ORIGINAL ARTICLE

Lipoprotein (A) Levels in Type 2 Diabetic Patients With Diabetic Retinopathy

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Summary

To examine a possible association between lipoprotein(a) [Lp(a)] levels and diabetic retinopathy in patients with type 2 diabetes mellitus. 100 type 2 diabetic patients were assessed with the following parameters: age, body mass index, duration of diabetes, blood pressure, fasting plasma glucose, total cholesterol, HDL-cholesterol, triglycerides, blood urea nitrogen, creatinine, Lp(a), and albumin excretion rate (AER). Retinopathy was classified as normal retina (NR), non-proliferative diabetic retinopathy (NPDR), and proliferative diabetic retinopathy (PDR) by an ophthalmologist. The PDR group had higher cholesterol ($t=-2.24$, $p<0.05$) and creatinine ($z=-2.547$, $p<0.05$) levels than the NPDR group. The PDR group had a higher value of AER ($z=-2.439$, $p<0.01$) than the NR group. The possibility of developing diabetic retinopathy after 10 years of diabetes was found to be 6.5 fold high (OR; 6.57, 95% CI 1.74-24.79; $p<0.05$). The Lp(a) levels were similar in the patients with retinopathy and those without retinopathy. In the study, there was no evidence for a relationship between the serum Lp(a) levels and diabetic retinopathy in type 2 diabetic patients.

Key Words: Type 2 Diabetes Mellitus, Diabetic retinopathy, Lipoprotein (a)

Introduction

Atherosclerotic vascular diseases such as coronary heart disease, cerebrovascular disease, and peripheral vascular disease are a major cause of morbidity and mortality in patients with diabetes mellitus[1]. Diabetic patients are also prone to develop microangiopathy clinically manifested as diabetic nephropathy, neuropathy and retinopathy[2]. Hence, the early diagnosis and treatment of the risk factors that are responsible for the development of these complications are very important in the follow-up and management of the disease. The factors which are assumed to account for the occurrence of diabetic retinopathy include advanced age, duration of disease, poor glysemic control, hypertension, proteinuria, high serum creatinine, cholesterol, triglycerides, lipoprotein(a) [Lp(a)] levels, and microalbuminuria[3,4].

Lp(a) is a macromolecular complex found in human plasma that combines structural elements from the lipoprotein and blood clotting systems and that is associated with premature coronary heart disease and stroke. Lp(a) is a plasma complex composed of apolipoprotein(a) covalently linked to apo B-100 by disulfide bridges[5]. Due to the structural similarity of apolipoprotein(a) to plasminogen, Lp(a) has been suggested to have antifibrinolytic properties and additionally shown to compete with plasminogen for the plasminogen binding site with an equivalent affinity and capacity. It has been estimated that, at plasma concentrations of 30 mg/dl, Lp(a) reduces cellular

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plasminogen binding by 20 per cent, thereby suppressing endothelial cell fibrinolysis and producing a procoagulent state[6]. Furthermore, high serum Lp(a) levels have thus been shown to be an independent risk factor for atherogenesis and thromboembolic events in both diabetic and nondiabetic subjects[7,8]. In this context, high serum Lp(a) levels might play a role in the occlusion of retinal capillaries leading to diabetic retinopathy. Controversial results have been obtained from limited studies both with type 1 and type 2 diabetic patients [9-15]. The aim of the present study was to evaluate serum Lp(a) levels and the relationship between these levels and diabetic retinopathy in type 2 diabetic patients.

Materials and Methods

Subjects and admission criteria

This was a cross-sectional study where 100 subjects of both sexes were enrolled. The study sample was recruited from 357 type 2 diabetic patients who were attending and being followed-up in the diabetic outpatient clinic at Haydarpasa Numune Education and Research Hospital in Istanbul, Turkey. The sample size required for the expected mean difference was calculated as 94 on the basis of the mean values which are 13.1±1.1 and 19.3±1.5 for the patients with normal retinopathy and with NPRP, respectively in literature number 13 (b=80 a=0.05). To conpensate for lost of follow-up, 115 patients were included. One of the three patients that applied to the outpatient clinic was randomly and sequentially included to the study. Of the 115 participants, 15 were excluded from the study for they had not had their blood chemistry tested because they had to be hospitalized due to their medical condition. This study was approved by the local ethical committee and written informed consent was taken from all participants.

