Hyperhomocyst(e)inemia is an important risk factor for vascular disease in subjects with high-molecular weight apo(a) isoforms

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Summary

Background: Homocyst(e)ine is reported to increase the binding of lipoprotein(a) [Lp(a)] to fibrin, which may increase the thrombogenic effects of Lp(a) in vivo. The aim of this study was to investigate whether there is a relationship between homocyst(e)ine and Lp(a) levels and vascular disease risk, and if the relationship depends on the apo(a) isoforms.

Methods: A case-control study was performed in 91 Caucasian male subjects with vascular disease due to atherosclerosis, and in 100 healthy age- and sex-matched control subjects.

Results: Both hyperhomocyst(e)inemia and elevated Lp(a) were significantly more prevalent in patients. Concordant elevated Lp(a) and hyperhomocyst(e)inemia were not associated with increased vascular disease risk (relative odds 2.96; 95% CI: 0.90-9.80), while hyperhomocyst(e)inemia in the absence of elevated Lp(a) was associated with increased vascular disease risk (relative odds 7.20; 95% CI: 2.37–21.91). Hyperhomocyst(e)inemia in individuals with high-molecular weight apo(a) isoforms [smaller apo(a) isoform > S3] was observed to be associated with increased vascular disease risk (relative odds 11.02; 95% CI: 3.54–34.30), while vascular disease risk in subjects with low-molecular weight apo(a) isoforms [smaller apo(a) isoform < S3] was not significantly increased, the relative odds being 1.92; 95% CI: 0.51–7.24.

Conclusions: We conclude that hyperhomocyst(e)inemia is an important risk factor in individuals with high-molecular weight apo(a) isoforms.

The association between elevated plasma Lp(a) levels and increased risk for vascular disease is well established, although negative findings have also been reported. A variation at the apo(a) gene locus and the apo(a) size polymorphism, which determines Lp(a) levels to a great extent, are also determinants of coronary artery disease (CAD) risk. Small apo(a) isoforms are associated with increased risk for CAD.

Although in vitro and population studies suggest that elevated plasma Lp(a) levels are causally related to atherosclerosis, the process of atherogenesis is not fully understood. Increased Lp(a) levels are associated with ischaemic heart disease in particular when LDL levels are also increased. Howard and Pizzo speculated that Lp(a) is not atherogenic on its own but needs to be modified structurally or needs the presence of evolving atherosclerotic vascular disease to exhibit its pro-thrombotic effects. Intact Lp(a) may cross the vascular endothelial layer, and in the intima it may undergo structural changes due to interaction with fibrin, free radicals, proteoglycans or glycosaminoglycans. After modification, Lp(a), like LDL, may be taken up by macrophage receptors, resulting in the formation of foam cells, although in vitro studies of Lp(a) uptake by macrophages have been less than convincing. Modified Lp(a) is also reported to increase monocyte chemo-attractant activity of vascular endothelial cells, stimulate smooth muscle cell proliferation, and impair endothelium-dependent vasodilation.

Due to the structural homology with plasminogen, Lp(a) may affect fibrinolysis by competing with plasminogen for binding to endothelial cells, fibrin, fibrinogen and fibrin fragments, mononuclear cells and platelets. The binding of plasminogen to fibrin is mediated by lysine–fibrin-binding sub-sites localised to Kringles I and IV of plasminogen. The accessibility of these binding sites as well as the individual’s Lp(a) phenotype may...
determine the ability of \( \text{Lp}(a) \) to compete with plasminogen for fibrin binding.\(^47,48\) As a result, \( \text{Lp}(a) \) acts as a competitive antagonist for plasminogen, and thrombogenesis may be promoted \textit{in vivo} if \( \text{Lp}(a) \) levels are increased. Even at low plasma concentrations, homocysteine increases the binding of \( \text{Lp}(a) \) to fibrin, especially when \( \text{Lp}(a) \) levels are increased, and this may contribute to the atherogenicity and thrombogenicity of \( \text{Lp}(a) \).\(^49\) Furthermore, free \( \text{apo}(a) \) can more readily inhibit the fibrinolytic system than complete \( \text{Lp}(a) \), and homocysteine is reported to release apolipoprotein(a) from \( \text{Lp}(a) \) when total homocyst(e)ine (sum of free and protein-bound homocysteine and homocysteine) exceeded 22 mmol/L.\(^50\)

