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## The Role of Hyperlipidaemia in Peripheral Arterial Occlusive Disease

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# The Role of Hyperlipidaemia in Peripheral Arterial Occlusive Disease

H. Drexel

**Abstract:** A recent report from the Physicians' Health Study proved elevated plasma cholesterol, elevated triglycerides, and low HDL-cholesterol predictive of the incidence of peripheral arterial occlusive disease. The strongest predictor was the cholesterol/HDL-cholesterol ratio. In contrast, new risk factors, eg lipoprotein (a), homocysteine and apolipoproteins A and B did not have additional predictive power for peripheral arterial occlusive disease, whereas C-reactive protein and fibrinogen were independently predictive of its incidence. Earlier cross-sectional studies also found lipoprotein lipids closely associated with arterial disease: VLDL-cholesterol, IDL-cholesterol, and LDL-cholesterol were directly, and HDL-cholesterol, $HDL_2$-cholesterol as well as $HDL_3$-cholesterol inversely related to the prevalence of peripheral arterial occlusive disease. Treatment recommendations are the same as have been established for other secondary preventive settings, eg coronary artery disease.

**Kurzfassung: Die Bedeutung der Hyperlipidämie als Risikofaktor für die periphere arterielle Verschlußkrankheit.** Neue Daten aus der Physicians' Health Study zeigen, daß erhöhtes Plasmacholesterin, erhöhte Triglyzeride und niedriges HDL-Cholesterin das Auftreten von PAVK voraussagen. Der beste Prädiktor ist der Cholesterin/HDL-Cholesterin-Quotient. Im Gegensatz dazu zeigten neuere Risikofaktoren – wie Lipoprotein A, Homocystein und Apolipoprotein A und B – keine zusätzliche Vorhersagekraft für periphere Verschlußkrankheiten. C-reaktives Protein und Fibrinogen waren andererseits wieder unabhängige Prädiktoren für die Krankheitsinzidenz. Diese prospektiven Daten ergänzen frühere Literaturberichte von Querschnittstudien, in welchen ebenfalls der Lipoproteinstoffwechsel eng mit der peripheren arteriellen Verschlußkrankheit assoziiert war: VLDL-Cholesterin, IDL-Cholesterin und LDL-Cholesterin waren direkt, HDL-Cholesterin, $HDL_2$-Cholesterin sowie $HDL_3$-Cholesterin invers mit der Prävalenz der peripheren arteriellen Verschlußkrankheit vergesellschaftet. Wie bei anderen klinisch bereits faßbaren Manifestationen der Atherosklerose gelten auch bei peripherer arterieller Verschlußkrankheit die strengen Lipidzielkriterien der Sekundärprävention. **J Kardiol 2003; 10: 146–8.**

## Introduction

This overview summarizes the role of plasma lipids and specific forms of hyperlipidaemia in the context of peripheral arterial occlusive disease (PAOD). The text is subdivided into three parts:

1. A new study on PAOD and lipids
2. Earlier studies on the topic
3. Treatment recommendations

## A New Study on PAOD and Lipids

Ridker et al. have published the results of a study on risk factors in PAOD [1]. The main aim of the study was to investigate the value of novel risk factors (in comparison to that of more traditional risk factors) as predictors of systemic atherosclerosis. The authors proceed from the background that new risk factors have been established; that there are no comparative data for the clinical usefulness of new and standard risk factors; and that, therefore, eleven biomarkers were investigated from the sample of the Physicians' Health Study.

**Table 1:** Risk factors for PAOD and endpoints of the study

| Predictors | Endpoints (Incidence) |
|---|---|
| Plasma cholesterol | Typical clinical symptoms of PAOD |
| LDL-cholesterol | Revascularisation |
| HDL-cholesterol | |
| Cholesterol/HDL-cholesterol | |
| Triglycerides | |
| Homocysteine | |
| CRP (high sensitivity) | |
| Lipoprotein(a) | |
| Fibrinogen | |
| Apolipoprotein A-I | |
| Apolipoprotein B-100 | |

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The investigation was designed as a case-control study. A cohort of 14,916 healthy U.S. physicians, aged 40–84, was prospectively studied. The mean period of observation was 9 years, after which 140 cases of symptomatic PAOD had occurred. The authors then selected 140 control subjects without clinically manifest PAOD who were matched to the 140 cases for age and smoking. Table 1 summarizes the risk factors used as predictors for the endpoints, which are also listed there.

