Chapter 2

Monitoring of inflammation in patients on dialysis: forewarned is forearmed

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Abstract

Current evidence about the effects of inflammation on the outcomes of patients with advanced chronic kidney disease (*CKD*) generally originates from single measurements of inflammatory biomarkers. Patients with CKD, however, are exposed to persistent low-grade inflammation and levels of serum inflammatory markers are subjected to a substantial variability over time, being influenced by multiple processes, such as transient infections, comorbidities, and the intermittent stimulus of dialysis. Understanding and evaluating inflammation in the context of its time-dependent oscillations in renal disease fluctuation is therefore important. Nevertheless, the relationship between longitudinal inflammatory variation and risk prediction has so far been addressed in only a few studies, not all of which have been sufficiently powered. Consequently, uncertainty exists about how to interpret the findings of these studies in the clinical setting. The purpose of this Review is to explore the reasons and implications of variability in levels of inflammatory biomarkers in patients with uremia, specifically focusing on C-reactive protein (*CRP*) measurements. We also discuss the value of repeated versus single measurements of inflammation in the clinical setting and provide solutions to reduce both sample size and intraindividual variability in hypothetical, randomized controlled trials aimed at reducing CRP levels in patients undergoing hemodialysis.

Keypoints:

- In patients with end-stage renal disease, inflammatory markers are subject to substantial variability over time, and are influenced by transient infections, comorbidities, and the intermittent stimulus of dialysis.

- Insufficient evidence exists about the implications of regular CRP screening in patients undergoing dialysis; multiple measures of CRP seem to offer predictive advantages with single determinations.

- Regular CRP screening could identify short-term variation in levels of inflammatory markers associated with mortality, which could facilitate risk stratification of patients with chronic kidney disease.

- Regular CRP screening for individual patients could enable extensive exploration of underlying causes of inflammation and the assignment of appropriate treatment.

- When designing a randomized controlled trial to lower CRP level in patients on hemodialysis, sample size and intrapatient variability can be reduced by estimating inflammation at each time point with averaged measurements for each individual.

Introduction

The high mortality risk of patients with chronic kidney disease (*CKD*)[1–3] has been partly attributed to the inflammatory state,[4,5] a condition encountered in the vast majority of patients with CKD, and especially in those with end-stage renal disease (*ESRD*). In patients with renal failure, the systemic concentrations of both pro-inflammatory and anti-inflammatory cytokines are several-fold higher than concentrations in healthy individuals,[6] as a result of both decreased renal clearance and increased production of cytokines. Indeed, several dialysis-related factors (such as membrane bioincompatibility, dialyzate backflow, and endotoxemia) and factors not related to dialysis (such as infections, comorbidities, intercurrent clinical events [including sepsis, exacerbation of pulmonary diseases, heart failure, gastrointestinal diseases] genetic factors, and diet) might contribute to increased cytokine production and, therefore, a persistent state of inflammation.[7–11]

The robust evidence available concerning single measurements of various inflammatory biomarkers as independent predictors of infectious complications and mortality in patients with CKD[12–15] has justified the use of such measurements for identifying patients at increased risk of inflammation. C-reactive protein (*CRP*) is the prototype marker currently used for inflammatory monitoring in clinical units.[16] In the uremic milieu, patients are exposed to a low-grade, persistent inflammation that is subject to a substantial intraindividual and interindividual variability.[7,17,18] The coexistence of CKD with background inflammation and fluctuation of cytokines emphasizes the importance of understanding and evaluating inflammation in the context of its time-dependent oscillations as the process of renal disease fluctuates. In this Review, we explore the reasons for, and the implications and clinical importance of inflammatory biomarker variability in the setting of uremia with a focus on CRP measurements given their extended use in the clinical setting. The advantages of regular monitoring of inflammation in patients undergoing dialysis as a means of risk stratification within patient groups is also discussed.