The parameters of the patients (67 female and 33 male) were assessed as follows; age, body mass index (BMI), duration of diabetes, blood pressure, fasting serum glucose, total cholesterol, HDL cholesterol (HDL-C), triglycerides, blood urea nitrogen (BUN), creatinine, Lp(a), and albumin excretion rate (AER). Arterial blood pressure was measured three times with a mercury sphygmomanometer in the sitting position after a 10-min rest, and the mean of the measurements was assessed.

After 12 hours of fasting, serum glucose, triglycerides, total cholesterol, HDL-C, BUN and creatinine were measured by I1ab 1800 autoanalyzer via enzymatic colorimetric methods (Roche Modular System-DPP). Serum Lp(a) levels were measured by turbumetric method (Behring, Germany). The plasma concentrations between 0-29.9 mg/dl of Lp(a) were accepted as normal. Twenty-four hour of urine samples were collected by the patients so as to determine the albumin excretion rate (AER) via radioimmunoassay. AER: 0-30mg/24 hours was defined as normoalbuminuria; AER: 30-300mg/24 hours was defined as microalbuminuria and >300mg/24 hours was defined as overt proteinuria.

Fundoscopic examination was performed by a senior ophthalmologist, using ophthalmoscope and/or biomicroscope through dilated pupils. The findings were graded as normal retina (NR), nonproliferative diabetic retinopathy (NPDR), and proliferative retinopathy (PDR).

Statistical analysis

The data are expressed as mean ± s.e. mean or median (range). Comparisons among three groups were made by analysis of variance with Duncan's multiple range test or Kruskal-Wallis test where appropriate. Comparisons between the normal group (NR) and diabetic retinopathy group (PDR+NPDR) were made by Mann-Whitney-U test and student t test where appropriate. The multivariate logistic regression was performed to find relative risk factors. P value <0.05 (two-tailed) was considered to be statistically significant.

Results

Among 100 patients; 38, 33 and 29 had NR, NPDR, PDR, respectively.

Table I illustrates the clinical and laboratory characteristics related to each of three groups. The patients with PDR had longer duration of diabetes ($z=-2.863$, $p<0.05$) than those with NR while no statistically significance was reached between PDR and NPDR groups. The PDR group expressed higher cholesterol ($t=-2.24$, $p<0.05$) and creatinine ($z=-2.547$, $p<0.05$) levels when compared to that of NPDR. In the case of creatinine levels, there was a difference between the patients with PDR and NR ($z=-2.417$, $p<0.01$). The PDR group had a higher value of AER ($z=-2.439$, $p<0.01$) and fasting serum glucose levels ($t=-2.11$, $p<0.05$) when compared to that with NR. Age, gender, BMI, blood pressure, triglycerides, HDL-C, BUN, uric acids, and Lp(a) concentrations were similar in the three groups ($p>0.05$).

The characteristics concerning the groups with diabetic retinopathy (NPDR+PDR) and without retinopathy (NR) are shown in the Table II. The patients with retinopathy had higher AER than the patients without retinopathy (z=-2.50, p<0.05). The group with diabetic retinopathy had a longer duration of disease (t=-3.53, p<0.001) and a higher value of fasting plasma glucose (t=-2.16, p<0.05) when compared to those with NR group. The Lp(a) levels were similar in the patients with retinopathy and those without retinopathy (p>0.05).

The factors associated with PDR were entered into a multivariate stepwise regression model (Table III). Independently from other risk factors, the possibility of developing diabetic retinopathy after 10 years duration of diabetes was found to be 6.5 fold higher (OR; 6.57, 95% CI 1.74-24.79; p<0.05).

Table I: Clinical and laboratory characteristics of the subjects according to retinopathy groups

	NR	NPDR	PDR
Number of cases (n)	38	33	29
Age (years)	56±2.9	57±3.23	60±2.74
Diabetes duration (years)	6±2.25	8±2.43	13±2.86*
Body mass index (kg/m2)	29±2.08	31±2.38	29±2.53
Systolic blood pressure (mmHg)	149±5.23	152±4.68	149±4.84
Diastolic blood pressure (mmHg)	88±4.24	83±3.53	84±3.24
Fasting serum glucose (mg/dl)	153±5.55	164±2.17	174±2.60*
Blood urea nitrogen (mg/dl)	16±1.86	16±2.17	17±2.60
Creatinine (mg/dl)	1.04±0.45	1.01±0.50	1.26±0.67*,••
Uric acid (mg/dl)	4±1.1	4±1.1	4±1.32
Cholesterol (mg/dl)	199±5.97	212±6.35	220±6.15••
HDL cholesterol (mg/dl)	42±3.52	43±3.21	45±3.44
Triglycerides (mg/dl)	150±8.13	153±10.47	178±10.77
Albumin excretion rate (mg/24hour)	38±8.47	47±8.41	280±9.11*
Lipoprotein(a) (mg/dl)	29.87±5.11	23.64±4.28	27.07±4.14

