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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.

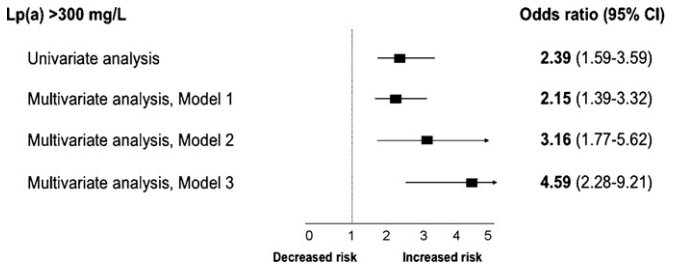

Fig. 1. Logistic regression analyses on the possible association between high Lp(a) levels and RVO. *Model 1*: Adjusted for age, gender, hypertension, diabetes, smoking habit. *Model 2*: Adjusted for age, gender, hypertension, diabetes, smoking habit, and triglycerides' levels. *Model 3*: Adjusted for age, gender, hypertension, diabetes, smoking habit, triglycerides, homocysteine and PAI-1 levels.

Subsequently, we investigated whether Lp(a) levels were different according to the type of the disease, as reported by either central or peripheral localization of the retinal thrombosis. Both types of the disease showed significantly higher Lp(a) levels compared to the control group ($p < 0.0001$ for all), but no significant differences between the different types of the disease were observed [central retinal vein occlusion: 186 (9–1828) mg/L vs. branch retinal vein occlusion: 190 (6–1285) mg/L; $p = 0.3$].

Finally, in order to search for a possible association between high levels of Lp(a) and RVO we performed a logistic regression analysis, which showed, at the univariate analysis, a significant association between Lp(a) > 300 mg/L (Fig. 1) and the disease. After adjustment for age, sex, hypertension, smoking habit, diabetes (Fig. 1, Model 1), triglycerides' levels (Fig. 1, Model 2) as well as for homocysteine and PAI-1 levels (Fig. 1, Model 3), high levels of Lp(a) remained significantly associated with the disease.

4. Discussion

The present case–control study performed in a consecutive number of RVO patients reported a significant association between alterations of Lp(a) and the occurrence of retinal vein occlusive disease. Indeed, patients with Lp(a) levels above the established cut-off for an increased risk of vascular thrombosis were found to be associated with an increased risk of RVO, after multiple corrections for confounding factors.

To the best of our knowledge, this is the largest study which has assessed the possible association between Lp(a) and RVO. Lp(a) is an emerging cardiovascular risk factor consisting of a low-density lipoprotein core associated with the apolipoprotein (a) [9]. Due to its structural homologies with plasminogen and cholesterol molecules, Lp(a) has been found to be implicated in the inhibition of fibrinolysis as well as in atherogenesis. Currently, epidemiological evidence has reported a pathogenetic role for high levels of Lp(a) in the occurrence of both arterial and venous thrombotic diseases [24,25] whereas few and conflicting results have been obtained relating to the occurrence of RVO [10–16].

In the present study we found significantly elevated concentrations of Lp(a) in patients with RVO, with no differences between central and peripheral localization of the occlusive disease. This finding is in keeping with some of the previous, limited, studies evaluating Lp(a) in the same type of patients [10–15]. In 1992, for the first time, Muller et al. reported increased Lp(a) levels in a limited group of RVO patients when compared to healthy controls [10]. Subsequently, other studies have confirmed such preliminary findings in other, larger (although still limited) study populations [11–15]. In our study, high Lp(a) levels have been found to be associated with an increased risk of RVO, after multiple statistical adjustments. This allows us to state that Lp(a) plays a relevant role in the pathogenesis of RVO. On the other hand, however, two previous studies, one by our group and the other from the cohorts of the ARIC and CHS studies did not observe an independent association between high Lp(a) levels and the occurrence of retinal occlusive disease after correction for confounding factors, which include other thrombophilic factors [5,16].

