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Serum Lipoprotein (a) Levels in Chronic Renal Failure and Liver Cirrhosis Patients. Relationship with Atherosclerosis

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ABSTRACT: This study was carried out to investigate the relationship between lipoprotein (a) levels and the development of atherosclerosis in chronic renal failure (CRF) patients with the possible role of the liver. Serum Lp (a) levels were measured in samples from 20 CRF patients on hemodialysis (HD), 20 liver cirrhosis (LC) patients, 20 patients having both CRF and LC and undergoing HD, and 20 normal control subjects. Renal function (blood urea nitrogen (BUN) and creatinine), hepatic function (transaminases (ALT and AST), alkaline phosphatase (ALP) and total bilirubin) investigations and serum cholesterol were carried out for all the subjects enrolled in this study. Serum Lp (a) concentration in CRF patients without LC was 87.25 ± 6.17 mg/dl, which was significantly higher than all the investigated groups ($P < 0.001$). Lp(a) concentration in patients with both CRF and LC was 24.65 ± 1.98 mg/dl, which was not significantly different from the controls, but was significantly higher than that in the subjects with LC only ($P < 0.001$) where the latter group had significantly low Lp (a) values (11.1 ± 0.99) relative to all the other groups ($P < 0.001$). Lp (a) correlated positively with cholesterol in all groups except the LC subjects, but did not correlate with age, or renal function in both CRF groups.

KEYWORDS: Lipoprotein (a), cholesterol, chronic renal failure, liver cirrhosis, atherosclerosis

INTRODUCTION

Patients with chronic renal insufficiency and end-stage renal disease (ESRD) form a group with a well-known high incidence of cardiovascular diseases [1,2]. Lipid metabolism abnormalities play a large role in the progression of renal diseases. Patients with ESRD suffer from an increased incidence of atherosclerotic diseases [2–4].

Increased lipoprotein (Lp(a)) levels may be the earliest and more consistent lipid alteration seen in predialysis renal failure patients. Several studies confirmed Lp(a) to be a risk factor for atherosclerosis alterations in end-stage renal disease (ESRD) independent of alterations in other lipid parameters. Plasma Lp(a) increases and attains maximal levels with mild/moderate reduction in renal function, and does not seem to change through late renal failure stage, or in relation to the introduction of hemodialysis [5–11]. Lp(a) is synthesized primarily, if not entirely in the liver. It constitutes a macromolecular complex in human plasma contained in LDL and consisting of an apoB-100 molecule and an apo(a) molecule linked together by a disulfide bond. Lp(a) plasma level is normally genetically determined and remains constant throughout adult life. An arbitrary normal upper limit of 30 mg/dl has been proposed for Lp(a) above which the risk for premature coronary heart diseases (CHD) increases [12–15].

Lp(a) levels in ESRD patients may reach 3–4 times higher levels than in normal subjects [2,18]

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independent of apo(a) isoform, which could be due to decreased Lp(a) catabolism, by the kidney and/or increased hepatic synthesis of apo(a). Lp(a) has been considered to be more strongly related to the risk of CHD than HDL-C and LDL-C, and independent of the other known risk factors. Lp(a) particles appear to bind preferentially to the arterial vessel wall. They may act synergistically with apolipoprotein B to promote atherosclerosis [1,3,4,12].

The present study aimed to investigate the effects of the functional state of kidney and liver, both individually and in combination, on the Lp(a) levels in CRF and/or LC patients with special emphasis on their association with the development and/or regression of atherosclerosis diseases associated with CRF.

SUBJECTS AND METHODS

Subjects

60 CRF and LC adult male patients were chosen from the dialysis unit and internal medicine department at Ain Shams University Hospital in Cairo, along with 20 healthy normal control subjects. The patients were divided into three groups, each consisting of 20 subjects, CRF patients group, LC patients group, and patients having both CRF and LC. They were thoroughly investigated and their clinical examination confirmed that they suffered only from CRF and/or LC. Duration of these disorders was five to seven years before carrying out this study. Patients with CRF have been undergoing hemodialysis for four hours, twice a week and on the basis of extensive clinical assessment, they were further subdivided into atherosclerotic and non-atherosclerotic subgroups. None of the CRF patients with LC was atherosclerotic. The mean age (mean ± SE) of CRF group was 51.95 ± 1.66 years, LC group was 52.05 ± 2.08 years, CRF with LC group was 52.40 ± 1.40 years and for the normal controls was 50 ± 2.22 years.

