JMB 2009; 28 (2) DOI: 10.2478/v10011-009-0004-0

UDK 577.1 : 61 **ISSN 1452-8258**

JMB 28: 82–88, 2009

Original paper
Originalni naučni rad

LIPOPROTEIN(a) IN CHRONIC RENAL FAILURE

LIPOPROTEIN(a) U HRONIČNOJ BUBREŽNOJ INSUFICIJENCIJI

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Summary: Cardiovascular diseases are the leading cause of mortality in patients with chronic renal failure. Among the parameters contributing to cardiovascular disease development is the elevated serum concentration of lipoprotein(a) diagnosed in these patients, especially in the terminal stage of CRF. However, an elevated concentration of lipoprotein(a) could influence the renal failure progression. The objective of this study is to examine the lipoprotein(a) serum levels in chronic renal failure, and to establish the relation between the stage of renal function preservation and the level of this lipoprotein. In this study 127 subjects were included, divided into three groups. The first group contained 42 subjects (15 females and 27 males) in different CRF stages, the second group contained 32 subjects (7 females and 25 males) on a chronic hemodialysis program, and the control group contained 53 subjects (22 females and 31 males) with regular renal function. The results obtained point to significantly higher frequency of hyper-Lp(a) lipoproteinaemia in dialysed patients compared to the control group, as well as significantly higher Lp(a) values in both groups of patients compared to the control group. It can be concluded that for the risk assessment of premature atherosclerotic changes, but also renal failure progression in patients with CRF, determination of the Lp(a) serum concentration is recommendable.

Keywords: chronic renal failure, lipoprotein(a)

Kratak sadržaj: Kardiovaskularne bolesti su vodeći uzrok mortaliteta kod bolesnika sa hroničnom bubrežnom insuficijencijom (HBI). Među faktorima koji doprinose razvoju kardiovaskularnih bolesti je i povišena serumska koncentracija lipoproteina(a) koja se beleži kod ovih bolesnika, naročito u terminalnom stadijumu HBI. Međutim, povišena koncentracija lipoproteina(a) mogla bi imati ulogu i u progresiji bubrežne insuficijencije. Cilj ove studije je da ispita serumske nivoe lipoproteina(a) u hroničnoj bubrežnoj insuficijenciji, kao i da utvrdi odnos između stepena očuvanosti bubrežne funkcije i nivoa tog lipoproteina. Ova studija preseka je obuhvatila 127 ispitanika koji su podeljeni u tri grupe. Prvu grupu su činila 42 (15 ž i 27 m) ispitanika u različitim stadijumima HBI, drugu grupu 32 (7 ž i 25 m) ispitanika na hroničnom programu hemodijalize, i kontrolnu grupu su činila 53 (22 ž i 31 m) ispitanika sa urednom bubrežnom funkcijom. Dobijeni rezultati ukazuju na značajno veću učestalost hiper-Lp(a) lipoproteinemije kod dijaliziranih bolesnika u odnosu na kontrolnu grupu, kao i značajno više vrednosti Lp(a) kod obe grupe bolesnika u odnosu na kontrolnu grupu. Može se zaključiti da je u cilju procene rizika za razvoj prevremenih aterosklerotskih promena, ali i progresije bubrežne insuficijencije, kod bolesnika sa HBI preporučljivo određivati serumsku koncentraciju Lp(a).

Ključne reči: hronična bubrežna insuficijencija, lipoprotein (a)

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List of abbreviations:

Lp(a) – Lipoprotein(a), GFR – Glomerular Filtration Rate, ClCr – Creatinine Clearance, CRF – Chronic Renal Failure, BMI – Body Mass Index, HD – Hemodialysis.

Introduction

Chronic renal failure (CRF) is a common health problem worldwide. The prevalence of chronic renal failure is on the rise, since it is a consequence of the increased development of diseases causing renal function disturbances, principally diabetes mellitus and arterial hypertension (1). In patients with chronic renal failure, and especially with end-stage renal disease, cardiovascular diseases are the leading cause of morbidity and mortality. Based upon data on renal patients from different countries, the cardiovascular mortality in this population is about 16 times higher compared to the healthy population (2). Numerous parameters contribute to accelerated atherogenesis and occurrence of cardiovascular diseases in patients with CRF, and the most important ones are: lipid metabolism disturbances, oxidative stress, inflammation, physical inactivity, hypertension, vascular calcifications, endothelial dysfunction and depressed nitric oxide availability (3–6).

