

# EFFECT OF C-REACTIVE PROTEIN ON LIPOPROTEIN A, PLASMA LIPIDS AND ALBUMIN IN HEMODIALYSIS PATIENTS

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## REZUMAT

**Introducere:** Pacienții hemodializați cronic au un risc foarte crescut pentru ateroscleroză, care a fost caracterizată ca o boală inflamatorie. La subiecții umani, proteina C reactivă (PCR) este un reactant major de fază acută, foarte sensibil. Ipoteza de lucru a acestui studiu este că activarea răspunsului de fază acută este responsabilă pentru statusul proaterogen al pacienților hemodializați. **Material și metode:** La 170 de pacienți hemodializați și la 50 de subiecți sănătoși (grupul de control) am determinat lipoproteina (a) [Lp(a)], lipidele, lipoproteinele și albumina serică, precum și legătura acestora cu PCR, ca marker sensibil al unui răspuns de fază acută. **Rezultate:** PCR serică a fost peste 10 mg/L la 69 (40,6%) din cei 170 de pacienți hemodializați cronic și a fost semnificativ mai mare la pacienții hemodializați comparativ cu grupul de control (44,62 mg/L vs. 8,75 mg/L,  $p < 0,01$ ). Lp(a) și trigliceridele serice au semnificativ mai mari la pacienții hemodializați comparativ cu grupul de control (31,37 mg/dL vs. 19,69 mg/dL,  $p < 0,01$ , și respectiv 2,76 mmol/L vs. 1,32 mmol/L,  $p < 0,01$ ). Colesterolul total și LDL-C serice nu au fost diferite față de grupul de control. HDL-C seric și albumina serică au fost semnificativ mai mici la pacienții hemodializați față de grupul de control (1,14 mmol/L vs. 1,35 mmol/L,  $p < 0,01$ , respectiv 34,92 g/L vs. 39,67 g/L,  $p < 0,01$ ). Pacienții care au avut PCR crescută au avut o Lp(a) semnificativ mai mare comparativ cu cei cu PCR în limite normale (35,39 mg/L vs. 28,6 mg/L,  $p < 0,01$ ). HDL-C seric și albumina serică au fost semnificativ mai mici la pacienții cu PCR reactivă crescută decât la cei cu PCR în limite normale (0,91 mmol/L vs. 1,29 mmol/L,  $p < 0,01$ , și respectiv 33,56 g/L vs. 35,86 g/L,  $p < 0,01$ ). Concentrația PCR a corelat pozitiv cu Lp(a) ( $R = 0,58$ ,  $p < 0,01$ ) și negativ cu HDL-C și cu albumina serică ( $R = -0,88$ ,  $p < 0,01$  și, respectiv,  $R = -0,87$ ,  $p < 0,01$ ) la subiecții cu PCR crescută, dar nu și la grupul de control și la cei cu CRP scăzută. Concentrația Lp(a) a corelat negativ cu albumina serică ( $R = -0,57$ ,  $p < 0,01$ ) la pacienții hemodializați cronic cu PCR crescută, dar nu și la grupul de control și la pacienții cu PCR normală. **Concluzii:** Conform acestor rezultate, un număr considerabil de pacienți hemodializați prezintă un răspuns de fază acută activat care este în strânsă relație cu un risc mult crescut de ateromatoză. PCR s-a corelat semnificativ cu lipidele plasmatice și cu albumina, care au fost dovediți ca predicatori ai mortalității cardiovasculare la pacienții hemodializați.

**Cuvinte cheie:** hemodializă, proteina C reactivă (PCR), răspuns de fază acută, lipoproteina (a), lipide, lipoproteine, albumină serică, boală cardiovasculară

