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Review

Postprandial lipoprotein metabolism in familial hypercholesterolemia: thinking outside the box

*Dick C. Chan, Gerald F. Watts**

Metabolic Research Centre, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia

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ABSTRACT

Familial hypercholesterolemia (FH) is a dominantly inherited disorder principally due to mutations in the low-density lipoprotein (LDL) receptor that classically cause markedly elevated plasma LDL cholesterol concentrations and premature coronary heart disease (CHD). However, elevated plasma LDL cholesterol alone does not fully account for the increase or variation in risk of CHD. We propose a hypothetical model for the role of postprandial dyslipoproteinemia based on the overproduction and decreased catabolism of triglyceride-rich lipoproteins, which may be a consequence of LDL receptor deficiency. Expression of postprandial dyslipoproteinemia in FH may also depend on the type of pathogenic gene variants and on coexistent conditions, particularly obesity and insulin resistance. Further research is required to investigate our model proposed and to test whether treating postprandial dyslipoproteinemia decreases CHD risk in FH incremental to standard therapy.

1. Introduction

Familial hypercholesterolemia (FH) is the commonest monogenic cause of hypercholesterolemia and premature coronary heart disease (CHD) [1-3]. Heterozygous FH occurs in the general population at a frequency of at least 1 in 500. The classic metabolic defect in FH is hypocatabolism of low-density lipoprotein (LDL) due to decreased LDL receptor activity [4,5]. Familial hypercholesterolemia markedly increases the risk of premature CHD, to the extent that approximately 50% of untreated men and 20% of female patients have fatal or nonfatal CHD events by the age of 50 years [6]. However, there is wide variation in the incidence of CHD among FH patients, even among family members with similar LDL receptor mutations and plasma LDL cholesterol concentrations. Hence, the classic mutational defect in FH, markedly elevated plasma LDL cholesterol, alone does not fully account for this variation in CHD or mortality [7-13]. Although some of this residual risk may be due to other coexistent cardiovascular risk factors, including diabetes, hypertension, smoking, and marked elevation in plasma triglyceride and lipoprotein (a) concentrations [11-13], it is possible that postprandial dyslipidemia may play a major contributory role [14]. Postprandial disturbance in lipoprotein metabolism has received little attention, however, as a specific metabolic defect and atherogenic risk factor in the context of FH.

2. Normal postprandial lipoprotein metabolism

After ingesting a fat meal, dietary cholesterol and triglycerides are packaged together with apolipoprotein (apo B-48) into

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* *Corresponding author*. School of Medicine and Pharmacology, Medical Research Foundation, Royal Perth Hospital, GPO Box X2213, Perth Western Australia 6847, Australia. Tel.: +61 8 9224 0245; fax: +61 8 9224 0246.
E-mail address: gerald.watts@uwa.edu.au (G.F. Watts).

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large chylomicron (CM) particles by the enterocyte. These lipoproteins are responsible for the transport of exogenous lipids from the intestine via the circulation to peripheral tissues, the so-called exogenous pathway of lipoprotein metabolism. Following lipolysis by lipoprotein lipase (LPL), CM remnant particles are produced; and these are in turn cleared by the liver via at least 5 liver surface cell receptors: the LDL receptor protein, the liver cell remnant receptor, the asialoglycoprotein receptor, the lipolysis stimulated receptor, and the classic LDL (or B/E) receptor [15]. The interaction of CM remnants with hepatic receptors is also dependent on the apoprotein ligand apo E.

Postprandial lipidemia is a normal physiological event that reflects chiefly the aforementioned metabolic pathway. The postprandial alterations in triglyceride and lipoprotein metabolism are transitory and usually last from 6 to 8 hours after ingesting a fatty meal [15]. Hypertriglyceridemia reflects the accumulation of triglyceride-rich lipoproteins (TRLs), CM, very low-density lipoprotein (VLDL), and their remnants.

