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Serum Apolipoprotein A-I Concentration Differs in Coronary and Peripheral Artery Disease

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Niina Khan^a, Jahangir Khan^b, Leo-Pekka Lyytikäinen^{c,d}, Terho Lehtimäki^{c,d}, Jari Laurikka^{b,c}, Niku Oksala^{a,c}

^aCenter for Vascular Surgery and Interventional Radiology, Tampere University Hospital, Tampere, Finland; ^bDepartment of Cardio-Thoracic Surgery, Heart Hospital, Tampere University Hospital, Tampere, Finland; ^cFinnish Cardiovascular Research Center – Tampere, Faculty of Medicine and Health Technology, Tampere University, Tampere, Finland; ^dDepartment of Clinical Chemistry, Fimlab Laboratories, Tampere, Finland

E-mail addresses for authors:

Niina Khan: khan.niina@gmail.com

Jahangir Khan: jahangir.khan@saunalahti.fi

Leo-Pekka Lyytikäinen: leo-pekka.lyytikainen@tuni.fi

Terho Lehtimäki: terho.lehtimaki@pshp.fi

Jari Laurikka: jari.laurikka@tuni.fi

Niku Oksala: niku.oksala@tuni.fi

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Corresponding author: Niina Khan, Center for Vascular Surgery and Interventional Radiology, Tampere University Hospital, Teiskontie 35 PO BOX 2000, 33521 Tampere, Finland; tel +358 311611; email: khan.niina@gmail.com

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Abstract

Coronary artery and peripheral artery disease represent different clinical outcomes of atherosclerosis and despite sharing common risk factors the ultimate reasons determining disease presentation are still unclear. The present study sought to define and compare the serum lipid and apolipoprotein profiles of patients undergoing coronary artery bypass grafting and those treated invasively for symptomatic lower extremity peripheral artery disease. Altogether 218 coronary and 280 peripheral artery disease patients treated between 2013 and 2014 in the Tampere University Hospital, Tampere, Finland, with available lipid measurements within two years prior to the intervention were retrospectively analysed. The Extended Friedewald formula neural network model was used to obtain apolipoprotein and lipoprotein subfraction values. Patients undergoing coronary artery bypass surgery had a clear male predominance (82% versus 53%, $p<0.001$), lower median age (69 versus 74 years, $p<0.001$) and a lower prevalence of smoking (18% versus 32%, $p=0.001$) and pulmonary disease (12% versus 20%, $p=0.023$) compared to peripheral artery disease patients. There were some differences in the serum lipid profiles between the study groups in the univariable analyses. When controlling for the statistically significant differences in age, sex, urgency of treatment and comorbidities between the groups in a multivariable logistic regression model, higher serum concentrations of apolipoprotein A-I were significantly and independently associated with coronary artery disease (OR 1.11 for 0.01 g/L increase, $p=0.044$). In conclusion, patients undergoing coronary artery bypass grafting appear to have higher apolipoprotein A-I levels when compared to patients treated for peripheral artery disease.

Keywords: Atherosclerosis, Coronary artery bypass grafting, Coronary artery disease, Lipids, Peripheral arterial disease

Introduction

Atherosclerosis is a leading cause of morbidity and health-care costs. Peripheral artery disease (PAD) and coronary artery disease (CAD) represent different manifestations of atherosclerosis and while coexisting conditions are possible, in most patients either PAD or CAD is dominant. The reasons behind varying disease presentation remain unclear. Risk factors for PAD and CAD are similar though their relative importance differs [1]. Dyslipidaemia is clearly associated with the development and progression of atherosclerosis. Particularly high serum total cholesterol (TC) and low-density lipoprotein cholesterol (LDL-C) have been considered important factors in the emergence and progression of PAD and CAD and lipid-lowering medical therapy is a cornerstone of conservative treatment for the diseases [2-6].