The risk for vascular disease associated with both hyperhomocyst(e)inemia and elevated plasma \( \text{Lp}(a) \) levels has been investigated in several studies,\(^8,9,24,51-56\) but in none of these studies has the possible interaction between the \( \text{apo}(a) \) isoform size, plasma total homocyst(e)ine concentrations and risk for vascular disease been analysed. The various \( \text{apo}(a) \) isoforms that are distinguished by a different number of Kring IV repeats differ also with respect to their affinity for fibrin.\(^47,48\) We hypothesised that the interactive effect between \( \text{Lp}(a) \) and homocysteine, which is postulated to enhance thrombogenesis \textit{in vivo}, may depend on the size of the individual \( \text{apo}(a) \) isoform. To investigate our hypothesis, we determined \( \text{apo}(a) \) phenotypes together with serum \( \text{Lp}(a) \) and plasma total homocyst(e)ine (tHcy) concentrations in patients with coronary or peripheral vascular disease (VD) due to atherosclerosis, and apparently healthy age- and sex-matched controls from the same geographic region.

**Aim**

The aim of the study was to assess whether there is a relationship between circulating \( \text{Lp}(a) \) concentrations, \( \text{apo}(a) \) isoform size, plasma tHcy concentrations and risk for vascular disease.

**Methods**

**Patients and controls**

Ethical approval was granted by the Human Ethics Committee of the University of Pretoria to perform this serial study on male Caucasian patients with clinical symptoms of vascular disease who were admitted for angiography to the Pretoria Heart and Unitas Hospitals. Apparently healthy male controls with no acute or chronic disease, or history of vascular disease were recruited from governmental and semi-private business institutions in such a way that the control group represented the same socio-economic subclasses that constituted the patient group.

From these two groups, 100 controls [mean (SD) age 49.1 (6.6)] and 91 patients with vascular disease due to atherosclerosis [mean (SD) age 49.5 (6.3)] were selected according to age, to perform a case-control study in which the possible interaction between plasma tHcy, \( \text{Lp}(a) \) and \( \text{apo}(a) \) isoform was assessed. Eighty-four patients had angiographically documented coronary artery disease (CAD) (> 50% stenosis of a major epicardial coronary artery), while four had angiographically documented peripheral vascular disease (PVD) of the iliac or femoral vessels, and three had both CAD and PVD. Of the 84 patients with CAD, 44 had survived a myocardial infarction, coronary artery bypass grafting or percutaneous transluminal angioplasty, but not within the three months preceding angiography. The rest of the patients had newly diagnosed VD. A questionnaire was completed by all subjects and provided information concerning age, general health status, current medication used, and current smoking practice.

**Laboratory analyses**

Blood samples with EDTA as anticoagulant, and clotted blood samples were collected from the patients after an overnight fast prior to angiography. Fasting blood samples were also collected from the apparently healthy controls. The EDTA samples were kept on ice until the plasma was separated within 30 minutes by low-speed centrifugation. The plasma was aliquoted and transported on dry ice to the laboratory where it was stored at \(-80^\circ\)C until the analyses were performed. The serum samples were left to clot and were separated within four hours at the laboratory. A biochemical profile was determined on all subjects with an automated analyser (results not shown) to identify individuals with renal or hepatic dysfunctions.

Plasma \( \text{Lp}(a) \) concentrations were measured in batches using a radio-immunoassay method [Mercodia Apo(a) RIA, Merckodia AB, Uppsala, Sweden] within six months of collection and were recorded in mg/dl. The day-to-day analytical coefficient of variation of the method was 4.6%.