Many of the renal disease patients have dyslipidaemia, often already in an early stage of renal failure (7, 8). Apart from quantitative abnormalities (hypertriglyceridaemia and hypo-HDL cholesterolaemia), in CRF there are also qualitative ones, i.e. disturbance in plasmatic lipoprotein structure (small dense LDL and HDL particles) (9). Furthermore, elevated lipoprotein(a) [Lp(a)] serum concentration was also reported.

Lp(a) is an LDL-like lipoprotein that consists of an LDL particle to which the glycoprotein apolipoprotein (apo)(a) is bound. Lipoprotein(a) serum levels vary widely, with a distribution that is skewed at low levels. The apo(a) gene is located on chromosome 6 and is the major gene controlling lipoprotein(a) levels. In Lp(a) catabolism, the liver is without any function, and it is supposed that kidney is the dominant organ. The presence of apo(a) fragments liberated from the lipoprotein complex was established in urine in quantity of 1% of the total Lp(a) catabolism, which is in correlation with its plasmatic levels (10). There is a possibility that it is an active tubular secretion mechanism.

Numerous studies reported elevated Lp(a) levels in patients with kidney diseases. This increase, however, depends markedly on the impairment of kidney function, the amount of proteinuria, and the treatment modality. In addition to these parameters, there is strong evidence that the relative increase of Lp(a) also depends on the apo(a) K-IV repeat polymorphism (11). Lipoprotein(a), a genetically determined lipoprotein in the blood, is one of the most powerful independent risk factors for cardiovascular disease (12). Lp(a) levels above 0.30 g/L were proposed to be associated with an increased risk. However, the Lp(a) level itself seems to be less discriminative for cardiovascular disease in kidney patients compared with the general population (11).

Based upon previous research, it is known that endothelial function disturbance, infiltration of intimal endothelial surface of the arterial wall with native LDL particles, their oxidative modification, monocyte mobilization, migration and proliferation of smooth muscle cells, extracellular matrix reorganization and growing fibrolipid plate are the key mechanisms of atherogenesis. Furthermore, the central part in the initiation of endothelial dysfunction is represented by LDL modification into the form of oxidatively modified LDL (oxLDL) (13). Hypertriglyceridaemia, present in CRF as a rule, brings about modifications of HDL and LDL particles' structure, resulting in the occurrence of small dense LDL with increased capacity of binding to the arterial wall, and a special tendency for oxidative modification. Reduced concentrations, as well as proactive abilities of modified HDL particles, represent an additional factor contributing to the premature atherosclerosis development in CRF (11).

Lp(a) lipoprotein is presumed to function as a dual pathogen, which is related to both atherogenesis and thrombogenesis. Apo(a) is an atherothrombogenic moiety, which can competitively inhibit plasminogen activity leading to impaired fibrinolysis. Lp(a) has also been implicated in enhanced oxidation and foam cell formation. Recently, it has been proposed that in settings of enhanced oxidative stress and increased Lp(a) concentrations, a proinflammatory milieu may predominate that contributes to the clinical expression of cardiovascular disease (12).

Apart from its role in atherogenesis, dyslipidaemia can have a potential role in kidney disease progression acceleration by a few mechanisms, such as: reabsorption of cholesterol and fatty acids, occurring in the filtrated protein structure (albumins and lipoproteins), by tubulocytes can stimulate the tubulointerstitial inflammation, formation of foam cells and tissue damage (14, 15). Lipoprotein accumulation in the glomerular mesangium can contribute to matrix production and occurrence of glomerulosclerosis (16). In this context, native and oxidized lipoproteins, particularly LDL, stimulate the production of matrix proteins by cultured mesangial cells and promote the generation of proinflammatory cytokines, which can lead to recruitment and activation of circulating and resident macrophages. Additionally, HDL-intervened reverse cholesterol transportation is disturbed, what can further contribute to tissue damage. In fact, hypo-HDL cholesterolaemia represents an independent risk factor for renal disease progression (17).