Methods

Fasting serum samples were used for this study. For the hemodialysis patients, blood samples were withdrawn just before starting dialysis. The renal function, hepatic function, and cholesterol assays were performed using Synchron CX5 Clinical System (Beckman, USA). Lp(a) was assayed immunologically [19] by enzyme-linked immunosorbent assay (ELISA) (Innogenetics, Belgium). The results were analyzed using SPSS package (Echo Soft Corp., USA, 1993). Analysis of variance (ANOVA) was applied to demonstrate the diagnostic value of the assayed parameters in the studied disorders.

Table 1
Statistical analysis of the results of the lipid parameters and age in the main investigated groups

	C	CRF	LC	CRF/LC	CRF & LC	CRF & CRF/LC	LC & CRF/LC
Cholesterol (mg/dL)							
mean ± S.E.	213.50 ± 4.68	241.95 ± 9.68	137.20 ± 6.56	130.30 ± 6.26			
t		− 2.65	9.47	10.64	8.96	− 9.69	− 0.76
P		< 0.01	< 0.001	< 0.001	< 0.001	< 0.001	> 0.05
Lp(a) (mg/dL)							
mean ± S.E.	25.25 ± 2.0	87.25 ± 6.17	11.10 ± 0.99	24.65 ± 1.98			
t		− 9.56	6.35	0.21	12.18	− 9.66	6.12
P		< 0.001	< 0.001	> 0.05	< 0.001	< 0.001	< 0.001
Age (years)							
mean ± S.E.	50.0 ± 2.22	52.05 ± 2.08	52.40 ± 1.40	51.95 ± 1.66			
t		− 0.67	− 0.91	− 0.70	− 0.14	− 0.04	− 0.21
P		> 0.05	> 0.05	> 0.05	> 0.05	> 0.05	> 0.05

Table 2
Statistical analysis of the results of the CRF subgroups

	Subgroup A (non-atherosclerotic) n = 10 mean ± S.E.	Subgroup B (atherosclerotic) n = 10 mean ± S.E.	t	*P*
BUN (mg/dL)	86.20 ± 12.59	86.70 ± 10.64	− 0.03	> 0.05
Creatinine (mg/dL)	12.90 ± 1.16	12.60 ± 0.76	0.21	> 0.05
ALT (IU/L)	11.80 ± 0.88	11.80 ± 0.99	0.08	> 0.05
AST (IU/L)	13.40 ± 1.28	14.90 ± 1.19	− 0.85	> 0.05
ALP (IU/L)	106.70 ± 5.95	106.20 ± 8.43	0.04	> 0.05
T. Bilirubin (mg/dL)	0.66 ± 0.09	0.49 ± 0.07	1.51	> 0.05
Cholesterol (mg/dL)	207.60 ± 5.88	276.30 ± 9.92	− 5.95	< 0.001
Lp(a) (mg/dL)	65.90 ± 6.44	108.60 ± 4.26	− 5.53	< 0.001
Age (years)	47.10 ± 1.44	57.0 ± 3.27	− 2.77	< 0.01

RESULTS

Cholesterol. The CRF subjects without LC had significantly higher cholesterol levels than the controls ($P < 0.01$) and the other patients' groups ($P < 0.001$) (Table 1). On the other hand, the CRF subjects who had LC and the LC patients had significantly lower levels than the control ($P < 0.001$), but non-significantly different from each other ($P > 0.05$). In this study, 50% of the CRF subjects without LC were atherosclerotic having significantly higher cholesterol levels than their non-atherosclerotic counterparts ($P < 0.001$) (Table 2). A significant positive correlation was found between cholesterol and age in all the patients' groups (in CRF subjects with LC, $r = 0.49448$; in CRF subjects without LC, $r = 0.54223$ (Fig. 1) and in LC subjects, $r = 0.41482$).

