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High lipoprotein (a) levels are associated with an increased risk of retinal vein occlusion

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ABSTRACT

Introduction: Retinal vein occlusion (RVO) is one of the most common retinal vascular disorders affecting ocular vessels. Few studies, with conflicting results and conducted in limited study populations, have hypothesised the role of high levels of lipoprotein (a) [Lp(a)] in the occurrence of RVO. The aim of this study was to investigate, in a large group of RVO patients, the role of such an emerging thrombophilic parameter on the pathogenesis of RVO.
Materials and methods: We compared 262 patients [median age: 66 years (15–88); 122 M, 140 F] with 262 age- and sex-comparable healthy subjects.
Results: Circulating concentrations of Lp(a) were found to be significantly different in patients when compared to healthy subjects [189 (60–1898) mg/L vs. 119.5 (6–1216) mg/L; $p < 0.0001$, respectively]. No significant differences were observed relating to the different types of occlusion (central or branch occlusion). In order to investigate the possible association between high Lp(a) levels and the disease we performed a logistic regression analysis. In the univariate analysis, Lp(a) levels > 300 mg/L were found to be associated with an increased risk of RVO (OR: 2.39, 95%CI 1.39–3.59; $p < 0.0001$). Following this, three models of multivariate analysis were performed, firstly by adjusting for age, gender, and traditional cardiovascular risk factors, secondly for triglycerides and thirdly for homocysteine levels. In all the models, Lp(a) levels > 300 mg/L confirmed their role as a risk factor for RVO [first model, OR: 2.15 (95%CI 1.39–3.32), $p = 0.0001$; second model, OR: 3.11 (95%CI 1.77–5.62), $p < 0.00001$; third model, OR: 3.48 (95%CI 1.88–6.43), $p < 0.00001$].
Conclusions: This study reports that, in a large population of RVO patients, high Lp(a) concentrations are significantly related to RVO, independent from other traditional and emerging risk factors, suggesting that they may play a role in its pathogenesis.

1. Introduction

Retinal vein occlusion (RVO) is a potentially vision-threatening retinal vascular disorder, representing the second most frequent disease of the eye [1,2]. RVO is a relatively frequent disease which has been reported to be associated with an increased risk of mortality from cardiovascular diseases [3]. To date, the pathogenesis of RVO is not fully understood. Atherosclerosis is considered to be the most important underlying condition and several traditional risk factors (hypertension, diabetes, and smoking habit) have been identified to play a role in the pathogenesis of the disease [4].

We have recently reported a role for emerging thrombophilic risk factors, haemorheology, and B-group vitamins on the occurrence of RVO [5–8], but an ongoing issue is the role of dyslipidemia and lipid parameters in the pathogenesis of RVO. Lipoprotein (a) [Lp(a)] is a specific class of lipoprotein particle composed of a single copy of apolipoprotein B-100 linked to an apo(a) component [9]. Due to its similarity with low-density lipoprotein particles, Lp(a) has been thought to have proatherogenic properties. Moreover, Lp(a) has been also demonstrated to have prothrombotic properties, mainly due to the high homology between certain kringle domains of apo(a) of Lp(a) and that of the fibrinolytic proenzyme plasminogen. In recent years, there has been increasing interest in the possible association between alterations of Lp(a) and RVO, but no conclusive data have been obtained [5,10–16]. Some studies

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reported increased levels of Lp(a) in RVO patients when compared to healthy controls [10–15], whereas others did not support these findings [5,16]. The aim of this retrospective case–control study was therefore to evaluate, in a large population of RVO patients, the possible association between Lp(a) and the occurrence of RVO.

2. Materials and methods

2.1. Study population

The study population comprised 262 consecutive patients [122 males, 140 females with a median age of 66 years (range: 15–88)] with an RVO diagnosis who had been referred to the Thrombosis Centre of the University of Florence, Italy. RVO was diagnosed in all patients within a period of 1–3 months before the examination, at the Department of Oto-Neuro-Ophthalmogical Surgical Sciences of the University of Florence, Italy. RVO was diagnosed by ophthalmoscopic fundus examination revealing disc swelling, venous dilation or tortuosity, retinal haemorrhages, and cotton-wool spots and by fluorescein angiography demonstrating extensive areas of capillary closure, venous filling defects and increased venous transit time.

The control population comprised 262 healthy subjects, selected to be of comparable age and gender to the patients [123 males, 139 females; median age: 65.5 years (range: 21–84)] from the staff of the University of Florence and/or from their friends or partners.

Patients and control subjects with a personal history of glaucoma or cardiovascular disease were excluded from the study. In order to identify symptom-free subjects and patients excluding those who were suspected of having any form of vascular disease, a detailed interview addressing personal and familial history was performed.

The subjects were classified as having hypertension according to the guidelines of The European Society of Hypertension/European Society of Cardiology [17] or if they reported taking antihypertensive medication, as verified by the interviewer. Diabetic subjects were defined in line with the American Diabetes Association [18] or on the basis of self-reported data (if confirmed by medication or chart review). Dyslipidemia was defined following the criteria of the ATP III Expert Panel of the US National Cholesterol Education Program [19]. Current smoking status was determined at the time of physical examination. All participants gave signed informed consent; the study was approved by the local Ethics Committee and complies with the Declaration of Helsinki.

