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Levels of Lipoprotein (a) in patients with coronary artery disease with and without inflammatory rheumatic disease: a cross-sectional study

Sverre Holm,[1,2] Ingvild Oma,[3,4] Tor-Arne Hagve,[4,5] Kjell Saatvedt,[6] Frank Brosstad,[1,4] Knut Mikkelsen,[2] Hans Rydningen,[7] Ivar Risnes,[7] Sven Martin Almdahl,[8] Thor Ueland,[1,4] Pål Aukrust,[1,4,9] Bente Halvorsen,[1,4] Ivana Hollan[2,3,10,11]

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For numbered affiliations see end of article.

Correspondence to
Dr. Sverre Holm;
sverre.holm@rr-research.no

ABSTRACT

Objectives Patients with various inflammatory rheumatic diseases (IRDs) have increased risk of atherothrombotic disease. Lipoprotein (a) (Lp(a)) is a risk factor for atherosclerosis but its role in IRD with accompanying coronary artery disease (CAD) is still unclear. We aimed to examine if serum Lp(a) levels differed between CAD patients with and without accompanying IRD.

Design A cross-sectional observational, patient-based cohort study.

Setting Referred centre for coronary artery bypass grafting in the South Eastern part of Norway.

Participants 67 CAD patients with IRD (CAD/IRD) and 52 CAD patients without IRD (CAD/non-IRD). All patients were Caucasians, aged >18 years, without any clinically significant infection or malignancy.

Methods Lp(a) levels in serum were analysed by particle enhanced immunoturbidimetric assay, and Lp(a) levels were related to clinical and biochemical characteristics of the patient population.

Results We found no differences in serum levels of Lp(a) between CAD patients with and without IRD. In general, we found that Lp(a) correlated poorly with clinical and biochemical parameters including C reactive protein with the same pattern in the CAD/non-IRD and CAD/IRD groups.

Conclusions Our data do not support a link between inflammation and Lp(a) levels in CAD and in general Lp(a) levels were not correlated with other risk factors for cardiovascular disease.

Strengths and limitations of this study

- The study investigates a unique and well characterised group of patients.
- We present measurement of Lipoprotein (a) in two distinct coronary artery disease populations, that is, patients with and without accompanying inflammatory rheumatic disease.
- The main limitation of the study is the relatively small sample size.
- Another limitation is that the design of the study does not allow for confirming of any cause–effect relationships.

INTRODUCTION

Patients with inflammatory rheumatic diseases (IRDs) have increased cardiovascular risk, primarily due to accelerated atherothrombosis.[1–4] The reasons are not fully understood, but seem to involve chronic inflammation as a common mediator of both IRD and atherosclerosis.[5 6] Thus, persistent chronic inflammation in IRD patients has been shown to contribute both to accelerated atherosclerosis[7] and cardiovascular events.[8] Besides chronic inflammation, traditional cardiovascular risk factors and genetic components are also implicated in the increased risk of cardiovascular disease (CVD) observed in patients with chronic IRD.[9]

Lipoprotein (a)[10] (Lp(a)) is composed of a low-density lipoprotein (LDL)-like particle bound with a cringle-structured glycoprotein, named apolipoprotein (apo) (a).[11 12] Epidemiological studies have suggested that elevated levels of Lp(a) is a significant risk factor for atherosclerotic disorders including myocardial infarction (MI) and ischaemic stroke.[12 13] In those with established coronary artery disease (CAD), high Lp(a) levels are associated with increased cardiovascular risk.[10 12] Moreover, Lp(a) seems to be a marker of atherosclerotic disorders and to exert both proatherogenic and prothrombotic effects, some of which are primarily related to the LDL component whereas others are apo(a)-dependent.[12 14]

Interestingly, besides genetic factors, also inflammation may influence Lp(a) levels. In support of this notion, interleukin 6 (IL-6) inhibition has been shown to down-regulate

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Lp(a) levels in patients with IRD.[15] Moreover, we have previously demonstrated that methotrexate and tumour necrosis factor inhibition down-regulate Lp(a) in patients with rheumatoid arthritis (RA).[16] In contrast, the majority of lipid-lowering strategies, except for lipid apheresis, have little influence on Lp(a) levels.[17 18]

Lp(a) levels have been reported to be elevated in IRDs including RA and systemic lupus erythematosus (SLE).[19] However, it is still unclear if the increased levels of Lp(a) in IRDs is modified by accompanying CAD. Our aim in this study was to investigate if Lp(a) levels differed between CAD patients with and without accompanying IRD. Our secondary aim was to examine if Lp(a) levels were associated with relevant clinical and laboratory variables in these patients.

