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Review

Dyslipidemias in clinical practice

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ABSTRACT

Most dyslipidemic conditions have been linked to an increased risk of cardiovascular disease. Over the past few years major advances have been made regarding the genetic and metabolic basis of dyslipidemias. Detailed characterization of the genetic basis of familial lipid disorders and knowledge concerning the effects of environmental factors on the expression of dyslipidemias have increased substantially, contributing to a better diagnosis in individual patients. In addition to these developments, therapeutic options to lower cholesterol levels in clinical practice have expanded even further in patients with familial hypercholesterolemia and in subjects with cardiovascular disease. Finally, promising upcoming therapeutic lipid lowering strategies will be reviewed. All these advances will be discussed in relation to current clinical practice with special focus on common lipid disorders including familial dyslipidemias.

1. Introduction

The term dyslipidemia refers to a disturbance of the lipid profile, including both hyperlipidemia and hypolipidemia. The latter may be associated in some cases to deficiencies of fat-soluble vitamins, like the homozygous form of abetalipoproteinemia and hypobetalipoproteinemia [1], which are characterized by the absence of apolipoprotein (apo) B in plasma, or disorders like chylomicron retention disease in which there is an impaired secretion of intestinally-derived lipoproteins [2]. Recently, a novel type resulting in reduced levels of low-density lipoprotein cholesterol (LDL-C), triglycerides (TG) and high-density lipoprotein cholesterol (HDL−C) has been described, the so called "familial combined hypolipidemia" [3]. In the heterozygous forms, these types of dyslipidemias do not have a clinical expression and are therefore, infrequently diagnosed. Others like hypoalfalipoproteinemia (low HDL−C) may in some instances be linked to increased cardiovascular risk [4].

In clinical practice, the most frequent and therefore the most relevant dyslipidemias are the hyperlipidemias [5]. Most of these dyslipidemic conditions have been linked to an increased risk of cardiovascular disease. In the case of severe hypertriglyceridemia (with plasma TG levels > 10 mmol/l) there is also an increased risk of pancreatitis. The nomenclature is rather simple: the term hypercholesterolemia is used when only plasma cholesterol is elevated, usually due to high LDL-C levels, hypertriglyceridemia is used when only plasma TG are increased and combined or mixed hyperlipidermia refers to both elevated LDL-C and plasma TG. Clinicians should be aware of the fact that TG-rich lipoproteins (very low-density lipoproteins (VLDL) and chylomicrons and their remnants) also carry cholesterol molecules. This explains why severely elevated TG are always accompanied by elevated plasma cholesterol levels. One should exclusively use the term "hypertriglyceridemia" when LDL-C levels are normal or low and the elevated plasma cholesterol is confined to the TG-rich lipoproteins. In this case plasma apo B is always within normal limits and this helps to discriminate between hypertriglyceridemia (with the elevated risk of pancreatitis) and combined or mixed hyperlipidemia (with increased cardiovascular risk).

Finally, a distinct type of dyslipidemia is mainly observed in type 2 diabetes mellitus (DM) or situations associated to the metabolic syndrome and insulin resistance: the high TG-low HDL-C dyslipidemia, also called "atherogenic dyslipidemia".

While the recognition of a dyslipidemic condition is not so difficult, clinicians should always try to establish the diagnosis underlying the phenotypic expression. This is of extreme importance to determine the prognosis and the choice of treatment. Furthermore, in the case of familial dyslipidemias, genetic counselling and family screening need to be implemented. First, one should differentiate primary from secondary hyperlipidemias. The latter are always the consequence of a different condition like for example obesity, hypothyroidism, nephrotic syndrome, obstructive liver disease, chronic renal failure or the use of medication [5]. When these causes have been ruled out, one should consider primary hyperlipidemia in which a differentiation can be

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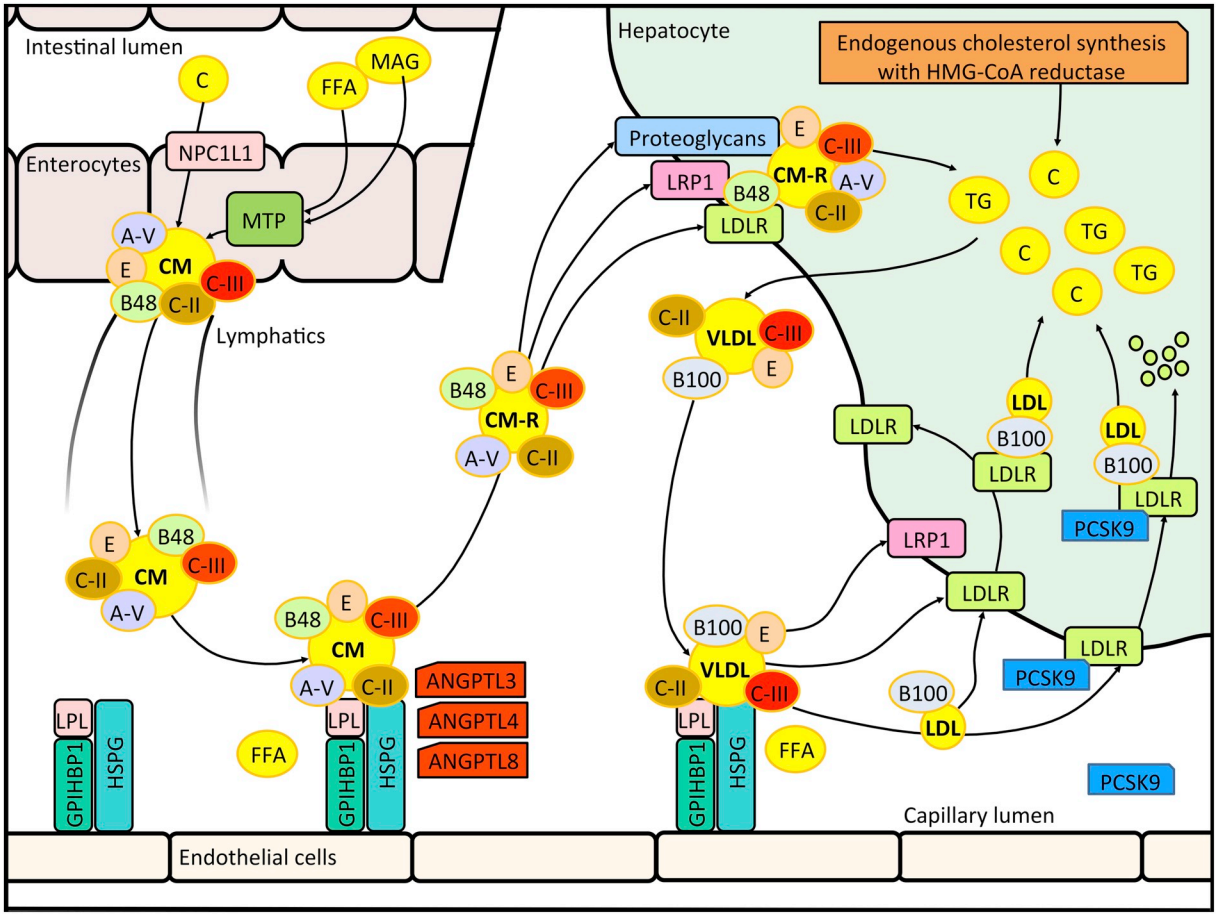

