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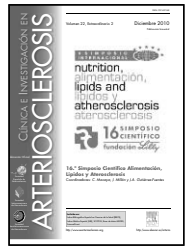

16.º SIMPOSIO CIENTÍFICO ALIMENTACIÓN, LÍPIDOS Y ATEROSCLEROSIS

Familial combined hyperlipidemia: an oligogenic disorder

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Familial combined hyperlipidemia (FCHL) was first described in Seattle and in Helsinki in the early 1970s. Since then it has been studied around the world[1]. Goldstein et al. reported that a portion of the families of probands with premature coronary artery disease have either hypertriglyceridemia or hypercholesterolemia or both in the same family which they described as a familial disorder with different combinations of dyslipidemia, thus FCHL. It was later shown that a single individual might be hypertriglyceridemic on one occasion and hypercholesterolemic on another with elevated apolipoprotein B in either VLDL or LDL, respectively.

This elevated apoB was found to be due to increased hepatic secretion of apoB in VLDL and LDL from pre-synthesized apoB by many laboratories. Although increased hepatic secretion of VLDL has been found consistently, increased apoB synthesis does not appear to account for this secretion. ApoB is constituitively synthesized in the liver, suggesting that the defect occurs post-translationally, perhaps due to impaired proteosomal degradation of preformed apoB that leads to the apparent increased secretion of the protein.

It has been confirmed that elevated triglyceride and/or cholesterol levels are characteristic of FCHL. Increased numbers of small-dense LDL have been noted by many investigators and in combination with elevated apoB levels. Whether there are increased levels of VLDL or LDL, elevated apoB levels in the presence of small-dense LDL seem to be present consistently[2]. FCHL might be a "two hit" disorder with one defect in apoB metabolism and the other associated with the dyslipidemia. Bimodal distribution of apoB is present in FCHL families, but only in those who have small-dense LDL[3]. In addition complex segregation analysis suggests that apoB level is inherited independently from LDL peak size or density[4]. One hit would be related to elevated apoB levels and apoB containing particle number, the other would be related to factors associated with hypertriglyceridemia, small-dense LDL particles and decreased HDL_2. One example of the dyslipidemia would be the obligate heterozygote parents of children with lipoprotein lipase deficiency who have such dyslipidemia[5]. Of note, about 20%of probands with FCHL have abnormal values of post-heparin plasma LPL activity[6]. More commonly central obesity with increased visceral fat and insulin resistance has been noted as the precursor to dyslipidemia[7]. However, this central obesity-insulin resistant syndrome does not account for the elevation in apoB levels[8]. The central obesity-insulin resistant syndrome (metabolic syndrome) occurs in type 2 diabetes, as well as in FCHL; these two disorders may account for most, if not all, of the premature coronary disease associated with the metabolic syndrome[9,10].

Plasma VLDL levels in FCHL are smaller than normal. These particles are more abundant, but contain less triglyceride per particle. This is in contrast to monogenic benign familial hypertriglyceridemia (FHTG) where VLDL particle number is normal but the particles are bigger than normal and very triglyceride-rich[11]. It also is not what would be expected as reported by others[12] where larger VLDL are proposed to be more predictive of atherosclerosis. Both FCHL and FHTG are associated with small-dense LDL, but the level of small-dense LDL is high in FCHL and low in FHTG. HDL is abnormal in both disorders, but due to different mechanisms. Large triglyceride-rich VLDL in FHTG lead to triglyceride-rich LDL and HDL via cholesteryl ester transfer protein, which become small-dense LDL and HDL particles in the in a normal weight patient with normal levels of hepatic lipase activity. In contrast small, triglyceride-poor VLDL exchange less with LDL and HDL, but this occurs in the presence of visceral obesity and elevated hepatic lipase activity. In FHTG the net effect is triglyceride enrichment of HDL with depletion of the cholesteryl ester core, while in FCHL the net effect is a decrease in the

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Table 1 It is hypothesized that interaction of 2 separate sets of defects, one related to apoB levels and one related to lipids, leads to familial combined hyperlipidemia (FCHL). Within each of these sets of defects multiple different abnormalities are likely to be involved

Genetics of FCHL Interaction of 2 defects?	
Apolipoprotein B	**Triglyceride/cholesterol**
Not LDL receptor	Upstream factor 1 (1q21) [Finland, Mexico, Holland, USA]
Not apoB gene	AI, CIII, AIV, AV (11q13-) [Finland, Holland, USA]
	Lipoprotein lipase (8p22)

buoyant HDL_2 particle that is alpha 3 or the apoAI without AII particle.

These differences in LDL size and number and the specific differences in HDL may explain the excess of coronary disease in FCHL in the Seattle Myocardial Infarction Studies of Goldstein et al. or the Seattle Hypertriglyceridemic Family Study of Brunzell et al. In a twenty year follow up of cardiovascular mortality of subjects from these two studies, premature coronary disease was very common in FCHL, but non-existent in FHTG[13].

The molecular and genetic defects have been elucidated in most of the Mendelian disorders of lipid metabolism (see Molecular and Metabolic Basis of Inherited Disease). This has not been the case for FCHL. If one accepts the "two hit" hypothesis that FCHL is oligogenic, perhaps due to genes associated with the triglyceride, small-dense LDL and decreased HDL2 component, the dyslipidemia can have different etiology in each family. As noted above, some families seem to have a monogenic disorder with 1/2 normal levels of LPL activity, while others are associated with the multiple components of the metabolic syndrome. Genome wide association scans have found genes associated with this atherogenic dyslipidemia. Upstream factor 1 on chromosome 1q21 has been associated with FCHL in families in Finland, Mexico, the Netherlands, and in the United States. Variation in the apoAI, CIII, AIV, AV locus on chromosome 11q13 has been found in FCHL in Finland and the Netherlands. Evidence for genes affecting apoB levels in FCHL has been scarce. The apoB and LDL receptor genes are not associated with FCHL. Although some evidence of GWAS for apoB has been found, this has not persisted after adjustment for the triglyceride and HDL cholesterol level or LDL particle size. The major gene, or more likely genes, accounting for elevated apoB levels remains an area of great interest.

In spite of the complexity of FCHL, treatment with combination drug therapy has been shown to have a major effect on coronary artery disease progression in small studies[14] effected, in part, by specifically decreasing the number of small-dense LDL via a drug induced reduction in hepatic lipase activity[15]. Two large studies are underway, Aim High and HPS Thrive, with combination drug therapy in such patients

Conflict of interest

The author declares he has not any conflict of interest.

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1. The author apologizes for not using multiple relevant references due to editorial restriction.
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