From Tables 2 and 3 it can be seen that cholesterol and triglycerides about equally distinguish between cases and con-

**Table 2:** Means of the eleven biomarkers of PAOD in patients and controls

| Variable (mg/dl) | Controls (n = 140) | Cases (n = 140) | p-value |
|---|---|---|---|
| Cholesterol | 210 | 221 | < 0.001 |
| LDL-cholesterol | 125 | 137 | 0.001 |
| HDL-cholesterol | 47 | 43 | 0.009 |
| Triglicerides | 114 | 141 | 0.001 |
| Cholesterol/HDL-cholesterol | 4.55 | 5.39 | < 0.001 |
| Apo A-I | 151 | 147 | 0.05 |
| Apo B-100 | 123 | 141 | 0.001 |
| Lp(a) | 75 | 89 | n.s. |
| Homocysteine | 0.00146 | 0.00149 | n.s. |
| Fibrinogen | 320 | 340 | 0.02 |
| CRP | 0.10 | 0.14 | 0.006 |

**Table 3:** Adjusted relative risk of the forth over the first quartile of patients

| Variable (mg/dl) | Relative Risk | p-value |
|---|---|---|
| Cholesterol | 3.1 (1.5–6.5) | 0.001 |
| LDL-cholesterol | 2.2 (1.1–4.7) | 0.003 |
| HDL-cholesterol | 0.5 (0.2–0.9) | 0.03 |
| Triglicerides | 2.8 (1.3–5.9) | 0.003 |
| Cholesterol/HDL-cholesterol | 3.9 (1.7–8.6) | < 0.001 |
| Apo A-I | 0.6 (0.3–1.1) | n.s. |
| Apo B-100 | 2.9 (1.5–6.3) | < 0.001 |
| Lp(a) | 1.1 (0.6–2.2) | n.s. |
| Homocysteine | 1.1 (0.5–2.1) | n.s. |
| Fibrinogen | 2.2 (1.1–4.7) | 0.02 |
| CRP | 2.8 (1.3–5.9) | 0.01 |

trols, as did LDL-cholesterol. The predictive value of HDL-cholesterol for protection from PAOD was also in the same order of magnitude. Hence, the best predictor among lipids was the cholesterol/HDL-cholesterol ratio. The plasma level of Apo A-I was less predictive than HDL-cholesterol, whereas the plasma level of Apo B-100 was about equally predictive as plasma cholesterol. Therefore the two apolipoproteins did not add to the predictive power of the lipids. More disappointingly, lipoprotein (a) (Lp(a)) was not associated with PAOD in this cohort but the authors concede that in larger populations Lp(a) could become such a marker. Also surprisingly, homocysteine was not a predictor of PAOD. On the contrary, fibrinogen and C-reactive protein (CRP), both markers of systemic or more generalized inflammation, proved predictive of PAOD. The main results of this study were that (i) about 1 percent of the patients reached an endpoint of PAOD, (ii) the middle observation period to the first clinical event was 60 months, whereas the total observation period was 108 months (9 years). (iii) The best predictor for the incidence of PAOD in this prospective study was the ratio of total cholesterol/HDL-cholesterol. (iv) This ratio remained the best predictor even upon control for age, smoking, hypertension, body-mass-index and family history of PAOD. (v) From the novel risk factors, the inflammatory markers CRP and fibrinogen proved to be additionally predictive. (vi) Apolipoprotein A-I, apolipoprotein B-100, lipoprotein (a) and homocysteine did not offer any additional value for the prediction of PAOD.

## Earlier Studies on the Topic

Mannarino et al. [2] investigated $HDL_2$- and $HDL_3$-cholesterol subfractions in normolipidaemic patients with peripheral vascular disease and found $HDL_2$ to be a stronger predictor of disease than $HDL_3$-cholesterol when comparing 27 patients with 27 controls whose cholesterol values were less than 250 and triglyceride values less than 200. Cases were defined by clinical PAOD, and all were documented by angiography. HDL-subfraction cholesterol was measured by polyethylene glycol precipitation.

Pilger et al. [3] in a study comparing 49 patients with 31 controls, which included also 17 patients and 2 controls with type-1-diabetes mellitus, used a sophisticated mathematical model for the discrimination of risk factors of PAOD. Their data proved serum cholesterol and serum triglycerides as well as LDL-cholesterol, HDL-cholesterol and apolipoproteins AI, AII and B of predictive value. In a further study of the lipoprotein profile in men with peripheral vascular disease, Senti et al. [4] investigated 102 patients with PAOD and 102 controls. Their data proved serum triglycerides but not serum cholesterol predictive of PAOD in a Spanish cohort. Also HDL and IDL-cholesterol (but not LDL-cholesterol) were predictive as were VLDL-cholesterol, IDL-triglycerides and VLDL-triglycerides. Taken together, their data point to a more important role of high triglycerides and low HDL in patients with PAOD. This view is also corroborated in our own study [5], involving 102 patients with PAOD and 100 controls. We investigated the predictors of the presence and extent of PAOD and used very precisely defined control patients – we only included patients who neither had coronary nor peripheral arterial disease. The exclusion of disease was made angiographically in both vascular beds.

