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On the Relation between Peripheral Atherosclerosis and Serum Lipoproteins

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ABSTRACT

The occurrence and degree of peripheral atherosclerosis in 30 male patients with symptoms of intermittent claudication were studied by arteriography. The changes observed in the angiograms were codified. In all patients the concentrations of triglycerides and cholesterol were determined in whole serum and in the three major lipoprotein classes - very low density, low density and high density lipoproteins. These data were compared with those of a control material and were also correlated to the codified angiographic findings in each individual patient.

Positive significant correlation was not found between the arteriographic changes and the serum concentrations of lipids and lipoproteins, which might be explained by an advanced stage of the disease where such relationships might not appear.

INTRODUCTION

An increased incidence of hyperlipidaemia and hyperlipoproteinaemia in patients with peripheral arterial disease (PVD) has been noted by several authors (1,4,5,15,16,17,22,24). Most of these reports, however, give quantitative information only about total plasma lipids and since most plasma lipids are transported in the form of lipoproteins, it is of major importance that these will be determined. There appear to be no reports in the literature on the relation between angiographic changes in peripheral arteries and serum lipoprotein levels. This investigation was therefore undertaken to study the correlation between atherosclerotic manifestations and the concentrations of triglycerides and cholesterol in whole serum and in the three major lipoprotein classes (very low density /VLDL/, low density /LDL/ and high density lipoproteins /HDL/). In this connection the recent report (2) that hyperlipoproteinaemic patients with PVD showed regression of the atherosclerotic changes after treatment with lipid-lowering agents is of interest.

It is always important to measure the atherosclerotic changes objectively.

Various densitometric and computerized methods have been suggested for this purpose. These are not very commonly used, however, and are still a matter of evaluation (11,12). It seems justified at present to assess the arteriograms by a more simple technique which we have used at our hospital for a long time, and the same type of gradation has been applied both for peripheral arteries and for the coronary arteries. In the study reported here we have tried to make an objective evaluation of the arteriographic changes in the distal aorta, the pelvic arteries and the arteries in the legs. These changes have been correlated to the concentrations of triglycerides and cholesterol in whole serum, VLDL, LDL and HDL.

MATERIAL AND METHODS

Material

Thirty men of ages 39-76 years, with a mean age of 60 years, were investigated. All patients had symptoms of intermittent claudication. They were hospitalized at the Department of Geriatrics in Uppsala and referred to the Department of Diagnostic Radiology of the University Hospital in Uppsala.

Five patients were overweight, defined as a weight/height index above 1.10 (weight in kg divided by height in cm -100). None of the patients suffered from thyroid dysfunction, diabetes, obstructive liver disease or nephrotic syndrome and none was being treated with any β-blocking or lipid-lowering agent.

Methods

Laboratory chemical methods

Blood was sampled in the morning after an overnight fast on the day of admission to hospital, in order to eliminate any effect of hospital diet.

Lipid-lipoprotein analysis

The ultracentrifugal lipoprotein separation was performed as described by Carlson (10). Whole serum as well as isolated lipoprotein fractions were extracted manually with isopropanol. Cholesterol and triglyceride concentrations were then determined by automated techniques, using an Autoanalyser Model 2 (Technicon Corporation) (21). The cholesterol values obtained with this method agreed well with those obtained by the Sperry-Webb method. The triglyceride values for whole serum were about 0.2 mmol/l higher than those reported by Carlson (7).

Reference group

Control subjects for lipoprotein comparisons (n = 61) have been described previously (8).

Radiological methods

All patients underwent peripheral arteriography with use of the Seldinger technique. A catheter was introduced into the femoral artery under local anaesthesia, its tip being placed in the distal aorta just above the bifurcation.

The investigation comprised the distal aorta and the arteries on the right and left side, including the distal part of the lower leg. In most patients special oblique projections were also used with regard to the deep femoral artery.