The dynamic inflammatory response

In response to tissue damage, bacterial particles, tissue necrosis, or other provoking stimuli, polymorphonuclear cells and monocytes are triggered and recruited to the affected area. These cells initiate the inflammatory cascade by producing a diverse range of proinflammatory and anti-inflammatory cytokines, which are involved in autocrine, paracrine, and endocrine communication.[19] Cytokines expand the inflammatory response to a systemic level via the endocrine pathway by initiating production of acute-phase proteins, including CRP, in the liver.[19] Systemic manifestation of this orchestrated system is soon apparent. Levels of proinflammatory mediators synthesized locally at the area of damage and/or infection, such as interleukin (*IL*)-6 or pentraxin 3 (*PTX-3*), are the first to increase systemically, typically 1.5–3.0 hours following tissue injury.[20–22] CRP levels, however, increase slightly later, about 6–8 hours following injury,[20,21] and peak after >24 hours from hospital admission in patients who have experienced myocardial infarction.[22,23]

Of all the acute-phase proteins and plasma markers of vascular inflammation, CRP has been studied the most extensively in patients with CKD. Depending on the severity of the inflammatory stimulus, CRP levels can increase by up to 500 times the normal level. CRP has a half-life of 19 hours,[24] this prolonged half-life makes it easy to detect CRP in the blood. Established methods for measuring CRP serum levels seem reliable, with relatively low coefficients of variation.[25] CRP is currently thought to be a 'bystander' marker of vascular inflammation, rather than a 'culprit' and risk factor for vascular disease.[11,26,27] Biological intraindividual and inter individual variability in CRP level exists, however, even among healthy individuals in whom CRP levels are low or undetectable.[28–30] This biological variability could be related to the reflective nature of CRP, and gradually increases in inflammatory and atherosclerotic conditions.[31] In early population studies, the 4-year reproducibility of CRP measurements was equivalent to those for cholesterol and blood pressure measurements.[30] Interindividual variability results from differences in both demographic factors and comorbidities between patients.[30,32–37] Intraindividual variability, on the other hand, is associated with the presence and influence of transient intercurrent events and the dynamic response of the immune system.[30] In 1,800 healthy Japanese patients who were tested twice during a 1-year period, increasing age was associated with larger intraindividual CRP variation in men than in women;[38] this difference could affect the risk assessment of CRP values, and, therefore, the sex of the patient needs to be taken into account when CRP is used to assess risk in age-related diseases.[39] Proinflammatory cytokines are also subject to a considerable day-to-day variation; intraindividual IL-6 variability was reported in healthy adults, with a mean age of 59 years, during six consecutive daily fasting measurements,[40] describing an index of individuality of 0.20 and a standard error of the mean (*SEM*) of 0.32 pg/ml. Such an SEM indicates that observed differences of ≤0.32 pg/ml in a trial should be understood as part of the normal daily fluctuation of IL-6 levels.

In patients undergoing dialysis, the intraindividual and interindividual variability of serum CRP levels might be even greater than the variability in the general population. However, this variability has been investigated considerably less in the dialysis population. The main cause of CRP variability in the setting of renal dialysis are intercurrent clinical events.[41–43] However, other factors could also contribute to variability, as intraindividual CRP variation in patients undergoing hemodialysis who are free from intercurrent clinical events is very high.[44] Additional interindividual variation might result from decreased renal function and the uremic environment, comorbidities, and protein-energy wasting.[18,45,46] Intraindividual variation, however, could be enhanced by membrane bioincompatibility, dialyzate backflow, endotoxemia and the intermittent nature of hemodialysis.[7,10,41,47–49] In addition, residual renal function can further contribute to variation in CRP levels among patients undergoing dialysis.[50]

Quantifying the magnitude of variability specifically attributable to dialysis-related and nondialysis-related factors is difficult in the clinical setting. However, as demonstrated by Kaysen et al.,[42] the intermittent activation of the acute-phase response often spans multiple dialysis sessions, thereby suggesting that the causative value of the dialysis session per se is of less importance in inducing and maintaining the inflammatory response. Finally, genetic determinants might influence the

intraindividual variability of the inflammatory response, as suggested for both CRP variance in relation to cardiovascular disease risk[51] and IL-6 response following vaccination in the general population.[52] In patients undergoing hemodialysis, Girndt et al. observed that a polymorphism in the gene encoding IL-10 associated with reduced production of IL-10 was associated with reduced intrapatient CRP variability assessed monthly over a 6-month period (**Figure 1**).[53]

