterohepatic circulation of bile acids by confiscating them, thereby preventing their re-absorption from the

gut. This increases the catabolism of plasma lipoproteins via the number of LDL receptors increases on the hepatic cell membrane thereby reduces LDL levels in blood circulation [22]. Adverse effects include- nausea, bloating, cramping, and an increase in liver enzymes. Flatulence is most commonly reported. Other potential adverse effects include impaired absorption of fat-soluble vitamins A, D, E, and K; hypernatremia and hyperchloremia; gastrointestinal obstruction [22].

6.3. Fibric acid derivatives (Clofibrate, Fenofibrate, Gemfibrozil, Benzafibrate, Ciprofibrate)

The plasma HDL-C concentration raised by approximately 20% in the presence of fibrates and plasma triglyceride levels can be reduced up to 50% by fibrates class of drugs [23]. The principal mechanism of action of fibrates is the modulation of the activity of peroxisome proliferator-activated receptor-α (PPAR-α) in the liver [24] which results in increased β-oxidation of fatty acid in the liver, increased activity of lipoprotein lipase and decreased secretion of hepatic triglyceride. Thus the net increase is in HDL, VLDL clearance, clearance of remnant particles [15]. Adverse effects include- Gastrointestinal grumblings happen in 3% to 5% of patients, rash in 2%, unsteadiness in 2.4%, and transient rises in transaminase levels and alkaline phosphatase in 4.5% and 1.3%, respectively. Clofibrate and, less usually, gemfibrozil may upgrade the arrangement of gallstones. A myositis disorder of myalgia, malaise, stiffness and rise in creatine kinase and aspartate aminotransferase may occur and conditions are more common in renal insufficiency patients [22].

6.4. Niacin (Nicotinic acid)

Hepatic synthesis of VLDL is reduced by Niacin (nicotinic acid). Decreased LDL cholesterol significantly reduces the catabolism of HDL and increases (HDL) and it's effective plasma concentration [25]. Older clinical trials suggested a reduction in cardiovascular events related to niacin treatment [26]. Niacin is first-line agent or alternative for the treatment of hypertriglyceridemia and diabetic dyslipidemia. However, niacin frequently causes light-headedness, cutaneous flushing, or pruritus [27].

6.5. Ezetimibe and colesevelam

Ezetimibe is used as combinational therapy with statins and other drugs, also as monotherapy. Ezetimibe meddles with the assimilation of cholesterol from the brush border of the intestine, a novel mechanism that settles on it a decent decision for adjunctive treatment [28]. A combination of fenofibrate and ezetimibe was recently shown to be safe and effective for patients with elevated triglyceride and LDL-C levels. Adverse effect include gastrointestinal upset [29].

7. EMERGING TREATMENTS

Glitazar drugs-Glitazar medications are dual agonists of peroxisome proliferator-activated receptor-like fibrates and thiazolidinediones also, hold hypothetical favorable circumstances for the treatment of type-2 diabetes and metabolic disorder. Anyway, an examination of clinical trial phase 2 and 3 preliminaries found noteworthy affiliations among muraglitazar and death, myocardial infarction and stroke. This agent and others of the class have been introverted from clinical use [30].

Rimonabant- These classes of drug act by inhibiting appetite, thereby reduces the appealing to food intake through cannabinoid-1 receptor antagonists [31, 32]. Clinical trial reports on this drug by Four phase-3 randomized, double-blind, placebo-controlled trials show successful, persistent reductions in obesity variables in the treatment groups, with concurrent improvements in triglycerides including metabolic biomarker [33]. However, adverse effects were also more common in those groups which include depression and anxiety. Nevertheless, rimonabant accounts to be a promising new treatment for obesity and dyslipidemia.