3. Postprandial dyslipoproteinemia

Pathological postprandial dyslipidemia or more precisely dyslipoproteinemia, refers to an increase in the magnitude and duration of TRLs response after a fatty meal [15]. These changes are loosely and globally reflected by the response of plasma triglyceride concentration to a meal. Postprandial dyslipoproteinemia may occur as a consequence of decreased receptor activity or a defect in the ligand for these receptors, and impaired lipolysis by LPL. Moreover, oversecretion of VLDL that competes with CM remnants for clearance can exacerbate the postprandial response. As discussed later, these metabolic defects can occur in FH. Postprandial accumulation of TRLs in plasma also enhances exchange their triglycerides for cholesterol esters from LDL and high-density lipoprotein (HDL) [16,17]. Under the action of lipolytic enzymes, triglyceride-enriched LDL and HDL particles become smaller, denser, and more atherogenic. Hence, the atherothrombotic effects of TRL imply that the postprandial state is highly significant for patients with FH.

4. TRLs and atherothrombosis

Epidemiological data suggest that fasting and postprandial hypertriglyceridemia is a risk factor for CHD [18,19]. A recent report from collaborative analysis of 101 studies supports a causal role for triglyceride-mediated pathways in CHD [20]. That notion is consistent with several clinical case-control studies showing enhanced accumulation of TRLs in plasma following a fat challenge in patients with coronary disease compared with those without coronary disease [21,22]. Longitudinal studies also indicate that progression of coronary atherosclerosis is independently related to TRLs [23,24]. Disturbances in postprandial dyslipoproteinemia have been observed in individuals with visceral obesity, type 2 diabetes mellitus, and metabolic syndrome [25-27]. These abnormalities may partly account for increased CVD risk in these subjects. The atherogenicity of TRLs relates to the smaller-sized remnant particles that accumulate in plasma following lipolysis of CMs and VLDLs [28-30]. Apolipoprotein C-III, an inhibitor of LPL, regulates this process and plays a crucial role on the pathogenesis of hypertriglyceridemia and atherosclerosis [31]. Triglyceride-rich lipoprotein remnants readily infiltrate the subendothelial space of the arterial wall where they are trapped by connective tissue matrix. These particles are enriched in cholesterol and apo E and are rapidly phagocytosed by arterial wall macrophages, which are then transformed into “foam cells,” the hallmark lesion of atherosclerosis [32]. Triglyceride-rich lipoprotein remnants further contribute to atherosclerosis by impairing endothelial function [33], as well as by activating monocytes and inflammatory signaling pathways [34]. Triglyceride-rich lipoprotein remnants also have a direct effect on thrombogenicity by stimulating the cellular release of tissue factor and the generation of thrombin, as well as by potentially inhibiting fibrinolysis [35,36]. Given their role in experimental atherothrombosis, TRL remnants have been shown to be directly related to the extent in progression of coronary and carotid artery disease [37,38]. Hence, TRLs are likely to exaggerate the atherogenic effect of LDL particles in patients with FH.

The association between the molecular defect in FH and fasting plasma triglyceride concentrations has been previously examined [39-49]. Souverein et al [39] found that elevated fasting plasma triglyceride concentration was not significantly associated with increased CVD risk in FH (hazard ratio, 1.03-1.14). However, the lack of significant association could be due to the confounding effect of other factors such as diabetes and/or low HDL cholesterol in the statistical models. Bertolini et al [40] found a small but nonsignificant increase in plasma triglyceride concentration in FH patients with CHD compared with those without CHD, but the definition of CAD in this study was not rigorous. Several studies have shown no significant impact of LDL receptor (such as null LDLR alleles vs defective alleles) or apo B-100 mutational class on fasting plasma triglyceride concentration [41-45]. However, these studies did not specifically examine the effect of individual molecular defect in FH on fasting plasma triglyceride concentrations. As we will discuss later, mutations in the binding domain of the LDL receptor (such as the exon 4 of the LDLR gene) could have a significant impact on TRL metabolism. Patients with FH with tendon xanthomas (which are associated with increased risk of premature CHD) have been found to have a trend to a significant increase in fasting plasma triglyceride concentration compared with those without tendon xanthomas [46,47], consistent with a meta-analysis of 22 studies [48]. It is important to note that none of these studies were carried out in the postprandial state. Whether this small increase in fasting plasma triglyceride levels in FH patients reflects a significant alteration in postprandial TRL metabolism remains unclear and merits further investigation. Importantly, a study by Kolovou et al [49] found that heterozygous FH patients had impaired triglyceride response to a fatty meal compared with non-FH controls with similar fasting plasma triglyceride concentrations. This observation implies that fasting plasma triglyceride alone may not be a sufficiently sensitive predictor of postprandial dyslipoproteinemia in FH.

