Postprandial lipaemia in familial combined hyperlipidaemia

M. Castro Cabezas

Department of Vascular Medicine F02.126, University Medical Center Utrecht, P.O Box 85500, 3508 GA Utrecht, The Netherlands

Abstract

FCHL (familial combined hyperlipidaemia) is the most frequent inherited disorder of lipid metabolism leading to premature atherosclerosis. The usual phenotype in FCHL is elevated fasting plasma triacylglycerols, low HDL (high-density lipoprotein)-cholesterol concentrations and elevated plasma apolipoprotein B concentrations. The metabolic basis for this phenotype is hepatic overproduction of VLDL (very-low-density lipoprotein), which is only partly linked to the insulin resistance associated with FCHL. At this stage the molecular basis for this VLDL overproduction is not known, but emerging evidence points to a disturbed trapping of peripheral fatty acids, resulting in enhanced hepatic flux of NEFA (non-esterified ('free') fatty acids). Postprandial hyperlipidaemia with accumulation of lipoprotein remnants and NEFA have been implicated in the development of atherosclerosis in this disorder. It has been proposed that, by VLDL overproduction, fasting hypertriglyceridaemia may lead to 'overflow' of the catabolic cascade for triacylglycerol-rich particles, thereby explaining the delayed catabolism of remnants in FCHL. Delayed clearance of remnants of VLDL and chylomicrons leads to enhanced interaction of these highly atherogenic particles with the endothelium, and enhanced trans-endothelial migration of the particles, resulting in a chronic inflammatory response that is the initiation of the atherosclerotic lesion. In this process, activated leucocytes (either directly by the remnants or indirectly by released NEFA) play an important role by adherence to the endothelium and migration into the subendothelial space, where the uptake of atherogenic remnants results in a vicious cycle of activation of endothelium, leucocytes and production of cytokines.

Introduction

FCHL (familial combined hyperlipidaemia) is the most frequent familial dyslipidaemia resulting in premature atherosclerosis [1–5]. Several reports have suggested that FCHL is a monogenic disorder with different modifying genes [6–8]. However, the gene directly responsible for FCHL has not been identified yet, although several candidates have been described [9,10]. A recently identified gene on chromosome 11, the apoAV (apolipoprotein AV) gene, seems to be one of the most promising candidates due to its strong effects on fasting plasma TG (triacylglycerol; triglyceride) concentrations in FCHL [11].

The diagnosis of FCHL is based on clinical criteria, such as the presence of ‘multiple type hyperlipidaemia’ [1–5], a positive family history of premature coronary heart disease and increased plasma apoB levels, reflecting overproduction of VLDL (very-low-density lipoprotein) [12,13]. Other metabolic characteristics in FCHL are impaired chylomicron remnant clearance [14,15], high levels of small, dense LDL (low-density lipoprotein) [16], the presence of insulin resistance [17,18], disturbed postprandial NEFA [non-esterified ('free') fatty acid] metabolism [19,20] and impaired NEFA uptake by fibroblasts and adipocytes [20], resulting in enhanced NEFA flux to the liver [19,20]. Finally, decreased in vitro activity of hormone-sensitive lipase has been described in Swedish FCHL patients [21], but not in Finnish patients [22] or in Dutch patients based on in vivo studies [23].

Based on the metabolic abnormalities described in FCHL [24], several investigators have attempted to reach a consensus on the clinical identification of the FCHL phenotype [25]. It was concluded that the hyper-TG/hyper-apoB is the most characteristic presentation of patients with FCHL. This approach is justified, because several metabolic disorders linked to different genes may ultimately lead to the same phenotype of hepatic apoB overproduction and fasting dyslipidaemia. The proposed definition will help to identify patients with the FCHL phenotype in clinical practice, as long as the genetic marker for this disease has not been found.

Physiology of TG metabolism and consequences in FCHL

In the fasting state, TGs are transported in the blood in VLDLs, which are liver-derived lipoproteins that have apoB100 as their structural protein. One apoB100 is associated with one VLDL particle. In the blood, VLDLs are converted into VLDL remnants (IDLs (intermediate-density lipoproteins)) by the action of LPL (lipoprotein lipase) attached to endothelial cells [26]. For the hydrolysis of TG by LPL, apoCII present on the surface of VLDL (and chylomicrons) is a necessary cofactor. A different apolipoprotein

Key words: atherosclerosis, familial combined hyperlipidaemia, triacylglycerol, non-esterified fatty acids (NEFA), postprandial hyperlipidaemia, very-low-density lipoprotein (VLDL).

