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# Cardiovascular Risk Factors and Inflammation in Patients with Chronic Kidney Disease

KEYWORDS: inflammation, C - reactive protein, cardiovascular risk, Cardiovascular disease (CVD),Chronic Kidney disease(CKD).

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**ABSTRACT** *Background. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). Markers of inflammation are also elevated in chronic renal patients. High levels of C- reactive protein (CRP) are a strong prognostic factor for cardiovascular morbidity and mortality both in non uremic and uremic patients. Increased CRP predicts cardiovascular mortality in hemodialysis patients (pts.). The aim of our study was to assess the relationship between the prevalence of CRP and the prevalence of cardiovascular disease in pre-dialysis and hemodialysis patients.Methods. 55 patients with CKD were enrolled in this study. 30 pts were in CKD not requiring dialysis (pre-dialysis) and were hospitalized at the Department of Internal Medicine in the University Hospital Center "Mother Teresa" in Tirana, Albania, during the period of September 2005 to May 2006, while 25 pts were dialyzed in Hospital Center of "Dr. Xh. Kongoli" Elbasan, Albania. The patients were divided in two groups based on the levels of CRP. The first group comprised patients that presented CPR levels lower than 6 mg/l and the second group comprised those presenting CRP levels higher than 6mg/l. For both groups we evaluated cardiovascular risk factors such as: systolic and diastolic blood pressure, albumin level, total cholesterol, anemia and dose of EPO treatment. Results: 50% of pre-dialysis and 52% of dialysis pts presented with elevated concentration of CRP > 10mg/l. In the first or pre-dialysis group, two patients (7%) presented with Ischemic Heart Disease, one patient (3%) had a history of myocardial infarction and 3 patients (10%) had congestive cardiac failure (CCF). In the dialysis group two patients (8%) presented ischemic heart disease and 5 patients (20%) with CCF. All patients with cardiovascular disease presented with elevated concentration of CRP. Considering all patients enrolled, a significant correlation (p<0.003), between elevated levels of CRP and cardiac morbidity has been found, but considering each group, pre-dialysis and dialysis, the correlation was not significant, most probably because of the limited number of patients enrolled.Conclusions. Regardless of the stage, CKD patients (pre-dialysis and dialysis) with elevated levels of CRP (as a single CVD marker) were associated with higher cardiovascular morbidity*

**Introduction**

Patients with chronic kidney disease (CKD) have a higher mortality rate when compared to the general population [1]. The risk of cardiovascular events is 100 times higher in end-stage renal disease (ESRD) patient when compared with age and sex matched controls. This burden of cardiovascular disease in CKD reflects the additive effect of the presence of traditional (such as hypertension, diabetes mellitus, obesity, hiperlipidemia and smoking) and non - traditional risk factors (C- reactive protein (CRP)) for cardiovascular events [2]. Cardiovascular risk in patients with CKD has gained crucial interest in the current clinical research. In addition, the cardiovascular risk in renal insufficiency is perceived as an important public health problem, and preventing and curing cardiovascular complications in patients with renal dysfunction is considered a true priority [4,6]. Cardiovascular complications are the leading cause of death in patients with end-stage renal disease (ESRD), accounting for 40% of deaths in these patients [9,10]. Markers of inflammation are also elevated in CKD patients [11,14,20]. Inflammation in CKD is a multifactor process, and it seems likely that this process, at least in part, mediates the effect of most traditional and nontraditional risk factors [24,29,30]. High levels of CRP are a strong prognostic factor for cardiovascular morbidity and mortality both in non uremic and uremic patients [9-11,30]. An elevated serum C-reactive protein has been shown to be strongly predictive of cardiac morbidity and mortality in dialysis patients [27,28]. However the significance of the higher levels in the pre-dialysis period has not been studied extensively. Several authors have found that overall cardiovascular morbidity and mortality were significantly higher in hemodialysis patients with elevated CRP levels [8,12,17]. Single measurements of CRP predict cardiovascular morbidity in patients with chronic renal disease. Therefore we investigated the effect of high concentrations of CRP on cardiovascular morbidity in patients with chronic renal disease. The aim of our study was to assess the relationship between the prevalence of CRP and prevalence of cardiovascular disease in pre-dialysis and hemodialysis patients.

**Material and methods**

We enrolled 55 patients, out of whom 30 patients were hospitalized as pre-dialysis and 25 were stable hemodialysis patients (mean age in pre dialysis 58 ± 15 and in dialysis 45 ± 12 years). Both pre-dialysis and dialysis patients were divided in groups according to the level of CRP (<6>mg/l). CRP was assessed using a high standard sensitivity test. At baseline, a complete clinical history was obtained and a physical examination performed. The presence of CVD was also examined by asking them for a former history of CVD, by physical examination and ECG.