Apart from the fact that increased lipoprotein(a) level is an independent risk factor for premature atherosclerosis development, there is an opinion that Lp(a) could also be important for renal disease progression (18). This lipoprotein has stimulatory effects in low concentrations, and cytotoxic effects in high concentrations on mesangial cells culture, which

can have a negative influence on renal disease progression *in vivo* (19). There are numerous data in literature, based upon *in vitro* examination on animal models, describing the possible mechanisms by which Lp(a) can induce or aggravate renal dysfunction (20, 21). While analogical and pathobiological processes (22) are included in glomerulosclerosis and atherosclerosis, and Lp(a) is an independent risk factor for premature atherosclerosis development, this particle could be a contributing factor in chronic renal insufficiency progression. However, there are other studies (23), pointing to the fact that plasma levels of Lp(a) do not predict progression of renal dysfunction.

The objective of this study is to examine Lp(a) values in patients with chronic renal failure, as well as to determine the relation between functional renal reserves and Lp(a) serum concentration in these patients.

Materials and Methods

In this study 127 subjects were examined, and their characteristics are represented in *Table I*.

Subjects in the first group were patients in various stages of CRF, and non-hemodialysed, while subjects in the second group were patients on a chronic hemodialysis program (HD). Blood samples were taken from these patients before the first hemodialysis in the week. Subjects of comparable age with regular renal function formed the control group.

In order to evaluate the functional renal reserves, the serum concentrations of creatinine and urea, as well as creatinine concentration in urine were determined by standard biochemical methods, using the analyzer Olympus AU400 and the commercial sets of the Olympus company (Ireland). After that, the creatinine clearance (ClCr) was calculated, and the obtained value was normalized in comparison to the body surface of 1.73 m^2.

Table I Subjects' features.

	I group	II group	III group
Subjects	Non-hemodialysed CRF patients	Hemodialysed patients	Control group
Number (f/m)	42 (15/27)	32 (7/25)	53 (22/31)
Creatinine (μmol/L)	126.8±49.5	940.8±148.1	86.1±15.7
Urea (mmol/L)	8.3±4.3	29.6±7.7	4.9±1.2
Creatinine clearance (mL/min/ 1.73 m^2)	59.3±28.7	–	105.5±12.1
BMI (kg/m^2)	26.3±4.6	24.0±5.0	23.3±3.0

Legend: CRF – chronic renal failure, BMI – body mass index.

On the same biochemical analyzer, the serum concentrations of apo A-I, apo B (Olympus, Ireland) and lipoprotein(a) (Sentinel, Italy), were also determined immunoturbidimetrically. Lipid status parameters were determined by standard biochemical methods with the commercial sets of the BioMerieux company, France, on the RA-XT analyzer.

Statistics

Statistic data processing was performed by using the Microsoft Office Excel program package 2003. Results were presented as mean value ± SD. The following statistic methods were applied: f-test, t-test, correlation and linear regression analysis.

Results

The values obtained for lipid status parameters apo A-I and apo B are represented in *Table II*.

Table II Lipid status parameters and apolipoproteins A-I and B.

Parameters (mmol/L; g/L)	Non-hemodialysed CRF patients	Hemodialysed patients	Control group
Atherogenic			
Total cholesterol	4.83±1.01**	4.72±0.91**	5.78±0.40
Triglycerides	1.69±1.01**	1.97±1.08**	0.95±0.39
LDL-C	3.40±0.81	2.78±0.65	3.91±0.42
Apo B	1.03±0.23	0.98±0.23	0.78±0.20
Protective			
HDL-C	1.28±0.41** ‡‡	1.05±0.23 **	1.41±0.32
Apo A-I	1.31±0.23** ‡‡	1.13±0.16 **	1.55±0.30
Relations			
LDL-/HDL-C	2.91±0.92	2.83±0.75	2.98±0.87
Cholesterol/HDL-C	4.11±1.18 ‡	4.56±1.10	4.23±0.91
Apo B/A-I	0.78±0.16**	0.89±0.29 **	0.52±0.15

Legend: *p<0.05,**p<0.01 compared to the control group ‡p<0.05, ‡‡p<0.01 compared to the hemodialysed patients.