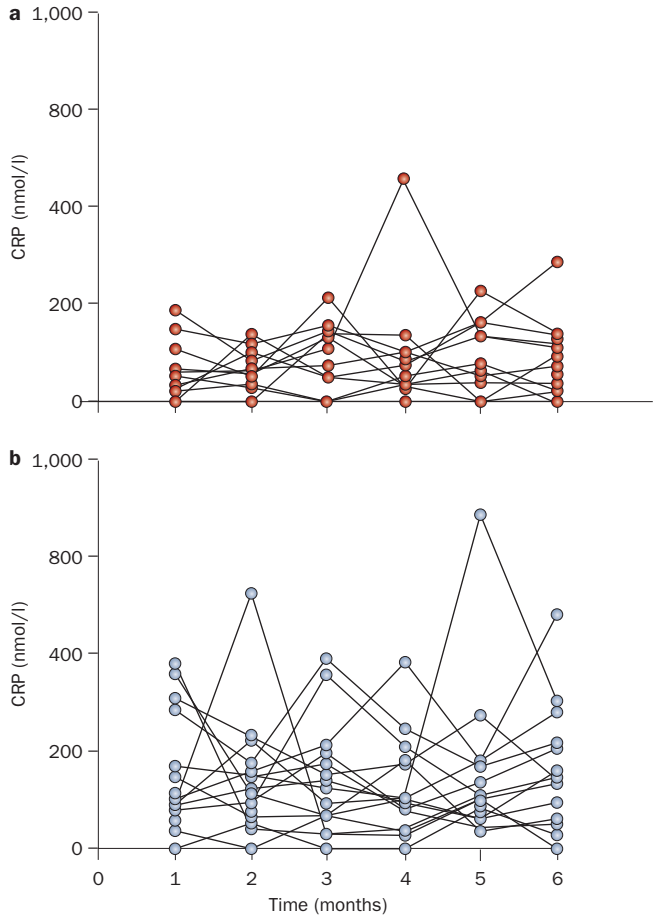

Figure 1. Course of CRP levels in three selected patients. Intraindividual CRP variability could, in part, be genetically determined. The figure depicts CRP values of 15 patients a) an IL-10 'high-producer' genotype or b) an IL-10 'low-producer' genotype. CRP measurements were taken during the first week of each month before dialysis, regardless of whether or not the patient had complications. The IL-10 'low-producer' genotype seemed to be associated with more frequent elevations in CRP than the 'high-producer' genotype. The mean CRP measurement in the 'low-producer' group was 173.3 nmol/l (18.2 mg/l) ± 15.2 nmol/l (1.6 mg/l), and in the 'high-producer' group the mean CRP measurement was 80 nmol/l (8.4 mg/l) ± 16.2 nmol/l (1.7 mg/l) (P = 0.002,Mann–Whitney test). To convert values to mg/l, divide by 9.524. Abbreviation: CRP, C-reactive protein. Permission obtained from Nature Publishing Group © Girndt. M. et al. Kidney Int. 62, 949–955 (2002).

Single measurement assessment

In the general population, strong links exist between elevated levels of systemic inflammatory markers during a single assessment and an increased risk of cardiovascular morbidity and mortality.[5,32] Such links are also observed for the majority of cytokines and acute-phase reactants in various subpopulations of patients with CKD, including individuals in the early stages of this disease,[5,54] patients with ESRD awaiting their first dialysis session,[55] individuals undergoing hemodialysis[12,14,56–63] and patients on peritoneal dialysis.[64–67] In addition, single CRP measurements have been positively associated with left ventricular hypertrophy (*LVH*),[67] myocardial infarction,[66] and hospitalization[68] in patients undergoing dialysis. Despite the fact that many comparative studies suggest that IL-6 might be the best outcome predictor in early and advanced CKD,[56,64,69,70] CRP measurement is still the prototypic marker of uremic inflammation, owing to the widespread availability of this method. Cytokines and acute-phase proteins are substantially elevated in patients with uremia.[71–73]

