Serum lipids act as inverse acute phase reactants and are falsely low in patients with critical limb ischemia

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Background: **Lipid levels generally fall after an acute myocardial infarction. This study was conducted to see what trends lipid levels had in patients who underwent operation for critical limb ischemia.**

Methods: **The study was prospective and included 30 patients who underwent operation for critical limb ischemia. Serum lipid profiles and C-reactive protein were analyzed before surgery and 3 months after peripheral bypass surgery. In addition, comparison of lipid levels after surgery was made with 287 healthy and 283 ischemic heart disease controls from The Copenhagen City Heart Study.**

Results: **Total, low density lipoprotein, and high density lipoprotein cholesterol levels were found to be significantly lower before surgery than 3 months after surgery ($P < .001$). In contrast, C-reactive protein was higher before surgery and decreased after 3 months ($P < .0001$). An inverse linear correlation was found between total cholesterol/low density lipoprotein cholesterol and C-reactive protein ($P < .001$ and $P < .04$, respectively). Comparison with controls showed that cholesterol levels 3 months after surgery were significantly lower ($P < .009$).**

Conclusion: **Serum cholesterol levels are not reliable in the preoperative period and should therefore be measured at least 3 months after surgery when they seem to approach a more representative level. (J Vasc Surg 2002;36:1005-10.)**

It is now well established that hyperlipidemia is a modifiable risk factor for atherosclerosis, conferring significant reductions in both cardiac morbidity and mortality rates.[1-5] In patients who undergo peripheral arterial revascularization, the presence of coronary artery disease has been identified in up to 90% after angiography.[6] The mortality rate in this group is about 10% to 20% per annum.[7,8] Therefore, active treatment of hypercholesterolemia could prove to be highly beneficial in this patient group, with regards to reducing cardiac morbidity and mortality rates,[8] even though the recent Heart Protection Study apparently showed a significant effect.[9]

Although evidence exists that every patient with manifestations of atherosclerotic disease would probably stand to benefit from treatment with antihyperlipidemics, current guidelines still dictate treatment protocols for most physicians. Therefore, instituting appropriate antihyperlipidemic treatment is entirely reliant on a dependable measurement of serum lipids.[10,11] Several studies have reported that serum lipids drawn on admission for an acute myocardial infarction are not representative of baseline values.[12-19] Whether this is also true in patients with severe peripheral arterial disease is, however, unknown. Consequently, treatment may be delayed or never instituted. Because of the benefits of medicinal lowering of serum lipids, current treatment guidelines advocate an aggressive approach.[10,11]

With this in mind, this study was initiated to: 1, determine the natural course of lipid levels in patients with critical limb ischemia, measured before surgery and 3 months after bypass surgery; and 2, to investigate whether lipids and C-reactive protein were interrelated. To set the blood values for our cases in perspective, two case-control studies were performed comparing cases with controls free of cardiac disease and controls with ischemic heart disease (IHD).

MATERIALS AND METHODS

Patients. This study included 30 consecutive patients with peripheral critical ischemia admitted to the Department of Vascular Surgery at Gentofte University Hospital for bypass surgery. Critical ischemia was defined according to the Second European Consensus document. No patient was currently or had previously been taking antihyperlipidemics, nor had any patient previously been treated with diet for hyperlipidemia. Serum lipids were drawn before surgery. To monitor nutritional status, albumin was also measured. Reassessment was performed 3 months after surgery in the outpatient clinic. All but one bypass graft were patent at 3 months postoperative control evaluated with ultrasound duplex scanning.

Controls. The 30 patients included in this study were matched for gender and age to participants in the Copenhagen City Heart Study, a population study with 10,049 participants. Participants in the Copenhagen City Heart Study were randomly selected from the city of Copenhagen, with the goal of obtaining a representative sample of

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Competition of interest: nil.