An automatic film changer (AOT, Siemens Elema, Solna, Sweden) was used. The film frequency was 1 exposure/s. The contrast medium was injected with a Sisal 2 pressure syringe (Siemens Elema, Solna, Sweden). In all investigations Angiografin (Schering AG, W.Germany) was used, in an amount of 30 ml which was injected at 15 ml/s. The film-focus distance was 100 cm.

The angiograms were analysed by a standardized method. The diameter of the superficial femoral artery was measured at the level of the lesser trochanter and 20, 10 and 0 cm above the knee joint. For measurement of the diameters a magnifying glass with an inbuilt scale and with an accuracy of 0.1 mm was used. The greatest and the smallest diameters were also noted in the different sections of the arteries. The changes in the different regions of the arteries from the aorta to the arteries of the distal lower leg were codified according to the following system. No changes = 0; diameter reduced by not more than 50% = 1; diameter reduced by more than 50% = 2; reduction of the diameter by more than 50% in several places in the arterial region = 3; and total occlusion = 4 (13).

The development of collaterals was also graded, using a 3-grade scale: 1 = a very small number of collaterals, 2 = a moderately large number and 3 = a large number.

The length of any total arterial occlusion was measured. The following arteries in addition to the aorta were studied: The common, internal and external iliac arteries, deep and superficial femoral arteries, popliteal artery, anterior and posterior tibial arteries and the fibular artery, i.e. nine different arterial regions. Thus the maximum sum of codes was 36.

Statistical analysis was performed as described by Snedecor (23).

RESULTS

The results of the radiographic analysis by means of the code system are presented in the form of histograms in Fig. 1. The lengths of the occlusions are shown in Fig. 2. Surprisingly long occlusions, up to 56 cm, were observed. Occlusions as short as 3 cm were also found. In most cases a large number of