5. Assessment of postprandial TRL metabolism

Although fasting measurements of TRLs (such as plasma triglyceride and apo B-48 concentrations) are predictive of postprandial dyslipoproteinemia, they do not reflect the full details or mechanisms of the metabolic changes in lipid and lipoprotein metabolism in the postprandial state. Standard methods for assessing TRL metabolism involve measurement of the response of plasma triglycerides, retinyl esters, remnant-like particle (RLP), or apo B-48 to an oral fat load following an overnight fast [50]. In practice, a creamy emulsion consisting of 35% to 40% fat (weight/volume) with a polysaturated to saturated fatty acid ratios of 0.05 to 0.06 is taken orally after an overnight fast; the total fat content of the emulsion is determined by body surface area (30-40 g/m^2). After the ingestion of the oral fat challenge, blood samples are taken every 1 or 2 hours over 10 to 12 hours. Postprandial responses are commonly analyzed as the area under the curve (AUC) following the oral fat challenge. Although measurement of plasma triglyceride is the most simple and reliable measure of postprandial dyslipoproteinemia, it does not quantitate the number of TRL particles or differentiate between apo B-48–containing and apo B-100–containing lipoproteins. An immunoseparation method to analyze RLP has been developed as a simple test for remnants, but does not distinguish between apo B-100–containing and apo B-48–containing lipoproteins. Retinol labeling is a conventional test for investigating postprandial dyslipoproteinemia. However, the postprandial response to a fat load is different from that of plasma triglyceride and RLP [51]. Accordingly, the retinyl palmitate levels may not be a suitable for evaluating postprandial dyslipoproteinemia. Apolipoprotein B-48 is an exclusive marker of the number of circulating particles of CM and their remnants [52]. Hence, apo B-48 is the most appropriate one to use to detect the presence of postprandial chylomicronemia. The kinetics of TRL metabolism may be further assessed using stable isotope labeling techniques. A ^{13}C breath test based on the injection of a remnant-like emulsion labeled with cholesteryl ^{13}C-oleate and subsequent measurement of $^{13}CO_2$ enrichment in breath has been described as a functional test for CM remnant metabolism in postabsorptive state [53].

6. Studies of TRL metabolism in FH

6.1. *Experimental studies*

Choi et al [54] found that an antibody raised against the LDL receptor delayed the clearance of ^{125}I-CM remnants from plasma by 30%. Ishibashi et al [55] reported that the AUC of plasma retinyl ester in the LDL receptor–deficient mice following a fat tolerance test was 4 times larger than that in wild-type mice. Martins and Redgrave [56]l showed that the clearance of CM remnants, as measured by the remnant-like emulsion breath test, was delayed in homozygous LDL receptor–deficient mice, consistent with a study in heterozygote and homozygote Watanabe heritable hyperlipidemic rabbits [57]. Using pulse-chase experiments and compartmental modeling in wild-type and LDL receptor–negative hepatocytes, Twisk et al [58] found that the absence of LDL receptor was associated with almost 2-fold higher apo B-100 and apo B-48 secretion rates compared with the wild-type cells. Taken together, these experimental studies demonstrate that a deficiency in the LDL receptor is associated with decreased catabolism and/or overproduction of TRLs.