## ABSTRACT

**Background:** Patients on chronic hemodialysis have one of the highest risks for atherosclerosis, which has been characterized as an inflammatory disease. C-reactive protein (CRP) is a sensitive major acute phase reactant in humans. We therefore hypothesize that an activated acute phase response is responsible for the atherogenic condition in hemodialysis patients. **Material and methods:** In 170 hemodialysis patients and in 50 healthy controls lipoprotein (a) [Lp(a)], lipids, lipoproteins and serum albumin were determined in relation CRP, as a sensitive marker of an acute phase response. **Results:** Serum CRP was found to be elevated more than 10 mg/L in 69 (40.6%) from the 170 patients on chronic hemodialysis. Serum concentration of CRP was significantly higher in hemodialysis patients than in control group (44.62 mg/L vs. 8.75 mg/L,  $p < 0.01$ ). Lp(a) and triglycerides serum levels were significantly higher in hemodialysis patients than in control group (31.37 mg/dl vs. 19.69 mg/dl,  $p < 0.01$ , and respectively 2.76 mmol/L vs. 1.32 mmol/L,  $p < 0.01$ ). Total cholesterol and low density lipoprotein cholesterol (LDL-C) serum levels in hemodialysis patients are similar to those found in the control group. Serum levels of high density lipoprotein cholesterol (HDL-C) and serum albumin were significantly lower in hemodialysis patients than in control group (1.14 mmol/L vs. 1.35 mmol/L,  $p < 0.01$ , respectively 34.92 g/L vs. 39.67 g/L,  $p < 0.01$ ). Patients with elevated CRP had significantly higher levels of Lp(a) compared with patients with CRP in normal range (35.39 mg/L vs. 28.6 mg/L,  $p < 0.01$ ). Serum levels of HDL-C and serum albumin were significantly lower in patients with elevated CRP than in patients with values in normal range (0.91 mmol/L vs. 1.29 mmol/L,  $p < 0.01$ , and 33.56 g/L vs. 35.86 g/L,  $p < 0.01$ , respectively). CRP levels correlated positively with Lp(a) ( $R = 0.58$ ,  $p < 0.01$ ) and negatively with HDL-C and serum albumin ( $R = -0.88$ ,  $p < 0.01$ , and  $R = -0.87$ ,  $p < 0.01$ , respectively) in patients with elevated CRP, but not in the control group and patients with low CRP. The Lp(a) levels correlated negatively with serum albumin ( $R = -0.57$ ,  $p < 0.01$ ) in hemodialysis patients with elevated CRP but not in the controls and in patients with low CRP. **Conclusion:** According to the results, a considerable number of hemodialysis patients exhibit an activated acute phase response which is closely related to high levels of atherogenic vascular risk. We found significant correlations of CRP with plasma lipids and albumin which have been proven as predictors of cardiovascular mortality in hemodialysis patients.

**Key Words:** hemodialysis, C-reactive protein (CRP), acute phase response, lipoprotein (a), lipids, lipoproteins, serum albumin, cardiovascular disease

## BACKGROUND

Cardiovascular disease is the main cause of morbidity and mortality in patients with chronic kidney disease and end-stage renal disease.<sup>1-3</sup> The morbidity and mortality of cardiovascular disease are substantially higher among dialysis patients, than in the general population.<sup>4-6</sup>

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Received for publication: Apr. 18, 2009. Revised: Sep. 15, 2009.

The annual mortality rate is 20% per year with over 50% of deaths due to cardiovascular disease.<sup>7</sup> This has led to the formulation of an «accelerated atherogenesis» hypothesis in uremic patients and has been commonly linked with the metabolic alterations associated with uremia.

Inflammation is considered one of the key factors in accelerating atherosclerosis and endothelial dysfunction and advancement in the understanding of the pathogenesis of atherosclerotic vascular disease in end stage renal disease, suggests a central contribution of inflammation, with involvement of a number of key mediators and markers of the inflammatory process. Inflammation involves complex interactions among immune cells and soluble proteins (cytokines, chemokines, adhesion and co-stimulatory molecules) occurring in affected tissues in response to infection, trauma, ischemia or autoimmune injury. Like most immune reactions, inflammation is a two-edged sword. It is an evolutionary advantage that usually leads to recovery from infection or healing. However, if the targeted defense or assisted repairs are not properly orchestrated, inflammation can cause progressive tissue damage by leukocytes and collagen causing atherosclerosis.<sup>8</sup> Recent epidemiological data have documented associations between C-reactive protein (CRP), the prototypical acute phase response protein, and cardiovascular disease in general population.<sup>9-11</sup> Given the lipoprotein binding and complement activation functions of CRP and its localization in atherosclerotic vessels, there is a strong likelihood that CRP may be involved in the atherosclerotic process.<sup>12</sup>

