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The relationship of early atherosclerotic vascular changes with serum lipoprotein(a) in predialysis chronic renal failure and maintenance hemodialysis patients

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ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2006, 23(5):514–520

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Σχέση πρώιμων αθηροσκληρυντικών αγγειακών αλλοιώσεων και λιποπρωτεΐνης(a) του ορού σε ασθενείς με χρονία νεφρική ανεπάρκεια πριν και μετά από την έναρξη της χρονίας αιμοκάθαρσης

Περίληψη στο τέλος του άρθρου

OBJECTIVE **Study of the effect of serum plasma Lp(a) levels on early structural atherosclerotic vascular changes in a group of CRF patients not yet on dialysis and end-stage renal disease patients under regular hemodialysis (HD).** METHOD **This was a cross-sectional study. 29 normal subjects (group one, F=17, M=12), 33 chronic renal failure (CRF) patients not yet on dialysis (group two, F=19, M=14) and 43 HD patients with end-stage renal disease (group three, F=19, M=24). For all patients serum Lp(a) was measured. Carotid intima-media thickness (IMT) was measured and carotid-femoral artery examined for plaque occurrence (plaque score) by B-mode ultrasonography was determined.** RESULTS **The mean±SD of serum Lp(a) in group one was 42.0±20.0 mg/dL, in the CRF group 57.0±23.0 mg/dL and in the HD group 55.0±16.0 mg/dL. The IMT of group one was 0.84±0.20 mm and the CRF group and HD group 1.30±0.40 mm and 1.10±0.30 mm, respectively. Ninety-three percent of persons of group one had zero plaque score while 39.4% of patients of group two (CRF) and 51.2% of patients in group three (HD) had zero plaque score while 6.8% of subjects in group one, 24.3% in group two and 25.6% of patients in group three had plaque scores of between 1 and 2. For plaque scores of 3 and 4, group one had none, group two had 36.4% and group three had 23.3%. Significant differences were found in IMT group one between group two (P<0.001) and group three (P=0.008), and also between group two and group three (P=0.023). Significant differences in Lp(a) between group one and group two (P=0.016) and group three (P=0.021) were demonstrated. No significant difference in Lp(a) between group two and group three (P>0.05) was found. Significant differences in plaque score between group one and group two (P<0.001) and group three (P=0.020) were found, but not between group two and group three (P>0.05). Positive correlations were found of serum Lp(a) with IMT and plaque score in HD patients.** CONCLUSIONS **This study showed a positive relationship of Lp(a) with IMT and arterial plaques in HD patients. Lp(a), as a non-traditional factor in the progression of atherosclerosis, could play an important role in the acceleration of rapid progressive atherosclerosis observed in HD patients, which needs further attention.**

Key words

Chronic renal failure
Hemodialysis
Intima-media thickness
Lipoprotein(a)
Plaque score

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Lipoprotein(a) [Lp(a)] when present in high levels in plasma is recognized as an independent risk factor for premature atherosclerotic coronary heart disease.[1] Studies in renal failure have revealed an increase in plasma concentration of Lp(a).[1–3] Elevated plasma Lp(a) levels in chronic renal failure (CRF) patients have been associated with a frequency distribution of apolipoprotein(a) [apo(a)] isoforms similar to those found in the general population, which indicates that elevated Lp(a) levels in CRF patients are not genetic in origin.[4–6] It has therefore been suggested that kidneys play an important role in Lp(a) metabolism, decreasing Lp(a) catabolism or increasing liver production.[7–10] Increased Lp(a) levels could be a contributing factor to the increased incidence of

atherosclerotic disease observed in CRF and hemodialysis (HD) patients.[11,12] The early stages of atherosclerosis are associated with changes in arterial structure. Subtle structural changes such as thickening of the arterial intima-media complex thickness (IMT) occur early in the atherosclerotic disease process.[12–14] Using B-mode ultrasonography (US) for assessing early atherosclerosis is a safe and non-invasive method of studying superficial vascular segments, such as the carotid or femoral artery.[11–13] In this way US evaluation of the carotid artery for IMT can identify patients at risk for cardiovascular disease.[12–14] Indeed the carotid arteries are an ideal site for studying the progression of atherosclerotic lesions from onset to fully developed plaque. Carotid IMT measurements are strongly related to the extent of atherosclerosis in other vascular sites.[11–14] Many well-known and conventional risk factors have been shown to be significantly associated with increased arterial wall thickness, consistent with their accepted role in atherogenesis. Much less is known, however, about the effects of Lp(a) on IMT in CRF and HD patients.[15] Therefore, this study was designed to investigate the effect of plasma Lp(a) levels on early structural atherosclerotic vascular changes in a group of CRF patients not yet on dialysis and end-stage renal disease (ESRD) patients under HD and to explore the correlation of carotid artery IMT and carotid and femoral artery plaques with serum and with the duration of disease.