Some explanations can be identified for the discrepancy in the results. First of all, the number of patients with RVO included in the previous studies is extremely variable, being in some cases too low to obtain reliable data. Secondly, the levels of Lp(a) found to be associated with an increased risk of the disease differ from one study to another. In the study by Wong et al. [16] an analysis of quartiles of Lp(a) was conducted, whereas in the vast majority of studies the cut-off of 300 mg/L was used. Thirdly, the methods used for the measurement of Lp(a) are different, especially in relation to the sensitivity and specificity for the identification of the wide variation of the apo(a) molecular weight. This could explain, at least in part, some of the differences observed in the studies that investigated Lp(a) in association with thrombotic diseases [26]. Finally, the parameters for which the statistical analysis has been adjusted vary substantially. In one of our previous studies [5] Lp(a) was adjusted for all the other thrombophilic risk factors, including some which are strictly linked to Lp(a), such as PAI-1, whereas in most of the other studies no, or very limited, adjustments have been performed.

RVO is one of the most common retinal vascular diseases, with a low prevalence in the general population [1,2]. During the few years, findings which demonstrate a significant association between RVO and cardiovascular mortality have been reported, so conferring on RVO an epidemiological relevance among vascular disorders [3].

To date, the pathogenesis of RVO has not been completely clarified [4]. A link between atherosclerotic risk factors and RVO has been widely suggested by many studies. In particular, a relevant role for hypertension has been reported. Indeed, almost all relevant studies have recorded a strong and consistent link between hypertension and the risk of RVO [1–4]. Our study population shows a consistent number of patients with RVO who recorded high blood pressure, thus hypothesising a possible influence of such a risk factor on the association between Lp(a) and the disease. However, after adjustments for traditional risk factors comprising hypertension, Lp(a) still remains associated with an increased risk of RVO. Recently, a meta-analysis by Janssen et al. [27] demonstrated that factors known to contribute to the risk of atherosclerosis might also be important in the pathogenesis of RVO, including some thrombophilic risk factors. In addition, we have also demonstrated in a large group of patients with RVO that homocysteine, as well as haemorheological variables and circulating vitamins, may predispose the occurrence of the disease [5–8]. Despite this, the full pattern of possible risk factors in its pathology has not been investigated and some issues remain open in terms of the pathological mechanisms that lead to the clinical thrombosis.

The present study, evaluating Lp(a) levels together with other traditional and emerging thrombophilic risk factors, in a relevant number of RVO patients and healthy subjects, support the previous evidence of a significant role of elevated levels of Lp(a) in the occurrence of RVO.

The association between Lp(a) and RVO can be explained by several mechanisms. Lp(a) can, in fact, act through different pathophysiological pathways to promote atherosclerosis and thrombosis. Lp(a) has been reported to enter into human atherosclerotic plaques and promote cholesterol accumulation in macrophages which form foam cells [28]. Moreover, it has been demonstrated that an interaction between Lp(a) and other lipid variables including low-density lipoprotein can exist, acting possibly through the activation of the protease region of apo(a) and a subsequent increase of the risk of atherothrombosis [29]. In addition, Lp(a) is able to promote smooth muscle cell proliferation

and migration in atherosclerotic lesions by inactivating transforming growth factor-beta [30], and, more importantly, to have an inhibitory effect on fibrinolytic mechanisms due to its structural similarity to plasminogen, which causes competition with plasminogen activators [31]. Other mechanisms that may contribute towards thrombus formation include inactivation of the tissue factor pathway inhibitor, thus promoting coagulation [31], and augmentation of oxidative stress via generation of reactive oxygen species [32].

Notably, the results obtained in the present study can be helpful in the clinical management of RVO patients. Up until now, no established treatment for RVO is available. The increasing role of hypercoagulability in these patients supports the use of antithrombotic drugs, but medical management of patients with RVO consists primarily of the treatment of the underlying systemic diseases. The presence of an altered lipid profile, on the other hand, can give physicians a further therapeutic option for the treatment of RVO patients, even in the current absence of an established efficient therapy for elevated Lp(a) levels. Some reports indicating the possible beneficial role of aspirin therapy in the management of RVO and high Lp(a) levels have been reported, but data are very limited [33]. Moreover, a possible beneficial effect of treatment with extracorporeal lipid-selective apheresis and niacin has been proposed in patients with a vascular occlusive clinical event and markedly elevated Lp(a) levels, thus possibly hypothesising a role for this technique also for RVO, even if data supporting this approach are limited [34].

In conclusion, the findings of the present study provide evidence for the possible pathogenetic role of high levels of Lp(a) on the occurrence of RVO, thus hypothesising the inclusion of such a parameter in the evaluation of this type of thrombotic disease. Larger controlled trials are recommended to clarify whether lipid-lowering techniques are beneficial in the treatment of these patients.

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