Table III Frequency of normal (<0.3), moderate (0.31–0.50) and extremely (>0.5) elevated serum Lp(a) levels.

Lp(a), (g/L)	Non-hemodialysed CRF patients	Hemodialysed patients	Control group
0–0.3	37 (90.5%)‡	22 (68.7%)*	48 (90.6%)
0.31–0.5	1 (2.3%)	5 (15.6%)	5 (9.4%)
>0.5	4 (9.5%)	5 (15.6%)	0
Total pathological values	5 (11.8%)‡	10 (31.2%)*	5 (9.4%)

Legend: ‡p<0.05 compared to the hemodialysed patients, *p<0.05 compared to the control group.

Table IV Serum lipoprotein(a) levels.

Lp(a), (g/L)	Non-hemodialysed CRF patients	Hemodialysed patients ($\bar{x}\pm SD$)	Control group ($\bar{x}\pm SD$)
0–0.3	0.10±0.07	0.07±0.06	0.05±0.05
0.31–0.5	0.31±0.31	0.37±0.04	0.36±0.07
>0.5	0.78±0.14	0.70±0.11	0
Summary ($\bar{x}\pm SD$)	0.18±0.21*	0.22±0.25‡	0.08±0.10

Legend: *p=0.01, and ‡p=0.006 compared to the control group.

In both groups of patients with CRF, significantly lower values of total cholesterol (C), HDL-C and apo A-I were established, i.e. significantly higher triglyceride values, as well as rate of apo B/A-I compared to the control group. In non-hemodialysed CRF patients, compared to the hemodialysed ones, significantly lower HDL-C and apo A-I values were present, as well as the cholesterol/HDL-C ratio.

Percentage distribution of Lp(a) lipoprotein serum levels is presented in *Table III*. The highest frequency of hyper-Lp(a) lipoproteinaemia was found in hemodialysed patients, which is significantly higher (p<0.05) compared to non-hemodialysed CRF patients and the control group.

Distribution of Lp(a) lipoprotein mean values is represented in *Table IV*. In patients with CRF, somewhat more so in HD patients, mean values of Lp(a) were significantly higher than in the control group.

In *Table V*, the correlation of Lp(a) with lipid parameters, BMI, age and dialysis treatment duration is represented. There is no significant correlation between Lp(a) serum levels and lipid status parameters, as well as BMI, age and dialysis duration.

Table V Lp(a) correlation with lipid parameters, BMI, age and hemodialysis duration.

	Non-hemodialysed CRF patients		Hemodialysed patients	
	r	p	r	p
Total cholesterol (mmol/L)	0.10	0.50	0.14	0.40
Triglicerides (mmol/L)	0.20	0.19	0.15	0.75
HDL-c (mmol/L)	0.04	0.71	0.10	0.75
LDL-c (mmol/L)	0.03	0.80	0.07	0.19
Apo A-I (g/L)	0.03	0.80	0.34	0.06
Apo B (g/L)	0.02	0.90	0.30	0.09
BMI (kg/m^2)	0.14	0.40	0.08	0.65
Age (year)	0.11	0.46	0.20	0.26
Dialysis duration (month)			0.16	0.36

Also, no significant correlation was established between the Lp(a) value and creatinine clearance as a filtration rate indicator.

Discussion

Lipid metabolism disturbances are frequently present in patients with chronic renal failure, representing an important factor in premature atherosclerosis development. They occur in 40–60% of patients with CRF (24) and their basic characteristics are: hypertriglyceridaemia (mild to moderate degree), normal or mild hypercholesterolaemia, reduction of HDL-C and apolipoprotein A-I values, increase of apolipoprotein B values (25, 26). The most frequent one is type IV hyperlipoproteinaemia, according to Fredrickson. In our study the same results were obtained, which was expected referring to the well known causes of lipid metabolism disturbance in CRF, such as: factors retarding the lipoprotein catabolism – reduced enzyme activity of lipoprotein lipase, hepatic triglyceride lipase and lecithin cholesterol acyltransferase, as well factors retarding the lipoprotein cellular transfer – modification of apolipoprotein content and modified lipid content, hormonal factors (hyper insulinaemia and secondary hyperparathyroidism).

