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Review article

Therapeutic approaches to drug targets in hyperlipidemia

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ABSTRACT

Hyperlipidemia is a metabolic syndrome characterized by diverse lipid profiles (e.g. hypercholesterolemia, hypertriglyceridemia, and familial combined hyperlipidemia) and may have significant adverse effects on health (e.g. atherosclerosis, cardiovascular diseases, diabetes, insulin resistance, obesity). Both genetic and environmental components are associated with hyperlipidemia sub-types. Effective drugs targeting hyperlipidemia sub-types are thus required. In the present review, we mainly focus on types of hyperlipidemia, digestion, and absorption of lipids as well as on their consequences on human health and on potential effective drug targets against hyperlipidemia. Omega-3 fatty acids have favorable effect on reducing postprandial triglyceride levels and will be beneficial if combined with statins.

1. Introduction

Hyperlipidemia is a heterogeneous disorder commonly characterized by an increased flux of free fatty acids (FFAs), raised triglycerides (TGs), low-density lipoprotein-cholesterol (LDL-c) (aka "bad cholesterol") and apolipoprotein B (apoB) levels, as well as by a reduced plasma high-density lipoprotein (HDL)-cholesterol concentration (aka "good cholesterol"), because of metabolic effects, or dietary and lifestyle habits [1]. The lipid abnormality in hyperlipidemia is an increase in circulating (nonesterified) FFAs originating from adipose tissue, and an inadequate esterification and FFA metabolism [2]. The reduced retention of fatty acids (FAs) by adipose tissue leads to an increased flux of FFA returning to the liver, which stimulates hepatic TG synthesis, promoting the production of apoB and the assembly and secretion of very low-density lipoprotein (VLDL). When plasma TG concentration subsequently increased, TG-rich HDL particles are formed and undergo catabolism. Elevated VLDL particles are lysed and hence fail to bind efficiently to LDL receptors, while the exchange of cholesterol esters with TGs forms TG-rich lipoproteins, resulting in formation of small dense LDL-c particles [3,4]. A strong association exists between elevated LDL-c levels and increased incidence of coronary artery disease [5]. The development of atherosclerotic plaques is associated with elevated levels of LDL-c, reduced receptor-mediated clearance, increased arterial wall retention and an increased susceptibility [6]. Cardiovascular risk factors such as hyperlipidemia,

Abbreviations: ACAT, Acyl-Co A: cholesterol acyltransferase; AMPK, AMP-activated protein kinase; apoB, Apolipoprotein B; ATP III, adult Treatment Panel III; CETP, cholesteryl ester transfer protein; CM, chylomicrons; DGAT, diacylglycerol acyltransferase; FCH, familial combined hyperlipidemia; FFA, free fatty acid; HC, hypercholesterolemia; HDL, high-density lipoprotein; HTG, hypertriglyceridemia; LDL, low density lipoprotein; NCEP, National Cholesterol Education Program; PPAR, peroxisome proliferator-activated receptors; TG, triglyceride; VLDL, very low density lipoprotein.