2.2. Blood measurements

Blood samples were collected from the antecubital vein into evacuated plastic tubes (Vacutainer), after an overnight fast. Sera samples were obtained by centrifuging blood collected in evacuated tubes without anticoagulant at $2000 \times g$ for 10 min at 4 °C, subsequently stored at −20 °C. Lp(a) levels were measured using the commercially available direct-binding double MAb-based method (Mercodia Apo (a) ELISA, Pharmacia Diagnostics, Uppsala, Sweden). Mercodia Apo (a) ELISA is a solid phase two-site enzyme immunoassay. It is based on the direct sandwich technique in which two monoclonal antibodies are directed towards separate antigenic determinants on the apolipoprotein (a) molecule. It is calibrated using a highly purified, fully validated commercial Lp(a) preparation. The Mercodia assay's isoform independent detection of apo(a) is reported in the study by Dembisnki et al. [20]. The results are expressed in mg/dL, where 1 U of apo(a) is approximately equal to 0.7 mg of Lp(a) (Mercodia Manual) [21–23].

The lipid profile was assessed by conventional methods. To determine homocysteine, whole venous blood was collected in tubes containing ethylenediaminotetracetate (EDTA) 0.17 mol/L, immediately put in ice and centrifuged within 30 min at 4 °C ($1500 \times g$ for 15 min). The plasma levels of total homocysteine (free and protein bound) were determined by fluorescence polarization immunoassay (IMX Abbott Laboratories, Oslo, Norway). PAI-1 levels were determined by immunoenzymatic assay (Asserachrome PAI-1, Diagnostica Stago, Asnieres, France).

2.3. Statistical analysis

Statistical analysis was performed using the SPSS (Statistical Package for Social Sciences, Chicago, USA) software for Windows (Version 13.0). The non-parametric Mann–Whitney test for unpaired data was used for comparisons between single groups. The Chi^2-test was used to test for proportions. A general linear model, after adjustment for age, gender, smoking habit, hypertension, and diabetes was conducted in order to investigate differences in Lp(a) between the patients and controls.

A logistic regression analysis was used to evaluate the risk of RVO according to Lp(a) levels > 300 mg/L. Variables which showed, at univariate analysis, a significant association with the disease were introduced into the multivariate model. During multivariate analysis, a first model (Model 1) was created by adjusting for age, gender, smoking habit, diabetes and hypertension. Subsequently, a second model (Model 2) was created by also adjusting for triglycerides' levels. Finally, a further fully adjusted model was created by introducing some thrombophilic risk factors such as homocysteine and PAI-1 levels, which have been demonstrated to be associated with RVO [5–7]. Odds ratios (OR) and 95% confidence intervals (CI) are presented. A p-value < 0.05 was considered to indicate statistical significance.

3. Results

Demographic, clinical and laboratory characteristics of the study population are reported in Table 1. Among the traditional cardiovascular risk factors, hypertension, smoking habit and diabetes, but not dyslipidemia, were significantly more frequent in patients than in healthy subjects.

Lp(a) levels were found to be significantly ($p < 0.0001$) different between patients and controls, with a median value of 189 (range: 6–1898) mg/L in patients compared to 119.5 (6–1216) mg/L in healthy controls. This significance was also confirmed using a general linear model adjusted for age, gender, smoking habit, diabetes, and hypertension. Furthermore, Lp(a) levels above the cut-off for an increased risk of thrombotic vascular diseases (>300 mg/L) were observed in a significantly ($p < 0.0001$) higher proportion of patients ($n = 90$, 34.4%) than healthy controls ($n = 47$, 17.9%).

Table 1
Clinical and laboratory characteristics of the study population.

Variable	Patients ($n = 262$)	Healthy subjects ($n = 262$)	p-value
Age (years)[a]	66 (15–88)	65 (21–84)	0.6
Males/Females, n	122/140	123/139	0.9
Hypertension, n (%)	124 (47.3)	38 (14.5)	<0.0001
Smoking habit, n (%)	69 (26.3)	43 (16.4)	0.006
Dyslipidemia, n (%)	86 (32.8)	68 (26)	0.08
Diabetes, n (%)	35 (13.4)	18 (6.9)	0.01
Lipoprotein (a)[a]	189 (6–1898)	119.5 (6–1216)	<0.0001
Total cholesterol, mg/dL[b]	221.5 ± 44.2	213.8 ± 45.1	0.1
LDL-cholesterol, mg/dL[b]	122.6 ± 37.5	110.2 ± 40.7	0.7
HDL-cholesterol, mg/dL[b]	57.2 ± 16.3	60.9 ± 15.3	0.3
Triglycerides, mg/dL[b]	145.5 ± 37.5	113.9 ± 59.9	<0.0001
PAI-1, UI/L[b]	29.9 ± 10.6	18.6 ± 12.3	<0.001
Homocysteine, μmol/L[a]	12.4 (5.9–53.4)	9.3 (4.4–66)	<0.0001

[a] Median and (range).
[b] Mean ± SD.