The lipid profiles were determined either the same or the following day. Serum total cholesterol (TC), determined with an automated analyser (Technicon DAX® System; Miles Inc, Tarrytown, New York 10591-5097, USA), and high-density lipoprotein cholesterol (HDL-C), determined with the CHOD-Iodide method (14350 Merckotest® Merck, Darmstadt, Germany), were used to calculate serum low-density lipoprotein cholesterol (LDL-C) concentrations. Serum triglycerides were determined with an automated analyser (Technicon DAX® System; Miles Inc, Tarrytown, New York 10591-5097, USA) and serum apolipoprotein A1 and B (Apo A and Apo B) were determined with nephelometry (Behringwerke AG, Marburg, Germany).

Apo(a) phenotyping was performed by SDS agarose gel electrophoresis. The method was based on the one described by Kraft \textit{et al.}\(^57\) Plasma samples (2–10 µl, depending on the plasma \( \text{Lp}(a) \) concentrations) were diluted with a reducing buffer to a volume of 100 µl and boiled for 10 minutes in a water bath. The buffer contained 3.8% (w/v) sodium dodecyl sulfate (SDS), 7.7% (v/v) β-mercaptoethanol, 0.077% (w/v) bromophenol blue and 0.77% (v/v) glycerol. The final \( \text{Lp}(a) \) concentration was approximately 20 ng/µl. The gel contained 1.5% (w/v) ultrapure agarose (Agarose, L, Cat. No. 17-04240-02, Pharmacia Biotech, Uppsala, Sweden), 90 mM Tris-HCl, 90 mM boric acid, 2 mM EDTA and 0.1% (w/v) SDS. The size of the gel was 15 × 25 × 0.4 cm (L × W × H) with 30 slots of 2-mm depth and 1.5-mm width. One micro-litre of the standard or sample was loaded under buffer into the slots.

Electrophoresis was performed at a constant 15 W for seven hours with a Pharmacia gel electrophoresis apparatus (GNA-200, Pharmacia Biotech, Uppsala, Sweden) and a
Pharmacia power supply (EPS 600 Pharmacia Biotech, Uppsala, Sweden). The gel was cooled down to 25°C in a buffer containing 45 mM Tris-HCl, 45 mM boric acid, 2 mM EDTA and 0.1% (w/v) SDS. Semi-dry electroblotting was performed to nitrocellulose filters (PolyScreen® PVDF Transfer membrane, Cat. No. NEF-1002, Du Pont Biotechnology Systems, Boston, Massachusetts, USA) with an LKB transfer system over 120 minutes at 2.5 mA/cm². A transfer buffer system was used with two anode buffers (0.3 M Tris, pH 10.4 and 25 mM Tris, pH 10.4) and one cathode buffer (25 mM Tris, 40 mM glycine and 40 mM 6-amino-n-hexanoic acid, pH 9.4), all containing 10% methanol. The gel was equilibrated for 5 min in the cathodic buffer and the transfer membrane was immersed in methanol for a few seconds, left in water for five minutes to elute the methanol, and equilibrated for five minutes in the second anode buffer.

The nitrocellulose filter was blocked overnight at 4°C in a solution of 1% (w/v) bovine serum albumin, 10 mM Tris-HCl, 85 mM NaCl and 0.2% Triton X-100. A solution of 1% (w/v) bovine serum albumin, 10 mM Tris-HCl, 85 mM NaCl and 0.2% Triton X-100 was incubated for two hours at 37°C, in blocking solution to which the first antibody, apo(a)-specific 1A2 monoclonal antibody was added. After extensive washing the blot was exposed for one hour to the second antibody, which was a horseradish peroxidase conjugated monoclonal (mouse-anti human) antibody (Cat. No. NA 9310, Amersham, Life Sciences, UK). After further washing, an ECL-detection system (ECL Western blotting detection reagents, Cat. No. RPN 2106, Amersham, Life Sciences, UK) was used for detection on a Fuji RX-V 18 × 24 PT 361515 film.