Although several, arguably, arbitrary CRP cut-off values have been suggested for patients with CKD.[12,54,67,74] At present, no consensual definition of 'uremic inflammation' exists in terms of levels of CRP and other inflammatory markers. Furthermore, safe target CRP values for patients with CKD are still undefined. Follow-up periods for studies in which single measurements of inflammatory biomarkers were used typically range from 2 years to 10 years.[5,12,14,54–67] From a clinical point of view, and misinterpreting traditional Cox models, it would be incorrect to assume that a single CRP measurement would predict the probability of death within 10 years. Indeed, conditional or time-stratified analyses show that CRP is an excellent predictor of risk in the short term (1 year of follow-up).[75] Over an extended period (2–3 years of follow-up) however, the association between CRP and mortality diminishes as other comorbidities and conditions take part in the patient's prognosis.[76] Using periodical CRP monitoring for short-term risk prediction only therefore seems pertinent.

Biological variance associated with single measurements of CRP could have been incorrectly misinterpreted as a negative aspect of using this biomarker as a clinical tool. Increased variation in CRP levels would, however, have imposed a reduction in point estimates towards the null hypothesis in all of the aforementioned studies that included a single baseline CRP measurement.[5,12,14,54–67] As such, the observed relative risk associated with inflammation might be underestimated compared with the true relative risk.[77] Platz et al. reassessed mortality risk ratios attributed to single CRP measurements by correcting for intraindividual and interindividual variances (calculated from three determinations 2 years apart) in 50 healthy men aged >55 years (mean age at baseline 64.9 years).[78] The investigators reported an intraclass correlation coefficient of 0.66 for CRP levels measured at three time points over a 4-year period, which we consider to indicate good consistency over time. This observation indicates the following: if the CRP level is measured once, and, assuming no other errors exist, if the observed relative risk for an elevated CRP level is 2.06, then the true relative risk equals 3.0. Thus, although a single CRP measurement probably underestimates the true risk, it could be considered a valid estimate. A single measurement, however, prevents clinicians from gaining important information on the variability of the inflammatory response and the underlying processes behind this variation. **Figure 2** demonstrates that a single measurement of CRP level is probably insufficient for medical decision-making in day-to-day clinical practice.

Longitudinal CRP changes

To the best of our knowledge (details on the literature search are specified in **Appendix 1**), as many as 10 small-to medium studies, all but one examining patients undergoing hemodialysis, have addressed the consequences of fluctuating levels of CRP, IL-6, or tumor necrosis factor (*TNF*) on mortality or cardiovascular disease (**Table 1**). with respect to study design and methods of analysis, these studies can be grouped into three different categories: 1) ' summary measures', 2) 'long-term fluctuation' and 3) 'intradialytic fluctuation'. In the first category, Snaedal et al. assessed whether summary measures of repeated measurements (average, median or upper/lower values

within a given time period) offer a predictive gain as compared with a single assessment.[18] In this report, CRP levels were measured every week over a 3-month period in 224 patients who were undergoing hemodialysis.[18] As shown in **Figure 3**, an elevation of 10 nmol/l (1 mg/l) in median or mean CRP levels contributes a statistically significant 1.2–1.3% increase to the all-cause mortality hazard ratio.[18] As an example, a patient with a mean CRP value of 143 nmol/l (15 mg/l) has a 15% increased risk of death during follow-up compared with a patient with a mean CRP value <48 nmol/l (<5 mg/l). As such, the results from this study indicate that multiple measurements might offer improved mortality prediction.