LPL (lipoprotein lipase) gene therapy- Lipoprotein lipase deficiency causes Type I hyperlipoproteinemia resulting in elevated chylomicrons [34]. Gene therapy, however, may help treat monogenic lipoprotein lipase deficiency [35], Since, lipoprotein lipase can be focused on skeletal muscle unobtrusive increment inactivity would then significantly diminish plasma triglyceride levels. Utilizing an advantageous allele of LPL gene therapy has remedied raised triglyceride levels in animals, which paves for preliminaries for trials involving people [36].

7.1. Immunotherapeutics approaches

Heat Shock proteins: In atherosclerosis induced immune response the autoantibody to heat shock proteins is one of the elements in the pathogenesis of atherosclerosis. These atherosclerotic lesion formation is inhibited in LDL-receptor-deficient mice by Repeated mucosal administration of Mycobacterium HSP60/65, both orally and nasally [37-39].

Lipid-based vaccines: Inhibition of atherosclerotic lesion formation is a principle role of this therapeutic approach [40].

Based on Epitopes of oxidized LDL: The oxidized LDL possess different epitopes that serve as an effective tool in the modulation of the immune response mediated by OxLDL. These epitopes of oxidized LDL are responsible for atherogenic induced immune response. Most of the studies concluded that this therapeutic approach reduces atherosclerosis [41].

7.2. New potential targets and treatments

7.2.1. Acyl-CoA cholesterol acyltransferaseinhibitors (ACAT)

ACAT has two isoforms ACAT1 and ACAT2. This class of enzymes plays an important role in catalyzing the conversion of cholesterol into cholesteryl esters. Thereby prevents the toxic accumulation of surplus cholesterol in a cell. ACAT1 contributes to the development, by foam cell formation that is the oxidized LDL attracts monocytes that are transformed into foam cell in the arterial wall and the development of atherosclerosis, so ACAT-1 inhibitors may have antiatherogenic effect and ACAT-2 inhibitor may play an important role in reducing cholesterol absorption in the intestine [42]. Furthermore, the significance of ACAT emerges from its significant job in the congregation along with the secretion` of apolipoprotein B containing lipoproteins in the liver and intestines [43]. Some of the potent ACAT inhibitors which are currently in clinical development belong to the class of naphthoquinone derivatives [44]. Avasimibe and Eflucimibe decrease the plasma cholesterol level and slow the progression and development of atherosclerosis by inhibiting (ACAT) Acyl-CoA cholesterol acyltransferase [45].

7.2.2. Microsomal triglyceride transfer protein (MTP) inhibitors

Microsomal triglyceride protein is an essential protein in the assembly of apo B containing lipoproteins. Microsomal triglyceride protein (MTP) catalyzes the transfer of neutrallipids, triglycerides and cholesterol esters between the membrane of the intestinal mucosa and lumen of microsomes isolated from the liver also called as lipid transfer protein. Now it is known that MTP has a prominent role in the biosynthesis of glycolipid presenting molecules and the regulation of cholesterol ester biosynthesis [46]. This approach of inhibiting MTP might be useful for reducing the atherogenic lipoprotein levels thereby significantly reduces blood lipoproteins such as plasma triglycerides, LDL, and VLDL cholesterol. *In vitro* and *in vivo* model was implicated to evaluate a series of newly synthesized phosphonate esters for their effects on MTP activity and they found to exhibit potent inhibition of MTP both *in vitro* and *in vivo* model. Data also suggest the potency of lomitapide (AEGR-733, formerly BMS-201038), a novel drug for hypercholesterolemia as MTP inhibitors [47].

7.2.3. Acyl coenzyme A: diacylglycerol acyltransferase (DGAT)

Diacyl glycerol acyltransferase (DGAT**)** is a key enzyme in triglyceride biosynthesis which belongs to the class of microsomal enzyme that catalyzes the addition of Acyl CoA to 1,2-diacylglycerol which is a final step in triglyceride biosynthesis. These two isoforms of DGAT found to be DGAT-1 and DGAT-2. The inhibition of DGAT1 is a good target in the treatment of hyperlipidemia as shown by several studies. *In vitro* studies have shown that a two weeks treatment with compound T863 decreased serum and liver triglycerides, and decreased serum cholesterol in mice. The compound T863 is a potent inhibitor for DGAT [48].