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hypertension, and thrombosis contribute to the underlying mechanisms of atherosclerotic disease, promoting endothelial dysfunction, oxidative stress, and proinflammatory pathways to peroxidation [4,6]. Lipid guidelines from the National Heart Foundation of Australia place great emphasis on LDL-c and HDL-c as atherogenic and antiatherogenic components, respectively. Indeed, high LDL-cholesterolemia is considered as one of the major modifiable risk factors for coronary heart disease, which continues to be the leading cause of death and morbidity in the United States [7]. Conversely to the Australian lipid guidelines, the Adult Treatment Panel III (ATP III) guidelines of the US National Cholesterol Education Program (NCEP) place greater emphasis on TG levels [4,8]. According to the National Health and Nutrition Examination Survey III, 24% of individuals aged >20 years had metabolic syndrome [9]. Metabolic syndrome is characterized by the coexistence of hyperinsulinemia, obesity, dyslipidemia, and hypertension. Dyslipidemia, the hallmark of the metabolic syndrome, is summarized by: (1) increased flux of FFAs; (2) raised TG values; (3) low HDL-c values; (4) increased of LDL-c values; and (5) raised apoB values [10]. Dyslipidemia is an independent risk factor for cardiovascular disease [11]. Low HDL-c and hypertriglyceridemia (HTG) have been found to be independently and significantly related to myocardial infarction/stroke in patients with metabolic syndrome [12]. The combination of high fasting glucose and low HDL-c were shown to have primary predictive ability for coronary heart disease [13]. Dyslipidemia may be caused by a combination of overproduction of VLDL, apoB-100, decreased catabolism of apoB containing particles, and increased catabolism of HDL-apoA-I particles. Insulin resistance may be the consequence of this abnormality [1]. Dyslipidemia may arise from genetic components (e.g. mutated LDL receptors, mutated apoB-100, mutated proprotein convertase subtilisin/kexintype-9) [14], with or without environmental component (e.g. improper diet, familial history of hypercholesterolemia, hyperlipidemia, and/or hypertriglyceridemia) [15]. Causes of secondary hyperlipidemia include diabetes, hypothyroidism, obstructive liver disease, chronic renal failure, and drugs that increase LDL cholesterol and decrease HDL cholesterol, such as progestine and corticosteroids [16].

2. Digestion and absorption of lipids

Lipid digestion begins in the oral cavity by the use of lingual lipase, an enzyme secreted by lingual gland in the tongue, and continues in the stomach with the both lingual and gastric enzymes. Lipids undergo emulsification in the stomach under the influence of peristalsis. Fine lipid droplets enter the duodenum, where they mix with bile and pancreatic juice to undergo marked changes in physical and chemical form. For absorption across the intestinal walls, hydrolysis and micellization take place in duodenum [17,18]. Diacylglycerol and FFAs are the major digestion products of this gastric phase, and facilitate the intestinal phase of digestion acting as emulsifying agents [19]. Pancreatic lipase cleaves the TG, yielding 2-monoglycerides (2-MGs) and FFAs. Pancreatic cholesterol esters hydrolase completely hydrolyzes cholesterol esters into FFAs and free cholesterol [20]. Dietary phospholipids are hydrolyzed by activated pancreatic phospholipase A2, yielding 1-lysophospholipids and FFAs [21]. FFAs and 2-MGs enter into bile micelles, which helps polar lipids to go through the unstirred water layer and reach the microvillous membrane where they are absorbed. Absorbed lipids are re-esterified to newly form TGs and in the smooth endoplasmic reticulum (ER). TGs can be synthesized via 2-MG or via 3-glycerol-phosphate. TGs, phospholipids, cholesterol, and apoproteins are used to synthesize chylomicrons (CMs), which are secreted to the lymph, and then to the blood stream through the thoracic duct. In the peripheral tissues, they are cleaved by lipoprotein lipase losing TG and giving CM remnants, which are taken up by the liver [21–23].

3. Hyperlipidemia profiles/sub-types

The classification of hyperlipidemia according to WHO is in Table 1 [17] and the constitution, composition and role of lipids in Table 2 [23].

3.1. *HTG*

Plasma TGs represent an important mechanism of whole body fatty acid delivery for tissue utilization or storage [23,24]. HTG is defined as an abnormally high concentration of TG in the blood. According to the NCEP ATP III guidelines, a normal TG level is <150 mg/dL [17]. In the United States, the prevalence of HTG, defined as a TG level >150 mg/dL, is 30%.

HTG is a risk factor for pancreatitis and it accounts for 1% to 4% of cases of acute pancreatitis [25]. HTG may be primary or secondary in nature. Primary HTG is the result of various genetic defects while the secondary causes are high fat diet, obesity, diabetes, hypothyroidism, and certain medications [26].

4. Patterns of HTG

Familial HTG is commonly seen in clinical practice and can have various lipid patterns [27].

4.1. *Hyperlipoproteinemia*

Most commonly, patients demonstrate type IV hyperlipoproteinemia, which includes elevated TG levels (250–500 mg/dL) and elevated VLDL levels that transport them, whereas normal LDL-c and apoB levels are observed [28].