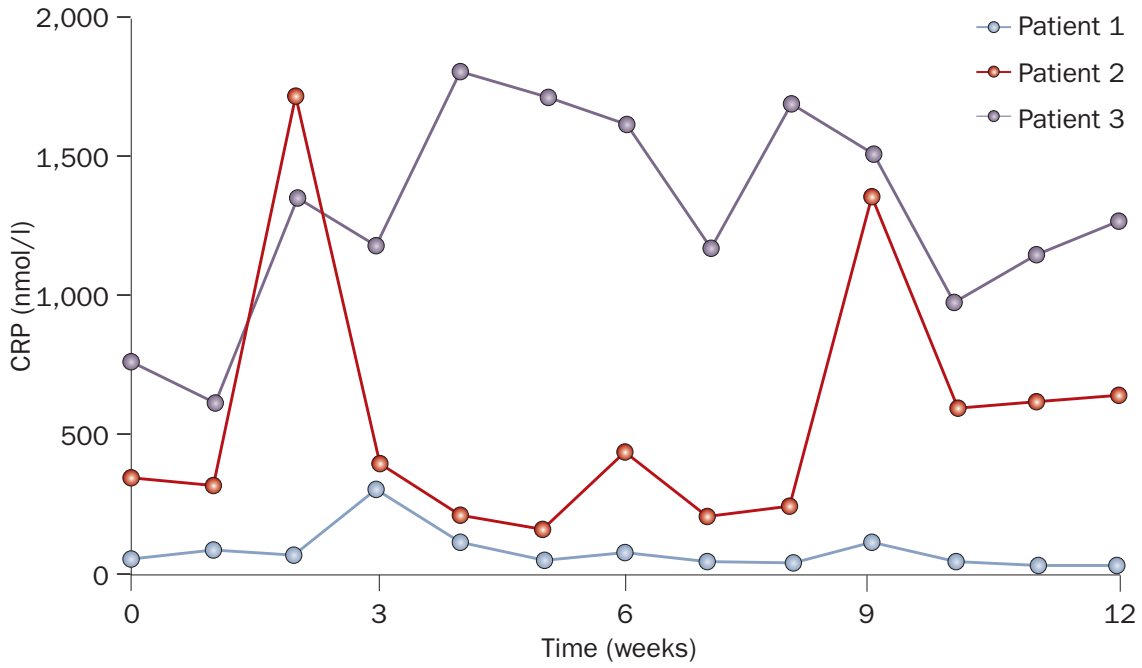

Figure 2. Weekly CRP variability in three selected hemodialysis patients at Karolinska University Hospital, Stockholm, Sweden. Three different hypothetical patients illustrate the usefulness of regular monitoring of the inflammatory response in patients undergoing dialysis. In patient 1, CRP levels remained low during the entire follow-up period apart from during a cold at week 3. In patient 2, CRP levels were, on average, within the 'smoldering' range (mostly remaining within the range 48–476 nmol/l (5–50 mg/l)). However, acute increases in weeks 2 and 9 denoted infections that were appropriately treated. In patient 3, CRP levels were high, indicating acute inflammatory processes that should have alerted the clinician about appropriate treatment and prognosis. Although a single measurement would have sufficed for patient 1, it would have provided misleading information in the other two cases. Regular monitoring in these cases could help to detect systemic CRP elevations warranting a work-up for the source of inflammation and appropriate palliative measures. To convert values to mg/l, divide by 9.524. Abbreviation: CRP, C-reactive protein.

A second category of studies assessed the temporal variation of inflammatory biomarkers during several consecutive measurements over a longer time period that spanned multiple dialysis sessions. In these reports, the analysis included three different categorization strategies: 1) persistently low CRP levels, 2) persistently high CRP levels, or 3) CRP elevations and/or decreases. Study periods varied from 3 months to 6 months.[74,76,79] These studies consistently showed that patients with persistently elevated CRP levels exhibited the worst prognosis (that is, all-cause mortality) as compared with the other groups, followed by patients that presented a rise or a fall in CRP during the observation period [74,76,79] (**Figure 4**). Such observations also seem to be valid for patients undergoing peritoneal dialysis [80] and are further reinforced by the results reported by Kim et al. who demonstrated that LVH was more prevalent among patients on hemodialysis who had persistently elevated CRP levels.[81] We could also demonstrate that this pattern of mortality linked to CRP variation is identical to that seen with variation in IL-6 and TNF.[79] An unexpected finding, however, was that the correlation between changes in these inflammatory markers was not very strong, leading to the hypothesis that various inflammatory pathways contribute in parallel to the pathogenesis of CKD.[79] In a more complex analysis, Rao et al. used a time-dependent Cox model to analyze, on a yearly basis, the influence of IL-6 levels on mortality in 206 stable patients undergoing hemodialysis.[82] In comparison with baseline values, hazard ratios were higher when IL-6 levels were incorporated as a time-dependent covariate.[82] These study results are similar to results from studies on the variability of parathyroid hormone[83] or hemoglobin,[84] which suggests that fluctuation in risk biomarkers in patients undergoing dialysis might affect both clinical decision-making and patient outcome.