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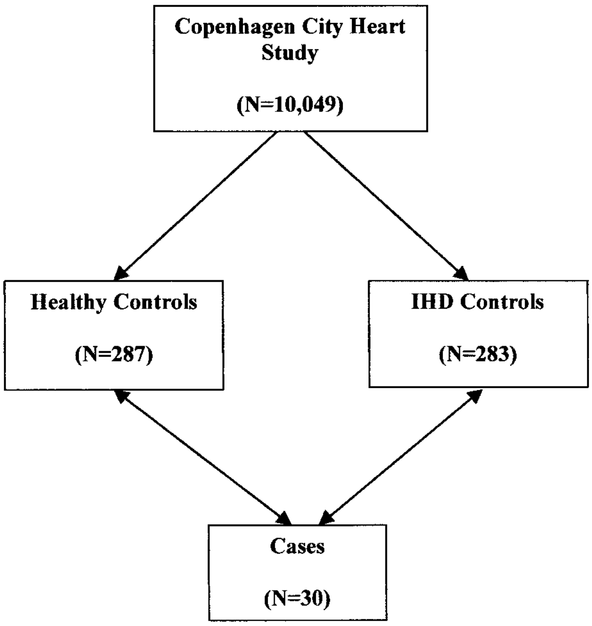

Fig 1. Study design.

Table I. Clinical characteristics of study participants

	Patient (n = 30)	Copenhagen City Heart Study: Healthy controls (n = 287)	Copenhagen City Heart Study: IHD controls (n = 283)
Smoking			
Current	64%	21%	25%
Former	23%	41%	30%
Never	13%	38%	45%
Hypertension	50%	58%	41%
Diabetes mellitus	26%	6%	33%
Cerebrovascular disease	20%	8%	–
IHD	17%	0	100%
Preoperative electrocardiogram			
Ischemia	20%	–	–
Myocardial Infarction	27%	–	–
Atrial fibrillation	20%	–	–
Normal	33%	–	–
Operative indication			
Rest pain	37%	–	–
Ischemic ulcer	37%	–	–
Gangrene	26%	–	–

the general adult Danish population. The study design can be seen in Fig 1. As illustrated, cases were compared with participants of The Copenhagen City Heart Study who remained free of cardiac disease (healthy) and those who had had IHD develop (verified until 1997 with review of all hospital admissions and diagnoses entered into the Danish National Hospital Discharge Register, all deaths entered in the Danish National Register of Cause of Death, and medical records from hospitals and general practitioners). We attempted to match a maximum of 10 healthy and IHD controls from The Copenhagen City Heart Study to each of the 30 patients who underwent operation for lower limb ischemia, but in some cases, fewer controls were found. The number of controls, however, was never less than 6 for each case, which resulted in a total of 287 healthy and 283 IHD control subjects.

Biochemical analysis. All preoperative and postoperative blood samples were determined from a venous puncture and analyzed by Gentofte Hospital laboratory staff. C-reactive protein was analyzed with the particle enhanced immunoturbidimetric method. Cholesterol (total, low density lipoprotein [LDL], and high density lipoprotein [HDL]), triglycerides, and albumin were analyzed with the enzymatic colorimetric method. Precision of laboratory cholesterol levels were assessed with two or three control seras. Coefficient of variation for total cholesterol was 1.4% and for LDL and HDL cholesterol was 3.0% and 2.7%, respectively. For triglycerides, the coefficient was 3.1%; for albumin, the coefficient was 3.2%; and for C-reactive protein, it was 3.4%. Furthermore, the laboratory was subjected to routine external quality control. In the Copenhagen City Heart Study, cholesterol (total, LDL, HDL) was also analyzed with the enzymatic colorimetric method. Coefficient of variation for total cholesterol was 2.1% and for LDL and HDL cholesterol was 1.9%.

Statistics. All statistical analyses were carried out on SPSS 10.0 (SPSS Inc, Chicago, Ill). Wilcoxon signed rank test and Mann-Whitney *U* tests were used to assess statistical significance. The R^2 values quoted on the scatter plots were based on Pearson correlations. *P* values of less than .05 were considered to indicate statistical significance.

RESULTS

Participant clinical characteristics are noted in Table I. The median age of the 30 patients (15 male, 15 female) was 71 years (range, 42 to 89 years).

After surgery, three patients had persistent intermittent claudication, one had critical ischemic pain from graft occlusion, and five had nonhealed ischemic ulcers; however, most patients had improved perfusion of the reconstructed lower limb, as evidenced by an increase in ankle/brachial index from 0.39 to 0.81 (Table II). In Table II and Figs 2, 3, and 4, the changes in laboratory blood values before and after surgery are shown. A highly significant elevation of the lipid profile up to 33% and a decrease in C-reactive protein of 81% were observed. Cholesterol levels for patients with critical limb ischemia 3 months after surgery were significantly lower for both total and LDL cholesterol compared with healthy controls and IHD control subjects. HDL cholesterol was significantly higher in patients 3 months after surgery compared with IHD control subjects (Table III).

