

Inflammation as a cardiovascular risk factor in patients with different stages of renal disease.

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KEYWORDS

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ABSTRACT:

Introduction: Cardiovascular disease (CVD) is a leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). Inflammatory markers are also elevated in patients with chronic kidney disease. High C-reactive protein (CRP) levels are important prognostic factors for cardiovascular morbidity and mortality in non-uremic and uremic patients. High CRP predicts cardiovascular mortality in haemodialysis patients.

Objectives: The aim of our study was to evaluate the association between CRP prevalence and cardiovascular disease in predialysis and haemodialysis patients..

Methods: In our study were included 55 patients with CKD. 30 patients with chronic kidney disease who did not require dialysis (predialysis) were hospitalized in the Department of Internal Medicine, University Hospital center "Mother Teresa", Tirana, and 25 patients were hospitalized in the Department of Internal Medicine, Xh. Kongoli – Elbasan. Patients were divided into two groups according to their CRP levels. The first group included patients with CRP levels below 6 mg/l, and the second group included patients with CRP levels above 6 mg/l. We evaluated cardiovascular risk factors such as systolic and diastolic blood pressure, albumin level, total cholesterol, anaemia, and EPO therapy in both groups..

Results: High CRP concentrations >10 mg/l occurred in 50% of predialysis patients and 52% of dialysis patients. In the first or predialysis group, two patients (7%) had ischemic heart disease, one patient (3%) had a history of myocardial infarction, and three patients (10%) had heart failure (CCF). In the dialysis group, 2 patients (8%) developed ischemic heart disease and 5 patients (20%) developed CCF. CRP concentrations were high in all patients with heart disease. When all enrolled patients were considered, there was a significant correlation between high CRP levels and the incidence of cardiovascular disease ($p < 0.003$), but the lack of significance when all groups, were considered..

Conclusions: High levels of CRP (as a CVD marker) were associated with more cardiovascular risk factors in all patients, regardless of CKD stage, demonstrating that markers of inflammation have an important impact for cardiovascular morbidities in this vulnerable population.

1. Introduction

Patients with chronic kidney disease (CKD) have a higher mortality rate than the general population (1). The risk of cardiovascular disease is higher in patients with end-stage renal disease (ESRD) compared with individuals of the same age and sex (2). Cardiovascular risk in patients with CKD is a current focus of clinical research. Understanding cardiovascular risk factors in chronic kidney disease is essential and crucial at the same time, for the prevention and treatment of chronic heart disease in CKD patients. Furthermore, the risk of cardiovascular disease from renal failure is recognized as a major public health problem, and prevention and treatment of cardiovascular complications in individuals with CKD are considered important (2,3). Cardiovascular complications are the leading cause of death in patients with end-stage renal disease (ESRD), accounting for 40% of patient deaths (4). Inflammation is a key process observed in patients with CKD, and CKD is considered a systemic inflammatory disease with many causes (5,6) and has been shown to predict the long-term risk of developing CKD (6,7).

High CRP levels are an important determinant of cardiovascular morbidity and mortality in non-uremic and uremic patients (8), as well as a strong determinant of cardiovascular morbidity and mortality in diabetic patients (9). However the significance of the higher levels in the pre-dialysis period has not been studied extensively. Several authors have found that all cardiovascular diseases and mortality are higher in haemodialysis (HD) patients with high CRP levels (8). A CRP test predicts cardiovascular disease in patients with chronic kidney disease. The aim of our study was to evaluate the relationship between CRP prevalence and cardiovascular disease in predialysis and haemodialysis patients.

2. Material and Methods

We enrolled 55 patients, out of whom 30 patients were hospitalized as pre-dialysis and 25 were stable haemodialysis 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.

Our cross-sectional study comprised 55 patients, 30 of whom were hospitalized as pre-dialysis and 25 of whom were stable haemodialysis patients (mean age in pre-dialysis 58 ± 15 years, mean age on dialysis 45 ± 12 years). Pre-dialysis and dialysis patients were divided into groups according to CRP (6 mg/l). The clinical data were extracted from the patient's medical history and by previously registered hospitalizations. The presence of CVD was also checked by questioning previous CVD history, physical examination and electrocardiogram. 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 the presence of antihypertensive therapy. 25 patients were treated with HD three times a week for 4 hours. The levels of Salb have been measured and hypoalbuminemia was defined as Salb<4gr/dl. Estimated GFR (eGFR) is calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) Equation (2021), from standardized creatinine, sex, race and age for each patient. BMI was calculated and expressed as kg/m². We evaluated the presence of anaemia for each patient, according to the level of haemoglobin (Hb<13mg/dl in men and <12mg/dl in women) and haematocrit < 33%. Serum C-reactive protein was analysed by enzyme-linked immunosorbent assay (ELISA) technique.

3. Statistical analysis

Statistical analysis was performed using SPSS version 25. Differences in parameters of interest between groups were sought by the Pearson's correlation. For comparison of qualitative variables Fisher's exact test and Student's test for quantitative variables was used. Statistical significance was assumed if $p < 0.05$.

