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Diagnosis and treatment of high density lipoprotein deficiency

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ABSTRACT

Low serum high density lipoprotein cholesterol level (HDL-C) <40 mg/dL in men and <50 mg/dL in women is a significant independent risk factor for cardiovascular disease (CVD), and is often observed in patients with hypertriglyceridemia, obesity, insulin resistance, and diabetes. Patients with marked deficiency of HDL-C (<20 mg/dL) in the absence of secondary causes are much less common (<1% of the population). These patients may have homozygous, compound heterozygous, or heterozygous defects involving the apolipoprotein (*APO)AI, ABCA1, or* lecithin:cholesterol acyl transferase genes, associated with apo A-I deficiency, apoA-I variants, Tangier disease , familial lecithin:cholesteryl ester acyltransferase deficiency, and fish eye disease. There is marked variability in laboratory and clinical presentation, and DNA analysis is necessary for diagnosis. These patients can develop premature CVD, neuropathy, kidney failure, neuropathy, hepatosplenomegaly and anemia. Treatment should be directed at optimizing all non-HDL risk factors.

High density lipoproteins (HDL) are generally spherical lipoprotein particles with a diameter of about 6–11 nm, and usually have α mobility on electrophoresis. HDL has been defined as having a density of 1.063–1.21 g/mL in plasma. Normal HDL particles contain (weight %) about 50% protein, 25% phospholipid, 20% cholesterol, and 5% triglyceride (TG). About 70% of the cholesterol is in the esterified form. In HDL the protein, phospholipid, and free cholesterol are on the surface, with cholesteryl ester (CE) and TG in the core. The major proteins of HDL are apolipoprotein (apo) A-I and apoA-II, present in a molar ratio of about 3:1, with many other proteins including apoA-IV, apoA-V, apoC-I, apoC-II, apoC-III, and apoE being found on HDL particles in much smaller amounts. The production and plasma residence time of HDL apoA-I in normal subjects are about 12 mg/kg/day and 4.0 days, respectively, while for apoA-II these values are about 3.0 mg/kg/day and 4.5 days, respectively. Other apolipoproteins within HDL have much lower plasma residence with these values of about 0.5–2.0 days. HDL has been further divided into HDL_2 of density 1.063–1.125 g/mL and HDL_3 of density 1.125–1.21 g/mL. In patients with low HDL, there is a much greater decrease in HDL_2 than in HDL_3.

HDL is quantified in the general laboratory by measuring its cholesterol content using automated enzymatic analyses after removing all other lipoproteins by precipitation. An HDL-C level of <40 mg/dL in men and <50 mg/dL in women has been defined as decreased, and has been associated with an increased risk of cardiovascular disease (CVD). HDL-C is

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Abbreviations and Acronyms

ABC = ATP binding cassette

APO = apolipoprotein

CE = Cholesterol ester

CETP = Cholesterol ester transport protein

CHD = Coronary heart disease

CVD = Cardiovascular disease

DM = Diabetes mellitus

FED = Fish Eye Disease

FH = Familial Hypercholesterolemia

FLD = Familial Lecithin: Cholesteryl Ester Acyltransferase Deficiency

HDL = High –density lipoprotein

HDL-C = High –density lipoproteincholesterol

LCAT = lecithin:cholesterol acyl transferase

LDL = Low-density lipoprotein

LDL-C = Low-density lipoprotein cholesterol

LIPG = endothelial lipase gene

Lp(a) = Lipoprotein a

MI = Myocardial infarction

SR = Scavenger receptor

TD = Tangier Disease

TG = Triglyceride

VLDL = Very low-density lipoprotein

VLDL-C = Very low-density lipoprotein cholesterol

one of the parameters used in the risk calculator for CVD risk.[1] It has been recommended by the guidelines that subjects with CVD, diabetes mellitus (DM), an elevated low density lipoprotein cholesterol (LDL-C ≥190 mg/dL) and an estimated 10 year CVD risk of ≥7.5% be considered for statin therapy in addition to lifestyle modification.[1,2] Recent expert opinion guidelines indicate that non statin agents such as ezetimibe, anion exchange resins, and proprotein convertase subtilisin kexin 9 inhibitors can be used along with statins to get at least a 50% decrease in LDL-C with an option to get LDL-C levels to <70 mg/dL in CVD patients and to <100 mg/dL in high risk patients.[3]

