Research Paper
The Inflammatory Markers C-reactive Protein and Mean Platelet Volume in Chronic Kidney Disease

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ABSTRACT

Background: People with chronic kidney disease (CKD) experience chronic systemic inflammation. Although a relationship exists between inflammation and renal injury, the association between inflammatory markers and renal disease has not been well-studied. As inflammation may be a trigger or a result of chronic disease, the kidney needs to be investigated to determine whether it is a clearer target for the devastating effects of persistent inflammation. Here, we report the relation of C-reactive protein and mean platelet volume levels with renal functions in chronic kidney disease patients.

Methods: This study was an observational retrospective single-center study conducted on the record of CKD patients to detect the outcomes over a median follow-up time of three years. Demographic, clinical, laboratory, medication, and outcome data were obtained from the electronic data records of the hospital. We investigated the multivariable association of plasma levels of C-reactive protein and mean platelet volume with the progression of CKD in the study participants.

Findings: Elevated plasma levels of C-reactive protein (r=0.13, P<0.001) and mean platelet volume (r=0.23, P<0.001) were associated with a greater loss of kidney function over time. The presence of diabetes mellitus was detected to be a risk factor for CKD progression (P=0.04). An inverse relationship was detected between sodium and creatinine (P<0.001). In addition, a weak association was detected between uric acid and creatinine (P<0.001).

Conclusion: Elevated plasma levels of C-reactive protein and mean platelet volume were associated with a decline in the estimated glomerular filtration rate in patients with CKD.
1. Introduction

Chronic kidney disease (CKD) is characterized by kidney damage or decreased kidney function for at least 3 months [1]. Diabetes mellitus, hypertension, polycystic kidney disease, glomerulonephritis, prolonged urinary tract obstruction, vesicoureteral reflux, recurrent pyelonephritis, and some medications are common causes of CKD. The last phase of CKD is end-stage renal disease (ESRD). Given its significant impact on morbidity and mortality, a key objective is to slow the progression of CKD, regardless of its underlying causes, and prevent the onset of ESRD.

The progression of renal disease is strongly related to its etiology. However, homeostatic mechanisms like hyperfiltration and compensatory maladaptive response lead to progressive damage on the nephrons independently from the activity of the main disease [2]. Besides the etiology and maladaptive responses, some other factors may have a partial role in the progression of CKD.

Inflammation is a function of the tissues during the battle against threatening factors. Sometimes this inflammation may be aggravated and may harm self-tissues. Systemic inflammation is closely associated with CKD, increased free radical production, and decreased antioxidant capacity [3]. Moreover, CKD itself has already been accepted as a chronic inflammatory state. Many patients and dialysis-related factors engender this state. The uremic milieu, infections, increased oxidative stress, and genetic factors are among these factors [4].

Uremic toxins cause both cellular and humoral immune deficiencies. CKD-associated immune deficiency resulting in defective elimination of intracellular pathogens like viruses has recently been shown during a pandemic with deeper lymphopenia in novel coronavirus disease 2019 (COVID-19) patients compared to patients without CKD [5]. Besides, in a meta-analysis, it has been reported that chronic kidney disease causes a more severe form of the disease in COVID-19 patients [6]. Patients with CKD were also shown to have a greater risk of mortality during COVID-19 disease [5].

C-reactive protein (CRP) is a member of the pentraxin superfamily. It is an important component of immunity and inflammation [7]. CRP may be a marker correlated with renal survival. For example, severe tubulointerstitial inflammation with upregulated proinflammatory cytokines, chemokines, and adhesion molecules are developed in human C-reactive protein transgenic mice [8].

Platelets participate in the coagulation process as their primary mission. However, the activation of platelets was shown to contribute to renal injury next to their beneficial roles in homeostasis [9]. Jansen et al. found platelet activation to induce renal inflammation and related injuries [10]. Mean platelet volume (MPV) is a measure of platelet activity and aggregation capacity [11]. MPV was also shown to be a possible biomarker in inflammation [12].

Inflammation and oxidant stress probably contribute to the progression of kidney diseases. Furthermore, immunosuppression associated with kidney disease causes prolonged hospitalization and increased mortality. CRP and MPV variability may be diagnostic and follow-up renal disease markers. In this study, we aimed to determine whether CRP and MPV, which indicate the severity of the inflammation, may predict the progression of CKD as a correlation.

2. Materials and Methods

Study design and subjects

This study was a retrospective observational case-control study with the recorded data of CKD patients of either gender without any age limitation from the nephrology outpatient clinic. The biochemical medical records of three consecutive years (2012-2015) were noted as 6 months apart. Demographical data about the patients were noted. Blood urea nitrogen (BUN), creatinine, creatinine clearance, sodium, chlorine, uric acid, CRP, and complete blood count parameters analyzed at the central laboratory were obtained. If needed, the CKD diagnosis was made based on biochemical parameters, clinical findings, imaging studies, and renal biopsy. Estimated glomerular filtration rate (GFR) values were calculated with the CKD-EPI formula [13]. Participants with an acute infection, malignancy, decompensated heart failure, severe fluid-electrolyte imbalance, or any other acute problem were excluded. Hypertension, diabetes mellitus, and coronary artery disease data were recorded as comorbidities. The medication history was taken carefully and comprehensively.