4. 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. In the first group 20% of patients were with Diabetes mellitus (DM), 23% with Renovascular Hypertension (RVH), 7% with chronic Glomerulonephritis (GN), and 50 % with chronic interstitial Pyelonephritis (IPN). In the second group of patients 4% were with polycystic kidney disease (Ren Polycystices), 24% with Diabet Mellitus type 2 (DM), 4% with chronic Glomerulonephritis (GN), and 68 % with Chronic Pyelonephritis (PN). 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	Group II	
	(CRP>6 mg/l)	(CRP≤6 mg/l)	P value
	n = 18	n = 12	
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	5444±1149	5000±1044.4	0.03

(IU/kg/week)		7	
Hb/EPO	0.0018±0.001	0.0020±0.000	0.004
		65	

Source: Authors

Clinical and biochemical characteristics of the study subjects for the second group (haemodialysis) presented in Table 2.

Table 2. Clinical and biochemical characteristics of the dialysis group

	Group I (CRP>6 mg/l) n = 18	Group II (CRP≤6 mg/l) n = 12	P-value
CRP (mg /l)	13.8(10-29.5)	1.65 (0.5-3.9)	0.001
Albuminemia (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

Source: Authors

The comparison of blood pressure, proteinuria, and CCr between two groups, with and without high CRP, in pre-dialysis patients are summarized in Table 3.

Table 3. The comparison of groups in pre-dialysis patients.

	Group I (CRP>6 mg/l) n =18	Group II (CRP≤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

Source: Authors

Belonging the prevalence of C- Reactive Protein among patients in pre-dialysis 58% of them had CRP > 6mg/l, and only 38% had CRP levels lower than 3 mg/l. (Fig.1)

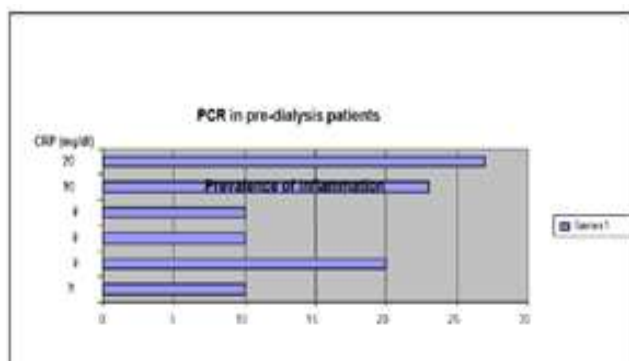


Figure 1. CRP among pre-dialysis patients. (Source: Authors)

Prevalence of C- Reactive Protein among patients in haemodialysis was 60% of them presented CRP levels > 6 mg/l and only in 40% of them CPR levels were lower than 3mg/l. (Fig. 2)

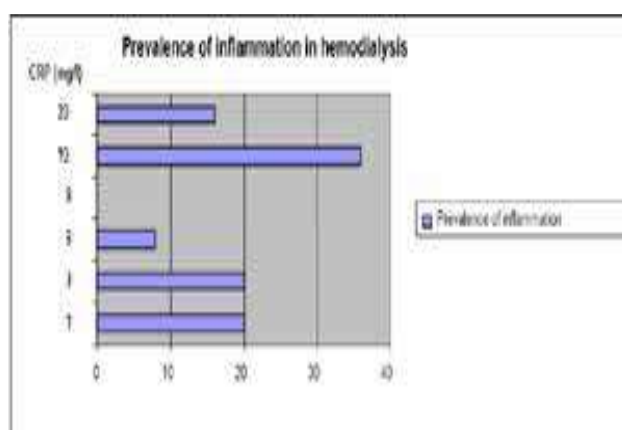


Figure 2. CRP among hemodialysis patients.
(Source: Authors)

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) (Fig.3)

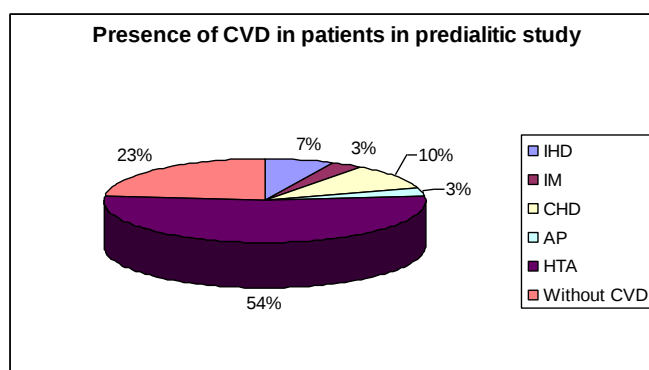


Figure 3. Cardiovascular Disease in pre-dialysis group. (Source: Authors)

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) (Fig.4).

