

# Is Lipoprotein(A) a Risk Factor for Atherosclerosis of the Retinal Arteries?

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## ABSTRACT

*Elevated plasma Lp(a) has been linked to development of coronary artery disease (CAD). There is no data about plasma Lp(a) and atherosclerosis of the retinal arteries. Therefore the purpose of this study was to assess the risk of retinal vessels atherosclerosis conferred by elevated plasma Lp(a) levels in 73 adult males. The results were compared with those in 45 matched apparently healthy males with no retinal vessel changes. The atherosclerotic changes of the retinal vessels were determined by direct ophthalmoscopy and graded (1–4) according to Scheie. Plasma levels of Lp(a) were measured by radial immunodiffusion. The results were compared using chi-square test. Although a very weak correlation between plasma Lp(a) levels and the incidence of retinal atherosclerosis was found, no significant association between the degree of atherosclerotic changes and plasma Lp(a) levels could be proven. Thus it could be concluded that plasma Lp(a) level is not a significant risk factor for atherosclerosis of the retinal arteries.*

## Introduction

An increasing number of studies suggests that lipoprotein(a) /Lp(a)/ might be an independent, discriminating risk factor for atherosclerotic disease in men<sup>1,2</sup>. This seems to be true not only for coronary artery disease (CAD) and myocardial infarction<sup>3–5</sup> but also atherosclerosis of carotid arteries and ischemic stroke<sup>6,7</sup> as well as atherosclerosis of peripheral

arteries, particularly of lower extremities<sup>7,8</sup>. Lp(a) is a plasma lipoprotein whose concentration is stable and genetically determined in an individual and whose composition closely resembles that of atherogenic LDL, but with one additional molecule of apoprotein(a) /apo(a)/<sup>10</sup>. Apo(a) is a large glycoprotein linked to apoprotein B (apoB) by a disulfide bond and structurally similar to plasminogen. It has been postulated that this similarity is one of

the mechanisms by which Lp(a) promotes atherosclerosis<sup>11</sup>. Namely, Lp(a) competes with plasminogen for binding to fibrin and to plasminogen receptors on the vascular endothelium surface thus interfering with fibrinolysis and accelerating atherothrombosis. Lp(a) also increases the activity of plasminogen activator inhibitor-1 (PAI-1)<sup>12</sup> and reduces the activity of transforming growth factor-beta (TGF-beta) resulting in inhibition of fibrinolysis and promotion of migration and proliferation of smooth muscle cells (SMC)<sup>13</sup>. It is well known that SMC migration and proliferation is an important feature of atherogenesis<sup>14</sup>. Lp(a) also binds to elastin via apo B, resulting in oxidation and oxidatively modified Lp(a) in a fashion similar to LDL, and such Lp(a) is then taken up by macrophages<sup>13,15</sup>. This process promotes the transformation of macrophages into foam cells which is an important step in early atherogenesis. There is currently no information on the effectiveness on either dietary or drug treatment which could decrease Lp(a) plasma concentration apart from observation that hormone replacement therapy<sup>16,17</sup> and antiestrogen tamoxifen<sup>18</sup> could do it.

Although atherosclerotic changes have been described in the retinal arteries half a century ago, there is no data in the literature about Lp(a) and retinal artery atherosclerosis. Therefore, the aim of this study was to assess whether any association exists between Lp(a) and atherosclerosis of retinal arteries in adult men.

## Material and Methods

### Subjects

The study group consisted of 73 males with atherosclerotic changes of retinal arteries and an age, smoking and BMI matched control group of 45 males with normal eye fundus. Neither of the subjects was acutely ill nor was receiving any

lipid lowering agents, antihypertensives, steroids, or any other drugs known to influence plasma lipids at the time of the study and over the 3 months prior to the study. Exclusion criteria were: diabetes or impaired glucose tolerance, hypertension (BP higher than 140/90 mmHg), clinical hypo- or hyperthyreosis, clinical adrenocortical hyperfunction or insufficiency, clinical liver disease, clinical renal disease, chronic or acute pancreatitis, former or present malignant disease, autoimmune diseases, extreme obesity (BMI >35), a history of drug abuse and/or a history of alcohol consumption greater than 21 units per week, as well as a history of myocardial infarction, angioplasty, stroke, or major surgery during the 6 months preceding the study.