MATERIALS AND METHODS

Study population

From the Norwegian Feiring Heart Biopsy Study, described elsewhere,[20 21] we examined CAD patients with IRD (CAD/IRD group; n=67) and CAD patients without IRD (CAD/non-IRD group; n=52). Briefly, all patients were Caucasians, aged >18 years, without any clinically significant infection or malignancy. The CAD groups were recruited among patients referred to coronary artery bypass grafting (CABG) due to CAD. The IRD diagnoses were confirmed according to accepted diagnostic criteria.[21] The patients were consecutively enrolled in the study. The CAD/IRD and CAD/non-IRD groups were matched for age and sex at group level.

The CAD/IRD group consisted of patients with RA (n=24), polymyalgia rheumatica (n=15), psoriatic arthritis (n=10), ankylosing spondylitis (n=6), giant cell arteritis (n=6), SLE (n=3), primary Sjögren's syndrome (n=1), reactive arthritis (n=1) and undifferentiated connective tissue disease (n=1).

Data collection

The CAD groups were examined by interview, physical examination, self-reported questionnaires and blood tests within 2 days before CABG. A positive family history of CAD was defined as CAD in first-degree relatives at age <65 years and hypercholesterolaemia as a total serum cholesterol level >5.5 mmol/L registered in medical records, or use of lipid-lowering drugs.[20]

Blood sampling protocol

Venous blood samples were collected after a minimum of 4 hours fasting. The samples were collected in sterile containers with EDTA (plasma) or without additives (serum). The EDTA tubes were immediately immersed in melting ice, and centrifuged within 30 min (2000 g for 10 min). The serum tubes were centrifuged after coagulation in room temperature (<2 hours). Plasma and serum were stored at −75 °C in multiple aliquots, and sent to the respective laboratory on dry ice. Samples were not thawed prior to the laboratory analyses, and they were analysed in batches, in random order and in a blinded manner.

Lp(a) assay

Lp(a) levels in serum were analysed by particle enhanced immunoturbidimetric assay, LPALX Tina-quant Lp(a) (Latex) (Roche, Rotkreuz, Switzerland). The precipitate was determined turbidimetrically at 552 nm, using Cobasc 501 system from Roche.

Miscellaneous

Plasma concentrations of plasminogen activator inhibitor were analysed by enzyme immunoassay provided from R&D Systems (Minneapolis, Minnesota, USA). Serum levels of C-reactive protein (CRP) were determined using a particle-enhanced, high-sensitive immunoturbidimetric assay (Tina-Quant CRP Gen.3, Roche). Routine test standards of the hospital laboratory were used to analyse erythrocyte sedimentation rate, leucocytes, neutrophils, triglycerides, total cholesterol, high-density lipoprotein (HDL) cholesterol and LDL cholesterol and uric acid.

Statistical analyses

Distributions of categorical variables were compared using χ^2 test. Comparisons of continuous variables in two groups were performed using Student's t-test (normally distributed variables) or Mann-Whitney U-test (non-normally distributed variables). The p values (two-sided) were considered significant when<0.05.

Patient and public involvement

The outcomes measures were selected based on the current level of evidence, which aims to contribute to the provision of the missing pieces. The plan for the study was developed in accordance with suggestions given by representatives and members of patient organisations, in particular the Norwegian Rheumatism association during frequent meetings/lectures about CVD in IRD. The patients wished to clarify reasons for the increased CV risk in IRD, especially with the aim to identify factors that could be possible to modify, and therefore ameliorate CVD morbidity and mortality in these diseases. The patients themselves were not involved in recruitment and conduction of the study. As for other substudies from this biobank, also this study will be disseminated to IRD patients through lectures for patient organisations and/or through popular scientific information in magazines published by these organisations.