Generally, the definition of controls is an important methodological issue. The Physicians' Health Study had the advantage of a prospective study. Therefore, the markers of disease were true predictors. The problem in this type of case-control studies is that although cases are properly defined, controls are not. They can already have clinically silent but important atherosclerotic disease, which escapes detection. Angiographic cross-sectional trials offer the advantage of better defining controls as the studies by Senti et al., Pilger et al., Mannarino et al. and also our study. Our study has the particular advantage that also significant atherosclerotic disease in the coronary bed was excluded.

In our study, presence of PAOD was defined as ≥ 1 narrowing of ≥ 50 %. Extent of disease was defined as the number of lesions with ≥ 50 % narrowing in the total of the iliacal, femoral, popliteal and crural beds of both sides. HDL-cholesterol subfractions were determined by the method of Warnick et al., which uses dextrane sulfate in increasing concentrations for the stepwise precipitation of non-HDL-lipoproteins and $HDL_2$, respectively. This method has been shown to give excellent agreement with HDL subfraction determination by rate zonal ultracentrifugation [6]. As shown in Table 4, the association of atherogenic lipids with presence of PAOD, cholesterol, LDL-cholesterol and, importantly, triglycerides well distinguished between the two cohorts as did apolipoprotein B.

We have thus a good accordance with the newer study from the Physicians' Health Study. Again, the elevation of triglycerides was more pronounced than the elevation of cholesterol in these patients. As shown in Table 5, $HDL_2$-cholesterol, but not $HDL_3$-cholesterol was associated with the presence of PAOD.

In a logistic model, significant markers of the presence of PAOD were LDL-cholesterol, Apo B, triglycerides, smoking, $HDL_2$-cholesterol and apolipoprotein A1, whereby, at the $p < 0,05$ level of statistical significance, LDL-cholesterol, triglycerides and smoking remained independent predictors.

By discriminant analysis, the association of risk factors with the extent of PAOD was determined. Here, HDL-choles-

**Table 4:** Atherogenetic lipids/apolipoproteins in patients with PAOD and controls

| Parameter* | Controls | Patients | p-value |
|---|---|---|---|
| Cholesterol | 217 ± 38 | 243 ± 48 | 0.0001 |
| LDL-cholesterol | 137 ± 36 | 156 ± 45 | 0.0003 |
| Apo B (g/l) | 1.1 ± 0.3 | 1.22 ± 0.34 | 0.0073 |
| Triglycerides | 133 ± 89 | 187 ± 69 | 0.0001 |

*mg/dl unless otherwise stated; means±SD

**Table 5:** Atherogenetic lipids/apolipoproteins in patients with PAOD and controls

| Parameter* | Controls | Patients | p-value |
|---|---|---|---|
| HDL-cholesterol | 55 ± 17 | 51 ± 15 | 0.0178 |
| $HDL_2$-cholesterol | 11 ± 10 | 9 ± 7 | 0.0085 |
| $HDL_3$-cholesterol | 44 ± 10 | 42 ± 10 | n.s. |
| HDL-Tg | 21 ± 8 | 21 ± 11 | n.s. |
| Apo A-1 (g/l) | 1.51 ± 0.25 | 1.49 ± 0.27 | n.s. |

*mg/dl unless otherwise stated; means ± SD

terol, $HDL_3$-cholesterol, apolipoprotein A1, smoking and fasting plasma glucose were predictors of disease, whereby independent prediction was provided by smoking and glucose.

Summarizing, all these lipid studies in PAOD point to a picture of lipid risk factors very similar to coronary heart disease studies: Cholesterol, triglycerides and low HDL-cholesterol were closely associated with disease. The cholesterol/HDL-cholesterol ratio in coronary disease was very similar to the values found for peripheral disease in the Physicians' Health Study as we showed in an earlier paper [7]. Therefore, it may be correct to use those lipid-lowering drugs in PAOD patients that have been proven to be beneficial in coronary disease, ie, pravastatin in primary prevention and simvastatin as well as pravastatin in secondary prevention.

## Treatment Recommendations

From these epidemiological findings, it appears consistent to give the following therapeutic recommendations: Peripheral atherosclerosis is associated with increased LDL-cholesterol (and total cholesterol) as well as increased triglycerides and lowered HDL-cholesterol. For primary prevention, we recommend that the LDL-cholesterol should be decreased below 130 mg/dl or, which could be a better marker, to a total cholesterol/HDL-cholesterol ratio lower than 5. This treatment target should be first tried to be obtained by dietary interventions especially if the patient is overweight or if triglycerides exceed 300 mg/dl. In the case of triglycerides over 300 mg/dl, a fibrate compound would be the first choice for pharmaceutical treatment, whereas, if triglycerides are lower than 300 mg/dl, pravastatin should be used as the first choice of compound.

For secondary prevention, it is suggested that treatment is tailored to an LDL-cholesterol of less than 100 mg/dl or, even better, to a total cholesterol/HDL-cholesterol ratio of lower than 4, whereby dietary and pharmacological treatment should be started together and as a first choice a statin (eg simvastatin or pravastatin) should be used if triglycerides are below 300 and a fibrate if they are above 300 mg/dl.

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