Reverse cholesterol transport substantially influences the individual risk of coronary heart disease in hypercholesterolaemic patients

See page 465 for the article to which this Editorial refers

The current extensive interest in research of infectious disease[1] or, more generally, participation of the immune response in the pathogenesis of coronary atherosclerosis[2] may partly be as a result of the role played by traditional risk factors in this disease. Although there is no doubt the multifactorial atherogenic process includes numerous pathogenic effects, a high intravascular concentration of LDL-particles, their accelerated inflow into the subendothelial space of the arterial wall, progressive chemical modification, and scavenger pathways of these modified particles by monocytes and foam cells play a crucial role in the development of coronary atherosclerosis. The monogenic defect in the LDL receptor locus — familial hypercholesterolaemia — is the best evidence supporting the lipid theory of atherosclerosis. Homozygotes with this defect develop vulnerable coronary plaques within the first years of life in the absence of any other coronary heart disease risk factor. Although coronary atherosclerosis develops in the heterozygous form much more slowly, the fact that their frequency in this form is more than a 1000-times higher compared to the homozygous form, constitutes a common feature of young myocardial infarction survivors.

Molecular genetics of familial hypercholesterolaemia has expanded the body of our knowledge of this autosomal dominant disease, and about 300 different defects in the LDL receptor gene locus have been described to date. ‘Null mutations’ generating no LDL-receptor protein are associated with high LDL-cholesterol concentrations and, probably, more frequent myocardial infarction in young age compared to other point mutations[3]. Despite this, a proportion of patients with the heterozygous form of familial hypercholesterolaemia survived to the 7th or 8th decade of life even before the ‘statin era’, and no explanation for this discrepancy, between high intravascular LDL concentrations and the absence of clinical complications, has been proposed as yet. Other than, for example, the low individual vulnerability of monocytes to convert into residual macrophages in these familial hypercholesterolaemia individuals without coronary heart disease until later in their life, their ability to transfer abundant LDL-cholesterol from peripheral tissue to the liver, have also to be considered. Data from Real and co-workers from the University of Valencia, published in this issue, support this explanation[4]. In this case-control study, 33 familial hypercholesterolaemia patients surviving myocardial infarction are compared to 33 controls, familial hypercholesterolaemia patients without clinical complications of atherosclerosis. The cases and controls were matched for age, sex and body mass index. The most important characteristic of the two groups was their identical prevalence of one of the 12 different LDL mutations. More than 505 patients in both groups displayed one of five ‘null mutations’ either with deletion or with a stop codon. The remaining mutations represent point mutations with a frequency from 2 to 8 in the total number of 66 patients. This complete molecular definition is essential as ‘null-allele’ defects — compared to other mutations in the LDL gene locus — may be associated with an increased likelihood of myocardial infarction. The molecular genetics-based definition of familial hypercholesterolaemia is substantial, as today it seems to be the only technique allowing differentiation of familial hypercholesterolaemia from the more severe forms of polygenous hypercholesterolaemia. In the presented papers, the subgroups of cases and controls are genetically very well defined and comparable.

Of all the coronary heart disease risk factors analysed, the cases and controls did not differ in blood pressure, diabetes prevalence, smoking, total cholesterol, LDL-cholesterol, VLDL-cholesterol, or apoprotein B; also the difference in triglyceride concentration did not reach statistical significance. Significantly lower HDL-cholesterol and increased higher total cholesterol: HDL-cholesterol ratios were found in cases compared to controls. The low
HDL-cholesterol levels associated with coronary heart disease, together with increased total cholesterol: HDL-cholesterol ratios suggest a decrease in reverse cholesterol transport. In this pathway[5], every peripheral cell may discard excessive molecules of intracellular cholesterol. Unesterified cholesterol is first transferred to nascent apoprotein AI-containing HDL particles with the participation of ATP cassette-binding protein 1. On reaching intravascular space, this cholesterol is esterified by lecithin-cholesterol-acyltransferase. HDL-cholesterol esters can be either transported to apoB-containing particles in exchange for triglyceride (through cholesterol ester transfer activity protein), or selectively taken up by the liver through the action of a scavenger receptor (SRB 1). During this process, vulnerable coronary plaques are able to decrease their cholesterol content, the presence of monocytes and macrophages, and progressively reach a more stable status. The activity of reverse cholesterol transport is influenced by both genetic and environmental factors. The absence of a difference in body mass index between controls and myocardial infarction survivors among familial hypercholesterolaemia patients may suggest that a difference in environmental factors is less probable, although inclusion of data about a possible difference in physical activity or alcohol consumption would have been a major plus. Then accelerated production of apoprotein AI and apoprotein AIV, or increased lipoprotein lipase activity or decreased activity of SRB 1 must be considered in familial hypercholesterolaemia individuals without clinical complications.

Even the difference in triglyceride concentration between controls and cases did not reach statistical significance; it was increased by 50% in cases. Given the well-known high triglyceride variability, this difference is not enough to reach statistical significance in these relatively small compared groups. As the triglyceride concentration in cases is much higher than the recently defined desirable upper level for serum triglyceride concentrations (1.6 mmol. l⁻¹) then more atherogenic remnant particles or intermediate density lipoproteins are likely to be presented in the plasma of cases. These data also suggest a higher frequency of individuals with small dense LDL particles among cases.

There has been a strong history in the treatment of coronary heart disease due to LDL particle concentration intervention, which is then shown to be beneficial in several randomized trials. New therapies for treatment of atherosclerotic coronary disease are still needed, especially those related to HDL metabolism and accelerated reverse cholesterol transport. A decrease in triglyceride-rich lipoprotein concentration together with a significant increase in HDL concentration by fibrate is one possible option[6]. Despite the changes, the next decade will witness the transition of molecular genetic knowledge and gene therapies, from the laboratory and pre-clinical studies to clinical trials[7]. For this approach, well genetically defined groups, as presented for example in Real’s paper, must be found and studied.

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References