4.2. *Chylomicronemia syndrome*

Familial chylomicronemia syndrome is a rare disorder of lipoprotein metabolism due to familial lipoprotein lipase (LPL) or apolipoprotein C-II deficiency or the presence of inhibitors to lipoprotein lipase [29]. The chylomicronemia syndrome is a disorder characterized by severe HTG and massive accumulation of CMs in plasma [30]. Finally, HTG may contribute to additional pathologic processes associated with metabolic syndrome and cardiovascular risk, including increased

Table 1 – World Health Organization (modified Fredrickson) classification of hyperlipidemias [17].

Type	Total cholesterol	LDL cholesterol	Plasma TGs	Lipoprotein abnormality	Primary causes	Secondary causes
I	Elevated	Low or normal	Elevated	Excess chylomicrons	Lipoprotein lipase deficiency, apoC-II deficiency	Systemic lupus erythematosus
II a	Elevated or normal	Elevated	Normal	Excess LDL	Familial hypercholesterolemia	Hypothyroidism
II b	Elevated	Elevated	Elevated	Excess LDL and VLDL	Familial combined hyperlipidemia	Nephrotic syndrome, diabetes, anorexia nervosa
III	Elevated	Low or normal	Elevated	Excess chylomicron remnants and Intermediate density lipoproteins	Familial type III Hyperlipoproteinemia	Hypothyroidis diabetes, obesity
IV	Elevated or normal	Normal	Elevated	Excess VLDL	Familial combined hyperlipidemia, Familial Hypertriglyceridemia	Diabetes, chronic renal diseases
V	Elevated	Normal	Elevated	Excess chylomicrons and VLDL	Familial hypertriglyceridemia, apoC-II deficiency	Alcohol, diuretics, β blockers, oral

apoC-II = apolipoprotein-C II; LDL = low-density lipoprotein; TG = triglyceride; VLDL = very low-density lipoprotein.

coagulability, impaired fibrinolysis, impaired endothelial function, and increased inflammation, although this remains uncertain [27,28,31].

4.3. HC

HC is one of the major causes of atherosclerosis and characterized by elevation of total cholesterol and usually normal levels of TG [32,33]. The population is considered to be unhealthy when its plasma concentration exceeds 5 mM and the incidence of CHD is usually low where plasma cholesterol concentration is low [34]. HC usually results from nutritional factors such as obesity and diet high in saturated fats along with genetic causes. The deficiency of adaptor protein Dab 2, or the clathrin coat adaptor AP-2 also leads to HC [32,35]. Patients with HC have plasma TG concentration of >10 mM owing to increase in both CMs and VLDL and, in such patients, plasma shows milky appearance [32]. Familial HC comprises a group of genetic disorders characterized by elevated plasma concentrations of LDL-c and premature cardiovascular disease due to a defective (mainly hepatic) metabolism of LDL [36]. Major genetic backgrounds of familial HC include loss-of-function mutations in the genes of LDL receptor, its ligand apoB or, gain-of-function mutations in the facilitator gene for hepatic LDL recepor degradation, the proprotein convertase subtilisin/kexin type-9 [35,37]. LDL receptors are predominantly found on hepatocytes and steroid hormone producing cells and are responsible for removal of cholesterol carrying LDL from plasma by a process of receptor-mediated endocytosis. The most important feature of untreated familial HC is the development of premature and extensive atherosclerosis leading to coronary artery diseases [38].

4.4. *Familial combined hyperlipidemia*

Familial combined hyperlipidemia (FCH) is the most common genetic hyperlipidemia in man and affects up to 5% of the general population [39]. HC, HTG, and elevated levels of apoB are the characteristics of FCH [40]. Other phenotypes of FCH are elevated levels of both LDL-c and VLDL, the presence of small dense LDL, and decreased levels of HDL-c. In addition, FCH is associated with obesity and insulin resistance [41,42]. Obesity results in an increase in number and size of adipocytes, which secrete leptin, a hormone involved in the regulation of the energy expenditure and appetite via hypothalamic receptors [43,44]. Both obesity and insulin

Table 2 – The constitution, composition, and role of lipids [23].