6.2. *Human studies*

Table 1 summarizes human studies of TRL metabolism in patients with FH. Twelve studies have been reported: 6 in the postprandial (2 under constant feeding condition) and 6 in the postabsorptive states.

Rubinsztein et al [59] used retinol labeling and found that the postprandial response to an oral fat challenge was not impaired in homozygous FH compared with normolipidemic controls. However, other reports showed elevated postprandial retinyl palmitate response in homozygous and heterozygous FH [60-62]. Using a primed, constant infusion of d3-leucine, Tremblay et al [63] found that apo B-48 secretion was almost 2-fold higher in heterozygous FH patients compared with normolipidemic controls, with no difference in fractional catabolic rate (FCR), consistent with experimental data [58].

Twickler et al [62] observed higher fasting RLP cholesterol and an increased postprandial RLP cholesterol response to a fat load in 7 heterozygous FH patients. This observation was consistent with 2 other reports demonstrating that fasting RLP cholesterol was elevated in heterozygous FH patients [64,65]. We and others have demonstrated that patients with heterozygous FH had elevated fasting apo B-48 concentrations [63,64]. There are only limited data on the study of postprandial apo B-48 response to a fat load in FH. Using a stable isotope breath test, we reported that, in the postabsorptive state, the FCR of CM remnants from plasma was not impaired in patients with homozygous or heterozygous FH [53]. We may infer 2 possibilities from these observations. First, CM remnants can be efficiently removed by other hepatic receptors that are genetically distinct from the LDL receptor, such as an apo E recognizing receptor and the liver cell remnant receptor [66]. Second, accumulation of TRL only occurs in FH after saturation of hepatic clearance pathway in the postprandial state.

Using stable isotope labeling, Schaefer et al [67] carried out a postprandial study and found that low levels of HDL cholesterol and apo A-I in a patient with homozygous FH were due to the combined metabolic defects of increased apo A-I catabolism and decreased apo A-I production. The findings were consistent with a study in Watanabe heritable hyperlipidemic rabbits [68]. The hypercatabolism of apo A-I may be related to increased apo E content in HDL particles that in turn enhances the removal of apo A-I from plasma [69]. However, the mechanism by which the lack of functional LDL receptor relates to overproduction of apo A-I is unclear and requires further study.

A number of in vitro studies have also suggested that the LDL receptor may play a role in the regulation of the hepatic production of apo B-100–containing lipoproteins. Using a primed, constant infusion of ^{13}C-leucine, Cummings et al

