Significance of high C-reactive protein levels in pre-dialysis patients

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Abstract

Background. An elevated serum C-reactive protein (CRP) has been shown to be strongly predictive of morbidity and mortality in dialysis patients. However, the significance of high CRP levels in the pre-dialysis period has not been studied extensively. The aim of our study was to analyse the evolution of our pre-dialysis population according to their basal levels of CRP.

Methods. A cohort of 66 pre-dialysis patients was followed for 1 year, after initial determination of serum CRP. The evolution of blood pressure (BP) control, CRP levels, nutritional data (body mass index, serum albumin, prealbumin, transferrin, cholesterol), proteinuria, calcium-phosphorus product, bicarbonate, haemoglobin (Hb), the weekly dose of erythropoietin (Epo)-kg body weight, and the Hb/Epo dose ratio were measured and compared between patients with high (>6 mg/l) or low (<6 mg/l) CRP levels at baseline. The decline in renal function, hospitalization, and death also were measured and compared between the two groups.

Results. At baseline, 23 patients (35%) showed high (>6 mg/l) CRP levels. CRP was higher in patients with a previous history of cardiovascular disease (P<0.01), as well as in patients in whom ischaemic nephropathy or nephrosclerosis was the cause of end-stage renal disease (P<0.01). There were no differences between diabetic and non-diabetic patients. During the study period, patients with higher CRP levels at baseline maintained higher levels (P<0.001). During this period, these patients showed lower (P<0.05) albumin concentration, higher bicarbonate levels, lower Hb concentration, and lower Hb/Epo ratio and needed higher Epo doses. There were no differences in systolic BP, the degree of proteinuria, and the decline in renal function between groups; diastolic BP was lower in patients with high CRP levels. Hospitalization was higher (P<0.005) in this group. Only one patient died.

Conclusions. The prevalence of inflammation is high in pre-dialysis patients. High serum CRP levels predict a constant inflammatory state on follow-up. As occurs in dialysis patients, pre-dialysis inflammation predicts lower serum albumin concentration, poorer response to Epo, and a higher hospitalization rate. The decline in renal function does not seem to be related to the inflammatory state. Mortality was not affected on short-term follow-up.

Keywords: erythropoietin response; hospitalization; hypoalbuminaemia; inflammation; pre-dialysis

Introduction

The mortality of patients with end-stage renal disease (ESRD) remains high, with most deaths resulting from cardiovascular disease [1]. Several authors [2,3] have found that overall mortality and cardiovascular mortality were significantly higher in haemodialysis patients with elevated C-reactive protein (CRP). As in the haemodialysis population, markers of inflammation in peritoneal dialysis patients also predict death [4]. In dialysis patients, high CRP levels are also associated with lower serum albumin [5–7] and with lower haemoglobin (Hb) levels resistant to Epo [8–10]. However, the significance of high CRP levels in pre-ESRD patients has not been studied extensively. The aim of our study was to analyse the evolution of a pre-dialysis population according to their basal levels of CRP. We analysed and compared the evolution of blood pressure (BP) control, nutritional status, calcium-phosphorus product, Epo response, the decline in renal function, hospitalization, and death between patients with high or low CRP levels at baseline.

Subjects and methods

A cohort of 66 pre-ESRD patients was prospectively followed for 1 year after initial measurement of CRP levels.
Their mean age was 59 ± 19 years (range: 19–93 years); 56% were male. Thirteen patients (20%) had diabetes and 17 patients (26%) had ischaemic nephropathy or nephrosclerosis as the cause of their chronic renal failure. Ischaemic nephropathy was diagnosed by angiography in 7 of 17 patients; the diagnosis of nephrosclerosis was confirmed by renal biopsy in 4 patients, and in 6 patients nephrosclerosis was diagnosed by clinical criteria. A history of cardiovascular events was present in 22 patients (33%). Of these, 11 had had myocardial infarction or clinical signs of ischaemic heart disease, 6 had peripheral ischaemic atherosclerotic vascular disease, and 5 suffered from cerebrovascular disease. The mean creatinine clearance of our cohort at the start of the study was 14 ± 4 ml/min (range: 4–20 ml/min). All patients were prescribed a low protein diet containing approximately 0.6 g protein/kg/day. Erythropoietin was prescribed for Hb levels below 10–10.5 g/dl. Angiotensin converting inhibitors were employed in most hypertensive patients.

During the study, 8 patients (12%) were started on dialysis. These patients were followed until the initiation of renal replacement therapy. The mean follow-up period was 10.2 ± 1.4 months (range: 6–12 months).