A third category of studies examines the association between intradialytic changes in serum CRP levels and death and/or development of cardiac disease. The investigators of these studies base their hypotheses on the putative intermittent proinflammatory stimuli of the dialysis procedure. Although some studies reported elevated CRP levels following a single dialysis session,[85–87] the effect of hemoconcentration during the hemodialysis session was taken into consideration. The observation of Park et al., that a proinflammatory response to a single hemodialysis session was associated with LVH, could be a consequence of this lack of correction.[58] The only study that, despite postdialytic CRP correction, showed an association between intradialytic CRP elevations and mortality[7] is, in our opinion, difficult to interpret in light of the biological plausibility of a rise in CRP within 6–8 h following tissue injury.[88] Indeed, similar analyses looking at intradialytic CRP changes from our group, including two independent cohorts of European patients undergoing hemodialysis, could not replicate these findings.[89] Moreover, as evidenced by statistically nonsignificant Pearson correlation coefficients, the congruency between CRP changes amidst consecutive dialysis sessions was poor.[89]

Monitoring inflammatory markers

In determining how inflammatory markers should be measured, the key points to consider are the reasons why CRP needs to be measured and the likelihood that diagnostic and therapeutic strategies not currently being used might change on the basis of these test results. A substantial amount of evidence included in the 2003 scientific statement by the American Heart Association (AHA) and Centers for Disease Control and Prevention (CDC)[90] is still applicable to patients undergoing dialysis. However, despite 10 years of extensive research on the causes and effects of uremic inflammation,[91] no randomized trials with testing of inflammatory markers as the primary intervention have been performed, nor have cost-effectiveness analyses been completed to assess additional costs or cost savings through the use of such tests. Consequently, the following suggestions about the routine monitoring of inflammatory markers are not evidence-based and reflect the authors' opinion only. Although lacking a precise definition, according to the literature from western countries, CRP levels in patients with uremia are usually higher than the >29 nmol/l (3 mg/l) level that indicates a high mortality risk in the general population.[92,93] A pragmatic cut-off value for serum CRP concentrations, which are typically observed in western patients with ESRD, would be 48 nmol/l (5 mg/l).[94] Individuals with CRP values <48 nmol/l (<5 mg/l), however, might still be at increased mortality risk. On the basis of published data from pooled European cohorts, a cut-off point of 95 nmol/l (10 mg/l) has been proposed for uremia-related inflammation[95] and is often used in research studies for the prediction of mortality. However, this cut-off value has not been approved for use in clinical practice. Notably, a substantially increased risk of mortality was already associated with a CRP concentration of 29 nmol/l (3 mg/l) in a large cohort of Japanese patients undergoing dialysis (adjusted HR 1.64, P = 0.04).[96] However, because ethnic differences exist, and lower CRP levels are found in Asian dialysis patients,[37] these results might not apply to other populations.

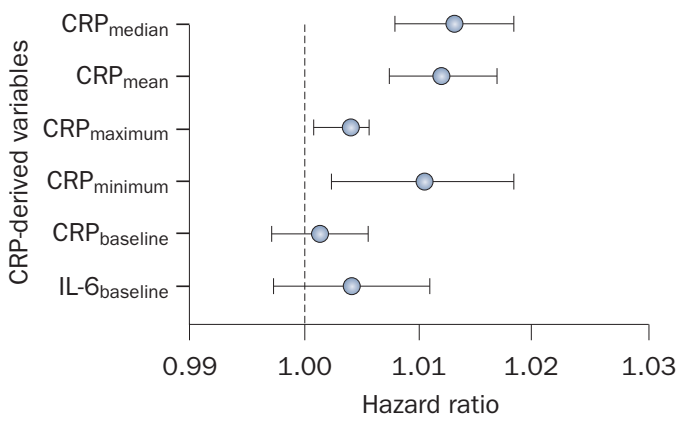

Figure 3. Prediction of all-cause mortality with single and averaged measurements in prevalent patients undergoing hemodialysis. Ratios indicate the increase in risk per 10 mg/L in CRP. Abbreviation: CRP, C-reactive protein. Permission obtained from Elsevier © Snaedal, S. et al. Am. J. Kidney Dis. 53, 1024–1033 (2009).

