Regression of Femoral Atherosclerosis

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The scientific community has by now generally accepted that human atherosclerosis development can be influenced by therapeutic means. This insight has mainly been based on studies of the coronary arteries, the conclusive one being the Cholesterol Lowering Atherosclerosis Study (CLAS)\textsuperscript{1} but supported by studies like the National Heart, Lung, and Blood Institute (NHLBI) study,\textsuperscript{2} the Helsinki Coronary Study,\textsuperscript{3} the Leiden Intervention Trial,\textsuperscript{4} the recently published Lifestyle Heart Trial,\textsuperscript{5} the Program on the Surgical Control of the Hyperlipidemias (POSCCH),\textsuperscript{6} and the Familial Atherosclerosis Treatment Study (FATS).\textsuperscript{7} Atheroma change was estimated by expert panels in all these studies except the FATS, in which a computer-assisted visual system was used,\textsuperscript{8} and the Lifestyle Heart Trial. Treatment has in all these instances been by plasma lipid regulation. Recently one study was published on the effect of the calcium-channel blocker nifedipine on coronary atherosclerosis progression.\textsuperscript{9}

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The first uncontrolled observations of human atherosclerosis regression after plasma lipid regulation was made of the femoral arteries.\textsuperscript{10} From these observations the Blankenhorn group in Los Angeles pioneered a method by which the subjective judgment by the human eye could be eliminated: computer estimation of atherosclerosis based on microdensitometric scanning of arteriograms.\textsuperscript{11} The group chose the femoral arteries because of the lesser difficulty in creating algorithms for computer estimation; the arteries are relatively straight, they do not move during the examination, and high resolution x-ray films could be obtained. Others followed the work of Blankenhorn et al and further developed methodological precision.\textsuperscript{12} This method is used in an ongoing study of the effect of probucol on femoral atherosclerosis.\textsuperscript{13} In the CLAS,\textsuperscript{1} sample size was estimated on the basis of the methodological variation of computer-estimated femoral atherosclerosis. From a study point of view, therefore, the results of the study by Blankenhorn and colleagues in this issue of Circulation\textsuperscript{14} is of great importance and interest, as it gives the results of the true major end point of the CLAS or the first outcome measure of the CLAS, according to the authors.\textsuperscript{15} It is also the first regression study yet published that completely relies on objective microdensitometric and computer estimation of atherosclerosis.

To be oversimplistic, the CLAS is a negative study, because the first outcome measure, the computer estimate of atherosclerosis, was not statistically different between treatment and control groups. However, if one takes a closer look at the data, interesting results emerge.

First, in those with moderate femoral atherosclerosis there was a significant difference between the treatment groups, there being a negative annual change rate in the drug group and a positive change rate in the placebo group. Second, using a per patient analysis not conceived or presented in the design paper\textsuperscript{15} and comparing the association of regression/progression with treatment showed that the rate of regression was significantly higher in the drug group. Third, significant differences were found between on-trial plasma lipoprotein concentrations and patient status (progressor, regressor, or unchanged). Of the different lipoproteins, plasma high density lipoprotein (HDL) cholesterol was related most persuasively with regression.

The results in the femoral arteries are in some contrast to those in the coronary arteries for the CLAS participants, as the global change score of the coronaries showed a more consistent benefit.\textsuperscript{1} One reason for this may be selection. Only patients with symptoms indicating coronary atherosclerosis were recruited into the CLAS and this may influence outcome. Another reason may simply be that femoral atherosclerosis is different from coronary atherosclerosis, as pointed out by Ross et al.\textsuperscript{16} Many of the lesions in the femoral artery are fibroproliferative and contain relatively little lipid.

There is evidence that the risk factors play different roles in different arterial beds. For example, Criqui et al\textsuperscript{17} studied peripheral arterial disease cross-sectionally and divided the patients into those with large vessel disease and small vessel disease. Although small vessel disease was not at all associated with the major cardiovascular disease risk factors, severe large vessel disease in men was associated with cigarette smoking, plasma glucose, and systolic blood pressure but not with total or low
density lipoprotein (LDL) cholesterol. Very low density lipoprotein (VLDL) and HDL were suggestively but not significantly associated with large and small vessel disease. We could thus trace a continuous change in risk factors for vessel disease from the coronary arteries out to the small vessels, the coronary arteries being susceptible to elevated LDL and VLDL cholesterol levels and low HDL cholesterol levels as well as elevated blood pressure and smoking. The large peripheral vessels are particularly susceptible to smoking, blood pressure, and "the metabolic syndrome" or insulin resistance, be it expressed as high levels of blood glucose or of VLDL or low levels of HDL cholesterol. This concept is further reinforced by our own findings in a representative sample of patients with intermittent claudication in Linköping. In these 154 men we found significantly higher levels of total, VLDL, LDL, and HDL triglycerides than in controls, although total, LDL, and HDL cholesterol did not differ between the two groups. Small vessel peripheral arterial disease does not appear to be related to any of the major risk factors but seems to be a separate disease entity. With this concept in mind, and considering that the CLAS patients were recruited because of coronary atherosclerosis, it is not astonishing that the outcome with the same treatment was less consistent in the femoral arteries than in the coronary arteries.