A common observation in the statin intervention trials was that patients with dyslipidemia (elevated TGs >200 mg/dL and decreased HDL-C <35 mg/dL) had the highest residual CVD risk. Moreover the addition of fenofibrate to statin therapy in DM subjects was not shown to provide significant benefit in CVD risk reduction, except in the dyslipidemic subgroup.[4] The same was true for the addition of niacin to statin therapy in CVD patients selected for having an HDL-C level <40 mg/dL.[5] Only those subjects with TG values >200 mg/dL and HDL-C values <32 mg/dL got benefit.[5] Interestingly, in the Japan Eicosapentaenoic Acid (EPA) Lipid Intervention Trial, the addition of EPA to statin therapy in hypercholesterolemic patients did lower CVD risk by 19%; however this risk reduction was most striking (–53%) in patients with dyslipidemia, despite no clinically significant effects on lipid levels.[6]

In studies of families with premature CVD it was originally documented that about 15% of these families had familial combined hyperlipidemia with elevations of both total plasma cholesterol and TG levels, and about 1% had familial hypercholesterolemia (FH).[7] In our own studies of families with premature CVD (age <60 years), we measured plasma concentrations of total cholesterol, TG, LDL-C, HDL-C, apoB, and lipoprotein (a) or Lp(a). We noted that 19% of families had Lp(a) excess, 15% had familial dyslipidemia (high TGs and low HDL-C), 14% had familial combined hyperlipidemia (mostly also with low HDL), 5% had isolated apoB elevation, 4% had isolated low HDL (hypoalphalipoproteinemia), and 1% had FH.[8,9] Cut points utilized were 10th and 90th percentile values for normal age and gender matched controls from the Framingham Offspring Study. These data indicate that low HDL-C in families with premature CVD is frequently associated with either elevated TGs or elevations of both TGs and LDL-C.

Our own early studies indicated that patients with very high TG levels (>500 mg/dL) had very low HDL-C values.[10] These patients were subsequently shown to have markedly enhanced clearance of HDL apoA-I.[11] Moreover in the Framingham Offspring Study low HDL-C levels were significantly associated with hypertriglyceridemia, obesity, DM, male gender, sedentary lifestyle, and cigarette smoking.[12] In men selected for CVD, low HDL-C (<40 mg/dL), LDL-C <140 mg/dL, and TG levels <150 mg/dL in the Veterans Affairs HDL Intervention Trial (VA-HIT), almost all subjects were overweight or obese, many were insulin-resistant, and 25% were diabetic.[13] Moreover in this trial the occurrence of new CVD and the benefit of fibrate therapy were much less dependent on levels of HDL-C or TGs than on the presence or absence of insulin resistance.[13] The overall data indicate that HDL-C levels in the general population are more strongly affected by TGs, body mass index and insulin resistance than genetic factors.

HDL Particle Analysis

HDL particles have been characterized by ultracentrifugation, nuclear magnetic resonance, one dimensional gel electrophoresis, high performance liquid chromatography, and ion mobility. These methods in our view lack the resolution and specificity provided by two dimensional gel electrophoresis of whole plasma followed by immunoblotting with apoA-I specific antibodies, developed by Asztalos and Roheim.[14] In this analysis there are five major HDL particles which are separated by size and charge. There are two major discoidal HDL particles: 1) very small preβ-1 migrating HDL of about 5.6 nm in diameter containing only apoA-I and phospholipid (about 6% of total apoA-I), and 2) small α-4 HDL of about 7.4 nm in diameter containing apoA-I, phospholipid, and free cholesterol (about 14% of total apoA-I). Then there are three larger spherical HDL particles all of which have α mobility: 1) medium α-3 HDL of about 8.1 nm in diameter containing both apoA-I and apoA-II, as well as phospholipid, free and esterified cholesterol, and TG (about 16% of total apoA-I), 2) large α-2 HDL of about 9.2 nm in diameter containing the same constituents as α-3 HDL (about 40% of the total apoA-I), and 3) very large α-1 HDL of about 11.0 nm in diameter containing the same constituents as α-3 and α-2 HDL except without apoA-II (about 16% of total apoA-I). About 8% of