The study complied with the Declaration of Helsinki. All subjects received oral and written information concerning the study prior to giving written informed consent.

### Analysis of the retinal arteries

In all the subjects the eye fundus examination was carried out by direct ophthalmoscopy performed after the pupil dilatation by the same ophthalmologist. The atherosclerotic vascular lesions in the retinal arteries were classified according to Scheie<sup>19,20</sup>. Namely, Scheie developed a four-scale classification of atherosclerotic changes of retinal arteries which was used in this study:

Stage 1 – A broadening of the light reflex from the artery can be seen, with minimal or no arteriovenous compression. This is the earliest sign of retinal artery atherosclerosis.

Stage 2 – The changes are similar to those in Stage 1 but more prominent.

Stage 3 – The arteries have a »copper wire« appearance and there is much more arteriovenous compression. These are se-

rious atherosclerotic changes of retinal arteries.

Stage 4 – The arteries have a »silver wire« appearance and the arteriovenous crossing changes are most severe. This is the most severe form of the atherosclerosis of the retinal arteries.

*Measurement of plasma Lp(a)*

All samples were collected between 8 and 9 am, after a 12–14 h overnight fast, and after 15 min of rest in supine position. Cubital venous blood was drawn into evacuated blood-collection tubes without anticoagulant. After clotting, each specimen was centrifuged at 1200 x g for 20 min at –4°C, immediately frozen and stored at –20°C for a maximum of one week. The plasma concentration of Lp(a) was measured by radial immunodiffusion<sup>21</sup> using the antisera from Immuno AG, Austria. Lp(a) was considered elevated if the concentration was higher than 0.3 g/L.

*Statistical analysis*

Plasma Lp(a) concentrations for patients with retinal artery atherosclerosis and subjects with no retinal artery changes were compared by using chi – square test. Statistical significance was assumed for p less than 5% (p < 0.05).

**Results**

Patients with the atherosclerosis of retinal arteries were 48.23 +/- 9.71 years old (range 25 – 69 years) and had a BMI 24.2 +/-2.4. Controls were 47.60 +/-9.22 years old (range 22 – 65 years) and had a BMI 24.1 +/- 2.0.

A very weak correlation between plasma Lp(a) levels and retinal vessels atherosclerosis was found ( $\chi^2 = 4.51008$ ; df = 1; p < 0.05). However, no significant association between the degree of atherosclerotic changes of retinal arteries and plas-

**TABLE 1**  
THE STAGE OF THE ATHEROSCLEROTIC CHANGES OF THE RETINAL ARTERIES AND PLASMA Lp(A) CONCENTRATION

Retinal arteries	Lipoprotein(a) (g/l)		
	< 0.3	> 0.3	Total
Normal	a 20	25	45
	b 44.4	55.6	38.1
	c 29.9	49.0	0
Stage 1	a 12	8	20
	b 60.0	40.0	16.9
	c 17.9	15.7	0
Stage 2	a 18	7	25
	b 72.0	28.0	21.2
	c 26.9	13.7	0
Stage 3	a 14	10	24
	b 58.3	41.7	20.3
	c 20.9	19.6	0
Stage 4	a 3	1	4
	b 75.0	25.0	3.4
	c 4.5	2.0	0
Total	a 67	51	118
	b 56.8	43.2	100.0

a = number of subjects; b = % horizontal; c = % vertical; <sup>2</sup> = 5.79935, df = 4, p > 0.1

ma Lp(a) concentration could be proved (Table 1).

**Discussion**

To our knowledge, this is the first report of a study investigating the relationship between Lp(a) and retinal artery atherosclerosis. Almost four decades ago it was noticed that 73% of patients with atherosclerotic retinal changes have atherosclerotic changes of other arteries as well, while 72% of the patients who had atherosclerosis of the arteries in some other part of the body had also atherosclerotic changes of the retinal arteries<sup>22–24</sup>. However, these investigators did not check Lp(a) in their patients.