The differences seen in total cholesterol and LDL cholesterol values were recognized as having an inverse linear correlation to C-reactive protein (P values $< .001$ and $< .04$, respectively). The correlation between

Table II. Median preoperative and 3-month postoperative blood values

	Median preoperative	*Range*	*Median postoperative*	*Range*	P *value*
Total cholesterol (mmol/L)	4.5	1.2-6.6	5.4	3.4-8.7	<.0001
LDL cholesterol (mmol/L)	2.4	0.4-4.5	3.2	1.4-5.9	<.0001
HDL cholesterol (mmol/L)	1.2	0.4-2.0	1.5	0.7-2.4	<.001
Triglycerides (mmol/L)	1.5	0.6-5.1	1.5	0.6-6.7	.08
Albumin (micromol/L)	422	211-649	579	394-704	<.0001
C-reactive protein (mg/L)	35	3.0-300.0	6.5	1.0-100.0	<.0001
Ankle pressure index (%)	0.39	0.0-0.71	0.87	0.45-1.1	<.0001

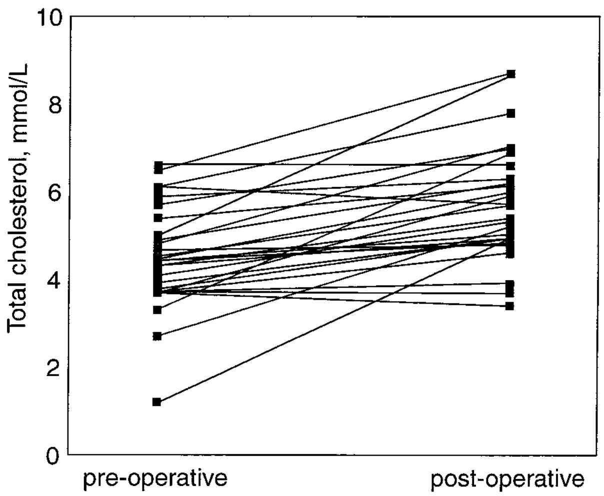

Fig 2. Preoperative and postoperative total cholesterol in mmol/L.

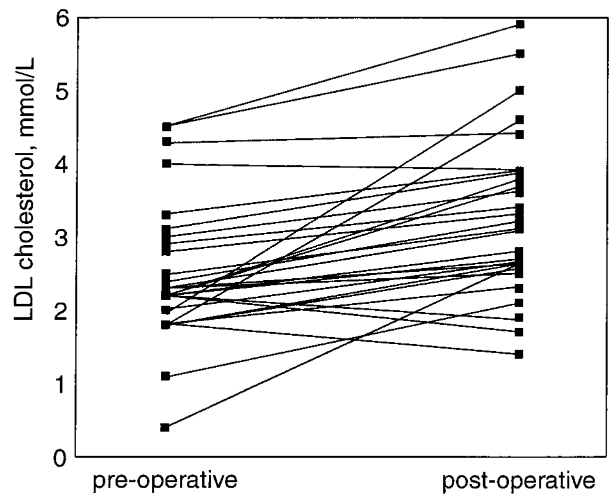

Fig 3. Preoperative and postoperative LDL cholesterol in mmol/L.

change in total cholesterol and C-reactive protein yielded an r^2 value of 0.40, indicating that 40% of the variability of the data could be explained by the association between these two variables. Likewise, 18% of variation of the change in C-reactive protein may be explained by LDL cholesterol (Figs 5 and 6). No significant correlation was noted between C-reactive protein and HDL cholesterol nor between C-reactive protein and triglycerides (data not shown).

Although 63% of the patients had ischemic ulcer or gangrene, no difference in C-reactive protein level was noted when compared with those with rest pain. Nor was the inverse relationship with lipids particularly notable among patients with ulcer/gangrene compared with those with rest pain.

DISCUSSION

In this study, we have shown that cholesterol levels are decreased before surgery in patients with critical limb ischemia and rise 3 months after surgery. In contrast, C-reactive protein decreased after bypass surgery. Furthermore, an inverse linear relationship was established between the rise of cholesterol values and the fall of C-reactive protein. Thus, serum lipids seem to act as "inverse" acute phase reactants. To our knowledge, however, nowhere in literature is there any biochemical explanation of this phenomenon.