The uremic state is associated with an altered immune response, which is associated with elevated proinflammatory cytokine levels.<sup>13-15</sup> Previous studies have also shown that T lymphocytes from hemodialysis (HD) patients are dysregulated and characterized by an increase in circulating Th1 cells with normal number of Th2 lymphocytes. This Th1/Th2 imbalance can be induced by inflammatory cytokines produced by monocytes and macrophages.<sup>16</sup> Intermittent stimulation by endotoxins originating from the dialysis water supply and artificial vein grafts or bioincompatibility caused increased circulating inflammatory proteins, such as plasma CRP.<sup>17-20</sup>

Peter Stenvinkel briefly outlined studies showing an inverse relationship between glomerular filtration rate and inflammatory biomarkers, such as CRP and tumor necrosis factor (TNF)- $\alpha$ .<sup>21</sup> CRP is the prototypical APR protein produced by the liver under the control of various proinflammatory cytokines, namely interleukin-6 (IL-6), interleukin-1 (IL-1) and tumor necrosis factor- (TNF-). Its uniqueness is due to rapid

(within 6 hours) and dramatic increases (up to 1000-fold) in circulating concentrations after a cytokine-mediated response to most forms of tissue injury, infection, and inflammation.<sup>22</sup> Moreover, it was shown that plasma half-life (19 hours) and fractional clearance rates of CRP were nearly constant in normal subjects, as well as in patients with infectious, inflammatory and neoplastic conditions.<sup>23</sup> This marks CRP as a «precise objective index» of overall inflammatory activity and a surrogate of underlying cytokine stimulus.<sup>24</sup> CRP predict cardiovascular events and many studies have shown that people with high CRP are at higher risk for heart attack, because «It's a marker for not being a healthy individual.» Measured by a simple blood test, high serum levels of CRP could be identified as a prominent risk factor for cardiovascular events in apparently healthy people.<sup>25</sup>

It is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipidemia. Chronic renal failure results in profound lipid disorders, which stem largely from dysregulation of high density lipoprotein (HDL) and triglyceride-rich lipoproteins metabolism. In addition, clearance of triglyceride-rich lipoproteins and their atherogenic remnants is impaired, their composition is altered and their plasma concentrations are elevated in chronic renal failure. The down regulation of the expression of several genes, along with the changes in the composition of lipoprotein particles and the direct inhibitory effect of various uremic 'toxins' on the enzymes involved in lipid metabolism, represent the most important pathophysiological mechanisms underlying the development of hypertriglyceridemia in renal failure.<sup>26-30</sup> Hypertriglyceridemia generates small dense LDL (low density lipoprotein) particles which are a very atherogenic. In hemodialysis patients LDL levels are usually not elevated. The reduced catabolism of LDL, in hemodialysis patients, is masked by the decreased production, resulting in near normal plasma levels of LDL-C (low density lipoprotein cholesterol).

Several mechanisms, working in concert, may underlie the reduction in HDL levels, which is usually indicative of impaired reverse cholesterol transport. Specifically, maturation of HDL is impaired and its composition is altered in chronic renal failure. Thus, uremic patients usually exhibit decreased levels of apolipoproteins AI and AII (the main protein constituents of HDL), diminished activity of lecithin-cholesterol acyl-transferase, the enzyme responsible for the esterification of free cholesterol in HDL particles, as well as increased activity of cholesteryl

ester transfer protein that facilitates the transfer of cholesterol esters from HDL to triglyceride-rich lipoproteins, thus reducing the serum concentration of HDL-C.<sup>31-33</sup> It has been shown that inflammation, has a inhibitory effect in the activity of enzymes involved in HDL metabolism.

Lipoprotein(a) [Lp(a)], is an LDL-like lipoprotein containing a unique apolipoprotein called apo(a). Apo(a) is very homologous to plasminogen and exhibits an extreme size polymorphism with the apo(a) isoproteins, ranging in size from 420 to 840 kDa.<sup>34</sup> Inherited in an autosomal codominant fashion, the apo(a) isoprotein is closely correlated with serum Lp(a) concentrations, with an inverse correlation between the size of the apo(a) isoprotein and the serum Lp(a) concentrations. Serum levels of Lp(a) are determined largely by genetic variation in the gene encoding for apo(a). Lp(a) has been implicated in the regulation of plasminogen activator inhibitor-1 expression in endothelial cells and shown to inhibit endothelial cell surface fibrinolysis to attenuate plasminogen binding to platelets and to bind to plaque matrix components.<sup>35,36</sup> Autopsy studies in humans have documented the presence of Lp(a) in aortic and coronary atherosclerotic plaques and an apparent colocalization with fibrin(ogen).<sup>37,38</sup> High plasma concentrations of Lp(a) are considered a major risk factor for atherosclerosis and cardiovascular disease.<sup>39,40</sup> Lp(a) levels are frequently elevated in patients receiving chronic hemodialysis treatment of end-stage renal disease.<sup>41,42</sup> It has been suggested that kidney have an important role in Lp(a) metabolism. In renal failure, there is a decrease in Lp(a) catabolism or increase in Lp(a) production by liver. In hemodialysis patients, Lp(a) has been shown to have the characteristics of an acute phase reactant.<sup>43</sup>