Ischemic heart disease (IHD) has been determined by the presence of chest pain, precipitated by exertion or stress and relieved by rest or nitrates, ECG evidences of myocardial ischemia, history or presence of myocardial infarction and coronary artery bypass. Hypertension was considered to be present when the sitting blood pressure (BP) was ≥ 140/90mm/Hg or when regardless of BP values, the patient was under antihypertensive therapy. Blood pressure was measured with the use of validated mercury sphygmomanometers. 25 patients were treated with HD three

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times a week for 4 hours. The levels of Salb have been measured and hypoalbuminemia was defined as Salb<4gr/dl. GFR was calculated using the Cockroft-Gault formula. BMI was calculated and expressed as kg/m2. We evaluated the anemia for each patient according to the level of haemoglobin (Hb<13mg/dl in men and <12mg/dl in women) and hematokrit < 33%.

**Statistical analysis**

The study was cross-sectional. Statistical analysis was performed using SPSS version 7.5. The initial estimated GFR and the biological, laboratory and inflammatory parameters expected to influence mortality were used as independent variables. Differences in parameters of interest between groups were sought by the Pearson's correlation. For comparison of qualitative variables we used Fisher's exact test and Student's test for quantitative variables. Data are expressed as mean ± SD. Statistical significance was assumed if P<0.05.

**Results**

Pre-dialysis group consisted of 16 men and 14 women (mean age 58± 15 years), while 14 men and 11 women were evaluated in the second group (HD patients) with mean age of 45 ± 12 years.

**Primary renal diseases in the pre-dialysis group were presented in Figure 1.**

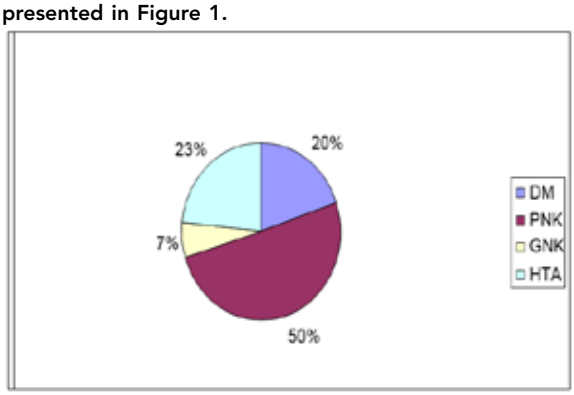


**Fig. 1.** Primary renal disease in the pre-dialysis group

**In the first group 20% of patients were with Diabetes mellitus (DM), 23% with Reno-vascular Hypertension (RVH), 7% with chronic Glomerulonephritis (GN), and 50 % with Chronic interstitial Pyelonephritis (IPN).**

**Clinical and biochemical characteristics of the study subjects for the first group (pre-dialysis) are presented in Table 1**

**Table 1.** Clinical and biochemical characteristics of the pre-dialysis group

| | Group I (PCR>6 mg/l) n = 18 | Group II (PCR≤6 mg/l) n = 12 | P value |
|---|---|---|---|
| CRP (mg /l) | 17.9 (8-93.3) | 4.015 (1-6) | 0.001 |
| Albuminemia (g/l) | 50.14±6.46 | 57.36±5.21 | 0.017 |
| Cholesterol (mg/dl) | 179.9±47.33 | 194.96±60.28 | NS |
| Hb (g/dl) | 8.79±1.41 | 9.27±1.32 | 0.05 |
| EPO-s (IU/kg/week) | 5444±1149 | 5000±1044.47 | 0.03 |
| Hb/EPO | 0.0018±0.001 | 0.0020±0.00065 | 0.004 |

**Data of prevalence of albuminemia levels, nutrition, anemia, and response to EPO therapy in the pre-dialysis group (Table 2).**

**Table 2.**

| | Group I (PCR>6 mg/l) n = 18 | Group II (PCR≤6 mg/l) n = 12 | Value of *P* |
|---|---|---|---|
| CRP (mg /l) | 17.9 (8-93.3) | 4.015 (1-6) | 0.001 |
| Albuminemia (g/l) | 5.0±0.6 | 5.7±0.5 | 0.017 |
| Cholesterol (mg/dl) | 179.9±47.33 | 194.96±60.28 | NS |
| Hb (g/dl) | 8.79±1.41 | 9.27±1.32 | 0.045 |
| Dosis of EPO(IU/kg/month) | 5444±1149.03 | 5000±1044.47 | 0.03 |
| Hb/EPO | 0.0018±0.001 | 0.0020±0.00065 | 0.004 |