Table 1 – Studies of TRL metabolism in FH

First authors	Clinical phenotype	No. of subjects	Principal marker	Findings	BMI	TG (mmol/L)	TC (mmol/L)	LDL-C (mmol/L)
Postprandial studies								
Rubinsztein et al	Homozygous [a]	5	TG, RP	Normal TG and RP AUC	N/A	N/A	N/A	N/A
Mamo et al	Homozygous [a]	6	RP, apo B-48	↑ RP and apo B-48 AUC	N/A	0.8 ± 0.3	8.5 ± 2.6	N/A
Cabezas et al	Heterozygous [b]	5	RP	↑ RP AUC in remnant fraction	27 ± 4	1.8 ± 0.6	9.7 ± 1.8	8.1 ± 1.4
Twickler et al	Heterozygous [b]	7	RLP-C	↑ RLP-C fasting and AUC	26 ± 2	1.4 ± 0.4	12.1 ± 1.9	10.3 ± 1.6
Tremblay et al	Heterozygous [a]	6	Apo B-48 kinetics	↑ Apo B-48 PR	22 ± 4	1.4 ± 0.2	9.5 ± 1.9	7.9 ± 1.7
Tremblay et al	Heterozygous [a]	6	Apo B-100 kinetics	↑ VLDL apo B-100 PR	22 ± 4	1.4 ± 0.2	9.5 ± 1.9	7.9 ± 1.7
Postabsorptive studies								
Dane-Stewart et al	Heterozygous [b]	15	Apo B-48, RLP-C	↑ Apo B-48 and RLP-C	27 ± 4	1.5 ± 1.8	9.9 ± 1.6	7.7 ± 1.5
de Sauvage Nolting et al	Heterozygous [c]	327	RLP-C	↑ RLP-C	26 ± 4	18 (1.2-2.4)	10.6 ± 2.7	8.4 ± 2.1
Watts et al	Homozygous [b]	10	^{13}C-breath test	Normal CM remnant FCR	23 ± 6	1.5 ± 1.5	14.8 ± 3.0	13.5 ± 3.0
Watts et al	Heterozygous [b]	15	^{13}C-breath test	Normal CM remnant FCR	27 ± 4	1.5 ± 1.8	9.9 ± 1.6	7.7 ± 1.5
Cummings et al	Heterozygous [b]	6	Apo B-100 kinetic	↑ VLDL apo B-100 PR	24 ± 3	1.5 ± 0.5	10.3 ± 1.5	8.5 ± 1.2
Millar et al	Homozygous [a]	7	Apo B-100 kinetic	↑ VLDL apo B-100 PR	23 ± 13	1.3 ± 0.8	13.2 ± 2.6	12.0 ± 2.4

BMI indicates body mass index; TG, triglycerides; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; RP, retinyl palmitate; RLP-C: remnant-like particle cholesterol; PR, production rate.
[a] Genetically defined FH.
[b] Phenotypically defined FH.
[c] Genetically or phenotypically defined FH.

[70] found that VLDL–apo B-100 secretion was almost 2-fold higher in heterozygous FH patients compared with normolipidemic controls. The findings were also consistent with an earlier report indicating that heterozygous FH subjects who carry a null LDL receptor gene mutation have elevated plasma concentrations of LDL partly because of increased production of apo B-100 [71]. The increased VLDL–apo B-100 secretion rate is more pronounced in FH homozygotes [72]. Two mechanisms could explain the increased hepatic secretion of apo B-100 in homozygous FH in this study. The first relates to a direct role of the LDL receptor in promoting presecretory degradation of apo B-100, which may in turn downregulate the intracellular processing of apo B-100 in the liver. The second relates to the effect of increased non–receptor-mediated uptake of cholesterol by the liver on apo B-100 secretion. It is also likely that increased competition for hepatic receptors between VLDL and CM remnants in the postprandial state could delay the uptake of VLDL and/or CM remnants by this pathway and exacerbate postprandial dyslipoproteinemia.

The increased hepatic secretion of apo B-100 could potentially influence HDL metabolism in FH. Frenais et al [73] carried out a kinetic study of HDL apo A-I kinetics in 7 patients with heterozygous FH. Although plasma apo A-I concentration was not significantly different from normolipidemic controls, both HDL–apo A-I catabolism and production were increased in the FH subjects. The findings were consistent with a study in a patient with homozygous familial defective apo B-100 (FDB) [74]. The disturbance of HDL metabolism in FH can exacerbate the impact of postprandial dyslipoproteinemia on other cardiovascular risk factors, such as procoagulopathy, oxidative stress, inflammation, and vascular dysfunction. The interrelationship between the exogenous and endogenous pathways of lipoprotein metabolism requires further investigation in FH.

Collectively, the evidence from experimental and human studies supports the notion that deficiency in LDL receptor function in FH may disturb TRL metabolism. The human studies have several limitations, however, including small sample size and differences in subject characteristics and protocols for assessing postprandial dyslipoproteinemia. For example, the confounding effects of obesity and type of mutations were not adequately addressed.