Constituent	Composition	Effect/role
Lipoproteins Chylomicrons	95% TG and 5% cholesterol	Mobilize dietary lipids, deliver dietary triglycerides to adipose tissues, muscles and dietary cholesterol to liver
VLDL	80% TG and 20% cholesterol	Transport triglycerols to extra hepatic tissues
IDL	50% TG and 50% cholesterol	They are either converted to LDL or taken up by the liver
LDL	10% TG and 90% cholesterol	Principal plasma carriers of cholesterol for delivering to peripheral tissues
HDL	5% TG and 95% cholesterol	The apolipoprotein-E in HDLs leads to an increase uptake of cholesterol and its catabolism by the liver to lower the levels of intracellular cholesterol

HDL = high-density lipoprotein; IDL = intermediate-density lipoprotein; LDL = low-density lipoprotein; TG = triglyceride; VLDL = very low-density lipoprotein.

resistance are characteristics of FCH, and therefore, it is likely that leptin is elevated in people with FCH [45]. Recently, in a large observational study, the calculated plasma non-HDL-c concentration was a stronger predictor of cardiovascular events than plasma cholesterol alone [46,47]. Partially lipolyzed TRL remnants (i.e. remnant-like particle cholesterol) are considered to be more atherogenic than larger newly secreted TRL because they can more readily penetrate the endothelial lining of the arterial wall [48]. In the metabolic syndrome, elevated levels of remnant-like particle cholesterol were a risk factor for cardiovascular disease and endothelial dysfunction, a predictor of coronary events [39,49]. FCH might be the result of a combination of an increased production of VLDL particles together with disturbances in their lipoprotein catabolism, such as a decreased LPL-activity [41]. The resulting partially hydrolyzed TG-rich remnant particles are more atherogenic than larger (newly-secreted) TG-rich lipoprotein particles, since the particles are smaller and thereby able to penetrate the endothelial barrier more easily [48,50]. A striking feature of FCHL is the presence of small and dense LDL particles, possibly consequent to hepatic overproduction of apoB [51–53]. Nondenaturing polyacrylamide gradient gel electrophoresis, which separates lipoprotein particles according to their size, has shown that the majority of the population can be characterized into two distinct, genetically determined, LDL subclass phenotypes [48]. Phenotype A is the most common phenotype and is found in individuals with a predominance of large LDL particles, whereas those with a predominance of small LDL particles have phenotype B [54]. Phenotype B often coexists with other lipoprotein abnormalities, notably raised plasma TGs and low HDL-c, in a condition that has been called 'atherogenic lipoprotein phenotype' [55]. Several regions on chromosomes including 2p, 6q, 8p, 9p, 10p, 11p, 16q, 19q, and 21q, have been reported to be associated with FCH [56]. The association of upstream stimulatory factor 1 with FCH however, was strongest in males with increased levels of TGs [57].

5. Current drug targets against hyperlipidemia

Conventional therapy for hyperlipidemia is as listed in Table 3 [28,58–62].