Previous longitudinal studies showed that hypoalbuminemia was associated with cardiovascular disease. Richard and colleagues first reported this association in the general population.<sup>44</sup> They did serum electrophoresis in 7434 middle-aged men free of an atherosclerotic disease at entry, and they monitored the development of CVD during an average of 6.6 years on average. Albumin level was significantly lower among myocardial infarction or sudden death. In dialysis patients, hypoalbuminemia is also known to be associated with cardiovascular disease and is a powerful risk factor for cardiovascular mortality.<sup>45,46</sup> Since albumin is a negative acute-phase reactant, non-nutritional factors like inflammation depress albumin synthesis in hemodialysis patients with elevated CRP.<sup>47</sup> It has been shown that inflammation causes a decrease in albumin synthesis and an increase in

albumin fractional rate, providing two mechanisms for hypoalbuminemia.<sup>48</sup> Although hypoalbuminemia and hypocholesterolemia have been reported to be independent predictors of high mortality in both older patients and patients with end-stage renal disease.<sup>49,50</sup> Some studies have demonstrated a significant inverse relationship between serum Lp(a) and albumin concentration in hemodialysis patients.<sup>51,52</sup>

We therefore hypothesize that an activated acute phase response is responsible for the atherogenic condition in hemodialysis patients. The purpose of this study was to explore in patients on chronic hemodialysis treatment whether the changes in plasma lipids, Lp (a) and serum albumin are influenced by activated acute phase reaction.

## **MATERIAL AND METHODS**

For this study we collected 170 blood samples of the patients with chronic renal failure, who were under haemodialysis in the Clinic of Internal Diseases from the Clinical Centre in Prishtina. Here are included patients who were treated with hemodialysis more than 6 months, which is considered as chronic hemodialysis. We initially determined CRP and the group of patients with high CRP was separated. Serum CRP concentrations over than 10 mg/L were found in 69 patients, 32 female and 37 male. These patients - based on age - were divided in two groups: a group of 20-40 years old patients and a group of 41-60 years old patients. In all patients we also have measured the serum levels of Lp(a), triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and serum albumin. Serum levels of CRP, Lp(a), triglycerides, total cholesterol, low density lipoprotein cholesterol (LDL-C), high density lipoprotein cholesterol (HDL-C) and albumin were also determined in 50 healthy people (20 females and 30 males), who represented the control group.

Measurements of CRP, Lp(a), lipids, lipoproteins and serum albumin were performed on fresh samples. The serum concentration of CRP was measured by turbidimetric method based on the combination of CRP with specific antibody to form insoluble antigen antibody complexes. Diazyme's Lipoprotein (a) assay is based on a latex enhanced immunoturbidimetric method. The normal range for CRP is less than 10 mg/L, and the range for Lp(a) is less than 30mg/dL. Total cholesterol and triglycerides were measured by enzymatic methods (cholesterol by CHOD-PAP and triglycerides by GPO). HDL-C was measured after precipitation with  $MgCl_2$ , and LDL-C was calculated

using the Friedewald formula. Measurement of serum albumin was carried out on serum using the bromocresol green method.

## RESULTS

Serum CRP was found to be elevated above 10 mg/L in 69 of 170 patients on chronic hemodialysis, respectively in 40,6% of them. Mean CRP values in patients were significantly higher than those in the control group (mean  $\pm$  SD,  $44.62 \pm 18.47$  mg/L vs.  $8.75 \pm 4.82$ , respectively  $p < 0.01$ ). Among the 69 HD patients with elevated CRP, mean CRP values were higher in older group (41 years or older) compared to those between 20 and 40 years ( $51.84 \pm 15.34$  mg/L vs.  $22.55 \pm 3.6$  mg/L,  $p < 0.01$ ). High CRP values are linked not only with age, but also with duration of hemodialysis.