CKD was described as decreased kidney function with a GFR of lower than 60 mL/min/1.73 m² or markers of kidney damage like albuminuria, urinary sediment abnormalities, electrolyte or other abnormalities due to tubular disorder, histological abnormalities, structural abnormalities on imaging and having a history of kidney transplantation, or both, of at least 3 months duration [14]. Acute kidney injury (AKI) was defined as an...
increase in serum creatine (Scr) by \( \geq 0.3 \) mg/dL (\( \geq 26.5 \) μmol/L) within 48 hours or to \( \geq 1.5 \) times of baseline or a urine volume less than 0.5 mL/kg/h for 6 h which is known or presumed to have occurred within the prior 7 days [15]; 24-h urine collection for creatinine clearance was used as the most common method for the measurement of GFR in clinical practice [16].

Statistical analysis

The data were statistically analyzed with the SPSS software, version 20.0. CRP, MPV, creatinine, and creatinine clearance were investigated and compared in the participants. The classical risk factors like diabetes mellitus (DM) and hypertension (HT) for CKD were also compared in both groups. The Mann-Whitney U and chi-square tests were used to compare participants’ data. The risk factors associated with CKD were evaluated using regression analysis. P<0.05 was interpreted as statistically significant.

We used the method that was recommended by Bland and Altman [17, 18] to calculate the correlation coefficients between repetitive measurements. Correlation coefficients were calculated using the repeated measures correlation (rmcorr) package included in R software [19].

3. Results

This study consisted of patients with CKD between 18 and 80 years of age. A total of 406 patients were included in this study, 184 patients (46%) were female, and 222 (56%) were female. The participants were divided into two groups: a 43-member group of patients with progressive disease (21 females, 22 males) and a 363-member group of control patients with stable disease (163 females, 200 males). Their mean age was 63.59±15.1 years for the stable group and 66.70±15.3 years for the progressive group.

There was no difference between the groups regarding gender (P=0.62). The average age (66.7) of the progressive disease group was similar to the stable control disease group (63.5). Hypertension was the most common comorbidity (n=308, 75.8%), followed by DM (n=142, 34.9%) and congestive heart failure (n=37, 0.09%).

No significant relationship was detected between the waist circumference and body mass index with CKD progression (P=0.86). Six patients with progressive disease and 100 patients with stable disease had diabetes mellitus. We found that DM is a risk factor for progressive disease (P=0.04). Systolic and diastolic blood measurements were also similar statistically. Baseline demographic, clinical, and biochemical characteristics did not differ significantly between the two groups (Table 1).

One of the patients with progressive disease and 36 patients with stable disease had congestive heart failure (CHF), which was not found to increase progressive disease risk (P=0.1). The initial presence of hypertension did not reach a statistical significance level for CKD progression (P=0.81). The presence of DM increased CKD progression risk (P=0.04).

<table>
<thead>
<tr>
<th>Table 1. Demographic and clinical characteristics of the study subjects</th>
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<tbody>
<tr>
<td><strong>Variables</strong></td>
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<td>----------------</td>
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<tr>
<td><strong>Stable</strong> (n=363)</td>
</tr>
<tr>
<td>Age (y)</td>
</tr>
<tr>
<td>Gender</td>
</tr>
<tr>
<td>Female</td>
</tr>
<tr>
<td>Male</td>
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<tr>
<td>Alcohol</td>
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<td>Smoking</td>
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<td>Diabetes Mellitus</td>
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<tr>
<td>Hypertension</td>
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<tr>
<td>Congestive heart failure</td>
</tr>
</tbody>
</table>

The chi-square test showed no association between stable disease and progressive disease in smokers and non-smokers (P=0.48). In addition, the test showed no association between stable disease and progressive disease in both alcohol users and non-alcohol users (P=0.83).

A statistically significant inverse relationship was found between sodium and creatinine (r=-0.13, P<0.001). A statistically significant inverse relationship was found between chlorine and creatinine (r=-0.13, P<0.001). A statistically significant but weak relationship was detected between uric acid and creatinine (r=-0.09, P<0.001). No association was seen between uric acid and creatinine clearance.

The effect of CRP and MPV on CKD progression

A statistically significant relationship was found between CRP and creatinine (r=0.13, P<0.001). Synchronously CRP was inversely related to creatinine clearance (r=-0.09, P<0.001) (Table 2). A statistically significant relationship was found between MPV and creatinine (r=0.23, P<0.001). Synchronously MPV was inversely related to creatinine clearance (r=-0.20, P<0.001) (Table 2).

4. Discussion

This study evaluated the relationship between CRP and MPV with CKD progression. Even though a cross-sectional study is good for descriptive analysis and generating a hypothesis, it may be difficult to determine whether CRP or MPV changes or CKD progression comes first, and the association identified may be difficult to interpret. Nevertheless, we found a strong relationship between CRP and creatinine. There was an inverse relationship between CRP and creatinine clearance. Also, we found a strong relationship between MPV and creatinine. There was an inverse relationship between MPV and creatinine clearance.

