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Review

Familial hypercholesterolemia and triglyceride metabolism

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A B S T R A C T

Familial hypercholesterolemia (FH) is a common autosomal disorder associated with hypercholesterolemia which usually results from a mutation in the coding region of the low density lipoprotein (LDL) receptor (R) activity. Only 20% of untreated heterozygote (h) FH men reach 70 years of age. Therefore, the diagnosis of hFH is a better predictor of coronary heart disease than risk-based algorithms.

Fasting and postprandial hypertriglyceridemia are also considered as risk factors for atherosclerosis. The plasma triglycerides (TG)s are formed from two major sources; intestinally-derived chylomicrons and hepatically-derived very low density lipoproteins (VLDL). Potentially, atherogenic remnants of TG-rich lipoproteins accumulate in the postprandial state. In addition, TG-rich lipoproteins may promote the formation of atherogenic small dense LDL. In FH subjects, lipoprotein metabolism seems to be impaired and may contribute to premature atherosclerosis. This was documented in many studies in which mice lacking LDLR present hypercholesterolemia, increased plasma TG-rich lipoprotein remnants and develop premature spontaneous atherosclerosis.

In this review, we focus on the current knowledge regarding TG metabolism on a selected clinically condition such as FH. Variation in clinical characteristics has been described between studies which may occur due to dissimilarity in the molecular defect of FH. Additionally, the relationship between TG levels in FH subjects and the development of atherosclerosis, as well as the appropriate treatment for these patients is analysed.

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1. Introduction

Familial hypercholesterolemia (FH) is a common autosomal dominant disorder associated with hypercholesterolemia which usually results from mutations in the coding region of the low density lipoprotein (LDL) receptor (R) activity [1]. The phenotype of FH is characterized by elevated LDL cholesterol (>4.9 mmol/l or >188 mg/dl), a positive family history of dyslipidemia and early coronary heart disease (CHD) as well as the presence of tendon xanthomas and premature atherosclerosis [2–4]. Causal mutations in other genes have been incriminated for hypercholesterolemia. The R3500Q mutation in the apolipoprotein (apo) B gene (familial defective apo B) results in a phenotype that is slightly milder than that caused by mutations in LDLR [5]. Mutations in a third locus, PCSK9, have been identified to result in hypercholesterolemia [6]. Analysis of family pedigrees has revealed the presence of an autosomal recessive hypercholesterolemia (ARH), where the disease-causing gene encodes an adaptor protein that binds to the LDLR clathrin-coat network [7]. The heterozygote (h) frequency is estimated to be 1/200–500 in most populations [3,4,8,9]. Clinically documented CHD usually occurs at a mean age of 45–48 years in men

and 55–58 years in women [4] while only 20% of untreated hFH men reach 70 years of age [4]. The plasma levels of LDL cholesterol in FH homozygotes are very high, irrespectively of diet or lifestyle variations. [10]. Nevertheless, the onset and severity of CHD varies among FH patients even with identical mutations [11,12]. This is even more pronounced in heterezygotes for FH where the level of LDL cholesterol can be additionally influenced by life style factors such as physical exercise, control of food calorie intake, psychological awareness of the disease and compliance regarding medications.

Epidemiological data support that elevated fasting plasma triglyceride (TG) concentrations also contribute to atherosclerosis and are an independent risk factor for CHD. Furthermore, the postprandial hypertriglyceridemia is considered as a risk factor for atherosclerosis, too [13–19]. Potentially atherogenic remnants of TG-rich lipoproteins, namely chylomicrons (CM), very low-density lipoproteins (VLDL), accumulate in the postprandial state [16,20,21]. The high levels of TG-rich lipoproteins may promote the formation of atherogenic small dense LDL [22,23]. Thus, one of the explanations of heterogeneity in the manifestation of atherogenic disease in FH patients could lie in the TG metabolism. Recent evidence raises the possibility that TG involvement has been significantly underestimated.

Here, we review the current knowledge regarding TG metabolism focusing on a selected clinically condition such as FH. This review also demonstrates the influence of TG on CHD manifestation in patients with FH.

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2. TG metabolism in the fasting state

Plasma TGs are formed by two major sources; intestinally-derived CM and hepatically-derived VLDL [24,25] (Fig. 1). CMs are characterized in our minds as solely TG-rich lipoproteins, although each particle contains 40 times more cholesterol than LDL [26] and CMs transport three times more cholesterol than LDL particles over a period of 24 h [27]. In the circulation, the TGs are hydrolysed by lipoprotein lipase (LPL) and they form CM remnants. The removal of CM remnants is carried out by muscle and adipose tissue [28] where endocytosis takes place. The endocytosis of CM remnants could be via the LDLR and LDLR related protein (LRP) as well as via other receptors.

The second source of TG derives from VLDL. The formation of VLDLs in the liver depends firstly on the availability of hepatic cholesterol substrate, that controls the expression of LDLRs and partly regulates the production of VLDL, and secondly on fatty acid supplies to the liver and hepatic TG pools [29]. High availability of cholesterol substrate reduces hepatic cholesterol synthesis and the secretion of VLDL decreases followed by the upregulation of LDLRs [29,30] (Table 1). This may enhance the removal of CM and VLDL remnants. The removal of VLDL follows the same pathway as the CM remnants [31].