Fig. 1. Schematic overview of lipid metabolism of apolipoprotein B containing lipoproteins. Abbreviations: ANGPTL = angiopoietin-like proteins, A-V = apolipoprotein A-V, B48 = apolipoprotein B-48, B100 = apolipoprotein B-100, C = cholesterol, CM = chylomicron, CM-R = chylomicron remnant, C-II = apolipoprotein C-II, C-III = apolipoprotein C-III, E = apolipoprotein E, FFA = free fatty acids, GPIHBP1 = glycosylphosphatidylinositol-anchored high-density-binding protein 1, HSPG = heparan sulphate proteoglycans, LDL = low-density lipoprotein, LDLR = low-density lipoprotein receptor, LPL = lipoprotein lipase, LRP1 = low-density lipoprotein like receptor 1, MAG = mono-acylglycerols, MTP = microsomal triglyceride transfer protein, NPC1L1 = Niemann-Pick-C1-like 1, PCSK9 = proprotein convertase subtilisin/kexin type 9, TG = triglycerides, VLDL = very low-density lipoprotein.

made between well-defined genetic hyperlipidemias and the so-called, most frequent, polygenic hypercholesterolemia in which environmental influences play a major role superimposed on a genetic predisposition.

2. Lipid metabolism of the atherogenic lipoproteins and their respective therapeutic targets

Knowledge of lipid metabolism is necessary in order to understand the pathophysiologic mechanisms of the different dyslipidemias but also to understand which therapy will be most appropriate. Therefore, lipoprotein metabolism will be discussed together with the clinically most relevant pharmacological targets (Fig. 1).

2.1. Intestinal chylomicron synthesis

All atherogenic lipoproteins are synthesized either by the intestine or the liver and are initially TG-rich lipoproteins. After food intake cholesterol is actively transported from the intestinal lumen into the enterocyte via the Niemann-Pick-C1-like 1 (NPC1L1) transporter [6]. NPC1L1 is the primary target of ezetimibe, which inhibits intestinal cholesterol absorption resulting in 20% reductions of circulating LDL-C levels. Ezetimibe has shown to reduce the absolute risk for major cardiovascular events by 2.0% in patients with an acute coronary syndrome when added on top of a statin over a median of 6 years [7]. In contrast to NPC1L1, the ATP binding cassette transporter-G5 and G8 (ABCG5/8) mediates cholesterol efflux from the enterocyte to the intestinal lumen contributing to transintestinal cholesterol excretion [8].

Food-derived TG are taken up as free fatty acids (FFA) and 2-monoacylglycerols (MAG) by the enterocytes after hydrolysis has taken place in the intestinal lumen. These are taken up by enterocytes through passive diffusion and specific proteins, like CD36 and various fatty acid transport proteins [9]. Once inside the endoplasmatic reticulum of the enterocyte, FFA and MAG are assembled into TG again and packed with cholesterol, phospholipids and apo B48 and apo A-IV to form lipid-rich chylomicrons, which consist for 85–92% of TG and 1–3% of cholesterol [10,11]. In this process, the microsomal triglyceride transfer protein (MTP) and the editing enzyme complex are paramount factors [12,13]. Especially the latter, which in humans is only present in the intestine, is crucial for the synthesis of apo B48, the structural protein of chylomicrons. Apo B48 is synthesized from the apo B mRNA strand following posttranscriptional editing with enzymatic deamination at nucleotide 6666, which results in truncation of apo B codon 2153, so that the mature protein consists of only 48% of the apo B100. After assembling, the chylomicrons can have a diameter up to 1000 nm. They are secreted into the lymphatics and enter the circulation through the thoracic duct. Within the circulation apo A-IV is exchanged for two other apolipoproteins, namely apo C-II and apo E [14]. These are involved in TG lipoprotein lipase (LPL)-mediated hydrolysis and receptor-mediated uptake, respectively.