RESULTS

Characteristics of the cohort

Characteristics of the study population are shown in table 1. Except for the use of immunosuppressive drugs, the two CAD groups were matched for most of the parameters. However, the CAD/IRD group had more often a history of previous acute coronary syndrome (ACS) and higher CRP levels (table 1).

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Table 1 Characteristics of the study population

	CAD/non-IRD (n=52)	CAD/IRD (n=67)	P value*
Age, years	68±10	67±10	0.684
Men	34 (65.4%)	42 (62.7%)	0.761
Body mass index, kg/m^2	25.7±3.3	25.5±4.3	0.822
Medical history			
History of MI	23 (44.2%)	38 (56.7%)	0.177
ACS	10 (19.2%)	19 (28.4%)	0.005
Family history of CAD	42 (80.8%)	49 (74.2%)	0.402
Diabetes	3 (5.8%)	2 (3.2%)	0.509
Hypertension	30 (57.7%)	40 (60.6%)	0.749
Hyperlipidaemia	46 (88.5%)	56 (83.6%)	0.691
Previous smoker	25 (48.1%)	26 (38.8%)	0.311
Current smoker	7 (13.5%)	15 (22.4%)	0.213
Biochemistry			
Cholesterol, mmol/L	4.91±1.17	4.92±1.28	0.966
HDL, mmol/L	1.21±0.32	1.25±0.36	0.556
LDL, mmol/L	3.18±0.96	3.12±1.05	0.761
TG, mmol/L	1.53±0.79	1.61±0.71	0.604
PAI-1, ng/mL	19.1 (13.4, 26.8)	20.1 (13.5, 28.8)	0.600
C reactive protein, mg/L	2.3 (1.2,4.4)	5.2 (2.3,14.0)	<0.001
Medication			
Oral glucocorticoids	0 (0%)	27 (40.3%)	<0.001
DMARDS	0 (0%)	22 (33.3%)	<0.001
COX2 inhibitors	0 (0%)	11 (16.4%)	<0.001
NSAID	0 (0%)	9 (13.4%)	<0.001
Lipid lowering drugs	42 (80.8%)	50 (75.8%)	0.514
Acetylsalisylic acid	47 (90.4%)	57 (85.1%)	0.387
Beta-blockers	42 (80.8%)	50 (74.6%)	0.427
ACE inhibitors	18 (34.6%)	21 (31.3%)	0.706
Duration of IRD, months	–	168 (73,260)	

Data are presented as n (%), mean ±SD or median (25th, 75th percentile) depending on variable type and distribution.
*P value from Student's t-test, Mann-Whitney U test or X^2 test depending on type and distribution of data.
ACS, acute coronary syndrome; CAD, coronary artery disease; COX2, cyclooxygenase 2; DMARDS, disease-modifying antirheumatic drugs; HDL, high-density lipoprotein; IRD, inflammatory rheumatic disease; LDL, low-density lipoprotein; MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drugs; PAI-1, plasminogen activator inhibitor 1; TG, triglycerides.

Serum LP(a) levels in CAD/IRD and CAD/non-IRD patients

As illustrated in figure 1, serum levels of Lp(a) were similar, with no significant differences between the CAD/IRD and CAD/non-IRD groups. As ACS and CRP was not associated with Lp(a) (see below), no adjustments were made when comparing levels between CAD/IRD and CAD/non-IRD groups.