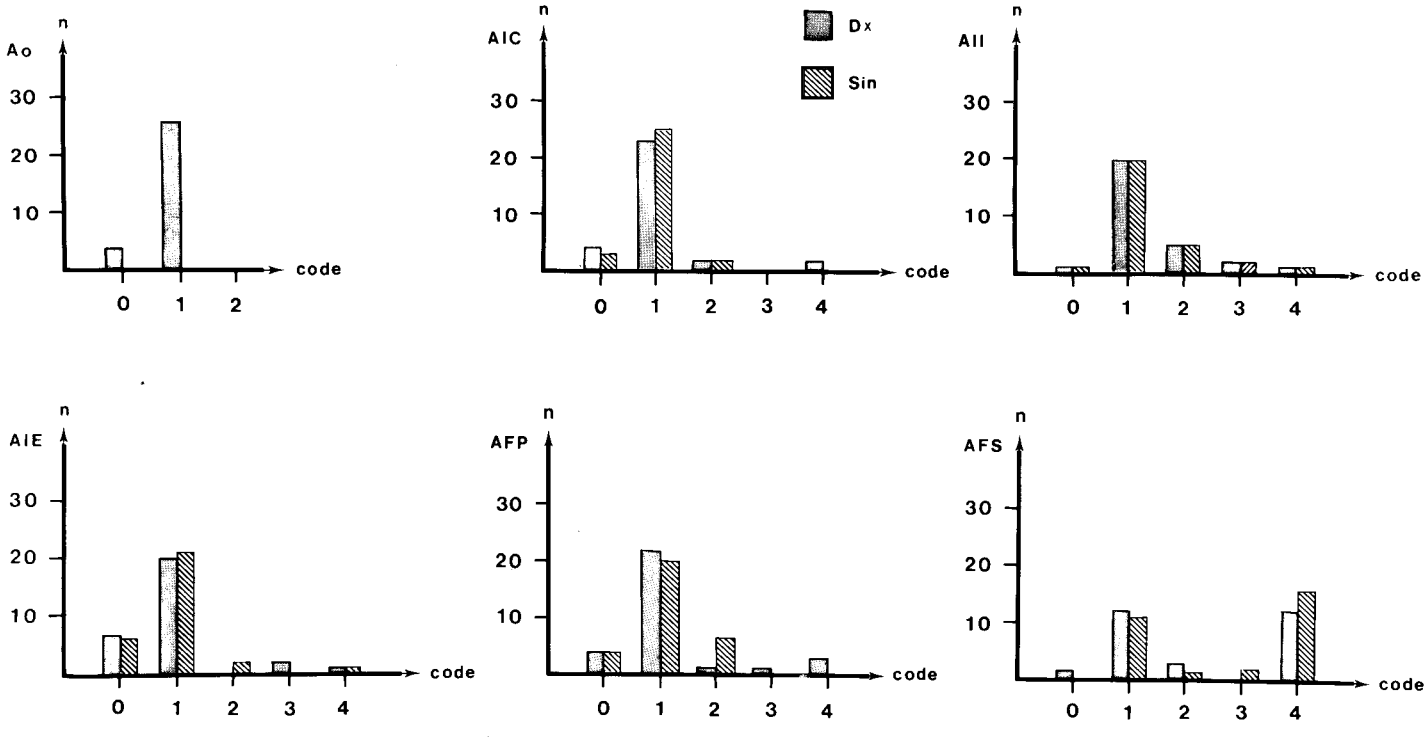

Fig.1. The codes (abscissa) represent the arteriographic changes in the aorta and in the nine separate, bilateral, arterial regions. The number of cases is given on the ordinate.

right leg left leg Ao = aorta, AIC = arteria iliaca communis, AII = arteria iliaca interna, AIE = arteria iliaca externa, AFP = arteria profunda femoris, AFS = arteria superficialis femoris, AP = arteria poplitea, ATA = arteria tibialis anterior, ATP = arteria tibialis posterior, AF = arteria fibularis

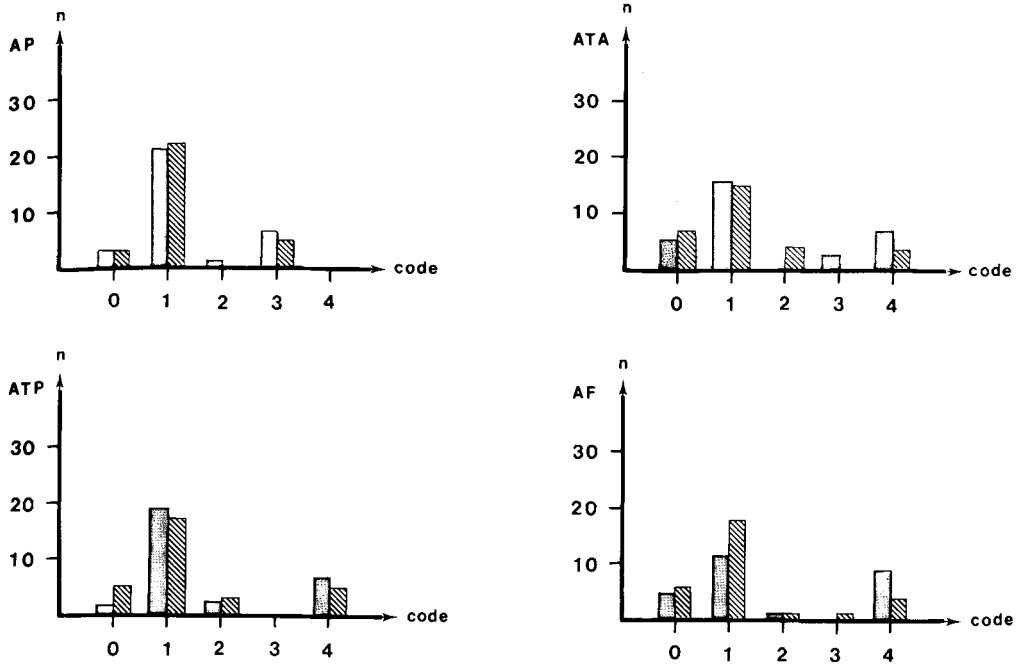

Fig. 1 (continuation)

