Familial Combined Hyperlipidemia and Insulin Resistance
Distant Relatives Linked by Intra-abdominal Fat?

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Familial combined hyperlipidemia (FCHL), originally identified by Goldstein et al., Rose et al., and Nikkila et al in the early 1970s, is a metabolic defect in lipoprotein metabolism that is associated with a predominance of small, dense LDL particles and appears to be a consequence of hepatic overproduction of apolipoprotein B-100 (apoB-100). Characteristic lipoprotein abnormalities include increases in apoB with variable manifestations of hyperlipidemia, including hypertriglyceridemia and/or increases in LDL cholesterol. Although FCHL has historically been viewed as a monogenic disorder, more recent analyses suggest that the disorder may be predicted by a threshold model in which apoB level genotype and LDL subclass phenotype interact to increase the risk of FCHL. Despite the fact that FCHL appears to be the most common genetic cause of hyperlipidemia and almost certainly predisposes to more coronary heart disease (CHD) events than any other known genetic disorder, the mechanism for increases in hepatic overproduction of apoB-containing lipoproteins remains unclear. Moreover, although genes have been identified that may contribute to the dyslipidemia of FCHL, a genetic explanation for the increases in apoB production is lacking.

Insulin resistance is also associated with small, dense LDL and lipoprotein abnormalities, including hypertriglyceridemia and/or reductions in HDL cholesterol. However, increases in apoB are not distinctive of reductions in insulin action. Presently, much of the evidence links the metabolic abnormalities of the insulin resistance syndrome to modifications of body fat distribution, ie, relative increases in intra-abdominal fat (IAF). Presently, it remains unclear whether FCHL is accompanied by increases in IAF; however, patients with FCHL are insulin resistant. Thus, it is important to discern the relative interdependence of insulin resistance and apoB, both potential explanations for the increase in CHD risk in FCHL patients.

The study reported by Purnell et al in this issue of *Arteriosclerosis, Thrombosis, and Vascular Biology* addresses this relationship in a small number (n=11, 6 men and 5 women) of well-characterized and zealously studied subjects with FCHL and age- and/or age- and weight-matched controls. Unfortunately, only 1 of the 22 age- and weight-matched controls was female. When compared with age-matched controls, FCHL subjects were again demonstrated to be insulin resistant, but not when compared with age- and weight-matched controls who also had increases in IAF. Importantly, the insulin resistance or amount of IAF in FCHL subjects failed to explain the levels of apoB, which were higher for any level of insulin action in FCHL subjects than in age- and weight-matched controls.

Thus, it would appear that the risk for CHD in FCHL extends beyond insulin resistance and increases in IAF and also likely beyond the presence of small, dense LDL, which occurs in both. ApoB and/or the lipoprotein(s) in which apoB is transported appear to be the culprit. This raises important questions for clinicians in how they assess cardiovascular risk in the presence of a lipoprotein phenotype that could typify insulin resistance and/or FCHL. If the presence of small, dense LDL were the most important determinant of increased CHD risk, then these lipoproteins should be quantified and therapeutic steps taken to reduce their quantity. However, despite the evidence for small, dense LDL as a predictor of CHD events, >90% of subjects with fasting triglycerides >200 mg/dL have small, dense LDL, and triglycerides >200 mg/dL alone are not strong, independent predictors of CHD. Yet FCHL with or without increases in LDL cholesterol is associated with a substantial increase in CHD risk. Why is this the case? Additionally, insulin resistance has increasingly been identified as a conglomerate of CHD risk factors, including hypertriglyceridemia and small, dense LDL. Yet the relative predictability of the insulin resistance syndrome for CHD appears to be largely dependent on the level of apoB. In the Quebec Cardiovascular Study, the impact of hyperinsulinemia, a marker of insulin resistance, on CHD events was substantially magnified by the presence of elevated apoB, ie, an apoB level >120 mg/dL. Is it then the insulin resistance or the number of circulating atherogenic lipoprotein particles superimposed on insulin resistance (FCHL?) that raises the greatest concern?

Published literature and the current report of Purnell et al would support the following approach to dyslipidemia in the setting of an increasingly adipose-centric population (amount and location of body fat). When fasting triglycerides (ie, >200 mg/dL) and LDL cholesterol (ie, >160 mg/dL) are both elevated and the family history is consistent with a similar lipid profile and/or premature CHD, small, dense LDL and elevations in apoB can both be assumed to be present, the latter because there is only 1 apoB molecule per particle and most of the apoB is carried in LDL. Thus, quantification of either is unnecessary. Familial dysbeta-lipoproteinemia should of course be ruled out. However, if fasting triglycerides are elevated (ie, >200 mg/dL) and LDL cholesterol is normal (ie, <130 mg/dL), small, dense LDL

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*Arterioscler Thromb Vasc Biol.* 2001;21:469-470.)

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again will be assumed to be present, but levels of apoB remain uncertain. In this clinical setting, apoB level should be measured by qualified assays, and, if elevated (ie, >120 g/dL), FCHL and increased CHD risk should be assumed. In this case, therapy should be targeted not only to LDL cholesterol goals (National Cholesterol Education Program [NCEP]) but also to reduce the number of potentially atherogenic (apoB-containing) particles. This approach circumvents the assessment of insulin resistance, which to a large extent requires an independent approach. Despite the connection between insulin resistance, IAF, and FCHL, apoB remains the important distinction that likely confers the increased CHD risk and needs targeted attention and therapy.

Because assays for apoB remain less than optimal, the addition of apoB to NCEP guidelines will likely be delayed past NCEP:ATP-III. Yet the utility of a reliable and validated assay for apoB can add much to the evaluation of patients with hypertriglyceridemia. Once LDL cholesterol levels are below goal, whether or not further reductions of apoB are associated with reductions in CHD risk remains untested. Nevertheless, at present it may be the best avenue to pursue. Reductions in insulin resistance independent of reductions in apoB may have a path of benefit on CHD outcomes entirely of their own. The article by Purnell et al helps to establish the relationship, but important differences remain between insulin resistance and FCHL.

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doi: 10.1161/01.ATV.21.4.469

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://atvb.ahajournals.org/content/21/4/469

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