Among dialysis patients, 25.3% had an Lp(a) level higher than 30 mg/dl, compared to 16% in the control group, with the difference being statistically significant. Mean Lp(a) values were significantly higher in hemodialysis patients than in healthy controls ( $31.37$ mg/dL vs.  $19.69$  mg/dL, respectively  $p < 0.01$ ). (Table 1) Mean Lp(a) values were significantly higher in patients exhibiting elevated CRP than in those patients with CRP values in normal range ( $35.39$  mg/L vs.  $28.6$  mg/L,  $p < 0.01$ ). (Table 2)

**Table 1.** Lipids lipoproteins and albumin in hemodialysis patients and healthy controls.

	All patients (N = 170)	Healthy controls (N = 50)	P <
Lp(a)	$31.37 \pm 11.25$	$19.6 \pm 7.87$	0.01
Tg	$2.76 \pm 0.89$	$1.32 \pm 0.56$	0.01
Chol	$4.46 \pm 0.9$	$4.37 \pm 0.64$	NS
HDL	$1.14 \pm 0.38$	$1.35 \pm 0.35$	0.01
LDL	$2.44 \pm 0.63$	$2.25 \pm 0.65$	NS
alb	$34.92 \pm 3.9$	$39.67 \pm 4.98$	0.01

**Table 2.** Lipids lipoproteins and albumin in hemodialysis patients with low and elevated serum.

	Levels of CRP		P <
	CRP > 10 mg/L (N = 69)	CRP < 10 mg/L (N = 101)	
Lp(a)	$35.39 \pm 13.7$	$28.6 \pm 8.21$	0.01
Tg	$2.83 \pm 0.99$	$2.71 \pm 0.82$	NS
Chol	$4.4 \pm 1.04$	$4.49 \pm 0.81$	NS
HDL	$0.91 \pm 0.27$	$1.29 \pm 0.37$	0.01
LDL	$2.32 \pm 0.55$	$2.15 \pm 0.78$	NS
alb	$33.56 \pm 4.58$	$35.86 \pm 3.14$	0.01

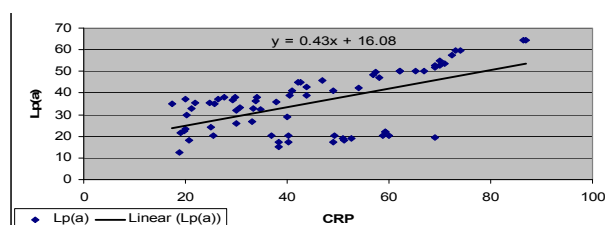
Triglycerides serum concentration was significantly higher in hemodialysis patients than in the controls, ( $2.76$ mmol/L versus  $1.32$  mmol/L, respectively

$p < 0.01$ ), but no difference was found between group of patients with elevated CRP and group of patients with low CRP. (Tables 1, 2)

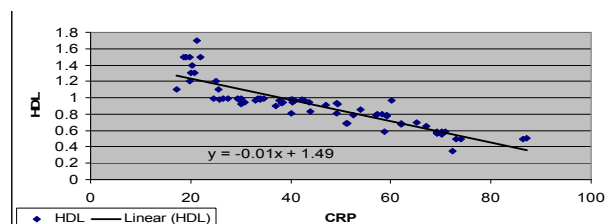
No significant difference was detected in total cholesterol and LDL-C serum concentration, between hemodialysis patients and control group and between group of patients with elevated CRP and group of patients with low CRP. (Tables 1, 2) Serum levels of HDL-C and serum levels of albumin, were significantly lower in hemodialysis patients than in the control group ( $1.14$  mmol/L vs.  $1.35$ mmol/L,  $p < 0.01$  and, respectively  $34.92$  g/L vs.  $39.67$ g/L,  $p < 0.01$ ). (Table 1)

Patients with elevated CRP had significantly lower serum levels of HDL-C and serum albumin than patients with values in normal range ( $0.91$  mmol/L vs.  $1.29$  mmol/L,  $p < 0.01$ . and  $33.56$  g/L versus  $35.86$  g/L,  $p < 0.01$ ). (Table 2)