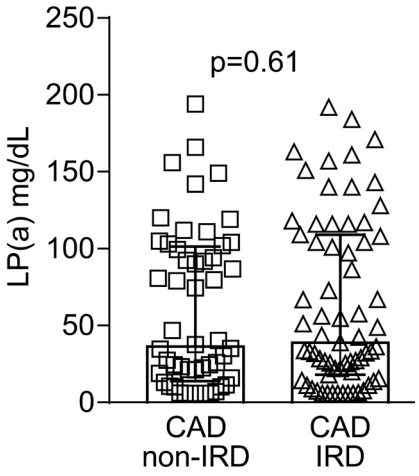

Figure 1 Lp(a) levels in CAD patients with (n=67) and without IRD (n=52). In addition to individual values, the figure shows median and 25th and 75th percentile levels. The comparison between the groups was performed by the Mann-Whitney U-test. CAD, coronary artery disease; IRD, inflammatory rheumatic disease; Lp(a), lipoprotein (a).

Associations between Lp(a) and relevant clinical and demographic variables

In general, Lp(a) correlated poorly with clinical and biochemical parameters in the study population as a whole, with the same pattern in CAD/IRD and CAD-non-IRD patients. This included correlations with age, gender and body mass index, medical history, biochemical parameters and medications, including CRP and a history of ACS that differed between the two CAD groups (table 2). However, Lp(a) correlated significantly with LDL-cholesterol in the study group as a whole, mainly reflecting a positive correlation in the CAD/non-IRD group (table 2). Moreover, whereas HDL cholesterol correlated positively with Lp(a) in the CAD/non-IRD group, Lp(a) was inversely correlated with HDL cholesterol in the CAD/IRD group (table 2).

DISCUSSION

In the present study we found no differences in serum levels of Lp(a) between CAD patients with and without IRD. Moreover, we found that Lp(a) correlated poorly with clinical and biochemical parameters including CRP with the same pattern in the CAD/non-IRD and CAD/IRD groups. These data do not support the notion that Lp(a) levels are driven by inflammation, as reflected by CRP levels, in these populations.

Several studies have shown that elevated serum Lp(a) levels are associated with a higher risk for developing CAD, and in those with established CAD, high levels of Lp(a) are associated with increased risk for cardiovascular events.[10 12 13] There are also some studies showing increased serum levels of Lp(a) in IRD patients,

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Table 2 Correlations between serum levels of Lp(a) and different clinical and biochemical characteristics of the study population

	All (n=119)	CAD/non-IRD (n=52)	CAD/IRD (n=67)
Age, years	−0.01	−0.01	−0.02
Men	−0.01	0.27*	−0.22
Body mass index	0.09	0.03	0.13
Medical history			
History of MI	0.01	−0.14	0.10
ACS	−0.05	−0.10	−0.03
Family history of CAD	−0.05	0.11	−0.16
Diabetes	−0.18	−0.14	−0.21
Hypertension	0.05	0.04	0.04
Hyperlipidaemia	0.00	−0.11	0.06
Previous smoker	0.00	−0.03	0.02
Current smoker	−0.09	−0.24	−0.01
Biochemistry			
Cholesterol	0.20	0.29	0.13
HDL	−0.02	0.37*	−0.29*
LDL	0.22*	0.30*	0.17
TG	0.04	0.06	0.04
PAI-1	0.02	0.00	0.04
C reactive protein	0.14	−0.02	0.22
Medication			
Oral glucocorticoids	−0.03	–	−0.12
DMARDS	−0.09	–	−0.15
COX2 inhibitors	0.10	–	0.13
NSAID	0.15	–	0.17
Lipid lowering drugs	0.04	0.05	0.04
Acetylsalisylic acid	0.13	0.15	0.12
Beta-blockers	−0.08	−0.14	−0.03
ACE inhibitors	0.07	−0.15	0.23
Duration of IRD, months	–	–	0.09

Data are given as Spearman correlation coefficients.
*P<0.05.
ACS, acute coronary syndrome; CAD, coronary artery disease; COX2, cyclooxygenase 2; DMARDS, disease-modifying antirheumatic drugs; HDL, high-density lipoprotein; IRD, inflammatory rheumatic disease; LDL, low-density lipoprotein; Lp(a), lipoprotein (a); MI, myocardial infarction; NSAID, non-steroidal anti-inflammatory drugs; PAI-1, plasminogen activator inhibitor 1; TG, triglycerides.