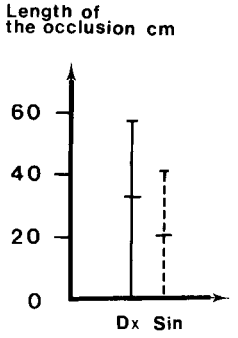

Fig. 2. The arterial occlusions found in 24 of the 30 patients are shown; mean value and range.

collaterals had developed (Fig. 3), indicating that the occlusions were of long duration. In Fig. 4 the diameters at different levels of the superficial femoral artery and the popliteal artery are given. It is seen that the diameters were clearly reduced at all levels. Total occlusions were most common in the superficial femoral artery and were relatively few in the arteries of the lower leg.

The lipid analysis showed that 70% of the patients with PVD had a normal lipoprotein pattern according to the system modified by Fredrickson (3). Seven per cent had type IV, 20% type II A and 3% type III A. The cholesterol

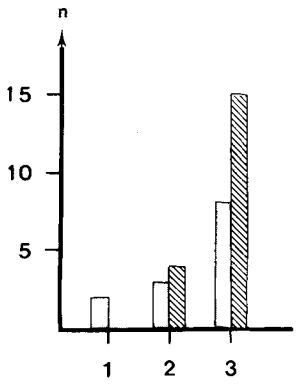

Fig. 3. The three classes of collaterals: 1 = a small number, 2 = a moderate number and 3 = abundent collaterals.

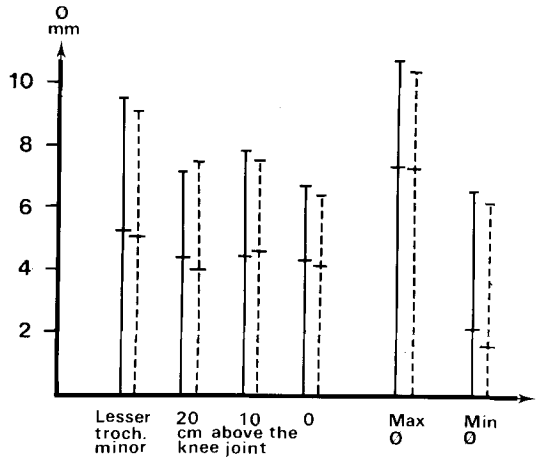

Fig. 4. The arterial diameters at four different levels, and the maximal and minimal diameters. The diameters are markedly reduced in many places.

concentration in the HDL fraction was significantly lower in patients with PVD than in the controls (Table 1).

Table 1. The concentrations of triglycerides (TG mmol/l) and cholesterol (chol mmol/l) in total serum and in the three lipoprotein classes VLDL, LDL and HDL (mean ± SEM) in control subjects and in patients with peripheral atherosclerosis. xxx indicates a statistically significant difference ($p < 0.001$).

	Total		VLDL		LDL		HDL	
	TG	CHOL	TG	CHOL	TG	CHOL	TG	CHOL
Controls								
N = 61	1.76	6.45	0.95	0.49	0.52	4.28	0.24	1.39
	±.08	±.15	±.07	±.05	±.02	±.13	±.01	±.05
PVD								
N = 30	2.35	6.68	1.55	0.80	0.58	4.46	0.23	1.08^{xxx}
	±.38	±.26	±.41	±.23	±.02	±.21	±.01	±.05

The results of correlation analysis of the angiographic code for the right + left limb versus the mean triglyceride and cholesterol concentrations in total serum and in the three lipoprotein classes (VLDL, LDL, HDL) in the 30 patients with PVD are presented in Table 2.

Table 2. Correlation coefficients (r-values) of the scoring code (the sum of the codes from the right and left legs) versus the mean triglyceride (TG) and cholesterol (Chol) concentrations in total serum and in the three lipoprotein classes VLDL, LDL and HDL in the patients with peripheral atherosclerosis. x indicates a statistically significant correlation ($p < 0.05$).