Lipoprotein(a). Wide variations were observed in Lp(a) levels among the patients' groups when compared with the controls. The CRF subjects without LC had significantly elevated Lp(a) levels ($P < 0.001$) (Table 1), while the CRF subjects with LC showed no significant change ($P > 0.05$), and the LC patients had significantly reduced levels ($P < 0.001$). Consequently, Lp(a) levels were significantly different among the three patients' groups ($P < 0.001$). Also, the atherosclerotic CRF subjects had significantly elevated levels compared with the non-atherosclerotic subjects ($P < 0.001$) (Table 2). In the CRF subjects without LC, no correlation was found between Lp(a) and either age, BUN or creatinine ($r = 0.2834$, $r = 0.27765$ and $r = 0.10057$ respectively). However, a positive correlation was found between Lp(a) and cholesterol (Fig 2) in this group ($r = 0.6878$) and in the CRF subjects with LC ($r = 0.68778$) although Lp(a) did not correlate to age in the latter group ($r = 0.08305$). On the other hand, no correlation was found between Lp(a) and either cholesterol ($r = 0.34979$) or age ($r = 0.31623$) in the LC subjects.

Renal function. The CRF patients, both with and without LC, showed significantly elevated BUN and creatinine levels compared with the controls ($P < 0.001$) (Table 3), with no significant difference between the atherosclerotic and non-atherosclerotic subjects ($P > 0.05$) (Table 2). The LC patients showed significantly decreased BUN levels compared with the controls, and consequently, with the other investigated patients' groups ($P < 0.001$), but showed non-significantly different creatinine levels from those of the controls ($P > 0.05$), but significantly lower than those of the CRF patients with and without LC ($P < 0.001$). The CRF patients who also had LC had significantly lower BUN and creatinine levels than those without LC ($P < 0.01$ and $P < 0.001$ respectively).

Hepatic function. The transaminases (ALT and AST), total bilirubin levels and ALP showed significant elevations in the CRF subjects who had also LC, and in the LC patients compared with both the controls and the CRF subjects who did not have LC ($P < 0.001$) (Table 3). This

Table 3
Statistical analyses of the results of the kidney and liver functions in the main investigated groups

	C	CRF/LC	CRF	LC	CRF/LC & CRF	CRF/LC & LC	CRF & LC
BUN (mg/dL)							
mean ± S.E.	13.90 ± 0.71	58.80 ± 5.30	86.45 ± 8.02	10.0 ± 0.51			
t		− 8.39	− 9.01	4.47	− 2.88	9.16	9.51
P		< 0.001	< 0.001	< 0.001	< 0.01	< 0.001	< 0.001
Creatinine (mg/dL)							
mean ± S.E.	0.70 ± 0.07	9.30 ± 0.54	12.75 ± 0.68	0.73 ± 0.07			
t		− 15.72	− 17.75	− 0.49	− 3.98	15.58	17.63
P		< 0.001	< 0.001	> 0.05	< 0.001	< 0.001	< 0.001
ALT (IU/L)							
mean ± S.E.	10.90 ± 0.79	51.15 ± 3.39	11.80 ± 0.64	35.20 ± 2.77			
t		− 15.17	− 1.13	− 11.11	16.92	3.83	− 11.47
P		< 0.001	> 0.05	< 0.001	< 0.001	< 0.001	< 0.001
AST (IU/L)							
mean ± S.E.	13.15 ± 0.83	62.65 ± 4.20	14.15 ± 0.87	50.58 ± 4.16			
t		− 11.56	− 0.83	− 8.90	11.30	2.0	− 8.65
P		< 0.001	> 0.05	< 0.001	< 0.001	< 0.05	< 0.001
ALP (IU/L)							
mean ± S.E.	65.10 ± 3.86	143.05 ± 5.11	106.45 ± 5.03	115.75 ± 7.53			
t		− 12.17	− 6.53	− 6.10	5.11	3.05	− 1.04
P		< 0.001	< 0.001	< 0.001	< 0.001	< 0.01	< 0.001
T. Bilirubin (mg/dL)							
mean ± S.E.	0.45 ± 0.06	2.51 ± 0.18	0.58 ± 0.06	1.05 ± 0.07			
t		− 11.03	− 1.52	− 6.17	10.42	7.65	− 4.98
P		< 0.001	> 0.05	< 0.001	< 0.001	< 0.001	< 0.001

P > 0.05: non-significant difference; P < 0.05: significant difference; P < 0.01 and P < 0.001: highly significant difference

Table 4
Analysis of variance (ANOVA)

	CRF (mean)	LC (mean)	CRF/LC (mean)	Fisher's-ratio (F-ratio)	*P*
Creatinine	12.75	0.73	9.30	151.090	< 0.001
Lp(a)	87.25	11.10	24.65	115.115	< 0.001
EPO	6.21	22.70	4.32	89.736	< 0.001
T. Bilirubin	0.58	1.05	2.51	76.266	< 0.001
Cholesterol	241.95	137.20	130.30	66.801	< 0.001
ALT	11.80	35.20	51.15	59.999	< 0.001
AST	14.15	50.85	62.65	53.80	< 0.001
BUN	86.45	10.0	58.80	48.504	< 0.001
Age	52.40	52.40	51.95	0.019	> 0.05

latter group showed non-significantly different levels from the controls (P > 0.05), with no significant difference between the atherosclerotic and non-atherosclerotic subjects as well (Table 2).