potentially associated with increased risk for developing atherosclerotic disease.[19] These latter studies may indicate an interaction between Lp(a) and inflammation. However, herein we found no differences in Lp(a) levels between CAD/non-IRD and CAD/IRD patients, although the latter group had significantly higher CRP levels. Indeed, we found no correlation between Lp(a) and CRP with the same pattern in the two CAD groups. Moreover, whereas therapeutic intervention targeting IL-6 by the IL-6 receptor inhibitor tocilizumab has been shown to down-regulate Lp(a) levels in patients with IRD,[22–24] we recently observed no effect of tocilizumab treatment on Lp(a) levels in patients with Non-ST-elevation MI.[25] Thus, at present the link between inflammation and Lp(a) levels is questionable, and our findings herein do not support the 'inflammatory-driven' Lp(a) hypothesis.

There are some reports of a positive correlation between Lp(a) and HDL cholesterol,[26] and in the present study this was also seen in the CAD/non-IRD group. In contrast, an opposite association was seen in the CAD/IRD, with a significant inverse correlation between Lp(a) and HDL cholesterol. At present we have no explanation for these different associations between HDL cholesterol and Lp(a) in the two CAD groups, and it could be by chance owing to a large number of correlation analyses. However, future studies exploring this pattern in larger study populations could potentially contribute to our understanding of the complex regulation of Lp(a) in CVD.

Although some correlation with LDL and HDL cholesterol, Lp(a) levels did not correlated with other risk factor for CAD. More recent studies have also noted that Lp(a) levels correlated poorly with other risk factors for CVD.[27 28] This does, however, not exclude that Lp(a) could contribute to development and progression of atherosclerotic disorders. Thus, Lp(a) has been suggested to promote atherogenesis and plaque instability by inhibiting angiogenesis, enhancing endothelial cell activation and thrombogenesis through inhibiting fibrinolysis and tissue factor inhibitor pathway and inducing platelet activation.[10 12 14] Lp(a) has also been shown to contribute to foam cell formation, and through binding to oxidised phospholipids it may cause plaque instability.[12] If these mechanisms are operating in the same degree in CAD patients with and without accompanying IRD has to this end not been studied.

This study has some potential limitations. First, due to a relatively small sample size, the apparent lack of differences and associations might be caused by type-II error and our data should be interpreted with some cautions. Second, the design of the study does not allow for confirming of any cause-effect relationships.

In conclusion, we found no differences in Lp(a) levels between CAD/IRD and CAD/non-IRD patients, and Lp(a) levels correlated poorly with other risk factors for CAD progression including CRP. Our data do not support a link between inflammation and Lp(a) levels in CVD.

Author affiliations
[1]Research Institute of Internal Medicine, Oslo University Hospital, Oslo, Norway
[2]Rheumatology Department, Hospital for Rheumatic Diseases, Lillehammer, Norway
[3]Department of Pathology, Sykehuset Innlandet HF Divisjon Lillehammer, Lillehammer, Norway
[4]Faculty of Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[5]Division of Diagnostics and Technology, Akershus University Hospital, Lorenskog, Norway

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[6]Department of Thoracic Surgery, Oslo University Hospital Rikshospitalet, Oslo, Norway
[7]Department of Cardiac Surgery, Feiring Heart Clinic, Feiring, Norway
[8]Department of Cardiothoracic and Vascular Surgery, University Hospital of North Norway, Tromso, Norway
[9]Section of Clinical Immunology and Infectious Diseases, Oslo University Hospital Rikshospitalet, Oslo, Norway
[10]Department of Medicine, Brigham and Women's Hospital, Boston, Massachusetts, USA
[11]Harvard Medical School, Harvard, Boston, USA

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Contributors SH, IO, BH and IH conceived and design research; T-AH and FB performed biochemical analyses; IO, KS, KM, HR, IR, SMA and IH recruited patients and collected samples; SH, IO, TU and IH performed statistical analyses; SH, PA and IH wrote the paper; SH, PA, BH and IH had the responsibility for the final content. All authors read, critically revised and approved the final manuscript.

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