Total		VLDL		LDL		HDL	
TG	CHOL	TG	CHOL	TG	CHOL	TG	CHOL
-. 23	$-.43^{x}$	-.22	-.27	-.05	-.18	-.22	-.07

There was a slight significant negative correlation between total cholesterol and the code symbolizing the atherosclerotic changes. This was due, however, to the patient with a type III pattern of lipoprotein abnormality.

DISCUSSON

Arteriographic changes in the lower extremity have been described earlier by Löhr and collaborators (18). They found that both early atherosclerosis in younger patients and atherosclerosis in elderly people were most common in the superficial femoral artery but were also present in the anterior and posterior tibular arteries and in the fibular artery. They did not, however, examine the relation between blood lipoproteins and atherosclerotic changes as on arteriograms. But they did report that among the patients with early atherosclerosis there was a high frequency of smokers, and that about 25% of the patients had diabetes mellitus. Their angiographic results are in accordance with ours.

When evaluating our results it must be kept in mind that arteriographic findings are always difficult to assess objectively. We have tried to avoid subjective judgement as far as possible. But codifying in itself involves an element of subjective evaluation. Nevertheless we have found this method usefut. The arterial diameters at the different standardized points are more reliable and the error of the method is 0.1 mm (14). These measurement points, however, cannot always be identical with the maximal and minimal diameters, so we have also included these diameters to better characterize the arterial changes. We have also included the length of the occlusion and have tried to assess the number of collaterals. All this together should increase the value

of the classification of the arterial changes, that is the degree of peripheral vascular disease in the legs.

The angiographic technique is also important. A sufficiently large dose of contrast medium and a sufficiently long series of exposures, with a large number of films, must be used to be sure that all parts of an artery are visualized. This is important as otherwise the number of collaterals may be underestimated and the length of a total arterial occlusion overestimated (19). This is especially true when an arterial region is filled in the retrograde direction via the collaterals. If the investigation time is too short an occlusion may be judged longer than it is in reality. We have tried in our investigations to avoid this and for this reason have avoided a so called stepwise technique, which means that the patient is automatically moved together with the table in relation to the X-ray tube, so that the same amount of contrast medium can be used almost throughout the whole series of investigation. This technique is very unreliable and is unsuitable for a study such as the present one. It should not be used in any preoperative investigation.

Values are not available for normal arterial diameters at different levels. But a comparison may be made with a material mostly of men reported by Erikson (14). This comprised a study of traumatic amputees in which the amputation stump and the healthy, intact leg were compared. From these arteriograms it is obvious that in our 30 patients with atherosclerotic disease the arterial diameters were greatly reduced. The degree of magnification was the same in the two materials. It seems that our arteriographic method is fairly objective and will describe the atherosclerotic changes fairly well. It thus seems justified to use this method for examining the relation between atherosclerosis and blood lipoprotein concentrations, even though a densitometric technique is probably superior.

It was a surprising finding that there was a very slight significant negative correlation between total cholesterol and the atherosclerotic changes. However, the arteriographies in our material obviously revealed all the typical signs of atherosclerosis, namely diametric reduction, occlusion and collaterals. The cholesterol concentration in the HDL fraction was significantly lower in our material than in the controls. This phenomenon has also been observed in survivors of myocardial infarction (8, 9). The role of a low concentration of HDL cholesterol in the development of atherosclerotic manifestations is not known. It is of interest, however, since HDL may transport cholesterol out of tissues (20), even from the arterial wall (6).

Our correlation data do not exclude the possibility of a causal relationship between abnormalities in lipoprotein metabolism and atherosclerotic changes, as the stage of the disease in the individual patient was not known.

In view of the regression of early femoral atherosclerosis observed in hyperlipoproteinemic patients after treatment with lipid-lowering agents (2), our patients might have been in a fairly advanced stage of the disease, where correlations between lipoproteins and atherosclerotic manifestations do not necessarily appear.

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