Health and Hypercholesterolemia

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Hypercholesterolemia is a major risk factor for coronary heart disease (CHD). Hypercholesterolemia can be divided into non-familial and familial conditions. The primary manifestation of both hypercholesterolemic conditions is an increased risk to CHD. Generally, blood cholesterol levels are in the range of 240-350 mg/dl in non-familial condition and the figures can even be as high as 290 mg/dl up to 400 mg/dl or higher in familial condition with serum triglyceride concentrations within the reference range.

Non-familial hypercholesterolemia is polygenic. It is the most common form of elevated serum cholesterol concentrations. This condition is due to a susceptible genotype aggravated by excessive saturated fat, *trans*-fatty acid, and cholesterol intake (the actual effect of cholesterol intake is small). The involved genes have yet to be discovered.

For familial conditions, they are monogenic disorders mostly caused by mutations in two major genes that control blood-cholesterol levels, i.e., low-density lipoprotein (LDL) receptor and apolipoprotein (apo) B genes. Mutations in the gene encoding for the LDL receptor cause familial hypercholesterolemia (FH), resulting in impaired binding and uptake of low density lipoprotein (LDL) from the circulation. FH is clinically characterized by autosomal dominant hypercholesterolemia, tendon xanthomas and coronary artery disease at an early age.[1] Now, over 900 different FH-related mutations at the LDLR locus have been identified worldwide. Mutations in apo B gene cause another dominantly inherited genetic disorder with similar clinical manifestations to FH, namely familial defective apo B-100 (FDB).[2] In this disorder, disruption of LDL - receptor mediated clearance is caused by a defect in the apo B-100 protein, the structural protein and ligand of LDL, due to a mutation in the corresponding gene. The defective binding of LDL to its receptor has been shown to be mainly due to a single amino acid substitution at position 3500 in apo B-100, viz R3500Q.

FH and FDB are the two most frequently inherited diseases that underline genetic defects in a small proportion of patients suffering from premature atherosclerotic heart disease. The frequencies of these disorders in heterozygous form are approximately 1 in 500 (0.2%) in most populations. However, in some populations the frequency of FH can be much higher due to founder gene mutations. In FH patients the CAD risk was 8.5 relative to unaffected family members, whereas FDB patients had a 2.7-fold higher risk of CAD than unaffected relatives.3 The frequency of FH was previously estimated to be 10-20% in CAD patients. Identification of these individuals with either FH or FDB are justified because prevention of atherosclerotic CAD can be manipulated via dietary control and/or cholesterol-lowering therapy (i.e., statins are effective in high-risk population). Treatment of patients with heterozygous FH should be considered from childhood. Nutritional advice, including energy intake to control overweight, avoidance of foods rich in saturated fat and cholesterol and inclusion of soluble fibers and soy protein in the diet may provide enough changes to satisfactorily control cholesterol levels in children. However, sometimes it is necessary to add cholestyramine, the only drug formally accepted for use in children after the age of 10. Early adoption of active physical exercise and education on the benefits of smoking avoidance is essential. In the most prevalent polygenic forms of primary hypercholesterolemia, the initial treatment is modifying lifestyles. Quitting smoking, dietary modifications and regular physical exercise may well normalize the lipid profile. The evolution should be monitored for up to two months (in secondary prevention or high-risk patients) or even up to six months (in primary prevention in low-risk patients) before adding any hypolipidemic medication. The choice of drugs depends on the prevalent lipid profile. In isolated moderate hypercholesterolemia, the first choice is a statin, the second is cholestiramine, and the third a 2nd generation fibrate (fenofibrate, bezafibrate or ciprofibrate).

Diagnosis of FH (or FDB) should be early and accurate, so that the treatment and prevention of CAD can be initiated since childhood. However, clinical and biochemical diagnoses of FH are inaccurate since phenotypes are variable. For example, xanthoma is scarcely found in most FH cases and hypercholesterolemia may be later expressed in life. These characteristic FH phenotypes may be untimely recognized, i.e., by the time of CAD or myocardial infarction expression. DNA-based diagnosis is now accepted as an unequivocal tool for identification of FH (and FDB) cases. Early diagnosis of family members or relatives of an FH (or FDB) case can be feasible by DNA tests. DNA diagnosis can identify cases at any age as well as assure non-cases who may be hypercholesterolemic from dietary or life-style factors, i.e., non-familial polygenic condition. Thus it initially requires different therapeutic approaches. Practically, clinical and biochemical diagnosis with indication of FH or possible FH (or FDB) in an individual should be identified and confirmed for a causative mutation at the DNA level which can be subsequently used to search for carrier(s) among the family members of an identified case. The carrier(s), if any, can be prevented from developing coronary artery disease with an appropriate diet, lifestyles and therapeutic treatment.

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