Atherosclerotic changes of the retinal arteries are characterized by the thickening of the arterial wall and lipid deposition in the intima often associated with fi-

brosis and even calcification of larger arteries. Sometimes in the literature the retinal arteries are called arterioles<sup>19</sup> but the arteries that are analyzed by ophthalmoscopy (branches of the central retinal artery) do have all the layers (intima, media, adventitia) and resemble all the small arteries in other organs including heart and brain<sup>25</sup>. Arterioles with the diameter smaller than 63 and 134 micrones<sup>26</sup> lack an internal elastic lamina, and a continuous layer of smooth muscle cells but they and the capillary vessels were not analyzed by ophthalmoscopy in this study<sup>27</sup>.

We have recently shown that atherosclerosis of the retinal vessels strongly correlates with plasma total cholesterol, LDL-cholesterol, triglycerides and apo-protein B levels which corresponds to the findings in CAD and ischemic stroke<sup>28</sup>. Therefore our results presented in this paper showing no correlation between plasma Lp(a) levels and retinal artery atherosclerosis were quite surprising.

However, despite the reports indicating that increased plasma Lp(a) is a risk factor for restenosis after balloon coronary angioplasty<sup>29</sup> and coronary by pass surgery<sup>30</sup> as well as several studies published in the last 20 years starting from the first one by Kostner et al<sup>31</sup> suggesting an association between Lp(a) and CAD<sup>5,32–34</sup>, there were opposing reports too. Several studies showed that plasma Lp(a) was not a predictor of future coronary

events<sup>35–38</sup> thus questioning the previously presented hypothesis. Our results are congruent with the results of these studies suggesting that clinical significance of increased Lp(a) concentration as a risk factor for atherosclerosis is questionable, at least for retinal artery atherosclerosis.

Although there was no previous study about Lp(a) and atherosclerosis of the retinal arteries, several studies have found an association between increased Lp(a) and central or branch retinal artery occlusion<sup>39–42</sup>.

There is no readily apparent source of bias to explain the discrepancy between the findings of our study which demonstrated a lack of association between Lp(a) and the risk of retinal artery atherosclerosis as well as other studies showing similar data for Lp(a) and CAD and studies which have found a link between elevated Lp(a) levels and the risk for CAD or retinal vascular occlusion. The results from any one study should be considered in the context of all other information. Thus our results do not negate the role of Lp(a) in atherogenesis in general and in all types of the arteries but further prospective studies are needed to explain whether susceptibility to atherosclerotic damage of the vascular walls and the role of Lp(a) in it is synchronous and uniform in different organs.

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## **JE LI LIPOPROTEIN(A) ČIMBENIK RIZIKA ZA ATEROSKLEROZU ARTERIJA MREŽNICE?**

### **S A Ž E T A K**

Povećana koncentracija Lp(a) u plazmi povezuje se s aterosklerozom koronarnih arterija srca. Međutim, nema nikakvih podataka o Lp(a) i aterosklerozi mrežničnih arterija. Stoga je cilj ovog istraživanja bio ustanoviti da li povećana koncentracija Lp(a) u plazmi predstavlja čimbenik rizika za aterosklerozu arterija mrežnice. U ispitivanje su uključena 73 odrasla muškarca s aterosklerozom arterija mrežnice, a rezultati su uspoređeni s onima u 45 zdravih muškaraca podjednake dobi, uhranjenosti i ostalih obilježja koji nisu imali nikakvih promjena na arterijama mrežnice. Aterosklerotičke promjene arterija mrežnice procjenjivane su uz pomoć direktne oftalmoskopije i stupnjevane su od 1 do 4 prema Scheieu. Koncentracije Lp(a) u plazmi određivane su radijalnom imunodifuzijom. Rezultati su uspoređeni hi-kvadrat testom. Iako je uočena

vrlo slaba povezanost između koncentracije Lp(a) i pojave ateroskleroze arterija mrežnice, nije se uspjela dokazati povezanost između stupnja aterosklerotičkih promjena mrežničnih arterija i koncentracije Lp(a). Stoga autori zaključuju da povećani Lp(a) nije značajan čimbenik rizika za aterosklerozu mrežničnih arterija.