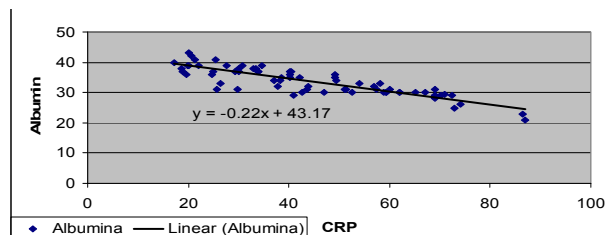
CRP levels correlated positively with Lp(a) ( $R = 0.58$ ,  $p < 0.01$ ) and negatively with total cholesterol, HDL-C and serum albumin ( $R = -0.64$ ,  $p < 0.01$ ,  $R = -0.88$ ,  $p < 0.01$ , and  $R = -0.87$   $p < 0.01$ ) in group of patients with elevated CRP, but not in the controls and in patients with low CRP. (Figs. 1-4) The Lp(a) levels correlated negatively with serum albumin ( $R = -0.57$ ,  $p < 0.01$ ) in hemodialysis patients with elevated CRP but not in the controls and in patients with low CRP. (Fig. 5)



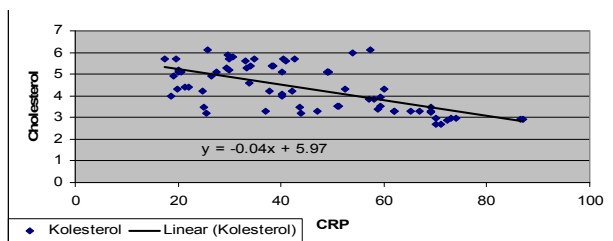
**Figure 1.** Correlation between CRP and Lp(a).



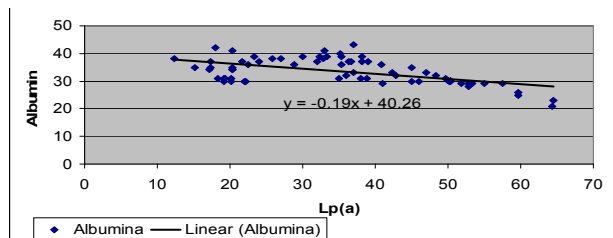
**Figure 2.** Correlation between CRP and HDL-C.



**Figure 3.** Correlation between CRP and serum albumin.



**Figure 4.** Correlation between CRP and total cholesterol



**Figure 5.** Correlation between Lp(a) and serum albumin

## DISCUSSION

Approximately 50% of patients with chronic renal failure, who are on hemodialysis, have evidence of chronic inflammation due to uremia and dialysis. Inflammatory processes play an important role for the progression of atherosclerosis.

An elevated serum level of acute-phase inflammatory markers is associated with an increased risk of cardiovascular disease. Recent epidemiological data have documented associations between CRP, the prototypical acute phase response protein, and cardiovascular disease in general population. In search for complement-activating molecules in human atherosclerotic lesions, it was demonstrated that CRP is ubiquitously present in all stages of human atherosclerosis and that it co-localizes with activated complement fragments.<sup>53</sup> A single determination of CRP is a powerful indicator of all cause and cardiovascular death even after a follow-up period of 4 years in patients on hemodialysis treatment.<sup>54</sup> Potential causes of inflammation in dialysis patients include volume overload, truncal obesity, membrane incompatibility, catheter biofilm, and thrombosed arteriovenous fistula.

In our study, a considerable proportion of patients (40.6%) exhibited an activated acute phase response, characterized by an increase of CRP concentration. We have found significant correlation between the CRP and lipoproteins which have been proven as having an atherogenic effect in blood vessels. During recent years, substantial evidence has accumulated suggesting that Lp(a) is another important risk factor for cardiovascular disease in the general population, as well as in dialysis patients. The mechanism of Lp(a) atherogenicity has not been elucidated, but likely

involves both its ability to influence plasminogen activation as well as its atherogenic potential as a lipoprotein particle after receptor mediated uptake. Lipoprotein(a) levels are frequently elevated in patients receiving chronic hemodialysis treatment.<sup>41,42</sup> In this study Lp(a) serum concentration was found to be elevated in 25.3% of hemodialysis patients. Lp(a) has been shown to have the characteristics of an acute phase reactant.<sup>43</sup>

Some studies have demonstrated a close relationship between high Lp(a) levels and the acute phase reaction, as shown by correlations with CRP, sialic acid and IL-6 in hemodialysis patients.<sup>55</sup> Because seven IL-6-responsive element sequence motifs can be identified in the 5' flanking regulatory region of the apo(a) gene on chromosome 6, it is likely that apo(a) responds as an acute phase reactant.<sup>56</sup> In the present study Lp(a) correlates in positive way with CRP, which confirm that Lp(a) reacts as an acute phase protein in hemodialysis patients.