A high-sensitivity assay for CRP was used. Serum CRP was measured by nephelometry (Behring Nephelometer BNA II). The detection limit of CRP was 3.25 mg/l and all values less than 3.25 mg/l were treated as 2 mg/l in the statistical evaluation. In the general population studied by this method, high levels are considered as those over 5 mg/l, but normal levels need to be defined in pre-dialysis patients. A cut-off level of 6 mg/l has been used in dialysis patients, employing nephelometry for measuring CRP [11]. In patients with normal renal function, it has been demonstrated that only values higher than 6 mg/l are predictive of cardiovascular events [12]. As a result, we defined a cut-off value of 6 mg/l for CRP. Patients were therefore divided into two groups, depending on their CRP levels at baseline being higher or lower than 6 mg/l.

During the study, patients were evaluated monthly or every 2 months. On each visit, BP and body weight were measured and body mass index (BMI) was calculated. The biochemical parameters measured at each visit included CRP level, nutritional data (serum albumin, prealbumin, transferrin, and cholesterol), proteinuria, calcium-phosphorus product, bicarbonate level, Hb, and the weekly dose of Epo/kg body weight. In each case, the Hb/Epo dose ratio was calculated in order to find a value that would reflect the response to Epo. Lower values of this ratio can indicate poorer response to Epo, since lower Hb levels result despite using larger doses of Epo. An average value of each of the parameters measured in each patient during the study period was calculated and this mean value was included in the database. The decline in renal function was calculated as the difference between the initial and final creatinine clearance. Hospitalization and death were also analysed. To evaluate hospitalization, we measured the number of admissions during the follow-up period; only those admissions more than 48 h in duration were included. The causes of admissions also were analysed, and grouped into three groups (cardiovascular, infectious, and other causes). The data obtained during follow-up were compared between patients with high (>6 mg/l, Group I) or low (<6 mg/l, Group II) CRP levels at baseline.

Normally distributed data are presented as mean values ± standard deviation and non-normally distributed data as median values and ranges. Computations were made using the SPSS package for Windows. Student’s t-test was used to analyse differences of quantitative variables between groups. The Mann–Whitney U-test was used for non-normal distributed variables. Differences in categorical variables were analysed using the chi-square test. Single regression was employed to correlate quantitative data. A probability of less than 0.05 was considered significant.

Results

The average value of serum CRP levels at baseline was 8.3 ± 14.2 mg/l (range: 2–95 mg/l; median 2 mg/l). Twenty-three patients (35%) showed high (>6 mg/l) CRP levels. The median CRP level was higher in patients with a previous history of cardiovascular disease (10.1 vs 2 mg/l, P < 0.01). There were no significant differences in CRP levels between diabetic and non-diabetic patients; median value of CRP was higher in those patients who had ischaemic nephropathy or nephrosclerosis as the cause of their ESRD (10.6 vs 2 mg/l, P < 0.01). Basal CRP levels correlated inversely (r = −0.45, P < 0.001) with serum albumin. We found no relationship between basal CRP levels and the other nutritional data (prealbumin, transferrin, cholesterol, and BMI). Proteinuria, creatinine clearance, and systolic BP also did not correlate with the basal CRP levels, whereas diastolic BP correlated inversely with CRP levels (r = −0.28, P < 0.05). A direct correlation between bicarbonate levels and CRP (r = 0.43, P < 0.001) was also found. At baseline, 29 patients (45%) were receiving Epo therapy. C-reactive protein did not correlate significantly with Hb values. Haemoglobin was higher, although not significantly, in patients with low basal CRP levels (12.2 ± 1.3 vs 11.5 ± 1.2 g/dl, P = 0.08).

During the study, Group I had higher CRP levels during follow-up when compared with Group II (21.6 vs 2 mg/l, P < 0.001). Group I showed lower S-albumin (3.5 ± 0.4 vs 3.8 ± 0.4 g/dl, P < 0.05) without significant differences in the other nutritional data (prealbumin, transferrin, and cholesterol). The mean value of Hb during the study was lower (P < 0.05) in patients with high CRP levels. In these patients, the weekly dose of Epo was higher (P < 0.05) and the Hb/Epo dose ratio was lower (P < 0.005), reflecting Epo hyporesponsiveness in the patients with markers of inflammation. The proportion of patients who received Epo therapy during follow-up was 65%. There were no significant differences in the ferritin levels during the study between the two groups. The comparison of nutritional data and anaemia correction on follow-up between patients with high or low CRP levels at baseline are expressed in Table 1.

Table 2 shows the comparison of the evolution of BP control, proteinuria, decline in renal function, bicarbonate levels, and the hospitalization rate between the two groups.