5.1. *Activators of peroxisome proliferator-activated receptor*

The peroxisome proliferator-activated receptors (PPARs) are members of the nuclear receptor superfamily that function as fatty acid-activated transcription factors [63]. PPARs are regulators of numerous metabolic pathways; hence there is huge increase in the development and use of agonists of these receptors as therapeutics for diabetes, dyslipidemia, and atherosclerosis [64]. Three different PPAR genes (α, β/δ, and γ) have been identified, each isotype displaying distinct patterns of tissues distribution and specific pharmacological activators, performing their distinct functions in different cell types [65]. PPARα is mostly expressed in the tissues involved in lipid oxidation, such as liver, kidney, skeletal, cardiac muscle, and adrenal glands. PPARα potentiates FAs oxidation in the liver, heart, kidney, and skeletal muscle. Activation of PPARα leads to an increase in expression of lipoprotein lipase and apoA-V and to a decrease in hepatic apoC-III. These actions lower plasma TGs in chylomicrons and VLDL particles, thus liberating FAs, which are taken up and stored as fat in adipocytes or metabolized in skeletal muscle [66]. In addition, PPARα activation increases hepatic apoA-I and -II expression, which raises HDL cholesterol levels, and promotes HDL-mediated cholesterol efflux from macrophages by inducing ATP-binding cassette A1 transporter [67]. PPARγ is expressed in adipose tissue, macrophages, and vascular smooth muscles, while PPARδ is mainly expressed in skeletal muscle and adipose tissues [68]. PPARβ/δ is best known for its role in skin homeostasis, and has recently been shown to play a role in HDL metabolism [64]. A combination of PPARα and PPARγ agonists would be expected to achieve beneficial effects on restoring metabolic disorders. Hence, a number of PPARα/γ dual agonists have been designed and developed. However, recently identified PPARα/γ dual agonists were ineffective because of undesirable side effects during preclinical or clinical trials. For example, muraglitazar, a synthetic PPARα/γ dual agonist, was aborted during clinical trials because of increased mortality, fluid retention, edema, and cancer [69]. PPARα regulates genes involved in FA uptake, β-oxidation, and ω-oxidation and down-regulates apolipoprotein C-III, a protein that inhibits TG hydrolysis by lipoprotein lipase, and it also regulates genes involved in reverse cholesterol transport, such as apolipoprotein A-I and A-II [68]. PPARα and PPARγ are the molecular targets of number of marketed drugs such as fibrates, the activator of PPAR α and the thiazolidinediones, the activators of PPAR γ [59].

5.2. *Cholesteryl ester transfer protein inhibitors*

Cholesteryl ester transfer protein (CETP) is a plasma glycoprotein that facilitates the movement of cholesteryl esters and triglycerides between the various lipoproteins in the blood by mediating the transfer of cholesteryl esters from the cardioprotective HDL-c to the proatherogenic LDL-c and VLDL-c [70]. Thus, the movement of cholesteryl esters from HDL-c to LDL-c by CETP has the overall undesirable effect of lowering HDL-c. It therefore follows that inhibition of CETP should lead to elevation of plasma HDL-c and lowering of plasma LDL-c, thereby providing a therapeutically beneficial plasma lipid profile [71]. Elevation in HDL levels is equally favored by diminished CETP-mediated transfer of CE and HDL to atherogenic acceptor lipoproteins (i.e. VLDL, LDL). Elevated CETP activity is a major player whose action underlies the atherogenic particle profile of both LDL and HDL in Type II diabetes [72]. Inhibition of CETP, a key protein involved in reverse cholesterol transport, can consequently lead to increases in HDL-c levels and thus, is under evaluation as an anti-atherogenic strategy. To date, anacetrapib demonstrates the greatest HDL-c raising and LDL-c lowering potential [73]. There are three CETP inhibitors that have been used in clinical trials. Torcetrapib was the first to go into human trials but was discontinued in Phase III because of excessive rates of mortality in the ILLUMINATE (investigation of lipid level

Table 3 – Pharmacotherapy of hyperlipidemia [28,58–62].

Drugs	Mechanism of action	Use	Effect on lipoproteins	Adverse effects
Statins Lovastatin (20–80 mg) Pravastatin (20–40 mg) Simvastatin (20–80 mg) Atorvastatin (10–80 mg) Fluvastatin (20–80 mg)	By inhibiting conversion of 3-hydroxy-3-methylglutaryl-coenzyme A-CoA to mevalonate.	Type IIa	LDL decreases 18–55% HDL increases 5–15% TG decreases 7–30%	SGOT, SGPT, Myositis, Lens opacity, Myopathy, Headache GI complaints, Increase liver enzymes Rhabdomyolysis Impaired cognitive function
Bile acid sequestrants Cholestyramine (4–16 g) Colestipol (5–20 g) Colesevelam (2.6–3.8 g)	By interrupting enterohepatic recycling of bile acids. FXR mediated CYP7A repression	Type IIa	LDL decreases 15–30% HDL increases 3–5% TG no change or increases	Constipation and bloating, Hemorrhoidal bleeding Dry flaking skin Gallstone Myopathy Flatulence
Fibric acid derivatives Gemfibrosil (600 mg) Fenofibrate (200 mg) Clofibrate (1000 mg)	Increase lipolysis of triglycerides via lipoprotein lipase. Act as agonist for PPAR-α, resulting in increased expression of lipoprotein lipase and inhibition of apolipoprotein-C-III gene transcription	Types III and IV	LDL decreases 5–20% HDL increases 10–20% TG decreases 20–50%	SGOT, SGPT, Myositis Gallstone Arrythmias
Nicotinic acid Immediate release (1.5–3 g) Extended release (1–2 g) Sustained release (1–2 g)	By decreasing flux of FFA to the liver. Through Gi coupled receptor (GPR109A, PUMA-G, HM74) By noncompetitive blocking of DGAT2	Types IIa and IV	LDL decreases 5–25% HDL increases 15–35% TG decreases 20–50%	Flushing SGOT, SGPT Tachycardia Pruritus Glucose intolerance Hyperuricemia Nausea Diarrhea Hepatotoxicity

