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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