Inflammation and cardiovascular risk in dialysis patients

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Background. Chronic inflammation, as evidenced by increased levels of C-reactive protein (CRP), predicts all-cause and cardiovascular mortality in hemodialysis patients in short-term studies. Whether CRP is also predictive in the long-term follow-up is unknown.

Methods. We conducted a 4-year follow-up of a cross-sectional study in a cohort of 280 stable hemodialysis patients. CRP was determined once at the beginning of the study, and all-cause as well as cardiovascular mortality was monitored prospectively.

Results. During follow-up, 123 patients (43.9%) had died, mostly from cardiovascular events (58.5%) corresponding to an annual mortality rate of 11%. Overall mortality and cardiovascular mortality were significantly higher in patients with a CRP more than 8 mg/L (73% vs. 39% and 87% vs. 55%, respectively). Multivariate Cox regression analysis demonstrated that age, CRP, and preexisting cardiovascular disease were the most powerful predictors, but the presence of diabetes, albumin, and BMI also remained in the model.

Conclusion. 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.

The inflammatory response to a given stimulus can be evidenced by a number of acute phase proteins; the most established is C-reactive protein (CRP) [1]. CRP is a prominent product of the inflammatory response syndrome and a marker of overall and cardiovascular death in the general population as well as in hemodialysis patients [2–4]. CRP is elevated 8–10-fold in hemodialysis patients as compared with healthy controls [3–5] and appears to be a common feature in chronic renal failure and dialysis patients. Chronic inflammation is linked to atherosclerotic cardiovascular disease by a number of mechanisms and contributes to the high mortality seen in this patient group. Chronic inflammation is accompanied by an increase in serum levels of other important acute phase proteins such as fibrinogen and lipoprotein(a) which also are atherogenic. On the other hand, levels of anti-atherogenic proteins such as apolipoprotein A-I (ApoA-I) and high density lipoprotein (HDL) cholesterol are reduced [3]. The modulation of the balance between atherogenic proteins, also called emerging new risk factors or non-traditional risk factors, and antiatherogenic proteins may explain the progressive nature of atherosclerosis in the absence of classic, traditional risk factors in dialysis patients. Because the levels of these proteins might undergo continuous modulation [6] by the acute phase stimuli, it remains unclear for what periods of time these proteins remain predictive in hemodialysis patients.

In the present study, we therefore evaluated the 4-year predictive power of acute phase proteins and its best known representative, CRP, in a cohort of 280 hemodialysis patients.

METHODS

The study population, baseline examination, sampling procedure, and laboratory analysis as well as statistical analysis have been described previously [3]. Briefly, between September and November 1995, patients from three outpatient dialysis centers entered the study (130 women and 150 men, mean age 62.4 ± 13.7 yrs). Patients were already on hemodialysis treatment for 55 ± 56 months. A follow-up investigation was performed at 12, 24, and 48 months, and the results of the latter evaluation are reported here. Data from all original 280 hemodialysis patients could be obtained for analysis of the four-year mortality, and no patient was lost in the follow-up. Date and cause of death were evaluated from records and from interviews with the physicians in the outpatient dialysis centers. Causes of death were classified as described previously [3].

RESULTS

The data of the two-year analysis have been reported previously [3]. During the follow-up period of four years, 123 out of 280 patients (44%) had died; most from cardiovascular events (72 out of 123, 58%), corresponding to an annual mortality rate of 11%. The death rate curve was linear. Patients with diabetes (N = 81) had a higher mortality rate at 4 years (65%) as compared with patients...
higher risk for cardiovascular mortality (87 vs. 50%; \( P < 0.0001 \)) during follow-up than those in the lowest quartile (less than 3.3 mg/L). Tables 1 and 2 outline univariate and multivariate stepwise logistic regression process by the Cox proportional hazards method.