The various apo(a) isoforms were designated according to the number of Kringle IV repeats by comparing the electrophoretic mobility of the isoforms with that of a standard in which the number of K-IV repeats had been determined by genomic southern blotting. To allow an adequate statistical treatment and also to enable comparability with previous studies with lower resolution, the following grouping was performed: apo(a) isoforms containing 11–13 Kringle IV repeats were summarised as F, 14–16 Kringle IV repeats as B, 17–19 Kringle IV repeats as S1, 20–22 Kringle IV repeats as S2, 23–26 Kringle IV repeats as S3 and those > 26 Kringle IV repeats as S4, in accordance with the original classification. In addition, the following phenotypic groups were constructed as described:31,34 phenotype group I: S4, 0; phenotype group II: S3, S3S4; phenotype group III: S2, S2S3, S2S4; phenotype group IV: phenotype combinations containing the isoforms F, B or S1. Phenotype groups II and I were regarded as high-molecular weight isoforms, and phenotype group III and IV as low-molecular weight isoforms.

Plasma tHcy concentrations were determined with HPLC as described,73,75 and total (free plus protein-bound) homocyst(e)ine was measured. The day-to-day analytical coefficient of variation of the method was 5.2%.

Statistical analyses

Analyses were performed with SPSS software. Between-group comparisons were performed with the student’s t-test or the Mann Whitney U-test for continuous variables depending on the distribution of the variable. The χ² test was used for contingency tables, and logistic regression was used to determine relative risk. A value of 12.0 μmol/l was used as cut-off level to establish vascular disease risk related to hyperhomocyst(e)inemia. Plasma Lp(a) concentrations above 30.0 mg/dl, the commonly accepted threshold, were regarded as elevated, which was less than the 75th percentile of control plasma Lp(a) concentrations of 32.7 mg/dl. Only one VD subject had increased serum urea and creatinine concentrations. As exclusion of this subject did not alter the statistical findings, and as none of the other variables measured could be regarded as a possible statistical outlier, the subject was included in the study.

Results

Risk profile of subjects and controls

No significant difference was observed in the prevalence of hypertension (diastolic blood pressure > 90 mm Hg and systolic blood pressure > 160 mm Hg / treated with anti-hypertensive drugs) between the two groups. The prevalence of tobacco smoking appeared to be much higher in the VD subjects, the observed prevalence of pipe or cigarette smoking being 61% for patients and 18% for control subjects, which is suspiciously low. Of the patient group, 37.4% were treated with cholesterol-reducing drugs, while 1% of controls were treated with these drugs. The serum TC concentrations of patients were significantly increased compared with controls (p = 0.035) despite more frequent cholesterol-reducing drug use, while the LDL-C, HDL-C and triglyceride levels did not differ significantly (Table I). Apo A and Apo B levels of patients were also less favorable in patients compared with controls (p < 0.001) (Table I).

Plasma Lp(a) concentrations as risk factor for VD

The median (IQD interquartile distance) plasma Lp(a) concentrations which are expressed as median (IQD). All variables are expressed as mean (SD), except plasma tHcy concentrations which are expressed as median (range), and plasma Lp(a) concentrations which are expressed as median (IQD).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Controls (n = 100)</th>
<th>Patients (n = 91)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>49.1 (6.6)</td>
<td>49.5 (6.3)</td>
</tr>
<tr>
<td>Hypertension^</td>
<td>17.0%</td>
<td>28.6%</td>
</tr>
<tr>
<td>Current tobacco smoking^</td>
<td>16/89 (18%)</td>
<td>35/57 (61%)</td>
</tr>
<tr>
<td>Serum TC (mmol/l)</td>
<td>5.63 (1.06)</td>
<td>5.98 (1.22)</td>
</tr>
<tr>
<td>Serum LDL-C (mmol/l)</td>
<td>4.06 (1.14)</td>
<td>4.37 (1.29)</td>
</tr>
<tr>
<td>Serum HDL-C (mmol/l)</td>
<td>1.05 (0.25)</td>
<td>1.02 (0.47)</td>
</tr>
<tr>
<td>Serum Apo A (g/l)</td>
<td>1.44 (0.22)</td>
<td>1.20 (0.24)^</td>
</tr>
<tr>
<td>Serum Apo B (g/l)</td>
<td>1.20 (0.34)</td>
<td>1.48 (0.38)^</td>
</tr>
<tr>
<td>Serum triglycerides (mmol/l)</td>
<td>2.33 (1.33)</td>
<td>2.34 (1.19)</td>
</tr>
<tr>
<td>Plasma tHcy (mmol/l)</td>
<td>8.34 (4.95–18.23)</td>
<td>10.15 (5.24–47.06)^</td>
</tr>
<tr>
<td>Lp(a) (mg/dl)</td>
<td>15.3 (27.7)</td>
<td>26.3 (46.1)</td>
</tr>
</tbody>
</table>

^Diastolic blood pressure > 90 mm Hg and systolic blood pressure > 160 mm Hg / treated with anti-hypertensive drugs.