Contemporary serum lipid parameters such as apolipoproteins and lipoprotein subfractions are increasingly recognised as complementary or even superior to the traditional lipid markers in cardiovascular risk assessment. Some guidelines recommend apolipoprotein B (apoB) and/or non-high-density lipoprotein cholesterol (non-HDL-C) measurements [7,8] and lipoprotein(a) – an apolipoprotein A (apoA) particle bound to a low-density lipoprotein cholesterol (LDL-C) -like particle – was discovered to be associated with PAD and its progression [9-13]. While the direct methods for obtaining apolipoprotein and lipoprotein subfraction concentrations are resource consuming, these can be estimated from traditional Friedewald inputs – serum total cholesterol (TC), triglycerides (TG), and HDL-C - by applying a neural network model, the extended Friedewald formula (EFW), accurately, swiftly and with lower costs [14].

The hypothesis for the present study was that the serum lipid and apolipoprotein profile is associated with the clinical manifestation of atherosclerosis. The serum lipid profiles were compared between patients invasively treated for PAD and those undergoing coronary artery surgery. Novel EFW lipid parameters were included.

Materials and methods

Patients and methods

The present study is a retrospective analysis comparing 218 patients that underwent isolated coronary artery bypass surgery and 280 patients that received invasive treatment – involving surgical, endovascular, or hybrid procedures – for peripheral lower extremity artery disease at Tampere University Hospital and Tampere University Heart Hospital between January 2013 and December 2014. The study subjects were identified from institutional prospective databases that contain information on all consecutive patients treated at the clinics. The clinical course of each case was reviewed and all patients whose serum lipid values had been measured within two years prior to the intervention were included in the analyses. The patients' demographic information, relevant medical history including statin use, urgency of the intervention as well as procedural details were recorded. If the same patient underwent treatment more than once during the study period, only the first treatment episode was included.

Lipid Analysis

Traditional serum lipid values including TC, HDL-C, and triglycerides (TG), were analysed using routine laboratory methods and were obtained from the Fimlab laboratories Ltd database. The median time interval between the lipid analysis and the treatment episode for PAD or CAD was 104 (range 0-728) days. The concentration of LDL-C was estimated by the traditional Friedewald formula [15]. If the serum lipid values of a patient had been measured more than once, the values closest to the index procedure were included. The Extended Friedewald formula -derived parameters - very-low-density lipoprotein triglycerides (EFW-VLDL-TG), intermediate-density lipoprotein cholesterol (EFW-IDL-C), low-density lipoprotein-cholesterol (EFW-LDL-C), high-density lipoprotein-cholesterol subfraction 2 (EFW-HDL₂), apolipoprotein A-I (EFW-ApoA-I) and apolipoprotein B (EFW-ApoB) - were determined as described by Niemi et al by using traditional serum lipid parameters as inputs [14].

Statistical Analysis

The study is of a descriptive nature and thus no prior power analysis was performed. All statistical testing was carried out with SPSS version 16.0 for Windows. The univariable comparisons of patient characteristics and serum lipid values between CAD and PAD patients were done using the Mann-Whitney U-test for noncategorical scale variables and the Chi-Square and the Fisher's exact test for categorical data. To control for the effect of group differences in the lipid values, statistically significant differences in the baseline characteristics – including age, sex, statin use, smoking, urgency of treatment and the prevalence of chronic pulmonary disease - were included in a multivariable logistic regression analysis. The statistical significance was set at $p < 0.05$. The study was performed according to the ethical principles of The Helsinki Declaration. Institutional review board approval was obtained.

Results

Altogether 218 patients treated for CAD and 280 patients treated for lower extremity PAD were included in the study. Critical limb threatening ischemia was present in 53.9% of PAD patients and 50.9% of patients that underwent coronary surgery were treated for acute coronary syndrome. The patients treated for PAD underwent operations comprising endarterectomies in 20%, bypasses in 26%, patch angioplasties in 10%, and/or hybrid or isolated endovascular procedures in 61% of cases. The patients undergoing coronary surgery were operated through standard median sternotomy and the median number of bypasses performed was three (range 1-7). The demographic information of the study groups is shown in Table 1. The patients undergoing coronary artery bypass grafting were more frequently male, somewhat younger, had lower rates of smoking and pulmonary diseases and higher rates of statin use. Also, urgent or emergency treatment was more common in patients undergoing coronary artery bypass grafting.