7. Gene variants and postprandial lipoprotein metabolism in FH

Familial hypercholesterolemia is mainly due to mutations in *LDLR*, *APOB*, and proprotein convertase subtilisin-kexin type 9 (*PCSK9*) genes [5]. Of these mutations, about 95% are in *LDLR*, 3% in *APOB*, and 2% in *PCSK9*. These mutations could have differential effects on lipoprotein metabolism in FH.

7.1. *LDLR*

The LDL receptor gene, located on chromosome 19, consists of a number of distinct functional domains (signal sequence, ligand binding, epidermal growth factor precursor homology, oligosaccharide, membrane spanning, and cytoplasmic domains) [75]. There are more than 1600 mutations in the *LDLR* gene that can cause FH [76], accounting for up to 95% of all cases (see also www.ucl.ac.uk/FH). Patients with FH with mutations in the ligand binding domain have higher plasma LDL cholesterol concentrations than patients with mutations in other *LDLR* domains [77]. These mutations could potentially impair TRL remnant catabolism, contributing to postprandial dyslipoproteinemia. It is well recognized that the exon 4 of the LDLR gene coding for repeat 5 of the binding domain of the LDL

receptor is critical for apo E–mediated removal of TRL remnants [78]. Accordingly, FH patients with this mutation have higher plasma triglyceride levels than patients with other LDLR mutations [79], possibly indicating an increased postprandial dyslipidemia in these patients.

7.2. *APOB*

Mutations in the *APOB* gene on chromosome 2 result in FDB and lead to defective binding of LDL to the LDL receptor [80]. Unlike FH due to the LDL receptor defect, subjects with FDB have normal clearance of the LDL precursors [81]. This is because triglyceride-rich particles can bind normally to the LDL receptor via apo E as a major ligand for the receptor. Patients with FDB tend to have plasma triglyceride concentration intermediate between that of control subjects and FH heterozygotes [81]. Kinetic data also demonstrate that, in the postabsorptive state, VLDL–apo B-100 secretion and FCR are not significantly different between FDB patients and controls [81]. These observations suggest that TRL metabolism may not be markedly disturbed in these subjects. However, the effect of mutations in the *APOB* gene on postprandial TRL metabolism has not yet been investigated in FDB patients.

7.3. *PCSK9*

The *PCSK9* gene, located on chromosome 1, is an important regulator of the LDL receptor and hence of LDL metabolism [82]. PCSK9 is a secreted protease produced mostly by the liver. In vitro and animal studies demonstrated that circulating PCSK9 binds to the LDL receptor and subsequently targets it for lysosomal degradation. Given the role of PCSK9 in the regulation of LDL removal by the liver, gain-of-function mutations in the *PCSK9* gene (such as p.D374Y) have been linked to more severe hypercholesterolemia than *LDLR* mutations [83]. Given the role of PCSK9 in the regulation of LDL receptor, it is conceivable that PCSK9 could also play an important role in postprandial TRL metabolism. Mice deficient in PCSK9 ($PCSK9^{-/-}$) are protected against postprandial hypertriglyceridemia, probably via the inhibition of TRL secretion and/or the upregulation of remnant uptake [84]. Consistent with this, Naoumova et al [85] reported that PCSK9 patients with the D374Y mutations have elevated fasting plasma triglyceride concentrations when compared with patients with *LDLR* mutation. The effect of PCSK9 mutations on postprandial TRL metabolism warrants further investigation in FH.

7.4. *ARH*

A rare autosomal recessive form of hypercholesterolemia (ARH) caused by mutations in a putative LDL receptor adaptor protein located on chromosome 1 has been described [5,86,87]. Patients with ARH have a clinical phenotype similar to homozygous FH, but the condition is less atherogenic and more responsive to cholesterol-lowering therapy [88]. In ARH, there is a defect in adaptor protein that is required for clathrin-mediated internalization of the LDL receptor by liver cells [5]. This defect appears to be specific for LDL uptake, but whether it is important on clearance of TRL remnants is unknown.