DGAT = diacylglycerol acyltransferase; FFA = free fatty acid; HDL = high-density lipoprotein; LDL = low-density lipoprotein; PPAR = peroxisome proliferator-activated receptor; SGOT = serum glutamic oxaloacetic transaminase; SGPT = serum glutamic pyruvate transaminase; TG = triglyceride; VLDL = very low-density lipoprotein.

management to understand its impact in atherosclerotic events) trial. Anacetrapib, which has a similar structure to torcetrapib but does not share its properties when it comes to the effects on aldosterone production, is presently in Phase III research. Dalcetrapib, which is structurally different than torcetrapib, is currently undergoing cardiovascular outcomes trials [74]. 2-Arylbenzoxazole, [75], tetrahydrochinoline (BAY 38-1335) [76], chromanol derivatives, and 2-(4-carbomylphenyl) benzoxazole are under development as CEPT inhibitors [77,78] .

5.3. *Cholesterol absorption inhibitors*

Ezetamibe is the only drug currently available from this class whose mechanism of action involves inhibition of dietary cholesterol absorption without affecting the absorption of fat-soluble vitamins, triglycerides, and bile acids [59,62,79]. Ezetamibe binds to cholesterol transporter NPL1L1 (Niemann-pick C1-like1) protein in the brush border of intestine as well as in hepatocytes [59,80]. Decrease in cholesterol absorption leads to compensatory up-regulation of LDL receptors on the cell surface and increased LDL cholesterol uptake into cells and decreases blood LDL cholesterol content [59,62]. Ezetamibe also exerts anti-inflammatory effect and also appears to improve renal function [81]. Some side effects of ezetamibe are diarrhea, abdominal pain, arthralgia, backache, myalgia, headache, sinusitis, hepatitis, aphylaxis, myopathy, and rhabdomyolysis [62]. This drug is contraindicated in active liver diseases [62]. Ezetimibe is primarily metabolized in the small intestine and liver via glucuronide conjugation with subsequent biliary and renal excretion [82]. After oral administration, ezetimibe is absorbed and extensively conjugated to a pharmacologically active phenolic glucuronide (ezetimibe-glucuronide), the drug and its metabolite have a half-life of approximately 22 hours [83].

5.4. *Cholesterol O-acyltransferase inhibitors*

Acyl-CoA: cholesterol O-acyltransferase (ACAT) is an important enzyme involved in re-esterification of absorbed cholesterol within enterocytes [84]. It is involved in the cholesterol metabolism in macrophages, liver, intestine and adrenal cortex and is believed to be involved in secretion of VLDL from liver and development of atherosclerotic lesion [85]. Two ACAT enzymes have been identified, ACAT1 and ACAT2. ACAT1 is found in the ER throughout the body, while ACAT2 is found in the ER of liver and intestinal tissues and may be responsible for the formation of cholesteryl esters [85]. In theory, inhibition of ACAT1 could prevent the transformation of macrophages into foam cells in the vessel wall and, thereby, slow the progression of atherosclerosis and prevent the development of vulnerable plaque and inhibition of ACAT-2 could decrease serum lipid levels by reducing the synthesis of lipoproteins [70]. HL-004 has been found preclinically to be an effective ACAT inhibitor [86]. Presently, specific ACAT 2 inhibitor, such as derivatives of fungal pyripyroneA, are under scrutiny [87].