Systolic BP, proteinuria, and the decline in renal function were not different between patients with low or high CRP levels. Diastolic BP, inversely correlated with CRP levels at baseline, remained lower (P < 0.05) in patients with markers of inflammation.
Table 1. Comparison of the evolution of serum CRP levels, nutritional status, anaemia correction, and Epo response between patients with high (Group I) or low (Group II) CRP levels at baseline.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I (CRP &gt;6 mg/l)</th>
<th>Group II (CRP &lt;6 mg/l)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRP (mg/dl)</td>
<td>21.6 (12.9–32.6)</td>
<td>2 (2–4.6)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Albumin (g/dl)</td>
<td>3.5 ± 0.4</td>
<td>3.8 ± 0.4</td>
<td>0.017</td>
</tr>
<tr>
<td>Prealbumin (mg/dl)</td>
<td>32.8 ± 8</td>
<td>31.7 ± 7.2</td>
<td>0.91</td>
</tr>
<tr>
<td>Transferrin (mg/dl)</td>
<td>192 ± 4.5</td>
<td>200 ± 34</td>
<td>0.49</td>
</tr>
<tr>
<td>Cholesterol (mg/dl)</td>
<td>182 ± 35</td>
<td>208 ± 52</td>
<td>0.065</td>
</tr>
<tr>
<td>Hb (g/dl)</td>
<td>11.6 ± 1.1</td>
<td>12.2 ± 0.8</td>
<td>0.045</td>
</tr>
<tr>
<td>Epo (IU/kg/week)</td>
<td>67 ± 32</td>
<td>43 ± 20</td>
<td>0.025</td>
</tr>
<tr>
<td>Hb/Epo</td>
<td>0.19 ± 0.08</td>
<td>0.32 ± 0.13</td>
<td>0.004</td>
</tr>
<tr>
<td>Ferritin (mg/dl)</td>
<td>116 ± 96</td>
<td>110 ± 80</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Median (interquartile range).

Table 2. Comparison of the evolution of blood pressure control, proteinuria, the decline in renal function, serum bicarbonate levels, and hospitalization between patients with high (Group I) or low (Group II) CRP levels at baseline.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Group I (CRP &gt;6 mg/l)</th>
<th>Group II (CRP &lt;6 mg/l)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Systolic BP (mmHg)</td>
<td>136 ± 18</td>
<td>140 ± 16</td>
<td>0.38</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>77 ± 9</td>
<td>83 ± 9</td>
<td>0.037</td>
</tr>
<tr>
<td>Proteinuria (g/day)</td>
<td>1.8 ± 2.4</td>
<td>3.3 ± 3.7</td>
<td>0.13</td>
</tr>
<tr>
<td>ΔCCr (ml/min)</td>
<td>-1.8 ± 2.3</td>
<td>-2.3 ± 2.1</td>
<td>0.8</td>
</tr>
<tr>
<td>Bicarbonate (mEq/l)</td>
<td>24.5 ± 2.7</td>
<td>22.4 ± 3</td>
<td>0.028</td>
</tr>
<tr>
<td>Hospitalization (n)</td>
<td>0.52 ± 0.8</td>
<td>0.03 ± 0.19</td>
<td>0.004</td>
</tr>
</tbody>
</table>

CCr, creatinine clearance.

The incidence of inflammation in uraemic patients is high [13]. Possible causes of inflammation include bacterial or viral infections, surgical trauma including vascular access surgery, heart failure, and renal or systemic inflammatory diseases. It has been suggested also that aspects of the dialysis procedure, such as the water source, the type of dialyser, or other processes, may cause inflammation [14]. Although our results do not rule out the influence of procedural variables on the inflammatory state, the high number of patients with high CRP levels in our pre-dialysis population (similar to the prevalence reported by Owen and Lowrie [8] in a dialysis population), suggests that the patients on dialysis with markers of inflammation could show signs of inflammation before the start of renal replacement therapy. In our study, a high CRP level at baseline predicts a constant inflammatory state during follow-up, which probably will be maintained after the start of dialysis therapy.

The decreased survival reported in dialysis patients with markers of inflammation is probably related to the association between inflammation and cardiovascular risk. This association has been described also in patients without renal disease [15,16]. Whether inflammation is the cause of cardiovascular disease or a marker of existing disease, or both, is an important unresolved question. Some argue that vascular disease is itself an inflammatory process [16] and that the markers of inflammation reflect existing vascular disease. Our pre-dialysis patients with previous histories of cardiovascular disease showed higher CRP levels. We cannot demonstrate a decreased survival in our patients with markers of inflammation since the observation period was very short. Nevertheless, hospitalization was higher even during a short follow-up in our pre-dialysis patients with high CRP levels. In this regard, some authors have reported recently that markers of inflammation are strong predictors of hospitalization in chronic haemodialysis patients [17]. The absence of a linear relationship between CRP and clinical events in our cohort suggests that, although inflammation can influence clinical outcome, the risk of hospitalization in inflamed patients is not strongly dependent on the level of CRP. A longer observation is required to confirm this notion.