These changes in cholesterol levels are well described for acute coronary events.[12-18] This paper supports these results but suggests that the degree of cholesterol reduction seen in patients with critical limb ischemia is more significant and possibly longer lasting or chronic. A single study has investigated the association between lipoproteins and acute phase reactants in patients with myocardial infarction,[19] but to our knowledge, this phenomenon has never been described in patients with critical limb ischemia.

A number of prospective epidemiologic studies have shown that serum total and LDL cholesterol can predict coronary artery disease.[20] Similarly, large randomized trials have shown that both primary and secondary prevention with cholesterol reduction with hydroxymethylglutaryl-coenzyme A reductase inhibitors (statins) can yield significant reductions in risk of nonfatal myocardial infarctions, need for coronary bypass surgery or angioplasty, and coronary death.[1-5] Because it is recognized that patients with peripheral arterial disease have an excessively high rate of concomitant coronary artery disease,[6] this is a group that would be expected to benefit from treatment with statins.

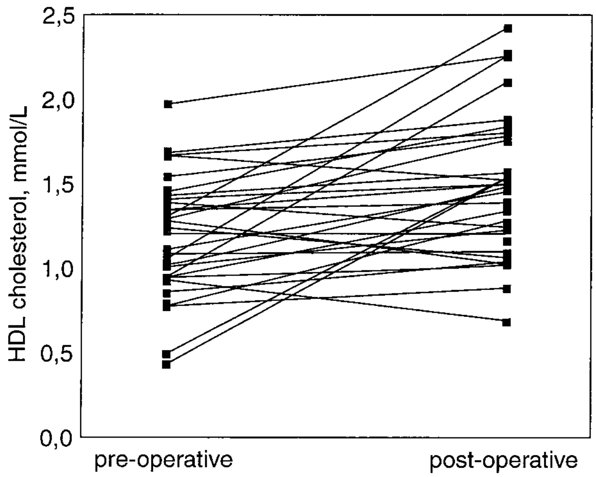

Fig 4. Preoperative and postoperative HDL cholesterol in mmol/L.

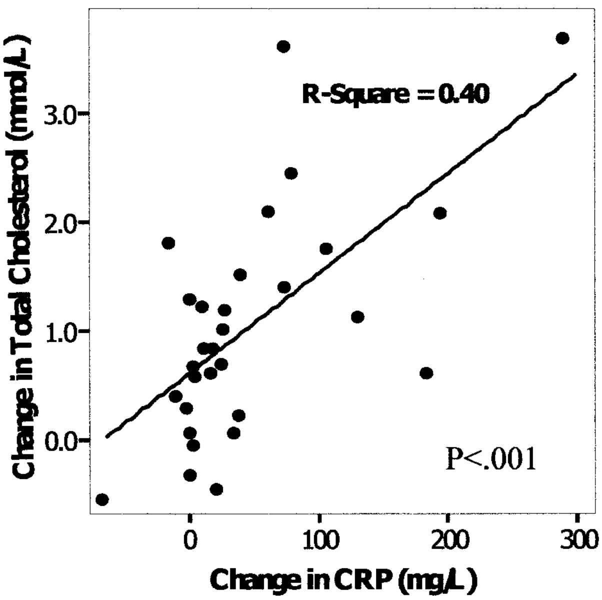

Fig 5. Correlation between change in total cholesterol and C-reactive protein before and after surgery.

The recent Heart Protection Study showed that patients with peripheral arterial disease and without clinical coronary artery disease had a reduction in the continued cardiovascular endpoint. However, the study has not been published, so exact data on the enrolled patients, randomization protocol, etc, remain unknown.[9]

Compared with healthy controls and individuals with IHD, patients with critical ischemia had significantly lower cholesterol levels even 3 months after surgery. This phenomenon may have several explanations. First, lipid levels may not have reached their maximum and assessment 3 months after surgery may be too early. Second, patients with critical limb ischemia may have been ill for a longer period of time before undergoing bypass surgery. This could affect lipid values because nutritional status of the patients is often suboptimal. Generally, albumin level may be a useful marker of preoperative nutritional status. However, in this study, albumin levels were hampered by the substantially elevated C-reactive protein level, a known "depressor" of albumin. Conversely, that albumin increased significantly after surgery may either be a result of an improved nutritional status or because of resolved inflammation, evidenced by the decreased C-reactive protein. Anyway, as national recommendations are based on actual lipid values, the main result of this study, that lipid levels measured around the time of surgery in this patient group will result in too low values, remains a critical issue in daily clinical practice. We did not address the question of dietary history because no information on this matter was available in the Copenhagen City Heart Study.