5.5. *Diacylglycerolacyltransferases inhibitors*

Diacylglycerolacyltransferases (DGATs) are enzymes involved in adipocyte lipid accumulation and catalyzes the final step reaction of triacylglycerol formation from diacylglycerol [88]. DGAT1 belongs to the same family of proteins as the ACATs [89]. In mammals, DGAT1 is expressed in skeletal muscle, skin, intestine (ileum, colon), and testis, with lower levels of expression in liver and adipose tissue, while DGAT2 is ubiquitous with high expression levels in hepatocytes and adipocytes [90].

5.6. *Microsomal TG transfer protein inhibitors*

Microsomal TG transfer protein (MTTP) is a heterodimeric lipid transfer protein that catalyzes the transport of TG, cholesteryl ester, and phosphatidylcholine between membranes [91]. MTTP is a protein located in intestine and liver tissues where it plays a role in lipid assembly, transport, and secretion of lipoproteins, triglyceride rich chylomicrons (in enterocytes), and VLDL (in hepatocytes) [92,93]. *In vitro* studies show that MTTP catalyses the transport of molecules between phospholipid membranes and is also involved in the synthesis of nascent lipoprotein particles within the lumen and ER [94]. The inhibition of MTTP by small molecules should lead to the reduction in plasma TGs and cholesterol levels [95].

Some clinical candidates, such as CP-346086 and BMS-201038, have been shown to inhibit MTTP in both the enterocytes and in the liver [96]. Dirlotapide is an enterocyte-specific MTTP inhibitor that has recently been approved by the FDA as an anti-obesity agent [97]. The most significant side effects involve elevation of hepatic transaminases, nausea, diarrhea, gassiness, and gastrointestinal cramping [98]. Of several MTTP inhibitors, only BMS-201038, now renamed AEGR-733, is still in development [98]. Microsomal triglyceride transfer protein inhibition with lomitapide may offer a treatment option for patients who cannot tolerate statin therapy or who experience insufficient LDL-c reduction with available therapies [95].

5.7. *Squalene synthase inhibitors*

Squalene synthase, a key enzyme in the cholesterol biosynthetic pathway, occupies the first and solely committed step towards the biosynthesis of the sterol nucleus of cholesterol; hence it is an attractive target for inhibition and the development of novel and improved antihypercholesterolemic agents [99]. Squalene synthase catalyzes one of the subsequent reactions in the cholesterol biosynthetic pathway (i.e. it reductively dimerizes two farnesyl pyrophosphate molecules to form squalene) which is the first intermediate committed to cholesterol [100]. Squalene synthase inhibitors are emerging new stars in the hypolipidemic drug sky and represent a novel class of antihyperlipidemics [59]. Squalene synthase is implicated in the late step in cholesterol biosynthesis and, the squalene synthase inhibitors exerts same effect as that of 3-hydroxy-3-methylglutaryl-coenzyme A-CoA reductase inhibitors, with decreased cholesterol production and up-regulation of LDL receptors [79]. Early inhibitors such as the zaragozic acids showed significant toxicity (acidosis), but a recent compound, lapaquistat, reached Phase III clinical trials [101,102]. EP2306 and EP2302 have been shown to possess antioxidant properties both *in vitro* and *in vivo* [103] as well as to inhibit squalene synthase activity and lipid biosynthesis *in vitro* [104].

5.8. *Thyroid hormone analogues*

Thyroid hormone has been known to lower total serum cholesterol for many years in hyperthyroidism and during thyroid hormone replacement therapy for hypothyroidism [105]. This action is the result of an accelerated LDL-c clearance rate [106]. T3 increases levels of both the hepatic LDL receptor and its mRNA [107,108]. Additional thyroid hormone actions on lipid metabolism include increasing the activity of lipoprotein lipase [106,109]. More recent understanding of thyroid hormone receptors has led to the development of thyroid hormone mimetics that have selective functions and are potential therapeutic agents to lower cholesterol [110]. Several thyroid hormone analogues have been developed, but the only one with published human data is eprotirome [98], a thyroid hormone analogue containing two bromines that only interacts with the β-receptors found primarily in the liver. It does not seem to have adverse effects on heart and bone [108,111].