In univariable analyses, the traditional lipid parameter distributions were similar between the groups aside from HDL-C, which was more favourable in PAD patients (Table 2). Similarly, there were no significant differences between the concentrations of EFW-VLDL-TG, EFW-IDL-C or EFW-LDL-C, but the EFW-HDL₂-subfraction concentrations and EFW-ApoA-I as well as the EFW-ApoB/ApoA-I were statistically significantly more favourable in patients with PAD (Table 2). Overall, EFW-ApoA-I levels were significantly higher in females when compared to males, 1.56 versus 1.33 g/L, $p < 0.001$, and in patients aged at least 70 years when compared to younger patients, 1.45 versus 1.35 g/L, $p = 0.001$, respectively. In the multivariable analysis (Table 3) older age and smoking were independently associated with a decreased risk of CAD as opposed to PAD. Conversely, statin use, male sex and a higher EFW-ApoA-I concentration were independently associated with a higher risk of CAD rather than PAD.

Discussion

The anatomical presentations of and the clinical syndromes caused by atherosclerosis are multiform and the factors influencing its manifestation are not completely understood. Atherosclerotic clinical conditions, such as PAD and CAD, share several risk factors though the gravity of each is variable. Serum lipid disorders are clearly associated with atherosclerosis. The present study sought to discern variances in the serum lipid profiles, including modern lipid parameters, between PAD and CAD patients and suggests an interesting difference between the atherosclerotic phenotypes.

The study included patients undergoing invasive treatment for PAD and those undergoing coronary surgery for CAD, essentially representing advanced stages of symptomatic atherosclerotic disease in both groups. The proportion of patients undergoing urgent or emergency coronary surgery in the present study is somewhat high but other series have also reported a similar change in the ratio possibly reflecting an ongoing trend towards percutaneous procedures in the treatment of elective CAD cases [16,17]. Overall, the presentation and disease severity of PAD patients in the current study is comparable to that in the literature [18]. As in earlier studies, there were some differences in the PAD and CAD patient cohorts. Firstly, PAD patients tended to be older which can be explained by the generally later clinical onset of the disease [1,19]. Secondly, the prevalence of smoking and pulmonary disease was higher in the PAD group. This is in line with previous studies as smoking is one of the most potent risk factors for PAD but its significance in CAD is less pronounced [1,20,21]. Thirdly, there was a clear male predominance in the CAD cohort, possibly explained by a tendency for selecting non-surgical revascularisation methods for female CAD patients, as elsewhere [16]. Male sex is a risk factor for both symptomatic CAD and PAD but sex differences in the incidence and prevalence of the latter are less pronounced [1,19,22]. Albeit statin medication is advocated for all symptomatic CAD and PAD patients, the rate of statin use in the present study was greater in CAD patients compared to PAD patients, which agrees with previous literature [23-27]. Although the included study groups somewhat differ, all in all, they should accurately reflect real life patients and clinical practice.

With regards to the lipid parameters, the present study found disease specific differences in lipid values between CAD and PAD patients. Of the traditional lipid

parameters, HDL-C values were higher in patients with PAD despite a lower use of statins, which tend to increase both HDL-C and ApoA-I levels [28], and an older median age, which has been found to be associated with a decrease in HDL-C concentrations [29]. Similar findings have been reported by other authors as well [19,20]. The difference may be partly explained by the greater proportion of females in the PAD cohort and was not evident after multivariable adjusting. Of the contemporary lipid parameters, EFW-ApoA-I, EFW-ApoB/ApoA-I ratio, and EFW-HDL₂ differed between the patient cohorts and were more favourable in the PAD group. However, in the multivariable analysis, higher EFW-ApoA-I was independently associated with CAD, which is a novel finding. Previously, ApoB/ApoA-I has been found to be an effective predictor of CAD in obese patients and the inclusion of EFW-derived apolipoprotein parameters has improved cardiovascular risk prediction [30,31]. In disease-free individuals, low levels of serum ApoA-I have predicted the development of or death due to both CAD and PAD [5,32]. In patients with established cardiovascular disease, low ApoA-I levels have been associated with a higher incidence of cardiovascular events and death [33,34], critical limb ischemia [35], as well as worse prognosis following coronary artery bypass surgery [36]. Furthermore, an inverse relationship between PAD and HDL-C as well as lower HDL-C levels in CAD patients compared to PAD patients have been reported in earlier literature [19,20]. A study by Tunstall-Pedoe et al [5] additionally discovered serum TC to be more predictive of CAD compared to PAD but failed to ascertain other differences in lipid profiles. Taken together, the combined evidence regarding the potential role of ApoA-I in determining the phenotype of atherosclerosis is thus far inconclusive. However, this interesting and novel finding warrants further research.