It is well known that patients with impaired renal function exhibit significant alterations in lipoprotein metabolism, which in their most advanced form may result in the development of severe dyslipidemia. Uremia can be considered to be a state of activated acute phase response. In the micro-inflammatory milieu, a number of atherogenic proteins like (Lp(a)) are elevated in serum and a number of anti-atherogenic factors like HDL-C are diminished. Decreased HDL-C is one of the main metabolic abnormalities of the lipoprotein profile in chronically uremic patients. Low serum concentrations of HDL-C are associated with increased cardiovascular disease risk in the general population, as well as in patients with chronic renal failure. It has been shown that HDL-C was significantly lower in hemodialysis patients with an activated acute phase response, which means that inflammation reduces the concentration and possibly compromises the anti atherogenic functions of HDL.<sup>57</sup>

SAA as an acute-phase reactant displaces apoA-I and, to a lesser extent, apoA-II from HDL and reduces the concentration of HDL-C.<sup>57</sup> The activity of enzyme lecithin-cholesterol acyl-transferase is also inhibited by cytokines such as tumor necrosis factor, and interleukin (IL)-1 which stimulates the liver to produce CRP.<sup>58</sup> In our study the levels of the antiatherogenic HDL-C was negatively correlated with CRP. These results indicate that the inflammatory condition may in part be responsible for low HDL-C levels and proves that lipoprotein profile of hemodialysis patients, with high CRP concentration, is a significant indicator for atherosclerosis and cardiovascular diseases.

Hypertriglyceridemia is a typical finding in

hemodialysis and represents an early feature of renal failure. Indeed previous studies have shown that patients with impaired renal function exhibit increased concentration of triglycerides even though serum creatinine levels are within normal limits. According to our results there was significant difference in triglycerides concentration, between hemodialysis patients and control group but no difference between group of the patients with elevated CRP and those patients with values in normal range. We also did not find any difference in LDL-C concentration in hemodialysis patients and control group, which confirmed that most hemodialysis patients do not have elevated LDL-C.<sup>58,59</sup>

Hypocholesterolemia has also been reported to be a predictor of high mortality in ESRD.<sup>49</sup> According to our results, the negative correlation between the CRP levels and total cholesterol shows that in hemodialysis, low cholesterol concentration can be caused not just because of malnutrition but also because of inflammation. This fact corresponds with study results, where the significant negative correlation was found, between the levels of IL-6, the major cytokine stimulus for CRP production and cholesterolemia.<sup>49</sup> These data support the hypothesis that an inflammatory condition may, in part, be responsible for the disturbed lipoprotein metabolism in chronic hemodialysis patients.

Hypoalbuminemia is known to be strongly associated with ischemic heart disease in dialysis patients and it is thought to be one of the cardiovascular risk factors in dialysis patients.<sup>45,46</sup> According to latest studies, inflammation results in hypoalbuminemia by increasing fractional catabolism of albumins and by damaging their syntheses.<sup>50</sup> A significant inverse relationship between serum albumin and Lp(a) has been reported in dialysis patients.<sup>60</sup> It has been showed that by increasing serum albumin levels, in hemodialysis patients, serum Lp(a) levels were decreased.<sup>61</sup>

According to our results, serum albumin levels were significantly lower compared with the control group. We found significant difference in albumin levels between group of the patients with elevated CRP and those patients with values in normal range. Albumin levels correlates negatively with CRP concentrations, which proves that hypoalbuminemia is a consequence of inflammation and that inflammation is an important factor which has an influence on albumin levels. There was a negative correlation between albumin levels and Lp(a), which according to literature is a significant indicator for cardiovascular death of hemodialysis patients.<sup>62</sup>

## CONCLUSION

According to our results, a considerable number of hemodialysis patients exhibit an activated acute phase response. The results further show that changes of the atherogenic risk profile in hemodialysis patients, namely elevated Lp(a), as well as decreased HDL-C and serum albumin, are partly the consequence of an activated acute phase response. We found significant correlations of CRP with Lp(a), HDL-C, and serum albumin, which have been proven as a predictors of cardiovascular mortality in hemodialysis patients.

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