Abbreviations used: apoA-I, apolipoprotein A-I; FCHL, familial combined hyperlipidaemia; IDL, intermediate-density lipoprotein; LDL, low-density lipoprotein; LPL, lipoprotein lipase; NEFA, non-esterified fatty acids; TG, triacylglycerol (triglyceride); VLDL, very-low-density lipoprotein.

e-mail m.castrocabezas@azu.nl

©2003 Biochemical Society
Figure 1 | Aspects of postprandial lipaemia in FCHL: consequences of VLDL overproduction and an impaired C3adesArg system

In FCHL, hepatic VLDL overproduction causes delayed clearance of postprandial TG-rich particles (TRPs) due to competition at the level of LPL (1). Impaired activity of the C3adesArg/acylation-stimulating protein (C3/ASP) system will lead to an enhanced flux of NEFA (FFA) to the liver, which will in turn up-regulate hepatic VLDL secretion (2). Another consequence of this enhanced hepatic NEFA flux will be increased levels of ketone bodies (HBA, hydroxybutyric acid) during the postprandial period. Increased concentrations of TG-rich particles will stimulate the formation of small, dense LDL (3), which is easily oxidized and migrates through the endothelial barrier, resulting in foam cell formation in the subendothelium. In addition, increased concentrations of TG-rich particles will activate blood leucocytes (neutrophils and monocytes) (4) and endothelial cells (ECs) (5), resulting in increased adherence of these inflammatory cells to the endothelium. Finally, many atherogenic apoB-containing particles will adhere to the endothelium, creating a ‘marginated pool’ that will easily penetrate the vessel wall and bind to receptors on inflammatory cells located in the subendothelium.

Aspects of Postprandial Lipemia in FCHL: Consequences of VLDL Overproduction and Impaired C3/ASP system

1. Overflow of Lipolytic cascade
2. Hepatic FFA flux
3. Small dense LDL
4. Activated leukocytes
5. Activated EC’s
6. Increased Marginalization of TRP's

VLDL remnants are enriched with apoE, the preferred ligand for the LDL receptor and the hypothetical remnant receptor. The LDL receptor binds both the C-terminal part of apoB100 and the apoE on IDL. Binding to apoE results in rapid internalization of particles, in contrast with apoB100 binding, which is a slow catabolic step. Under physiological conditions, IDL is taken up by these receptors into the liver, where the lipoproteins are degraded and cholesterol is removed from the body by excretion into the bile. Part of IDL is degraded to LDL by the action of a different enzyme localized in the liver sinusoids, hepatic TG lipase.

In the postprandial state, most TGs are transported by chylomicrons, which are intestinally derived lipoproteins. These chylomicrons contain apoB48 (identical to 48% of the N-terminal part of apoB100), which is produced only in the intestine in humans. Analogous to VLDL, chylomicrons share the same metabolic pathway as VLDL and are converted into remnants by the action of LPL. Since apoB48 lacks the C-terminal moiety of apoB100, apoB48 does not bind to the apoB-binding domain of the LDL receptor, and binding and internalization is apoE-dependent.

In the event that the liver is overproducing VLDL particles, as in FCHL, the common catabolic steps for VLDL and chylomicrons will become saturated, resulting in accumulation of both VLDL and chylomicron remnants (Figure 1). This may occur at the level of LPL, hepatic TG lipase or the cellular receptors involved in the removal of these
particles. An increased residence time of these atherogenic lipoproteins in plasma will result in their enhanced binding to the endothelium, thereby creating a margined pool of endothelial cell-bound lipoproteins. This theoretically will increase the level of activation of these cells, which will expose more adhesion molecules on their surface. These series of events will ultimately lead to the adhesion of inflammatory cells (monocytes and macrophages) to the activated endothelium. Recent evidence from our laboratory has shown that this margined pool of atherogenic lipoproteins is larger in patients with FCHL than in normolipidaemic controls, and that it decreases significantly after therapy with atorvastatin [27]. This may represent an additional anti-atherogenic effect of treatment with statins that cannot be detected by measuring only fasting plasma lipids. Future studies should evaluate the importance of this margined pool of atherogenic lipoproteins in different disorders in relation to atherosclerosis. Moreover, since normalization of this margined pool was not achieved in FCHL by monotherapy with atorvastatin [27], more aggressive interventions will be necessary in patients with FCHL.