Finally, although 29 of 30 patients had patent bypass grafts after 3 months, several still had tissue loss and ulcers in the healing phase. This may also contribute to the lower lipid levels observed in patients compared with controls. Although lipid levels remained lower after 3 months, there is evidence today that even at lower levels all patients with atherosclerotic disease seem to benefit from lipid-lowering therapy.[9]

Because subjects with critical limb ischemia often have ongoing inflammatory processes from infections in necrotic and ischemic tissue, C-reactive proteins may be a useful marker for predicting when serum lipids are about to reach their "normal" level. In light of this trend, the lipid levels of a patient who after 3 months has persistent tissue loss or ulcers and thereby elevated C-reactive protein should not be regarded as baseline. Rather a normalization of the inflammatory processes should be sought before evaluation.

Although changes in lipid and acute phase reactant levels have been noted for patients with myocardial infarction and stroke, the relationship has not been described for patients with peripheral vascular disease. Lipids and acute phase reactants are produced in the liver and hence inherently related. However, to our knowledge, no proof exists concerning the exact mechanism behind this lipid depression in acute and chronic illness.

Study limitations. One potential limitation of this study was the risk of a type 2 error from the sample size of 30 patients. However, the observed statistical differences were consistent and highly significant. Thus, we believe that these differences are a true phenomenon and not a result of multiple comparisons. Furthermore, the results are in line with known lipid depression in other chronic illnesses like stroke and IHD.

The study population may not be representative for the entire critical limb ischemia population because none of these consecutive patients were taking lipid-lowering drugs. However, in Denmark and in most of the European

Table III. Comparison of lipid values for cases versus healthy and IHD controls from Copenhagen City Heart Study

Median value (mmol/L)	*Cases* (n = 30)*	*Copenhagen City Heart Study* Healthy controls (n = 287)	P *value*	*IHD controls (n = 283)*	P *value*
Total cholesterol	5.4	6.0	<.007	6.2	<.002
LDL cholesterol	3.2	3.6	<.009	4.3	<.0001
HDL cholesterol	1.5	1.5	.45	1.2	<.0001

*Values for cases are postoperative.

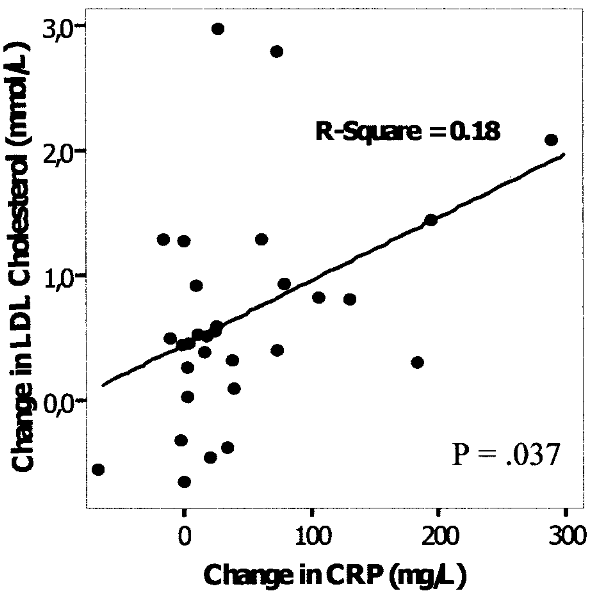

Fig 6. Correlation between change in LDL cholesterol and C-reactive protein before and after surgery.

countries, patients with claudication or critical limb ischemia are not routinely given lipid-lowering treatment. Current guidelines indicate benefit only in patients with IHD. Furthermore, a study of 147 consecutive patients in our clinic who underwent operation for critical limb ischemia in 1998 showed that only 5% received statins.[7] Unfortunately, we do not systematically register the use of lipid-lowering treatment in our clinical database. Therefore, we are not able to characterize this population further.

In conclusion, on the basis of these results, we suggest that preoperative lipid profiles are deceptively low in patients with critical limb ischemia when inflammatory markers are strongly elevated. Reassessment is necessary at least 3 months after peripheral bypass surgery to approach a more representative level.

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