**DISCUSSION**

This study confirms that inflammation is associated with an increased overall and cardiovascular mortality in hemodialysis patients and adds data that prediction is even maintained after prolonged periods of observation. It is puzzling and still unresolved how a single and cross-sectional obtained level of a plasma protein with a short half life (19 h) may yield such important information concerning the long-term prognosis in hemodialysis patients. Many centers today measure CRP on a routine basis but no further data are yet available that add knowledge. Pankow et al investigated familial aggregation of CRP in a large, cross-sectional study conducted in four US communities. They found a substantial heritability (35–40%) for CRP levels suggesting that genetic factors determine, at least in part, a given basal CRP level in serum [7]. Opinions have been brought forward to use the mean of multiple measurement, or the delta of two subsequent measurements, or even the area under the curve of several measurements. Further studies must show whether these approaches are superior to a single measurement in a given patient without infection.

**Vascular disease and the predictive value of CRP in dialysis patients**

Apparently we may see exactly the same thing in uremic patients that we see in healthy subjects, only at a higher level of expression and in a shorter period of time. CRP measured years before the acute event independently predicts future risk [3, 4, 8]. In addition, CRP levels are also associated with an increased intima-media carotid artery area in predialysis patients [9]. Other negative and positive acute phase reactants, such as albumin, fibrinogen, ApoA-I, and lipoprotein(a) correlate with serum concentrations of CRP. Figure 1 demonstrates Kaplan-Meier estimates of survival during follow-up with regard to all-cause (A) and cardiovascular mortality (B) in relation to quartiles of serum concentrations of CRP.

![Fig. 1. Kaplan-Meier estimates of survival during follow-up with regard to all-cause (A) and cardiovascular mortality (B) in relation to quartiles of serum concentrations of CRP.](image)
Table 1. Predictors of four-year mortality in the univariate Cox regression analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Units</th>
<th>All-cause mortality</th>
<th>Cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\chi^2$</td>
<td>Relative risk</td>
<td>$P$</td>
</tr>
<tr>
<td>Age</td>
<td>Years</td>
<td>35.09</td>
<td>1.05</td>
</tr>
<tr>
<td>Gender</td>
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<td>4.94</td>
<td>0.67</td>
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<tr>
<td>Diabetes</td>
<td>Ref. = male</td>
<td>28.71</td>
<td>2.57</td>
</tr>
<tr>
<td>BMI</td>
<td>kg/m$^2$</td>
<td>4.50</td>
<td>0.95</td>
</tr>
<tr>
<td>CRP</td>
<td>mg/L</td>
<td>40.02</td>
<td>1.17</td>
</tr>
<tr>
<td>Pre-existing CVD</td>
<td>Ref. = no CVD</td>
<td>31.39</td>
<td>2.66</td>
</tr>
<tr>
<td>Fibrinogen</td>
<td>g/L</td>
<td>16.25</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Abbreviations are: $\chi^2$, the chi-square statistic; BMI, body mass index; CRP, C-reactive protein; CVD, cardiovascular disease.

Table 2. Independent predictors of four-year mortality in hemodialysis patients in the multivariate Cox regression analysis

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Units</th>
<th>All-cause mortality</th>
<th>Cardiovascular mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\chi^2$</td>
<td>Relative risk</td>
<td>$P$</td>
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<tr>
<td>Age</td>
<td>Years</td>
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<tr>
<td>BMI</td>
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<td>0.93</td>
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<td>CRP</td>
<td>mg/liter</td>
<td>26.27</td>
<td>1.15</td>
</tr>
<tr>
<td>Pre-existing CVD</td>
<td>Ref. = no CVD</td>
<td>17.01</td>
<td>1.52</td>
</tr>
</tbody>
</table>

$\chi^2$ means the chi-square statistic. Statistical parameters were established after a multivariate stepwise logistic regression process by the Cox proportional hazards method. Abbreviations are in Table 1.

synthesis of CRP is the sole determinant of its plasma concentration. But which signal has stimulated endothelial cells, monocytes, T-lymphocytes, or mast cells to secrete these mediators? We do not yet know, but most likely enhanced formation of oxygen-free-radicals are involved or have a well defined place in this cascade. To clarify this issue, an intense search for endogenous as well as exogenous factors is currently under way. Since patients with chronic renal failure, not yet on maintenance hemodialysis, or continuous arterial peritoneal dialysis (CAPD) patients exhibit a similar degree of elevation in CRP levels [9], probably factors unrelated to the hemodialysis procedure but more related to accumulation of toxins are more likely to play the predominant role. In peritoneal dialysis (PD) patients, peritoneal transport rate during the first year of treatment is linked with inflammation and declining RRF. It is possible that inflammation may cause both an increase in peritoneal transport rate and a decline in RRF, or that the decline in RRF further aggravates inflammation because of less efficient removal of cytokines [14]. Further studies should investigate at what stages of declining renal function the cascade of inflammation is turned on. These studies should be designed in order to control for a maximum of confounding factors, and they should include repeated measurements during a longitudinal follow-up. Most ideally, the intervention of a potent antioxidant such as an ACE-inhibitor or a statin is appreciated [15].