The main limitations of the study include its retrospective nature, single centre setting and restricted cohort size. The inclusion of patients with preceding lipid measurements may have caused patient selection. Furthermore, possible concomitant CAD or PAD was not controlled for, but the treatment was given for the disease that was clinically relevant at the time. The differing baseline characteristics of PAD and CAD patients are also a potential source of bias in univariable analyses. However, these were accounted for in the multivariable analysis. All in all, the results of the current study must be viewed with caution, but they suggest previously unrecognised lipid profile differences between PAD and CAD patients.

In conclusion, patients undergoing coronary artery bypass surgery appear to have higher apolipoprotein A-I levels when compared to patients treated for peripheral artery disease. Other differences in the serum lipid profiles are likely to be explained by variance in the baseline characteristics such as age and sex.

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Tables

Table 1. Demographic data of study groups. Statistically significant differences between groups are highlighted in bold.

	Coronary bypass surgery patients	Lower extremity artery disease	p-value
Number of patients	218	280	
Male (%)	82	53	<0.001
Median age (years, range)	69 (42-89)	74 (45-95)	<0.001
Diabetes (%)	38	40	0.645
Statin use (%)	79	51	<0.001
Hypertension (%)	74	75	0.771
Smoking (%)	18	32	0.001
Urgent treatment (%)	51	25	<0.001
Chronic pulmonary disease (%)	12	20	0.023

Table 2. Serum lipid profiles of patients undergoing isolated coronary artery bypass grafting or interventional treatment for lower extremity artery disease.

	Coronary surgery patients	bypass Lower extremity artery disease	p- value
Total cholesterol (mmol/L)	4.2	4.5	0.353
LDL-cholesterol (mmol/L)	2.31	2.39	0.772
HDL-cholesterol (mmol/L)	1.18	1.27	0.006
Triglycerides (mmol/L)	1.27	1.34	0.824
EFW-VLDL-TG (mmol/L)	0.73	0.76	0.993
EFW-IDL (mmol/L)	0.21	0.21	0.706
EFW-LDL (mmol/L)	2.51	2.60	0.797
EFW-HDL₂ (mmol/L)	0.69	0.77	0.004
EFW-ApoA-I (g/L)	1.37	1.46	0.006
EFW-ApoB (g/L)	0.89	0.91	0.942
EFW-ApoB/ApoA-I	0.66	0.61	0.032

Table 3. Multivariable logistic regression analysis including significant preoperative patient characteristics and the serum lipid measurements. The Odds ratios are calculated for having coronary artery disease instead of peripheral artery disease and represent an increase of 0.01 mmol/L for cholesterol and triglyceride and 0.01 g/L for apolipoprotein levels.

	Odds Ratio	p-value
Male sex	4.01	<0.001
Age ≥ 70	0.51	0.005
Statin use	3.90	<0.001
Smoking	0.26	<0.001
Chronic pulmonary disease	0.56	0.063
Total cholesterol	0.90	0.389
LDL-cholesterol	1.11	0.343
HDL-cholesterol	0.97	0.835
EFW-VLDL-TG	1.04	0.491
EFW-IDL	1.00	0.931
EFW-LDL	0.97	0.389
EFW-HDL2	1.06	0.209
EFW-ApoA-I	1.11	0.044
EFW-ApoB	1.05	0.522
EFW-ApoB/ApoA-I* 0.5-0.7	0.55	0.160
EFW-ApoB/ApoA-I* >0.7	0.41	0.207

*Reference value <0.5

Independent variables are highlighted in boldface.

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