MATERIAL AND METHOD

This was a cross-sectional study of patients with CRF not yet on dialysis and ESRD patients undergoing maintenance HD treatment. For patient selection exclusion criteria were: Cigarette smoking, body mass index (BMI) of >25, anti-lipid drug treatment, recent myocardial infarction or vascular diseases, active or chronic infection and diabetes mellitus. Group one consisted of healthy persons who had no history of hypertension or renal disease. Group two consisted of CRF patients not yet on HD and group three of patients who were undergoing regular HD because of end-stage renal failure. For laboratory tests, blood sampling was made after 14 hour overnight fasting. For groups one and two blood samples were taken from the antecubital vein and for group three blood samples were obtained from the venous line of the HD apparatus at the beginning of dialysis. Fasting blood sugar (FBS), Lp(a), triglyceride (Tg), cholesterol (Chol), HDL-cholesterol (HDL-C), LDL-cholesterol (LDL-C), BUN, creatinine were measured. Lp(a) was measured by enzyme immunoassay (ELISA) by immuno-biological laboratories (IBL) kit of Hamburg. The other lipids, BUN, creatinine and FBS were measured by standard kits. Serum LDL-C was calculated by Friedewald's formula.[16] Creatinine clearance was evaluated from serum creatinine, age and body weight.[17] Subjects in group one were interviewed using a questionnaire prior to consent to ascertain that they were free from any clinical evidence or history of diabetes, cardiac or vascular disease and had no past or current history of hypertension or renal disease. The clinical history of patients in groups two and three was retrieved from the hospital medical records. Ninety-eight percent of the patients in groups two and three were hypertensive but taking antihypertensive therapy and their blood pressure levels were near normal. Carotid and femoral artery ultrasonography (US) were performed by a single sinologist, who was unaware of the history or laboratory data of the patients. Using a Honda-Hs-2000 Sonograph with 7.5 MHZ linear probe IMT in mm was measured and the carotid and femoral arterial plaques (plaque score) were determined. The procedure was done at the end of the diastolic phase. The sites of measurements were at the distal common carotid artery, the area of bifurcation and the first proximal internal carotid artery and IMT was measured at the plaque free areas. For the examination the subjects were in the supine position with neck hyperextension and rotation of head for facilitation of the procedure. On US, the carotid artery is found to have three different echoes. IMT was defined as the distance from the leading edge of the lumen-intima interface of the far wall to the leading edge of the media-adventitia interface of the far wall. IMT of >0.8 mm was considered abnormal. For statistical analysis the mean of the right and left carotid artery IMT was used. Sonography for plaque was made on the right and left carotid and femoral arteries and scored from 0 (no plaque) to 4 (plaque presence at all four sites), regardless of the number and size of the plaques in each site. Plaque was considered as a local intimal thickness more than 1 mm. For plaque measurement the largest longitude was considered. For statistical analysis descriptive data are expressed as mean±SD and frequency distributions. For comparison between groups ANOVA, Scheffe and chi-square tests were used. For correlations, partial correlation test and stepwise regression analysis were used. All statistical analyses were performed using SPSS (version 11.00). Probability (P) was considered significant when $P<0.05$.

RESULTS

The total number of subjects studied was 105 (F=55, M=50), consisting of 29 (F=17, M=12) normal, healthy subjects (control group, group one), 33 (F=19, M=14) CRF patients not yet on HD (CRF group, group two) and 43 (F=19, M=24) HD patients with end-stage renal disease (HD group, group three). Table 1 shows the characteristics of the subjects. Table 2 shows the mean±SD of the laboratory data of the subjects. Table 3 shows the frequency distribution of the plaque score in the 3 groups.