It is of interest that the effect of lipid lowering in the CLAS was located proximally and not distally in the femoral artery (i.e., in the segments not typical for the location of femoral atherosclerosis, which is more distally in the adductor channel19). It is tempting to speculate that the more proximal femoral atherosclerosis more closely reflects coronary atherosclerosis. If so, it might constitute a model for the study of coronary atherosclerosis. This is of great potential interest because the proximal part of the femoral artery is more readily accessible for noninvasive atheroma measurements.

Femoral atherosclerosis is, however, also multifactorial, and the characteristics of the atherosclerosis probably differ depending on the dominant risk factor. The method of selecting patients therefore plays a crucial role in the relation between risk factors and disease. For example, when we studied asymptomatic patients with marked hyperlipoproteinemia by means of femoral angiography we found visual atherosclerosis in 72-78% in the different types of hyperlipoproteinemia.19 In this study of patients with hyperlipidaemia we could also show that the presence of femoral atheroma was related above all to levels of LDL cholesterol.

The CLAS research into femoral atherosclerosis joins the many regression studies pointing to the importance of a high plasma HDL cholesterol for regression. This finding is in line with the NHLBI study on coronary atherosclerosis, the Helsinki Study, and the Leiden Study. The results are, however, at variance with the CLAS coronary study in the same patients in which a new risk indicator, apolipoprotein C-III in HDL, emerged as a determinant for coronary atherosclerosis progression. The partition of apolipoprotein C-III between triglyceride-rich lipoproteins and HDL is thought to reflect the efficiency of the metabolism of triglyceride-rich lipoproteins; the finding indicates the importance of these lipids in the development of coronary atherosclerosis. In the paper by Blankenhorn et al27 no mention is made of the relation between this newly detected factor and patient status. One looks forward to further results in this area of research.

Two other controlled studies of the development of femoral atherosclerosis after plasma lipid regulation and its relation to plasma lipoprotein have been published. Duffield et al21 treated hyperlipidemic patients with intermittent claudication with cholestyramine, nicotinic acid, or clofibrate and compared femoral atheroma growth in these patients with that in a group receiving usual care. Significantly fewer arterial segments showed detectable progression after 19 months of treatment compared with arterial segments from controls. On treatment, only LDL cholesterol was significantly related to progression, the ratio of LDL cholesterol to HDL cholesterol being of borderline significance.

In a recently published study22 we followed femoral atherosclerosis by taking two arteriograms 1 year apart in 45 hyperlipidemic but asymptomatic men, half of them receiving diet plus nicotinic acid and fenofibrate, half of them diet plus placebo. Femoral atherosclerosis was estimated by an expert panel as an overall atherosclerosis score. Marked plasma lipid alterations were achieved by the treatment. Progression was found in 24% and 40% of subjects, respectively, in the treatment and control groups, and the corresponding figures for regression were 29% and 0%, indicating a highly significant difference in distribution between the groups. Regression of femoral atherosclerosis was related to decreases of VLDL cholesterol and of systolic blood pressure, and no relation was found with decreases in LDL cholesterol. Again, the study points to the importance of triglyceride-rich lipoproteins in peripheral arterial disease.

The three published controlled studies on regression of femoral atherosclerosis thus show different relations between atheroma change and plasma lipoproteins, the CLAS demonstrating the relation of atheroma change with HDL cholesterol upon treatment, the Duffield study its relation with LDL cholesterol, and our own its relation with VLDL cholesterol. The three studies included different patient groups: CLAS coronary patients, the Duffield study claudicants, and our own asymptomatic markedly hyperlipidemic subjects. It is probable, as suggested above, that the recruiting mechanisms had an impact on the type of femoral atherosclerosis studied, and different relations between plasma lipoprotein changes and atherosclerosis development are therefore to be expected.
Controlled atherosclerosis regression studies are a recent development in clinical studies, the first one being published only in 1983.22 With the present landmark publication of the first outcome results of the CLAS regression studies,14 the standard is set as to how to treat the data. With the imminent emergence of noninvasive techniques for atheroma change estimation, an abundance of such studies are to be expected in the near future. Results should then be reported on a per patient basis or with appropriate correction for within-subject correlation25 when arterial segments or lesions are used as end points. Very recent publications still do not take this into account.5,29 The CLAS and the NHLBI regression studies have set the standards for treatment of data in atherosclerosis regression studies.

References

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