7.5. *LPL, APOE, APOCIII, and APOAV*

Gene variants in proteins involved in TRL metabolism may also govern postprandial dyslipoproteinemia in FH. Wittekoek et al [89] reported that FH patients with the *LPL* N291S mutations have elevated fasting plasma triglyceride concentrations compared with FH patients without the mutation. Hopkins et al [90] reported that FH patients with an *APOE2* allele had elevated plasma triglyceride concentration compared with FH patients without the *APOE2* allele (ie, *APOE3/E3*, *APOE4/E3*, and *APOE4/E4*). This observations was consistent with 2 other reports demonstrating that plasma triglyceride concentration was elevated in FH patients carrying 1 or 2 *APOE2* alleles [40,91]. However, the effects of these genetic mutations on postprandial TRL metabolism have not yet been demonstrated in FH. Gene variants in other apolipoproteins, such as apo C-III and apo A-V, have also been shown to play a central role in regulating the metabolism of TRLs [31,92]. Bertolini et al [40] found that FH patients carrying the –1131C allele of apo A-V had higher plasma triglyceride concentration compared with FH patients with the –1131TT genotype. The genetic effect of these apolipoproteins on postprandial TRL in FH warrants further investigation.

8. Obesity, insulin resistance, and other factors beyond FH

Triglyceride-rich lipoprotein metabolism is well recognized to be disturbed by obesity and insulin resistance (IR) [17]. The prevalences of obesity and type 2 diabetes mellitus in FH are about 30% and 6%, respectively [13]. Increased adiposity markedly increases the flux of free fatty acids to the liver. This not only stimulates hepatic gluconeogenesis and triglyceride synthesis, but also impairs hepatic extraction of insulin. Insulin resistance may further increase both de novo hepatic lipogenesis and postprandial delivery of fatty acids and triglyceride to the liver, and subsequently the accumulation of liver fat and the secretion of VLDL. Hepatic IR may also impair LDL receptor expression and activity and hence the catabolism of LDL–apo B-100. Postprandially, IR is also recognized to stimulate the intestinal secretion of CM particles [93]. Hence, obesity and IR can contribute to the accumulation of TRL in FH. Constitutional, environmental, and hormonal factors, such as increasing age, male sex, high–saturated fat diet, high alcohol intake, hypothyroidism, and menopause, may also disturb TRL metabolism and exacerbate postprandial dyslipoproteinemia in FH [94].

9. Hypothetical model integrating lipoprotein metabolism in FH

From the evidence reviewed, we propose a hypothetical model integrating the exogenous and endogenous pathways of lipoprotein metabolism in FH that could explain why this condition may be associated with postprandial dyslipoproteinemia (Fig. 1). In addition to reducing the catabolism of LDL–apo B-100, LDL receptor dysfunction in FH also increases the secretion of VLDLs. Although previous studies suggest that the