^Smoking refers to percentage of subjects who currently either smoked a pipe or cigarettes.

All variables are expressed as mean (SD), except plasma tHcy concentrations which are expressed as median (range), and plasma Lp(a) concentrations which are expressed as median (IQD).

Significance of differences: *p < 0.05, **p < 0.001, ***overall chi-square 28.83, p-value < 0.001.
cen-
tration of the patients was 26.3 (46.1) mg/dl, which was 
significantly elevated compared with control concentrations 
of 15.3 (27.7) mg/dl (Table I). Elevated Lp(a) concentrations 
(> 30 mg/dl) were observed in 30.7% of controls and 48.0% 
of patients. Also this difference was significant ($\chi^2 = 7.02; 
p = 0.008$), showing that VD was significantly associated 
with elevated Lp(a) levels, and the relative risk associated 
with VD due to increased Lp(a) concentrations was 2.02 
(95% CI: 1.14–3.59).

**Relation between VD risk and plasma total 

homocyst(e)ine**

Median (range) plasma tHcy concentrations of 10.15 µmol/l 
(5.24–47.06) for VD patients were significantly elevated 
compared with 8.34 µmol/l (4.95–18.23) for controls (Table 
I). Hyperhomocyst(e)inemia (> 12.0 µmol/l) was prevalent 
in 34.0% of the patients and was significantly associated 
with VD (relative risk 5.94; 95% CI: 2.56–13.79).

**Interaction between Lp(a) and homocysteine**

Potential interaction between Lp(a) and homocyst(e)ine was 
tested by assessing risk relating to excess of a risk factor 
in the presence of excess or absence of the other risk factor 
(Table II), as previously reported. Concordant excess 
of Lp(a) and hyperhomocyst(e)inemia did not result in 
significantly increased VD risk (relative odds 2.96; 95% 
CI: 0.90–9.80), whereas hyperhomocyst(e)inemia in the 
absence of excess Lp(a) resulted in a 7.20-fold increase in 
VD risk (95% CI: 2.37–21.91).

Table III shows the risk of VD associated with elevated 
plasma tHcy concentrations after stratification of the data 
into high- and low-molecular weight apo(a) isoform groups.

**Discussion**

Both elevated plasma Lp(a) concentrations and hyper-

homocyst(e)inemia appear to be associated with increased 

risk for VD in Caucasian South African males. Concordant 

Lp(a) excess and hyperhomocyst(e)inemia are expected 

to increase VD risk significantly. The possible interaction 

between Lp(a) and homocyst(e)ine was investigated by 

Hopkins et al. These researchers reported a significant 

interaction between Lp(a) and homocyst(e)ine, based on 
calculated relative odds of VD of 31.7 (95% CI: 6.5–155), 

if both risk factors were elevated. In our study we found 

that concordant excess of plasma total homocyst(e)ine and 

Lp(a) was not significantly associated with VD risk (Table 

II) (relative odds 2.96; 95% CI: 0.90–9.80).

The study by Hopkins et al. was performed in patients 

with familial CAD who had survived a myocardial infarc-

tion, percutaneous transluminal angioplasty, or coronary 

artery bypass grafting. Patients with such a profile consti-
tuted only 48% of our patient population. These differences 

may explain the different relative risks between our study 

and that of Hopkins et al. Application of Hopkins et al.’s 

higher threshold values for elevated Lp(a) (40 mg/dl) and 

hyperhomocyst(e)inemia (15 µmol/l) to our data did not 

alter our findings. Concomitant hyperhomocyst(e)inemia 

and Lp(a) excess may however be ascribed to renal impair-

ment, which was not taken into account in Hopkins et al.’s 

study. In our study we found that neither hyper-

homocyst(e)inemia nor Lp(a) excess could be explained by 

renal impairment.