C-reactive protein levels in our pre-ESRD patients correlated inversely with serum albumin, as in the dialysis population, and high CRP levels predict lower serum albumin concentrations on follow-up. Albumin, like other nutritional markers, such as prealbumin and transferrin, is a negative acute-phase protein [18]. The synthesis of these proteins decreases during inflammation, as does their serum concentrations, changes that are entirely independent of nutritional status [18,19]. Stenvinkel et al. [20] established that patients with pre-ESRD who were judged to be malnourished had markers consistent with the presence of inflammation. Our pre-ESRD patients with high CRP levels showed lower S-albumin concentrations, but without inflammation, although the overall mortality was not affected on short-term follow-up.

Discussion

Our results suggest that the prevalence of inflammation among the pre-ESRD population is high and that an increased CRP in pre-dialysis patients predicts a constant inflammatory state on follow-up. As in the dialysis population, high CRP levels in pre-dialysis patients predict lower serum albumin concentration and lower Hb levels with poorer response to Epo. The decline in renal function, on the contrary, seems not to be related to the inflammatory state. Hospitalization also was higher in our patients with markers of
the presence of other criteria of malnutrition. Mean S-transferrin and prealbumin were not statistically different between patients with low or high CRP levels. It is possible that more severe inflammation is needed to reduce the serum concentration of these proteins.

Our patients with high CRP levels at baseline were more anaemic during follow-up, in spite of receiving higher doses of Epo, suggesting poorer response to Epo in this group. Thus, the Hb/Epo dose ratio was lower during the study in the group of patients with markers of inflammation. The hematopoietic response to inflammatory disease includes anaemia secondary to decreased erythropoiesis [21]. This has been attributed to the inhibition of Epo secretion by pro-inflammatory cytokines [22]. Inflammation can also induce a functional iron deficiency, as cytokines can inhibit the delivery of iron from the reticulo-endothelial cells to the hematopoietic cells [23]. It has been reported that the dose of Epo required to maintain a certain Hb level in dialysis patients may be increased by 30–70% in those individuals with serum CRP >20 mg/l as compared with patients who have lower CRP levels [9]. Doses higher than 200 IU/kg/week may sometimes be necessary. Despite the poorer response to Epo detected in our patients with markers of inflammation, the dose of Epo they required to achieve the target Hb level was much lower than doses given to dialysis patients, even to patients with higher CRP levels.

In our patients, the decline in renal function does not seem to be related to the inflammatory state. These results should be analysed with caution, in view of the narrow range of glomerular filtration rate at the start of the study and the relatively short observation period. It is noteworthy, however, that systolic BP and proteinuria, factors that could influence in the decline of renal function, were not different during the study between patients with high or low CRP levels; diastolic BP, on the contrary, correlated inversely with basal CRP levels, and patients with higher levels maintained lower diastolic BP values on follow-up. Stenvinkel et al. [20] noted that the incidence of carotid plaques was significantly elevated in patients with signs of inflammation; patients with carotid plaques also had significantly lower diastolic BPs. Therefore, the lower diastolic BP values detected in our patients with higher CRP levels could be related to the presence of atherosclerotic changes, as CRP levels were higher in patients with a previous history of cardiovascular events.

Surprisingly, basal CRP levels in our patients correlated directly with serum bicarbonate, and patients with signs of inflammation maintained higher bicarbonate values along the study. Higher use of diuretics in the higher CRP group might explain these results, but we have not studied the use of diuretics in the two groups. Other authors [24] have detected higher bicarbonate levels in malnourished peritoneal dialysis patients, compared with patients without signs of malnutrition. In view of the association between malnutrition and inflammation, bicarbonate concentration could be elevated in patients with inflammatory signs.

In summary, our study shows a high rate of inflammation in pre-ESRD patients. High CRP levels in pre-dialysis patients predict a constant inflammatory state on follow-up, which might be maintained after the initiation of dialysis. Thus, we can identify those patients with inflammation signs during the pre-ESRD phase. Further studies are necessary to confirm the decreased survival rate of these patients after the start of renal replacement therapy. As in dialysis patients, high CRP levels in pre-dialysis predict lower serum albumin concentrations, poorer Epo response and higher hospitalization rate. Longer observation is required to analyse the influence of inflammation on mortality in pre-dialysis patients.

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