Table 4 represents the different analysed parameters arranged in descending order according to their diagnostic importance in CRF and/or LC patients as revealed by ANOVA test.

DISCUSSION

Chronic renal failure (CRF) develops due to irreversible renal function deterioration as a consequence of destruction of over 80% of the nephrons. ESRD is finally reached when more than 90% of the nephrons have been destroyed, and the renal functions are impaired in such manner that is life-threatening. Regular dialysis

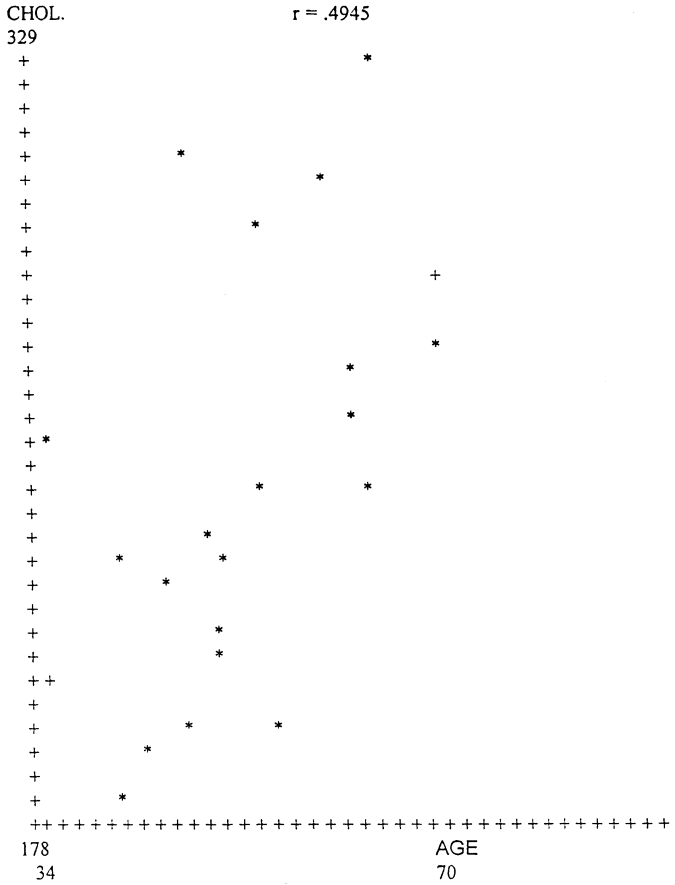

Fig. 1. Linear regression analysis showing the correlation between age and cholesterol in the CRF group.

is then essential to sustain life [20,21].

This study was constructed to investigate the functional state of the kidney and liver in CRF and/or LC patients, and the influence of each one on the other.

As the impaired function of the kidney and/or liver is manifested biochemically, association of both diseases together resulted in either intensification or amelioration of the biochemical changes.

On investigating the lipid parameters, the CRF subjects who had LC together with the LC subjects were found to have significantly reduced cholesterol levels compared with the controls ($P < 0.001$) as a consequence of liver damage, while the CRF subjects without LC had significantly elevated cholesterol levels compared with the controls ($P < 0.01$), and consequently with the two other patients groups ($P < 0.001$). 50% of the patients in this latter group were atherosclerotic, while none of the CRF subjects with LC was atherosclerotic. The atherosclerotic CRF subgroup showed a significant increase in cholesterol, Lp(a) and age compared to the non-atherosclerotic CRF patients ($P < 0.001$, $P < 0.001$ and $P < 0.01$ respectively).