Mean±SD of the known disease duration in the CRF patients was 36±20 months. The mean±SD of the length of the time the patients had been on HD was 44±31 months. Group one had normal creatinine clearance and the mean±SD of creatinine clearance of group two was 31±18. For the HD group creatinine clearance of <10 mL/min was envisaged. The Lp(a) values in group one, the CRF group and the HD group were 42.0±20.0, 57.0±23.0 and 55.0±16.0 mg/dL, respectively. The mean±SD of IMT in group one was 0.84±0.20 mm, in the group CRF 1.30±0.40 mm and in the HD 1.10±0.30 mm. Ninety-three percent of the subjects of group one had zero plaque score while 39.4% of patients of group two and 51.2% of patients in group three had zero plaque score. Plaque scores of 1–2 were observed in 6.8% of subjects in group one, 24.3% of patients in group two and 25.6% of patients in group three. No subjects in group one had plaque scores of 3–4 but in group two 36.4% and in group three 23.3% had plaque scores of 3–4. All of the plaques were calcified.

By ANOVA testing significant differences in IMT (P<0.001), LDL-C (P<0.001), Chol (P<0.001) and Lp(a) (P=0.006) were observed between the three groups. No significant difference in Tg and HDL-C was found between the three groups (P>0.05). Significant differences in IMT were observed between group one and both group two (P<0.001) and group three (P=0.008), and also between group two and group three (P=0.023) (Scheffe test). Significant differences in Lp(a) were found between group one and both group two (P=0.016) and group three (P=0.021) but no significant difference between group two and group three (P=0.962) (Scheffe test). Significant differences of plaque score between the three groups was observed (P=0.02) (chi-square test). The Scheffe test showed significant difference between

Table 1. Frequency distribution of age (years), duration of disease (DD) (months) and creatinine clearance (CLcr) (mL/min) in the three study groups. MT: Intima-media index.

Variables		Mean±SD	Minimum	Maximum
Group 1	Age	45±10.4	20	70
	DD	-	-	-
	CLcr	103±4	98	110
	IMT	0.84±0.20	0.50	1.20
Group 2	Age	62±14.5	30	88
	DD	36±20	2	76
	CLcr	31±18	10	70
	IMT	1.30±0.40	0.60	2.0
Group 3	Age	47±16.4	15	78
	DD	44±31	6	108
	CLcr	<10	<10	<10
	IMT	1.10±0.30	0.50	1.70

DD in group two: Known duration of CRF

DD in group three: The length of the time patients had been on HD

Table 2. Frequency distribution of lipids (mg/dL) in the three study groups. Lp(a): Lipoprotein (a), Chol: Cholesterol, LDL-C: LDL-cholesterol, HDL-C: HDL-cholesterol, Tg: Triglycerides.

Variables		Mean±SD	Minimum	Maximum
Group 1	Lp(a)	42.0±20.0	10	94
	Chol	203±41	125	340
	LDL-C	126±34	75	230
	HDL-C	41±10	25	65
	Tg	154±73	50	325
Group 2	Lp(a)	57.0±23.0	15	135
	Chol	211±70	100	390
	LDL-C	136±52	45	300
	HDL-C	33±13	15	85
	Tg	171±100	60	550
Group 3	Lp(a)	55.0±16.0	25	95
	Chol	148±35	95	930
	LDL-C	97±28	40	160
	HDL-C	33±18	20	90
	Tg	145±62	40	230

Table 3. Frequency distribution of plaque score in the three study groups.

	Plaque score	Frequency	Percent
Group 1	0	27	93
	1	1	3.4
	2	1	3.4
	3	0	0
	4	0	0
Group 2	0	13	39.4
	1	5	15.2
	2	3	9.1
	3	3	9.1
	4	9	27.3
Group 3	0	22	51.2
	1	3	7
	2	8	18.6
	3	2	4.7
	4	8	18.6