7.2.4. Squalene Synthase Inhibitors

Squalene synthase (SqS) is the first committed step in sterol synthesis, the enzyme catalyzes farnesyl pyrophosphate to form squalene, and one of these sterols includes cholesterol. Squalene synthase inhibitors have a promising role in drug discovery as a lead compound in the development of potential agents to treat hyperlipoproteinemia. It has been reported that after oral administration of BMS-188,494, a potential inhibitor of SqS, was found to reduce plasma levels of cholesterol in experimental rats [49].

7.2.5. Cholesteryl ester transfer protein (CETP) inhibitors

CETP involved in proatherogenic activity by initiating reverse cholesterol transport. In the liver, it mediates the transfer of cholesteryl ester to proatherogenic apolipoprotein B containing lipoproteins such as VLDL, LDL from anti-atherogenic HDLs. Furthermore, most studies showed that there is evidence that inhibition of CETP decelerate the progression of atherosclerosis [50]. Dalcetrapib and anacetrapib are found to be a novel class of compounds in Phase III of clinical trials. Dalcetrapib raised HDL cholesterol levels by 31% without

influencing LDL Levels and reduced CETP activity by 50% [51].

7.2.6. Role of Nutraceuticals in treatment of hyperlipidemia

Nutraceutical, is a term coined in 1989 by Stephen DeFelice, and combination of 'nutrient' (a nourishing food or food component) with 'pharmaceutical' (a medical drug), and indicates that these products have a potential application in pathological conditions, and hence should be treated in a similar way to pharmaceuticals [52]. They are 'a food or part of a food that provides medical or health benefits, including the prevention and/or treatment of disease' [53], The probability of executing a non-pharmacological nutraceutical based treatment for hyperlipidemia is getting expanding consideration and is considered to be an important [54].

Polyphenols - Polyphenols are well known for their anti-oxidant properties possessing multiple phenolic groups that are widely distributed in plant origin. Various plants are rich in polyphenols exhibiting medicinal properties; these constituents are rich in green tea, grapes, olives, fruits, and vegetables. It has been postulated to inhibit HMG-CoA reductase, as well as acetyl-CoA acetyltransferase and microsomal triacylglycerol transport protein, justifying their hypocholesterolemic effect [55].

Flavonoids-Flavonoids and are found in fruit, vegetables, grains, bark, roots, stems, flowers, tea and belong to a group of natural substances with variable phenolic structures. Flavonoids were isolated as the effective compounds. More than 4000 varieties of flavonoids have been identified, some Main groups of flavonoids are Flavones, Flavanones, Catechins, Anthocyanins. Flavonoids are likely to have a major influence on the vascular system, because of their antioxidative properties. Oxygen radicals promote the atherosclerotic changes by oxidizing LDL, which injures the endothelial wall contributing to hyperlipidemia. The activity may be due to the presence of polyphenolic compounds flavonoids, tannins and proanthocyanidines in the ethanol extracts, which reduce oxidation of LDL-c [56].

8. CONCLUSION

Hyperlipidemia is a clinical condition characterized by an elevation of lipid profile and/or lipoproteins, mainly total cholesterol, triglycerides and low-density lipoproteins along with the diminished level of high-density lipoproteins are recognized to cause hyperlipidemia which is the main root cause of cardiovascular, cerebrovascular diseases. Condition of hyperlipidemia can be treated with pharmacological treatments with recent advancements in the prevention of hyperlipidemia and considering the side effects that are associated with drugs. Several studies have been examined on the natural crude drugs which are rich in medicinal active constituents such as flavonoids, polyphenols was found to possess antioxidant and anti-hyperlipidemic activity.

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