It has been proposed that the dialysis procedure per se may be responsible for the inflammatory reaction in the patients [5, 16]. Lipopolysaccharide, through dialysate contamination, may stimulate cells to secrete cytokines and to initiate an inflammatory reaction. Indeed, a recent work of Sitter et al [17] suggests that the use of ultrapure dialysis solution will lower plasma CRP in dialysis patients as compared with conventional dialysis. The vascular access or the hemodialysis membrane itself may also be candidates to maintain chronic stimulation of CRP. The presence of an arteriovenous graft is a significant predictor, associated with high CRP and reduced albumin [6]. Schindler et al [5] investigated the impact of hemodialysis using cuprophane, polyamide, and polycarbonate membranes in a crossover design on serum levels of IL-1 receptor antagonist and CRP in 18 patients. Dialysis with cuprophane significantly stimulated the acute phase response as compared with the more biocompatible membranes.

Does oxidative stress cause inflammation? Compelling evidence now exists that dialysis patients are exposed to enhanced oxidative stress. Oxidative stress is initiated by the generation of oxygen free radicals, mainly in tissue and probably in the circulation. The most potent and so far best investigated O$_2$-generating proteins are oxidatively modified lipoproteins, mainly oxidized (ox)-LDL. A similar and comparable inflammatory milieu may be created by advanced glycation and oxidaton end products (AGEs, AOPPs). Both molecules, oxLDL and AGEs may be potent stimulators of oxygen-free radicals via an NADP/NADPH-dependent process. Oxidative and carbonyl stress may stimulate cells and the endothelium.
to produce IL-6 which in turn activates the liver to secrete CRP and other acute phase proteins such as fibrinogen and lipoprotein(a). Indeed, oxidative stress is present in HD patients [18], and free radical generation is involved in many processes that may initiate atherosclerosis. The view has been brought forward that a chronic inflammatory response may be the primary cause of increased oxidative stress in malnourished CRF patients [19]. However, it could also be vice versa: Recently, Nguyen-Khoa et al [20] found that the inflammatory status and duration of dialysis treatment are the most important factors relating to oxidative stress in HD patients. The imbalance between free radical formation and neutralization in dialysis patients, which deteriorates over time, may be the causative factor for the activation of an inflammatory cascade by a variety of potential stimulators in uremia and dialysis. A common signaling occurs via generation of oxygen-free radicals, activation of the transcription factor nuclear factor-kappa B (NF-κB) and induction of a number of genes such as adhesion molecules, cytokines, and chemokines. The result may be IL-6 stimulated production of CRP by the liver.

**What therapeutic approaches are available?** Based on the available information, it can be assumed that oxidative stress is the underlying basic mechanism driving the inflammatory response. Antioxidant therapy might be the treatment options to control inflammation. But what anti-oxidative substances are available today? Münnzel and Keaney claimed that angiotensin converting enzyme (ACE) inhibitors represent a “magic bullet” against vascular oxidative stress, as has been suggested by several trials [21]. Indeed ACE inhibitors ameliorate vasoconstriction and increase the bioactivity of nitric oxide (NO). There is also evidence that some of the effects of statins in preventing second myocardial infarction (CARE study) appeared to be caused by an anti-inflammatory effect [15]. Further data from studies using cerivastatin support the concept. Statins are able to reduce oxidative stress via reduction of vascular NADPH oxidase expression [22].

In summary, chronic inflammation, as evidenced by increased levels of pro-inflammatory cytokines and CRP, is a common feature in hemodialysis patients. Chronic inflammation may cause progressive atherosclerosis, and CRP is a reliable marker of the disease over a period of four years.

**REFERENCES**


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