In 1974, Dahlen [23] first described an association between Lp(a) and CHD. Most studies on Lp(a) in chronically hemodialyzed patients with intact liver have reported significantly elevated Lp(a) levels in those patients, in agreement with our findings [1,5, 18,24–39]. Only some studies described Lp(a) values in CRF patients not significantly different from those in the controls [7,40–45]. However, in a recent study by Kronenberg et al. [46], which included 534 HD

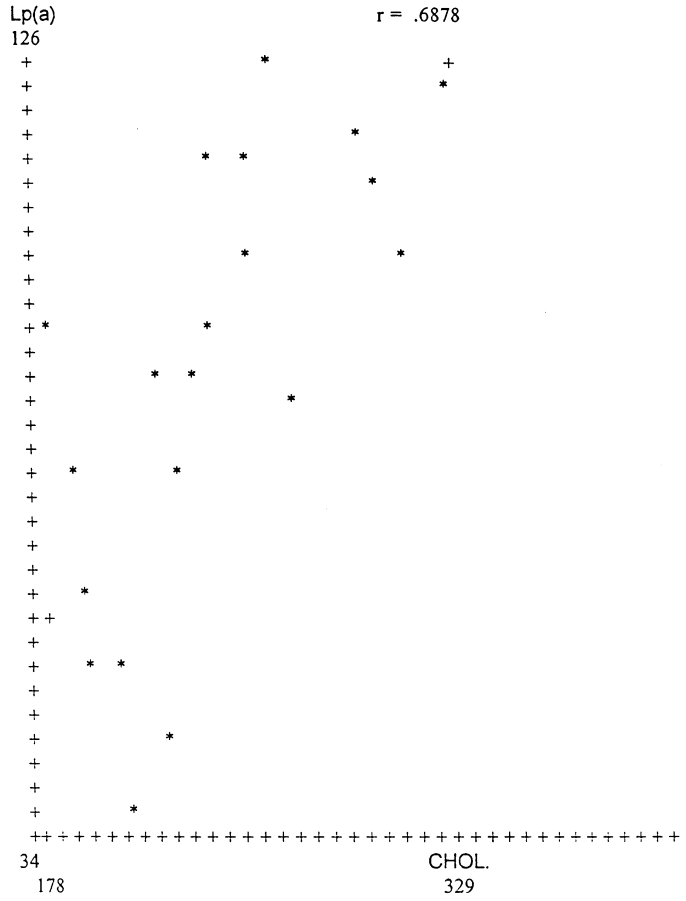

Fig. 2. Linear regression analysis showing the correlation between lipoprotein (a) and cholesterol in the CRF group.

patients, significantly elevated Lp(a) levels were found compared with the controls.

In the present study, CRF patients who did not have LC had mean Lp(a) level approximately 3.5 times higher than both the mean level of the control subjects and the assumed normal upper lineout of 30 mg/ ML. This agrees with two reports [2,18] in which approximately 3–4 times higher Lp(a) levels were found in ESRD patients than in the normal controls.

The elevation observed in the atherosclerotic CRF subjects compared with the non-atherosclerotic ones in our study agrees with report of Cressman et al. [34] who found significantly higher Lp(a) levels (> 73 mg/ ML) in HD patients with clinical events attributed to atherosclerosis than in those patients without such events. Also, Docci et al. [47] reported the presence of significantly higher mean Lp(a) level in HD patients with CHD than those without CHD, with lack of correlation between Lp(a) and cholesterol in the former group, although a significant positive correlation existed between both parameters when all the HD patients, with and without CHD, were investigated as a single group, which agrees with the significant positive correlation we found between Lp(a) and cholesterol in CRF patients without LC. On the other hand, other investigators did not find this correlation in CRF patients [16,18,41,48].

Hernandez et al. [49] confirmed the presence of higher Lp(a) levels in HD patients with failure of vascular access than those without failure of vascular access, but this difference did not reach a statistical significance. These authors reported lower vascular access survival in patients with

Lp(a) between 50 and 75 mg/dl than those with Lp(a) < 50 mg/dl, but higher survival than patients with Lp(a) > 75 mg/dl. Several other studies, mostly with small patient groups, confirmed Lp(a) to be a risk factor for atherosclerotic alterations in ESRD, independent of alterations in other constituents [5–11]. Other studies were against Lp(a) establishment as an independent atherosclerotic risk factor [25,30,37,50]. However, a recent study by Ritz [51] held strong evidence for the atherosclerotic role of Lp(a), as this investigator found consistently higher levels of total cholesterol, low-density lipoprotein cholesterol (LDL-C), apoB and other coronary risk indicators except Lp(a) in survivor HD patients than in those dying from cardiovascular causes.