Parsons et al. reported that 20% of patients with mild 

renal impairment had both risk factors present, whereas 

58% of patients with a GFR less than 10 ml/min had 

both hyperhomocyst(e)inemia and Lp(a) excess. In another 

study, mean plasma tHcy, fibrinogen and Lp(a) levels were 

reported to be substantially increased in end-stage renal 

disease patients. Prevalent CAD was however not associ-

ated with levels of plasma tHcy, fibrinogen or Lp(a) in the 
maintenance dialysis population. Kronenberg et al. found 

that the prevalence of peripheral arterial calcifications in 

patients with ESRD was related to Lp(a) and homocyst(e)ine 

levels and suggested that the progression of arterial calcifica-

tions is related to hyperhomocyst(e)inemia. Application of 

Hopkins et al.’s study. In our study we found that neither hyper-

homocyst(e)inemia nor Lp(a) excess could be explained by 

renal impairment.

A prospective study would probably be the ideal study 
design to investigate the cumulative or additive effect of 

concomitant hyperhomocyst(e)inemia and Lp(a) excess, 

although long-time storage of samples may affect the 

measurement of Lp(a). This may have been the case in a 

prospective study performed in Finland, which evaluated 

vascular risk relating to plasma concentrations of Lp(a) 

and homocyst(e)ine, and found that neither of these two risk 

factors contributed to VD prevalence.
Our results suggest that hyperhomocyst(e)inemia is an important risk factor for VD, especially in individuals with Lp(a) levels of < 30.0 mg/dl (Table II) (relative odds 7.20; 95% CI: 2.37–21.91), which are by default individuals with the larger apo(a) isoforms. Logistic regression analyses on the data, stratified according to high- or low-molecular weight apo(a) isoforms, showed that the risk of VD relating to elevated plasma tHcy concentrations was highly significant in subjects with high-molecular weight apo(a) isoforms (relative odds 11.02; 95% CI: 3.54–34.30) (Table III).

Kronenberg et al. recently demonstrated that the decrease of Lp(a) concentrations following kidney transplantation was caused by changes in the expression of HMW apo(a) isoforms.84 They concluded from this study that an interaction of apo(a) genetic variability and kidney function on Lp(a) concentrations exists.84 Renal function is one of the main determinants of plasma tHcy concentrations.51–55 Whether the association between hyperhomocyst(e)inemia and high-molecular weight apo(a) isoforms is causally related to VD risk and whether this relation to VD risk can be explained by renal function needs to be clarified.

Findings by Huby et al.85 show that ‘mini-Lp(a)’ containing the C-terminal domain of apo(a) (comprising the region from Kringle IV–V to the protease domain) linked to apo B exhibits binding affinity to fibrin, whereas the repeated Kringle IV-2 domain does not appear to possess lysine-binding sites. Steric changes within the Kringle IV-2 repeat region would therefore not affect binding to fibrin within this region, but could facilitate binding within the C-terminal domain to fibrin. Conformational changes of apo(a) induced by homocysteine may therefore have a greater impact on VD progression in the high-molecular weight apo(a) isoforms compared with the low-molecular weight apo(a) isoforms.

Eritsland et al.92 performed a study in which the influence of serum Lp(a) and homocyst(e)inemia on vein graft patency after coronary artery bypass grafting was assessed. Neither Lp(a) nor homocysteine could explain occlusion of the grafts, but the number of vein graft occlusions was significantly higher in the lowest quartile of Lp(a) concentrations [therefore in the individuals who probably had high-molecular weight apo(a) isoforms] than in the higher three quartiles of Lp(a) concentrations. This study may support the notion that high-molecular weight apo(a) isoforms may also play a significant role in VD progression.

Conclusion

The present data show that homocyst(e)inemia is an independent risk factor for VD in individuals with high-molecular weight apo(a) isoforms, who up to now have been considered to be at low risk because of their low Lp(a) levels. Determination of plasma tHcy concentrations seems imperative in these subjects.

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