5.9. *Lanosterol synthase inhibitors*

Oxido-squalene-cyclase (lanosterol synthase, LSS) is the second enzyme below the farnesyl pyrophosphate branch point that has been identified as a target for novel anti-cholesterolemic drugs that could complement statins [112]. LSS is located in the ER and converts 2,3-oxidosqualeneto lanosterol, the initial four-ringed sterol intermediate in the cholesterol synthesis pathway. The 24(S),25-epoxycholesterol is a ligand of liver X receptor [113]. It also sets the template for the design of inhibitors with improved pharmacological properties for cholesterol lowering and treatment of atherosclerosis. Through the dual mechanism of LSS action (formation of lanosterol; formation of ligands for liver X

receptor), LSS inhibitors have a potential to decrease plasma levels LDL-c and to prevent cholesterol deposition within macrophages [59].

5.10. *Cholesterol metabolizing cytochrome P450: implication for cholesterol lowering*

From the family of P450s, the 7A1, 27A1 and 46A1 are the most important enzymes involved in the control of cholesterol levels in the periphery and brain [114]. CYP7A1 is an important determinant of plasma cholesterol levels and is considered as target for cholesterol lowering [115].

CYP27A1 converts cholesterol to 27-hydroxycholesterol by oxygenation reaction and this is suggested to be important reaction for cholesterol elimination from human lung macrophages and cells in arterial endothelium [116].

5.11. *AMP-activated protein kinase activator*

AMP-activated protein kinase (AMPK), a heterotrimetric energy sensing protein, which restores cellular energy balance by promoting ATP-generating pathways (e.g. FA oxidation) and inhibiting ATP-utilizing pathways (e.g. FA synthesis) [117]. AMPK system plays a major role in regulating glucose and lipid metabolism by effect on energy metabilism and long-term effect on gene expression in the liver [118]. In liver, activation of AMPK results in decreased production of plasma TG and cholesterol and enhanced FA oxidation [119,120]. WS070117 is synthetic lipid lowering agent that is approved preclinically as an effective activator of AMPK with potential capability of inhibition of *de novo* hepatic lipogenesis [121].

5.12. *Omega-3 FAs*

Omega-3 belongs to the polyunsaturated FA family (n-3 PUFA), which includes the 20-carbon eicosapentanoic acid and 22-carbon docosahexaenoic acid, which lowers the TG levels and atherogenic remnant lipoproteins [81]. These FAs are derived from marine sources, especially salmon, mackerel, sardines, and tuna [28]. Omega-3 FAs at 4 g/day usually have favorable effect in lowering TG concentration particularly in the postprandial state and their addition to statins significantly decreases TG, VLDL, and non-HDL-c levels compared with simvastatin alone [122]. Omega-3 FA inhibits expression of SREBP-1, which is involved in the synthesis of FAs [80]. Another broad variety of biological actions shown by omega-3 FAs are hypotriglyceridemia, antiaggregatory, anti-inflammatory, and antiarrythmatic responses [4]. The most common adverse events shown by omega 3 fatty acids in clinical trials are eructation, infection, dyspepsia, and flu syndrome [8].

6. Conclusion

Hyperlipidemia is a metabolic disorder characterized by HC and HTG. FHC is one of the types of hyperlipidemia with a genetic basis. In the present review we mainly focused on the new therapeutic drug targets in the treatment of hyperlipidemia. PPARs are regulators of numerous metabolic pathways; hence there is huge increase in the development and use of agonists of these receptors as therapeutics of dyslipidemia. Inhibition of CETP should lead to elevation of plasma HDL cholesterol and lowering of plasma LDL cholesterol. Ezetamibe is the only drug available today that acts by inhibition of dietary cholesterol absorption without affecting the absorption of fat-soluble vitamins, TGs and bile acids. The inhibitors of ACAT, DGAT, and MTTP, along with thyroid hormone analogue, cholesterol-metabolizing cytochrome P450, AMPK activators, and omega-3 FAs, will be the new therapeutic drug targets in treatment of hyperlipidemia. The inhibitors of certain enzymes such as squalene synthase and lanosterol synthase contribute to the reduction of hyperlipidemia.

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