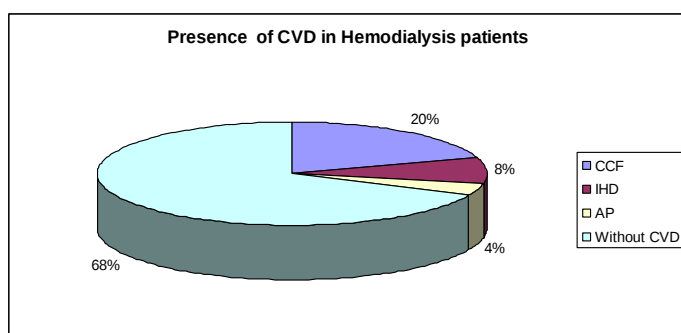


Figure 4. Cardiovascular Disease in Hemodialysis patients. (Source: Authors)

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.

5. Discussion

Cardiovascular disease is the driving cause of morbidity and mortality in chronic kidney disease. CVD mortality risk doubles and triples in stages 3 and 4 of CKD, respectively (10). CVD accounts for 40% of deaths, 10-30 folds higher than in the healthy population. This relationship is complex and bidirectional, with each condition increasing the incidence and progression of the other (11,12,13)

There are so many traditional and non-traditional risk factors that play a significant role in the development and progression of CVD in CKD patients. Increased inflammation is one of non-traditional risk factors and the effects of local inflammatory stimuli such as oxidation products, end advanced glycosylation products and chronic infective processes modify blood vessels in the sense of atherosclerosis development. In later stages of CKD, the systemic

concentrations of both pro- and anti-inflammatory cytokines are significantly higher as production has increased, coupled with decreased renal clearance (5,6,7) Uremia itself is considered an inflammatory condition (14).

In our study the prevalence of inflammation is high for both groups, CRP levels were elevated in 50% of patients pre-dialysis, and CRP levels were >10 mg/l in 52% of dialysis patients, suggesting that the process of inflammation in CKD starts before dialysis and it is not entirely dialysis related, as seen in many studies (15).

According to our data, 23% of pre-dialysis patients have signs of CVD; 7% have IHD, 3% have myocardial infarction, 10% have heart failure, and 3% have AP. Also, 32% of dialyzed patients have signs of CVD, 20% of them have chronic heart failure, 8% have IHD, and 4% AP. They all present higher levels of C-reactive protein > 6 mg/ l. These data are similar to previous study where C-reactive protein has been reported to be highly valuable in predicting cardiovascular risk in CKD patients (16,17). This link is well-documented in many studies. Inflammation contributes to endothelial dysfunction, atherosclerosis, and vascular calcification, all of which are pathways that increase cardiovascular risk. (4-11) Another large study with 12,410 patients that evaluated CRP in CKD and beyond, demonstrated the prognostic value of CRP monitoring as there was a positive relationship between its values and mortality from cardiovascular causes and mortality from all causes. (18)

Our patients who have higher levels of CRP presented lower haemoglobin levels. These patients had used higher doses of EPO in the past but did not respond adequately to this treatment. EPO resistance in haemodialysis patients was associated with low albumin and BMI (68%) $p<0.025$. Many studies have demonstrated that persistent inflammation may contribute to the variability in Hb levels and hyporesponsiveness to erythropoietin stimulating agents (ESA), which are frequently observed in CKD patients (19). This relationship is primarily driven by the interplay between inflammation and erythropoiesis through implications of some mechanisms such as hepcidin upregulation, erythropoietin resistance, or bone marrow suppression by inflammation. Numerous studies indicated that the inflammatory state influences the development of renal anaemia, and have demonstrated that lower average CRP values were associated with better Hb control (19,20)

In our patients in the pre-dialysis period, CRP was higher but albumin levels were not lower. 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 ($r = -0.25$, $P < 0.03$). C-reactive protein correlated negatively with serum albumin, a finding similar to previous studies (21,22). CRP and serum albumin are markers of inflammation and independent predictor of all-cause mortality in CKD patients, regarding of whether the patient is on HD or not (22, 23) Low albumin levels and high CRP levels can reflect the dual burden of malnutrition and inflammation, both of which can contribute to poor health outcomes in CKD patients. In this patient group, malnutrition and inflammation are coexisting, and together are responsible for adverse outcomes, as demonstrating many studies. (24,25)

6. Conclusions

Our study shows a high coefficient of inflammation in CKD patients with CVD. 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, anaemia which interrelated with each-other potentially increasing the risk of CVD.

In summary, elevated CRP levels in CKD patients, regardless of the stage, are a significant indicator of increased cardiovascular morbidity. Addressing inflammation and other cardiovascular risk factors is essential in managing these patients to improve outcomes. Futures long term studies, to assess how changes in CRP levels over time correlates with cardiovascular outcome in CKD patients; to evaluate if CRP levels can be used to stratify cardiovascular risk more accurately in these patients in combination with other biomarkers and to investigate the efficacy and safety of anti-inflammatory drugs in reducing this risk, are needed.

Conflict of interest: None

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