All the worsening factors for CKD have not been discovered yet. As a most discovered risk factor, DM was a risk factor for CKD progression in our study. Diabetic nephropathy is the leading cause of chronic kidney disease. Diabetes is also responsible for approximately half of all end-stage renal disease cases. It contributes significantly to the morbidity and mortality of patients with diabetes. Our findings are in line with the available information. As a possible risk factor for CKD progression, we focused on two inflammatory markers; CRP and MPV. Inflammation seems to be one of the sneaky enemies in renal studies. Inflammatory cell migration to the renal tissue creates renal scarring by triggering mesangial cell proliferation [20-23]. So, the excess inflammatory process should be accepted as an independent risk factor independent of the first renal disease. Because of its insidious nature, inflammation usually accompanies CKD without symptoms.

CKD triggers a sophisticated immune system dysfunction with chronic inflammation and insufficient immune protection. For example, the production of indoxyl sulfate increases through the effects of differentiated intestinal microbiota [24]. In addition, phenols increase because of decreased renal elimination [25]. In some studies, molecules like indoxyl sulfate and phenols were shown to disrupt immune functions [26, 27]. Additionally, tumor necrosis factor α and interleukin 6 were also shown to increase in CKD patients. A direct relationship was detected between proinflammatory cytokines and GFR decline [28]. Furthermore, hemodialysis treatment provokes immune system dysfunction in CKD patients due to dialysate pollution, biocompatibility defects of the dialysate membranes, and blood-pumping effects [29].

In addition to this chronic inflammatory environment, defective neutrophil chemotaxis [30], decreased neutrophil phagocytosis [31], weakened adaptive lymphocyte functions [32], and humoral immunity [33] contribute to the immune deficiency of uremia. So, despite the chronic inflammation in CKD, better immune protection cannot

Table 2. The correlation coefficients between repetitive measurements

<table>
<thead>
<tr>
<th>Variables</th>
<th>r</th>
<th>%95 Confidence Interval</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP-creatinine</td>
<td>0.13</td>
<td>0.08, 0.18</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>CRP-creatinine clearance</td>
<td>-0.09</td>
<td>-0.13, -0.04</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean platelet volume-creatinine</td>
<td>0.23</td>
<td>0.18, 0.27</td>
<td>&lt;0.001*</td>
</tr>
<tr>
<td>Mean platelet volume-creatinine clearance</td>
<td>-0.20</td>
<td>-0.24, 0.15</td>
<td>&lt;0.001*</td>
</tr>
</tbody>
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*Significant relationship
be achieved. But instead, more frequent and more severe infections occur [34]. These infections also increase the mortality rate in these patient groups [35].

Chu et al. found a higher AKI development in SARS (severe acute respiratory syndrome) patients in a study conducted on 536 patients infected by the SARS-CoV outbreak in 2005. Almost all of those patients (91.7%) had died when compared to a pretty low mortality rate of the patients without AKI (8.8%) [36]. Likewise, kidney disease was detected to be associated with more severe disease in a meta-analysis of COVID-19 [6].

As an inflammatory marker, CRP increases during CKD progression [37]. Besides being an inflammation-indicating sign, CRP also accumulates in tubular cells’ glomerular endothelium and cytoplasm, eventually inducing inflammation and fibrosis [38, 39]. Coagulation and inflammation increase renal injury together. Platelets are one of the main players in this process [9]. Platelet activation and platelet-granulocyte activation were shown to exacerbate renal inflammation and further renal injury by Jansen et al. [10]. Besides, CKD is already known to cause platelet defects [40, 41]. The effects of renal functions on platelet parameters were also investigated in some studies. However, some contradictory results have been reached so far. Some investigators found higher MPV levels in CKD patients [42, 43]. In another study, an increase in MPV levels was found to be directly related to decreased renal functions, but that study was conducted in only hemodialysis patients on a limited number of 20 patients [44]. Nevertheless, MPV was found to decrease during hemodialysis treatment in another study. [45] In our research, creatinine value increases as CRP increases synchronously. As CRP increases, creatinine clearance decreases. In addition, as MPV increases, the creatinine value increases. Synchronously, as MPV increases, creatinine clearance decreases. In summary, we found elevated plasma levels of CRP and mean platelet volume associated with a greater loss of kidney function over time. These inflammatory markers may be accepted as potential follow-up markers and therapeutic targets in CKD if further studies support the data we found.

5. Conclusion

In conclusion, reversing inflammation-mediated processes in CKD may be a new target in terms of slowing the progression of renal disease in the future. This study may better understand the role of inflammation on CKD progression. The association between inflammation and CKD progression needs further clarified with prospective studies.

The first limitation of our study was that it was a single-center retrospective study. Second, the sample size of the study was small. Third, difficulties with creatinine clearance measurement may affect results because of problems, including difficulty in sample collection, inconvenience to patients, and waste of time.

Ethical Considerations

Compliance with ethical guidelines

This research was approved by the Trakya University Ethics Committee (Code: 14002370).

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Authors’ contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interest.

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References