The LDLR acts as both apo B-100- and apo E receptor. However, LDLRs have a higher affinity for apo E-containing particles compared with the binding to LDL, which has only apo B-100 as a structural apolipoprotein [32]. It was shown that lipoproteins containing apo E have better affinity for LDLRs than those containing only apo B [33]. The relative contribution of the LDLR for the clearance of CM remnants is still unclear and controversial [34–42].

2.1. TG metabolism postprandially

The rate of TG clearance is the result of many variables [14,43] such as the size of capillary beds, the amount of active LPL and the competition between VLDLs and CMs. Xiang et al. have shown that the removal of TG from CMs is 10 times greater than that from VLDL after a mixed meal [44]. Furthermore, the number of VLDL particles is much higher than that of CMs in the postprandial state (about 20:1) and the increase in VLDL particle number in the postprandial state is greater than the increase in CM particle number [24,45]. In the early postprandial period (the first 3 h after a meal) smaller sized CMs are secreted. Later in the postprandial period, de novo-formed larger

CMs are secreted [46,47]. The smaller sized CMs are considered to be atherogenic [46,48]. In healthy subjects, VLDLs secreted by the liver are not considered to be atherogenic.

In the hyperTG state (transient accumulation of CMs, VLDLs and their remnants), the rate of cholesteryl ester transfer from high density lipoprotein (HDL) to VLDL is elevated resulting in the secretion of large VLDL particles and the formation of small dense LDL particles [49,50]. It has been proposed that elevated plasma TG concentration promotes the cholesteryl ester exchange reactions mediated by cholesteryl ester transfer protein (CETP, glycoprotein secreted mainly from the liver) [51,52]. When the level of VLDLs is within the normal range, the CETP-mediated transfer of HDL cholesteryl esters is directed preferentially to LDL particles [53]. When the concentration of VLDL particles is increased, the cholesteryl esters of HDL are preferentially transferred by CETP to larger VLDL particles [53] (Table 1). Overall, during alimentary lipemia, the CETP-mediated transfer of neutral lipids (cholesteryl esters and TGs) between plasma lipoprotein particles is increased [54–56], allowing transformation of cholesteryl ester-enriched HDL into TG-rich HDL particles which become a substrate for hepatic lipase [57,58] and are cleared more rapidly from the circulation [59], leading to low serum HDL cholesterol levels [60].

3. FH and TG metabolism in the fasting state

In FH subjects, TGs are not usually elevated, suggesting that production and clearance of CMs are normal. In 1980, Angelin [61] studied the plasma endogenous TG kinetics in five unaffected and eight affected (heterozygous) siblings with FH and concluded that abnormal plasma TG metabolism was not a feature of heterozygous FH. Since then many studies, including ours, have been evaluated the TG metabolism in FH subjects (as will be discussed in the later part) (Fig. 2). Radiolabeling studies indicated that patients with FH are characterized by a decreased clearance of LDL particles [62], which is in agreement with the underlying LDLR defect. In the absence of LDLR, the upregulation of VLDLR in the liver is observed [63]. Cummings at al. [62] reported an increased secretion of VLDL apo B. Also, Tremblay et al. [64] reported 50% and 109% increases in VLDL apo B production in heterozygous and homozygous FH, respectively. Furthermore, Horton et al. [65] have demonstrated that knockout mice showed an increased apo B secretion in the absence of the LDLR. Similarly, Liao et al. [66] found that hepatocytes from LDLR knockout mice secreted
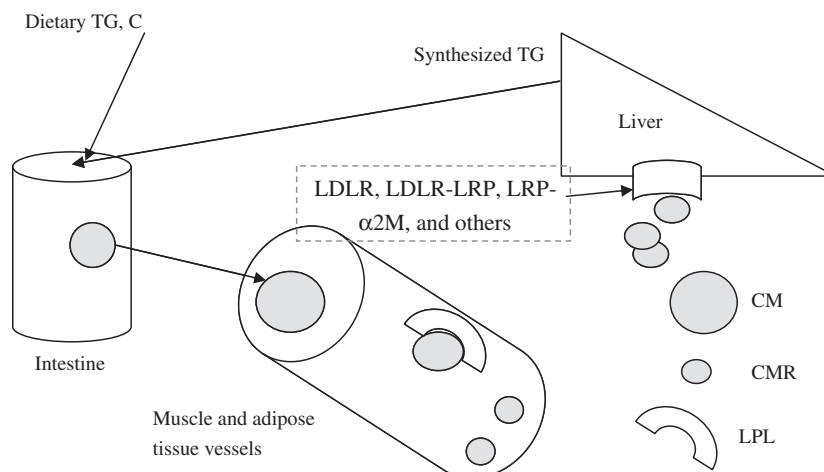
C = cholesterol, CM = chylomicrons, CMR = chylomicron remnants receptors,
LDLR = low density lipoprotein receptor, LDLR-LRP = LDLR-related protein,
LPL = lipoprotein lipase, LRP-α2M = LRP-α2-macroglobulin, TG = triglycerides.

Fig. 1. TG metabolism.