group one and both group two (P<0.001) and group three (P=0.020), but no significant difference in plaque score between group two and group three (P>0.05). There was a significant positive correlation between IMT and age in group one (P=0.035), group two (P=0.017) and group three (P=0.019) (regression analysis with stepwise method). In healthy persons (group one) significant positive correlation of IMT with LDL-C (r=0.350, P=0.03), significant linear inverse correlation of IMT with HDL-C (r=-0.405, P=0.02) and marginal correlation of IMT with Tg (r=0.310, P=0.05) were found. Significant positive correlation was not found of IMT with Lp(a) (r=0.240, P>0.05) or Chol (r=0.260, P>0.05), of IMT with plaque score (r=0.101, P>0.05) or of plaque score with serum Lp(a), LDL-C, HDL-C, Chol, and Tg (P>0.05) (partial correlation test after adjustment for age). In the CRF group, significant positive correlation of IMT with plaque score (r=0.500, P=0.002), but not of IMT and plaque score with serum Lp(a), LDL-C, HDL-C, Chol or Tg (P>0.05) (partial correlation test after adjustment for age, creatinine clearance and known duration of disease). In this group significant linear inverse correlation of creatinine clearance with Lp(a) (r=-0.441, P=0.040) (fig. 1) was seen, but no correlation of IMT and plaque score with creatinine clearance (P>0.05) was found (partial correlation test after adjustment for age). In the HD group, significant positive correlation was found of IMT with Lp(a) (r=0.298, P=0.029) (fig. 2), and of plaque score with Lp(a) (r=0.375, P=0.008) (fig. 3). No correlation of IMT and plaque score with Chol, LDL-C, HDL-C or Tg were found (P>0.05), or of IMT with plaque score (r=0.222, P>0.05) in this group (partial correlation test after adjustment for age).

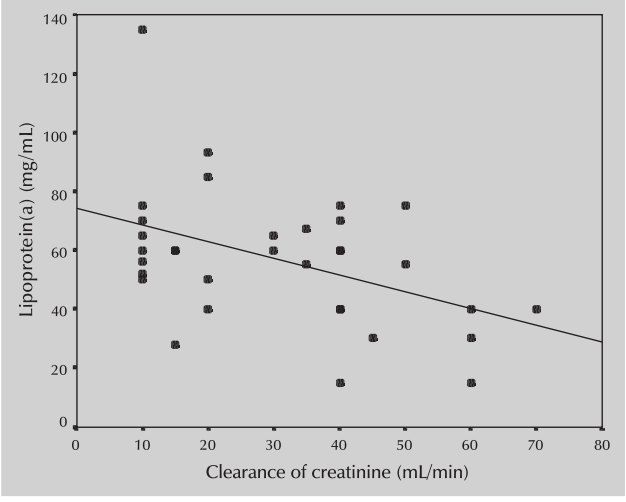

Figure 1. Significant linear inverse correlation of Lp(a) with creatinine clearance in the chronic renal failure group (group 2) [partial correlation test after adjustment for age (r=-0.441, P=0.06)].

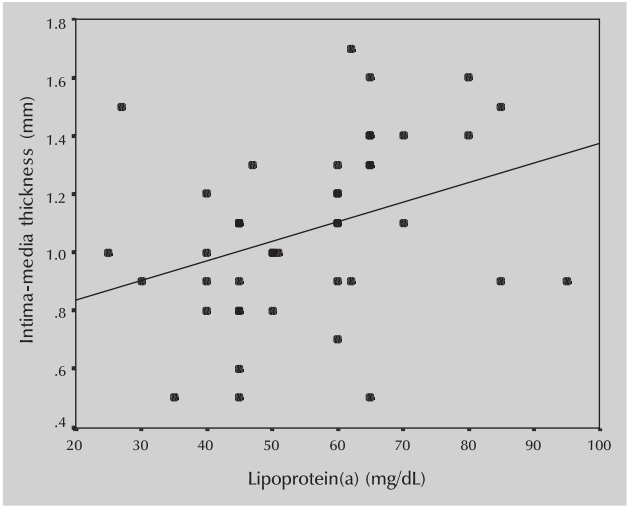

Figure 2. Significant positive correlation of intima-media thickness with serum Lp(a) in the hemodialysis group (group 3) (r=0.298, P=0.029) (partial correlation test after adjustment for age).

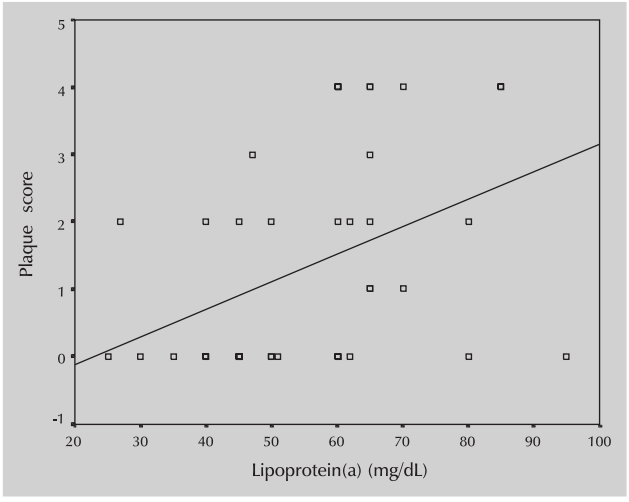

Figure 3. Significant positive correlation of plaque score with Lp(a) in the hemodialysis group (group 3) (r=0.375, P=0.008) (partial correlation test after adjustment for age).