**The comparison of blood pressure, proteinuria, and CCr between two groups in pre-dialysis patients (Table 3).**

**Table 3.**

| | Group I (PCR>6 mg/l) n =18 | Group II (PCR≤6 mg/l) n =12 | Value of *P* |
|---|---|---|---|
| Systolic pressure (mm Hg) | 166.67±17.49 | 177±17.12 | NS |
| Diastolic pressure (mmHg) | 98.06±9.42 | 104±8.74 | 0.04 |
| Proteinuria | 1.54 ±2.04 | 1.2 ± 1.54 | NS |
| Δ CCr (ml/min/1.73 $m^2$) | 15.68±10.5 | 19.03±13.35 | NS |

**Prevalence of C- reactive protein among patients in pre-dialysis (Fig 2).**

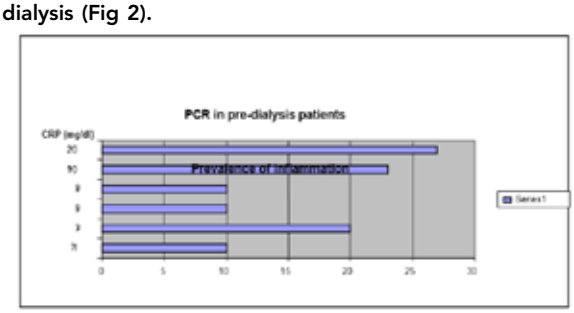


**Fig. 2. Prevalence of CRP among patients in pre-dialysis stage**

(58% presented CRP levels > 6 mg/l and only in 38% of them CPR levels were lower than 3mg/l).

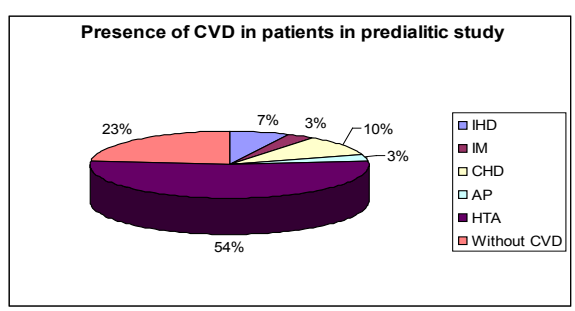


**Fig. 3 CVD (Cardio Vascular Disease) in predialitic group.**

In the first or pre-dialysis group: two patients (7%) presented IHD (Ischemic Heart Disease, one patient (3%) a history of IM (myocardial infarction), 3 patients (10%) CCF (congestive cardiac failure) and one patient, (3%) presented AP (Angina Pectoris)

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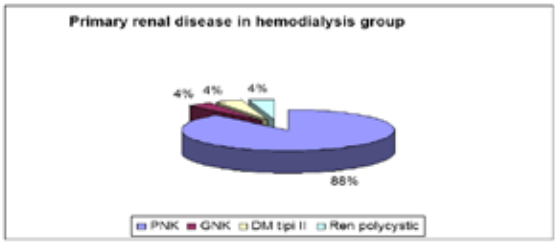


**Fig.4 Primary renal disease in hemodilysis group.**
In the second group of patients 4% were with polycystic kidney disease (Ren Polycistices), 4% with Diabet Mellitus type 2 (DM), 4% with chronic Glomerulonephritis (GN), and 88 % with Chronic Pyelonephritys PN.

**Clinical and biochemical characteristics of the study subjects for the second group (hemodialysis) Tab 4**

**Table 4.**

| | Group I (PCR>6 mg/l) n = 18 | Group II (PCR≤6 mg/l) n = 12 | P-value |
|---|---|---|---|
| CRP (mg /l) | 13.8(10-29.5) | 1.65 (0.5-3.9) | 0.001 |
| Albumine-mia (g/l) | 3.63±0.48 | 4±0.33 | 0.025 |
| Cholesterol (mg/dl) | 175.23±30.88 | 175.75±29.67 | NS |
| Hb (g/dl) | 8.15±1.43 | 8.73±1.9 | 0.05 |
| EPO-s (IU/ kg/week) | 4769.23±2241.8 | 5500±1732.05 | 0.03 |
| EPO/Hb | 632.68±333.98 | 664.14±260.34 | 0.004 |