Nearly every study that reported elevated Lp(a) levels in renal disease, whether in favor of or against the idea of Lp(a) atherogenicity, suggested a role of the kidney in Lp(a) metabolism. Elevated Lp(a) level in CRF was suggested to be of non-genetic origin and secondary to the renal disease. This is consistent with the normalization in Lp(a) levels following renal transplantation, which also argues against an elevation induced by an acute phase reaction in ESRD [51–55].

Two explanations have been suggested for Lp(a) elevation in CRF [32]. First, the kidney might have an indirect influence on Lp(a) synthesis in the liver, probably through a factor that is secreted by the kidney and regulates Lp(a) synthesis. The second explanation is that the kidney may have a direct metabolic function, and degrades Lp(a), since various renal cell types express the LDL receptor-related protein believed to play a role in Lp(a) catabolism [54]. Also, the kidney with its dense capillary network provides an imposing endothelial surface. Due to the high homology between apo(a) and plasminogen, a high density of plasminogen receptors is also available for apo(a) [55]. Impairment of these receptor systems in CRF might also influence the regulatory mechanisms of the hepatic synthesis and/or catabolic sites. Although some investigators are in favor of attributing the control of Lp(a) levels to increased hepatic production induced by proteinuria [41,56]. This route could only be valid in patients undergoing continuous ambulatory peritoneal dialysis (CAPD), as HD patients hardly suffer from any substantial protein loss [1].

In our study, we found significantly reduced Lp(a) levels in LC patients. This finding agrees with other reports [1,57–60]. The two contradictory mechanisms of CRF and LC influencing Lp(a) plasma level counterpoised in the patients investigated in this study that had both diseases. Consequently, those patients showed apparently normal Lp(a) levels although normal Lp(a) metabolism was not maintained in them.

In CRF patients with and without LC, BUN and creatinine levels increased significantly as a result of the impaired excretory function of the failed kidneys in those patients, while in LC patients BUN levels decreased significantly due to impaired urea formation by the cirrhotic liver. Although the CRF subjects with LC had elevated BUN and creatinine levels, BUN levels were significantly lower than those of the CRF subjects without LC, due to the combined effect of both CRF and LC together, yet exerting opposite influence on BUN level i.e., LC causing reduced hepatic synthesis of urea while CRF reducing urea excretion resulting in elevation of BUN level relative to the urea initially synthesized by the cirrhotic liver. As a result, those patients had significantly lower BUN levels than those with CRF only ($P < 0.001$). However, the role of the kidney in this case was more pronounced than that of the liver. This is confirmed by the positive significant correlation that was found between BUN and creatinine in both CRF groups.

Concerning the liver function in the studied groups, the highest significant elevations in ALT, AST, and bilirubin were always found in LC and CRF with LC groups. However, CRF with LC showed a significant increase over LC alone in the three parameters ($P < 0.001$, $P < 0.05$ and $P < 0.001$ respectively) (Table 3). This implies that renal failure may have an influence in liver function on those patients.

The elevation that was found in ALP levels in CRF and in LC patients could attribute the

extreme elevation that was found in the enzyme levels in the CRF subjects with LC to the association of both diseases together. These results are in accordance with those of Woitge et al. [22], who also found significantly increased ALP levels in CRF and in LC patients, and explained that the elevation found in LC was due to the release of the enzyme from the damaged hepatocytes into the plasma, however, the elevation observed in CRF was of non-hepatic origin, and may be due to increased bone turn-over in those patients.

In this study, no correlation was found between Lp(a) and either age, or renal function in CRF patients, which agrees with the reports of other investigators who found no correlation between Lp(a) and either of these parameters in CRF patients [1,16,18,61,62]. Despite the significant positive correlation found in this study between Lp(a) and cholesterol in both CRF groups, the latter was positively correlated to age, while in both CRF groups Lp(a) was not correlated to age. These findings emphasize the role of Lp(a) as the primary, and independent, cause of atherosclerosis in the investigated CRF patients.

ANOVA test showed that, among the investigated parameters in CRF and/or LC patients, creatinine was the most important diagnostic marker according to its F-ratio, followed by Lp(a), total bilirubin, cholesterol, ALT, AST, BUN, and finally ALP.

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