DISCUSSION

The principle findings of this study were, firstly, higher serum levels of Lp(a), more thickening of the carotid intima-media complex and more carotid-femoral artery plaque occurrence in patients with CRF, both predialysis and those on HD, and secondly, positive correlation

of serum Lp(a) with IMT and plaque score in HD patients only.

Pascasio and colleagues observed a large number of vascular plaques in uremia patients, and concluded that the process of advanced atherosclerosis might be started with the beginning of renal failure. They suggested that HD treatment may not be a potential factor in the acceleration of atherosclerosis, and concluded that the progression of atherosclerosis might be related to atherogenic factors operative before regular dialysis is in effect.[18] Damjanovic and colleagues evaluated the IMT of 45 dialysis patients and found higher mean carotid IMT in HD patients than in a control group with a positive correlation of IMT with certain risk factors for atherosclerosis (age, duration of dialysis and lipid parameters).[19] Correlation of IMT with age and duration of dialysis in HD patients was evaluated by Shoji and Hojs who found no clear relationship of IMT with the duration of HD treatment.[20,21] Hojs also, in his study, 28 HD patients, observed that age was the only significant determinant of the number of plaques, and he concluded that HD patients had advanced atherosclerosis in the carotid arteries compared with normal subjects.[21] In addition, Hojs in a more recent study showed no difference in plaque occurrence between 28 HD patients with 28 ESRD patients prior to HD.[22] Savage and colleagues in a study on 24 dialysis patients noted the prevalence of plaque in the carotid and femoral artery and showed the relationship between femoral artery plaque and age of the subjects, and also the correlation of age with carotid artery IMT in HD patients.[23] A recent study by Kato and colleagues showed a significant correlation of IMT with age in 219 HD patients.[12] Papagianni and colleagues in a study on 112 HD patients showed a positive correlation of plaque score with age.[13]

The present study showed a positive relationship of Lp(a) with IMT, but no clear relationship between Lp(a) and IMT in the CRF group. No differences were found between the Lp(a) and IMT of the CRF and HD groups of patients. Studies concerning the effect of Lp(a) on IMT of normal persons have showed various results. Sramek and colleagues in a study on 142 asymptomatic men found no increased IMT in the carotid or femoral artery at high levels of Lp(a) and concluded that Lp(a) levels are not associated with early atherosclerotic vessel wall changes in the carotid or femoral arteries.[24] Dentil and colleagues in a study on 100 elderly subjects (aged 78.5±0.6 years) showed no association between carotid IMT and Lp(a), and concluded that the Lp(a) was unrelated to the severity of extra-cranial vessel atherosclerosis.[25] Conversely, Baldassarre and colleagues in a study on 100 type 2 hypercholesterolemic patients showed higher values of carotid IMT in hypercholesterolemic patients with plasma Lp(a) levels >30 mg/dL than in those with lower levels. They concluded that elevated plasma levels of Lp(a) can be considered an additional independent factor associated with carotid artery thickening in patients with severe hypercholesterolemia but not in those with moderate hypercholesterolemia or normocholesterolemic subjects.[26] Finally, Raitakari and colleagues in a study on 241 healthy subjects revealed no association between IMT and Lp(a) but significant positive correlation with total cholesterol, LDL-C, LDL/HDL ratio, age and Tg.[1]

In renal failure patients the process of accelerated atherosclerosis is frequently observed. As an extraordinarily high mortality in ESRD patients under HD is due to cardiovascular disease, there is increasing interest in non-traditional atherosclerotic cardiovascular disease risk factors that are prevalent in ESRD, such as Lp(a), which needs to be given more attention because of its effect on the acceleration of rapid progressive atherosclerosis seen in HD patients.