Data are means ± SEM. •• p<0.05; NPDR vs PDR, * p<0.05; NR vs PDR, ** p<0.05; NDPR vs NR
NR; normal retina
NPDR; nonproliferative diabetic retinopathy
PDR; Proliferative retinopathy

Table II: The characteristics of the groups with diabetic retinopathy and without retinopathy

	DR* (-)	DR(+)
Number of cases (n)	38	62
Fasting blood glucose (mg/dl)	153±5.55	169±6.38•
Albumin excretion rate (mg/24hour)	38±8.47	156±7.61•
Diabetes duration (years)	6±2.25	10±2.74••

Data are means ± SEM •; p<0.05,••; p<0.001
*DR; Diabetic Retinopathy

Table III: Multiple regression analysis for proliferative diabetic retinopathy

	OR	95% CI		P value
		Lower	Upper	
Gender	0.661	0.239	1.828	.425
Age >50 (years)	1.421	0.460	4.388	.541
Total Cholesterol	0.998	0.987	1.008	.732
Fasting serum glucose (mg/dl)	1.010	0.998	1.023	.112
Creatinine (mg/dl)	1.923	0.408	9.069	.408
Albumin excretion rate (mg/24hour)	1.002	0.998	1.006	.982
Lp (a)>29.9 (mg/dl)	1.092	0.405	2.940	.862
Diabetes duration				
0-2.9 years	Ref.			.010
3-9.9 years	1.718	0.528	5.595	.369
≥10 years	6.579	1.746	24.797	.005

OR= Odds Ratio

Discussion

The investigations designed to examine a relationship between Lp(a) levels and diabetic retinopathy have revealed controversial results. The reasons responsible for such discrepancies have not been completely explored, but assumed to be due to the type of diabetes, classification of retinopathy, or ethnic groups in each of the studies. Several studies carried out with type 2 diabetic patients reported that serum Lp(a) concentrations are associated with diabetic retinopathy[10,13], on the contrary, other investigators did not determine any relationship between these two parameters[14,15]. Similarly, in this cross-sectional study, we did not find any relationship between serum Lp(a) levels and diabetic retinopathy in type 2 diabetic patients. Under the scope of the conflicting results, it seems not feasible to suggest that the type of the disease is responsible for the different results obtained in various studies. Thus, in support of this conclusion, similar controversial results were reported in type 1 diabetic patients[9,11]. The second assumption was that the classification of retinopathy might bring about conflicting results. In this context, Korean type 2 diabetic patients with PDR were found to have higher serum Lp(a) levels[13], whereas no difference between NPDR and PDR existed even though serum Lp(a) levels were high in both groups[16]. In contrast, high serum Lp(a) levels showed no correlation with either PDR or NPDR in the present study. Hence, further investigation is needed to understand the actual impact of classification towards the controversial results. Ethnic variations might account for the contradiction mentioned above, and accordingly, the differences in allele frequency of apo(a) phenotypes was shown to be associated with retinopathy in previous studies[9,12]. In contrast to our results, in a recent study with Turkish type 2 diabetic patients, the investigators indicated a positive correlation between Lp(a) levels and PDR[10]. The reason for the conflicting findings might be due to the genetic heterogeneity of Turkish patients coming from different ethnical groups. Further prospective studies are needed to determine the relationship between Lp(a) and retinopathy in Turkish type 2 diabetic patients.

Besides Lp(a), a number of medical risk factors were investigated and many of them were significantly related to retinopathy in the present study. These included duration of disease, increased level of fasting serum glucose, high levels of creatinine, cholesterol, and albumin excretion rate. After adjustment for those confounding factors in the stepwise multiple regression model, only the duration of diabetes remained associated with PDR.

Several studies showed that the duration of diabetes is found to be significantly associated with diabetic retinopathy in both type 1 and type 2 diabetic patients[17-19]. In agreement with those studies, the group with diabetic retinopathy, especially with PDR, had a longer duration of disease compared to that with NR in the

current study. Independently from the other risk factors, the possibility of developing PDR after 10 years of disease duration was found to be 6.5 fold high.

In conclusion, we could not find any association between serum Lp(a) levels and diabetic retinopathy in our type 2 diabetic patients. However, further prospective studies are needed to determine this relationship.

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