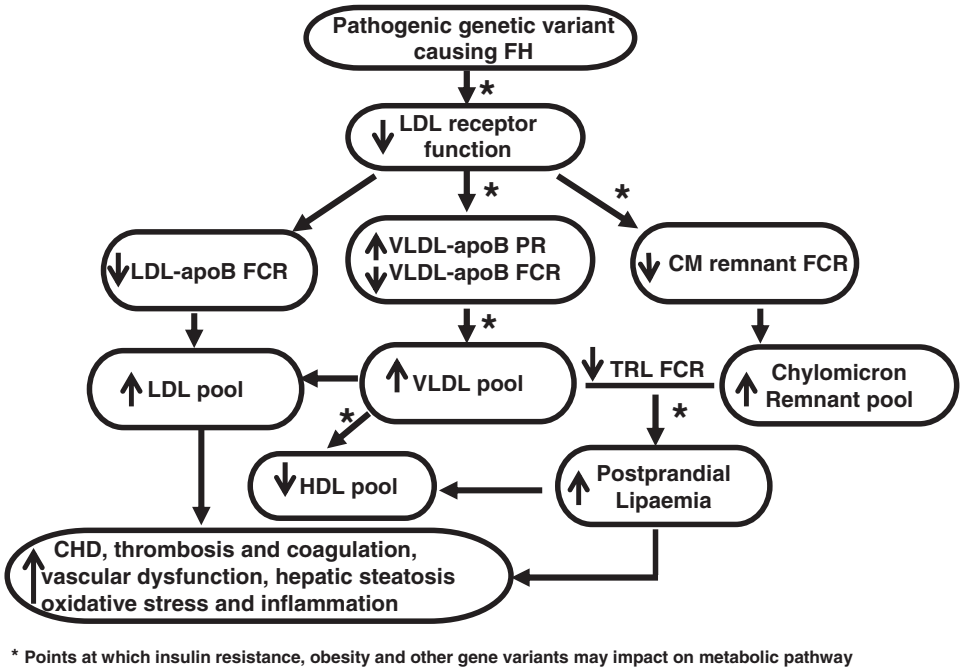

Fig. 1 – Hypothetical model integrating endogenous and exogenous lipoprotein metabolism in FH.

catabolism of VLDL–apo B-100 in FH is not different from controls, we consider that, in the postprandial state, the defects in TRL secretion in FH are likely to be further exacerbated by decreasing hepatic removals of TRLs due to increased competition between VLDL and CM remnants. Accumulation of VLDL and CM particles in plasma may enhance the formation of small, dense LDL and HDL particles that in turn can aggravate endothelial dysfunction, thrombosis, and coagulation and hence increase the risk of CHD. These pathways are considered to be disturbed by the gene defect responsible for FH and by the type of mutation in these genes. The metabolic defects shown in Fig. 1 are also to be compounded by coexistent conditions, especially obesity and type 2 diabetes mellitus. We concede that the molecular defect in FH may per se only have a small incremental effect on TRLs. However, in the presence of other factors (such as obesity and type 2 diabetes mellitus) that increase the secretion of apo B-48 and apo B-100, this molecular defect could have a major impact on postprandial lipid and lipoprotein metabolism. Hence, in our model, FH may be viewed as a necessary, but insufficient, causal factor for postprandial dyslipoproteinemia.

More research is required to fully explore our model for postprandial dyslipoproteinemia in FH. We propose further studies using larger sample sizes, mixed meals, and well-validated methods for investigating postprandial lipid and lipoprotein metabolism. A kinetic analysis of postprandial TRL metabolism using stable isotope and compartmental modeling may provide critical information on the secretion, interconversion, and catabolism of TRLs in the postprandial state. Future studies should address the impact of different genetic mutations and the effect of IR, obesity, and diabetes on postprandial TRL metabolism. The effect of postprandial dyslipoproteinemia on cardiovascular end points, such as endothelial dysfunction, also merits investigation.

10. Conclusion

We have proposed a model that integrates endogenous and exogenous lipoprotein metabolism in FH and could explain the occurrence of postprandial dyslipoproteinemia in this condition. The model, which is supported by experimental and clinical studies, may account for some of the variation in CHD risk in FH and requires to be rigorously tested.

However, postprandial dyslipoproteinemia is not a focus of standard therapy in FH at present. From a clinical perspective, treatment with statins (with or without intestinal cholesterol absorption inhibitor) is the primary treatment strategy to achieve LDL cholesterol lowering by at least 50%. Statins also contribute to modest reductions in plasma triglyceride and TRL concentrations in direct proportion to LDL cholesterol lowering [95], but are not as effective as other triglyceride-lowering agents, such as fibrate or niacin. For those FH patients on a statin with residual hypertriglyceridemia (>2.0 mmol/L fasting triglycerides), treatment should follow recently published guidelines [19,96]. This involves correcting secondary causes for hypertriglyceridemia, intensifying lifestyle modification, and probably additional therapy with fibrates, niacins, or n-3 fatty acid ethyl esters.

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Conflict of Interest

None declared.

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