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ΠΕΡΙΛΗΨΗ

Σχέση πρώιμων αθηροσκληρυντικών αγγειακών αλλοιώσεων και λιποπρωτεΐνης(a) του ορού σε ασθενείς με χρονία νεφρική ανεπάρκεια πριν και μετά από την έναρξη της χρονίας αιμοκάθαρσης

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ΣΚΟΠΟΣ Η μελέτη της επίδρασης της συγκέντρωσης της Lp(a) στον ορό στην εμφάνιση πρώιμων αθηροσκληρυντικών αγγειακών αλλοιώσεων σε ασθενείς με χρονία νεφρική ανεπάρκεια (ΧΝΑ) που δεν υποβάλλονται σε χρονία αιμοκάθαρση (ΧΑ) και σε ασθενείς με ΧΝΑ τελικού σταδίου που υποβάλλονται σε ΧΑ. **ΥΛΙΚΟ–ΜΕΘΟΔΟΣ** Πρόκειται για συγχρονική μελέτη, στην οποία περιελήφθησαν 29 φυσιολογικά άτομα (ομάδα 1, 17 γυναίκες και 12 άνδρες), 33 ασθενείς με ΧΝΑ που δεν υποβάλλονταν σε ΧΑ (ομάδα 2, 19 γυναίκες και 14 άνδρες) και 43 ασθενείς με ΧΝΑ τελικού σταδίου (ομάδα 3, 19 γυναίκες και 24 άνδρες). Σε όλα τα άτομα της μελέτης μετρήθηκαν τα επίπεδα της Lp(a) στον ορό. Επίσης, μετρήθηκε το πάχος της έσω-μέσης στιβάδας των καρωτίδων (ΙΜΤ) και εξετάστηκαν οι καρωτίδες και οι μηριαίες αρτηρίες για την ύπαρξη πλακών (προσδιορισμός βαθμού πλάκας) με B-mode υπερηχογραφία. **ΑΠΟΤΕΛΕΣΜΑΤΑ** Η μέση τιμή (±SD) της συγκέντρωσης της Lp(a) στον ορό ήταν στην ομάδα 1, 42±20 mg/dL, στην ομάδα 2, 57±23 mg/dL και στην ομάδα 3, 55±16 mg/dL. Αντιστοίχως, το ΙΜΤ ήταν 0,84±0,20 mm, 1,30±0,40 mm και 1,10±0,30 mm. Μηδενικό βαθμό πλάκας είχε το 93% των ατόμων της ομάδας 1, το 39,4% των ασθενών της ομάδας 2 και το 51,2% των ασθενών της ομάδας 3. Βαθμό πλάκας 1–2 είχε το 6,8% των ατόμων της ομάδας 1, το 24,3% των ασθενών της ομάδας 2 και το 25,6% των ασθενών της ομάδας 3. Βαθμό πλάκας 3–4 δεν είχε κανένα από τα άτομα της ομάδας 1, ενώ είχε το 36,4% των ασθενών της ομάδας 2 και το 23,3% των ασθενών της ομάδας 3. Η διαφορά του ΙΜΤ μεταξύ της ομάδας 1 αφενός και των ομάδων 2 και 3 αφετέρου ήταν στατιστικά σημαντική ($P<0,001$ και $P<0,008$, αντιστοίχως), καθώς και μεταξύ των ομάδων 2 και 3 ($P=0,023$). Σημαντικές διαφορές ως προς τα επίπεδα της Lp(a) στον ορό παρατηρήθηκαν μεταξύ της ομάδας 1 αφενός και των ομάδων 2 ($P=0,016$) και 3 αφετέρου ($P=0,021$). Δεν παρατηρήθηκαν σημαντικές διαφορές ως προς τα επίπεδα της Lp(a) στον ορό μεταξύ των ομάδων 2 και 3 ($P>0,05$). Θετικές συσχετίσεις παρατηρήθηκαν μεταξύ των επιπέδων της Lp(a) αφενός και του ΙΜΤ και του βαθμού πλάκας στους ασθενείς της ομάδας 3. **ΣΥΜΠΕΡΑΣΜΑΤΑ** Η Lp(a) ενδέχεται να διαδραματίζει κάποιο σημαντικό ρόλο στην εξέλιξη της αθηροσκλήρυνσης που παρουσιάζουν οι ασθενείς με ΧΝΑ, ο οποίος χρήζει περαιτέρω μελέτης.

Λέξεις ευρετηρίου: Αιμοκάθαρση, Βαθμός πλάκας, Έσω-μέση στιβάδα, Χρονία νεφρική ανεπάρκεια, Lp(a)

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