**Postprandial lipaemia and atherosclerosis in FCHL**

Native chylomicron remnants are atherogenic lipoproteins [28] that can induce foam cell formation without any modifications, in contrast with LDL particles, which must be modified before they can induce the transformation of monocytes/macrophages into foam cells [29]. In patients with FCHL, the vessel walls of these subjects are exposed to elevated concentrations of these atherogenic lipoproteins throughout the day [30,31]. The consequence is impairment of vessel function and increased subendothelial accumulation of remnants, leading to plaque formation [32,33]. Indirect detrimental effects of this postprandial hyperlipidaemia may be uncontrolled activation of leucocytes by TG-rich particles and their remnants [34,35]. This may result in activation of endothelial cells, leading to enhanced adherence of pro-inflammatory cells to the endothelium, causing damage to the endothelial barrier by the production of oxidative stress and by cytokines [33] (Figure 1). The role of blood-derived leucocytes in postprandial lipaemia has not been studied in detail, and future studies will investigate this aspect in FCHL subjects.

A different aspect of the inflammatory effects of postprandial lipaemia is activation of the complement system [35,36]. It has long been known that one of the complement-derived factors (C3adesArg; acylation-stimulating protein) plays an important role in the metabolism of NEFA by peripheral cells, especially adipocytes [20]. C3adesArg is a potent stimulator of cellular NEFA uptake and its intracellular esterification into TGs [20]. These NEFA are released in the circulation upon hydrolysis of TG-rich particles, and therefore C3adesArg is an important molecule in the postprandial channelling of NEFA. Evidence has been provided that, during postprandial lipaemia, C3 plasma concentrations increase significantly in patients with premature atherosclerosis and in healthy controls, reflecting activation of this precursor of C3adesArg (a split product of C3) [36]. This has not been shown consistently by other groups, but this discrepancy may have been caused by the different meal compositions used in the different studies [37]. In addition, treatment with statins has been shown to reduce complement activation, paralleled by a decrease in postprandial lipaemia in normolipidaemic patients with coronary heart disease [36]. In patients with FCHL, an abnormal postprandial C3 activation pattern has been demonstrated [35]; this occurs in both males and females [38], and is not fully normalized after therapy with statins, despite improvement of postprandial triglyceridaemia. This impaired C3 activation in FCHL has been linked to the enhanced hepatic NEFA flux characteristic of FCHL and the delayed clearance of postprandial atherogenic remnants [31,35,38] (Figure 1).

**FCHL and the metabolic syndrome**

Since FCHL and the metabolic syndrome share so many clinical characteristics and metabolic disturbances [5,17,18], it has always been difficult to separate the two disorders. One of the striking differences may be the mode of inheritance and the effects of environmental factors on the expression of the two phenotypes. While in FCHL a clear dominant inheritance pattern is observed, with the environment as important modifier, the influence of diet and lifestyle has a more potent impact in the metabolic syndrome. For example, dietary interventions and lifestyle modifications may be sufficient to correct several metabolic abnormalities in the metabolic syndrome [39], whereas drug treatment is almost always necessary in FCHL [5]. Furthermore, the prevalence of the metabolic syndrome is much higher than the predicted prevalence of FCHL [40]. Finally, derangements of carbohydrate metabolism seem to play a more important role in the expression of the metabolic syndrome than in FCHL, and plasma apoB levels in FCHL are not directly associated with insulin resistance [41].

**Conclusions**

In conclusion, in addition to the well-known direct effects of chylomicron remnants on the endothelium, postprandial hyperlipidaemia as a consequence of enhanced hepatic flux of NEFA and VLDL overproduction in FCHL result in an enlarged pool of atherogenic margined lipoproteins. Postprandial activation of blood-derived leucocytes and chronic stimulation of the endothelium are additional atherogenic mechanisms that play a role in postprandial atherogenesis in FCHL. Since normalization of postprandial hyperlipidaemia in FCHL is difficult to achieve, aggressive intervention will be necessary to correct this abnormality. Future studies should be designed to investigate whether improvements in postprandial NEFA metabolism in FCHL will correct the hepatic VLDL overproduction and the
fasting hyperlipidaemia, and ultimately decrease the risk of atherosclerosis [42].

References