Although there were numerous studies exploring relations between Lp(a) and renal functional status in patients with CRF, contradictory results were obtained. Some studies revealed an increase in the

plasma concentration of Lp(a) in these patients. Similarly to the study by Haffner et al. (27), in our research a low correlation coefficient was also obtained ($r=0.1$, $p=0.54$) between the Lp(a) serum values and creatinine clearance, as a glomerular filtration indicator. Considering the possible role of kidneys in Lp(a) catabolism, a result like this is somewhat contradictory to the expectations, due to the fact that by the reduction of functional renal reserves, this catabolism should also be reduced. Apart from this, there are also studies, as the one performed by Sechi et al. (28), examining Lp(a) serum concentrations in CRF initial phases, where a considerable inverse correlation exists between log Lp(a) and creatinine clearance ($r=0.243$, $p<0.001$), as well as a considerably higher Lp(a) level in patients with GFR<90 mL/min per 1.73 m^2 in comparison to patients with GFR >90 mL/min per 1.73 m^2. Although, based upon these results, it can be expected that Lp(a) concentrations, even at higher degrees of renal function reduction, would be in correlation with the creatinine clearance value, in our study the degree of this correlation was insignificant. Presumably, these results were caused by the fact that creatinine clearance determination in our test group was performed in ambulance conditions, implicating the possibility of nonadequate collection of twenty-four hour urine. Thereby, for more relevant insight into the degree of renal function preservation, especially in ambulance patients, apart from creatinine clearance determination, using some other markers (cystatin C) for glomerular filtration evaluation would be relevant.

In our study, Lp(a) values in patients with CRF, both hemodialysed and non-hemodialysed, were considerably higher compared to the control group. Similar results were obtained in the study by Lahrach et al. (29), while a somewhat lower mean value of Lp(a) in HD patients was obtained by Labudović et al. (0.17 ± 0.17 g/L) (30), however, it was not significantly different in comparison to the control group. Although neither the relation between the glomerular filtration reduction degree and Lp(a) level, nor the influence of elevated Lp(a) values on CRF progression were monitored in this study, there are some data in literature suggesting that elevated Lp(a) values in patients with HBI could influence the renal disease progression. Also, the apolipoprotein(a) isoforms were not established, but it was determined that in subjects with regular renal function Lp(a) levels were higher in case of existence of the low-molecular (LMW) apo(a) phenotype, in comparison to those with high-molecular phenotype (HMW), while Lp(a) values in patients with CRF, especially in advanced phases, converge to high values. Results of the CHOICE Study (31) in a dialysis cohort, showed that high lipoprotein(a) concentration, when measured by the ELISA assay, prospectively predicts cardiovascular disease, as does LMW apolipoprotein(a) size. It is of particular importance to say that patients with increased Lp(a) plasma level and LMW apo(a) isoform develop cantering atherosclerosis and progressive renal damage (32), because apolipoprotein(a) has a high degree of homology with plasminogen and LMW isoforms bind more strongly to fibrin than larger isoforms, suggesting that the LMW isoform size itself plays a role in atherogenesis. Furthermore, Lp(a) usually accounts for <10% of LDL-cholesterol. Therefore, if Lp(a) acts only through its lipid portion, even a relatively large elevation in its level might have relatively small atherogenic effects (33).

In accordance with considerably higher Lp(a) values in end-stage renal disease patients, in our study also a significantly higher presence of hyper-Lp(a) lipoproteinaemia has been established in comparison to the control group of subjects. Although Lp(a) serum values were significantly higher in non-hemodialysed patients with HBI in comparison to the control group, the presence of hyper-Lp(a) lipoproteinaemia was non-significant.

In our study, in contrast to the study of Haffner et al. (27), in which the correlation between Lp(a) and apo B was significant ($r=0.104$, $p=0.027$), Lp(a) was not in correlation with apo B or apo A-I, neither with lipid status parameters, nor with the age of subjects or duration of hemodialysis.

Considering the results of this study, which point to the fact that Lp(a) values are significantly higher in patients with CRF in comparison to the population with regular renal function, it can be concluded that the determination of Lp(a) serum concentration would be advisable for a more complete risk assessment of premature atherosclerotic modification development, but also of possible further progression of CRF.

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Received: September 10, 2008

Accepted: January 10, 2009