**Prevalence of C- reactive protein among patients in hemodialysis is show in Fig 5.**

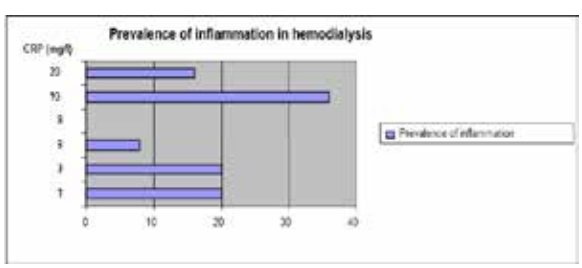


**Fig.5**
60% presented CRP levels > 6 mg/l and only in 40% of them CPR levels were lower than 3mg/l.

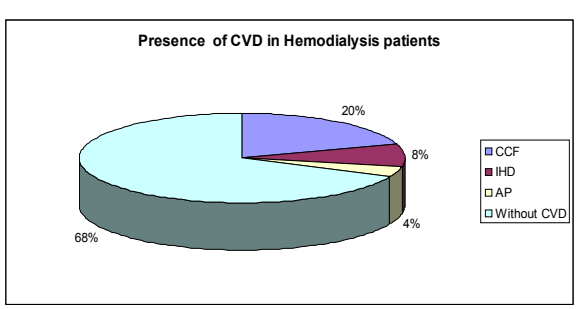


**Fig.6 CVD (Cardio Vascular Disease) in Hemodialysis patients.**
In the dialysis group: two patients (8%) presented IHD (Ischemic Heart Disease), five patients (20%) CCF (congestive cardiac failure) and one patient (4%) AP (Angina Pectoris). All the patients with cardiovascular disease presented elevated concentration of CRP. Considering all patients enrolled, a significant correlation (p <0.003), between elevated levels of CPR and cardiac morbidity has been found, but considering each group, pre-dialysis and dialysis, the correlations were not significant, because the limited number of patients enrolled.

## Discussion

CVD is the main cause of mortality and morbidity among patients with CRF.CVD accounts for 40% of deaths, 10-30 folds higher than in the healthy population. Uremia itself is considered to be an inflammatory status [8].Our data suggest that prevalence of inflammation is high for the two groups of patients; 50 % of the pre-dialysis patients presented higher levels of CRP and 52% of dialyzed patients present higher levels of CRP >10 mg/l. This is due to the fact that the mean age of the patients in the two groups was relatively young. Our hemodialysis center is a very new center, so the study includes a limited number of patients. According to our data 23% of pre-dialysis patients have signs of CVD; 7% have IHD, 3% have myocardial infarction IAM , 10% have CCF (congestive cardiac failure), and 3% have AP.Also 32% of dialyzed patients have signs of CVD, 20% of them have chronic heart failure (CCF), 8% have IHD and 4% AP. All of them present higher level of C- reactive protein CRP > 6mg/ l.Patients who have higher levels of CRP presented lower hemoglobin levels. These patients, who used to take higher dose of EPO, did not respond sufficiently to this therapy.Also CRP did not correlate with creatinine clearance level. We found that the EPO resistance correlated with low levels of albumin and BMI in hemodialysed patients (68 %) p< 0.025. Our patients in pre-dialysis stage who have higher levels of CRP, did not present lower levels of albumin. Levels of CRP indirectly correlated with levels of albumin (r = -0.5, P < 0.025).Our dialyzed patients who have higher levels of CRP present lower albumin levels and levels of CRP indirectly correlate with albumin levels (r =-0.25, P < 0.03). Albumin levels and CRP levels (high in patients with CVD) probably reflect the presence of the Malnutrition, Inflammation in dialyzed patients.

## Conclusion

Our study shows a high coefficient of inflammation in patients with CVD ( Cardiovascular Disease).High prevalence of CRP is shown at the pre-dialysis stage, so that the monitoring and its correction at this stage would be one of the efficient methods to reduce cardiovascular morbidity and mortality. Patients with elevated levels of CRP manifested lower value of Hb and they resisted to the EPO treatment (i.e. its normalization should be considered before start with EPO therapy, aiming at its cost reduction).CRP correlated in our study with non traditional risk factor like albuminemia, anemia which interrelated with each-other potentially increasing the risk of CVD. Finally, regardless of the stage, CKD patients (pre-dialysis and dialysis) with elevated levels of CRP (as a single CVD marker) were associated with higher cardiovascular morbidity.Conflict of interest statement. None declared.

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31. Novel Cardiovascular Risk Factors in End-Stage Renal Disease **Carmine Zoccali, Francesca Mallamaci and Giovanni Tripepi** *CNR-IBIM, Epidemiologia Clinica e Fisiopatologia delle malattie Renali e dell'Ipertensione Arteriosa, Reggio Calabria, Italy.*