Table 1. Studies addressing the effect of multiple measurements of inflammatory marker levels on mortality or on a cardiovascular end point

Study	Number of patients, type of dialysis	Dialysis vintage (months)	Marker, baseline levels	Measurements[3]	Follow-up (months)	Outcome measurement	Conclusion
Summary measures							
Snaedal *et al.*[17]	224, HD	28 (14–57)**	hs-CRP	3 months, 12	29.0 (11)#	Mortality	Average CRP levels superior to baseline in predicting mortality
Long-term fluctuation							
Nascimento *et al.*[70]	180, HD	59 (36)#	CRP	6 months, 12	21	Mortality	Persistent high > solitary high > persistent low[3]
Den Elzen *et al.*[72]	635, HD and PD	3	CRP	3 months, 2	27.2 (0.0-78.5)##	Mortality	Persistent high > solitary high > persistent low[3]
Kim *et al.*[77]	52, HD	41.8 (33.7)#	hs-CRP	3 weeks, 2	Cross-sectional	LVH	Persistent high > persistent low[3]
Ates *et al.*[76]	98, CAPD	>3	CRP	20 months, 5	33.9#	Mortality	Persistent high > solitary high > persistent low[3]
Meuwese *et al.*[75]	201 HD [2] 472 HD	28 (15–57)** 3	(hs-)CRP, IL-6 and TNF	3 months, 2	38.4 (17.4-45.1)** 27.2 (11.9-47.9)**	Mortality	Persistent high > increase > decrease > persistent low
Rao *et al.*[78]	198, HD[1]	44.4 (52.8)#	IL-6	4 years, 1–5	31.2 (20.2)#	Mortality	Time dependent IL-6 levels > baseline values[3]
Intradialytic fluctuation							
Korevaar *et al.*[6]	115, HD	9 (5)#	CRP	1 HD session, 2	22.5 (17.4)#	Mortality	Intradialytic CRP increase predicts mortality[3]
Park *et al.*[54]	118, HD	23 (2–225)§§	CRP	1 HD session, 2	Cross-sectional	LVH	Intradialytic CRP increase associates with LVH[3]
Meuwese *et al.*[85]	190, HD‡ 94, HD	29 (15–57)** 6 (6–12)**	CRP hs-CRP	1 HD session, 2	41.3 (22.2–48.5) 18.4 (9.3–41.6)	Mortality	Intradialytic CRP variation does not predict mortality[3]

Hemodialysis (HD), peritoneal dialysis (PD), continuous ambulatory peritoneal dialysis (CAPD). [1]A sample from the Hemodialysis (HEMO) study. During the 5 years of follow-up, 10 out of 198 patients could fulfill all 5 measurements. The dialysis vintage was retrieved from Cheung et al.[116] [2] In this study, two cohorts were included in which separate analyses were performed. [3] Period during which measurements took place and number of measurements. Total include baseline measurements. [3]Highest mortality in groups in order. Characteristics of LVH in most prevalent in groups are displayed in the following order:#Mean (standard deviation), **Median (IQR), ##Mean (range), §§Median (range). When summaries were given for separate groups in a study, a pooled estimate for the total population was calculated. Abbreviations: CAPD, continuous ambulatory peritoneal dialysis; CRP, C-reactive protein; hs-CRP, high sensitivity CRP (nmol/l), HD, hemodialysis; interleukin-6 (pg/ml), LVH, left ventricular hypertrophy; PD, peritoneal dialysis; TNF, tumor necrosis factor (pg/ml).

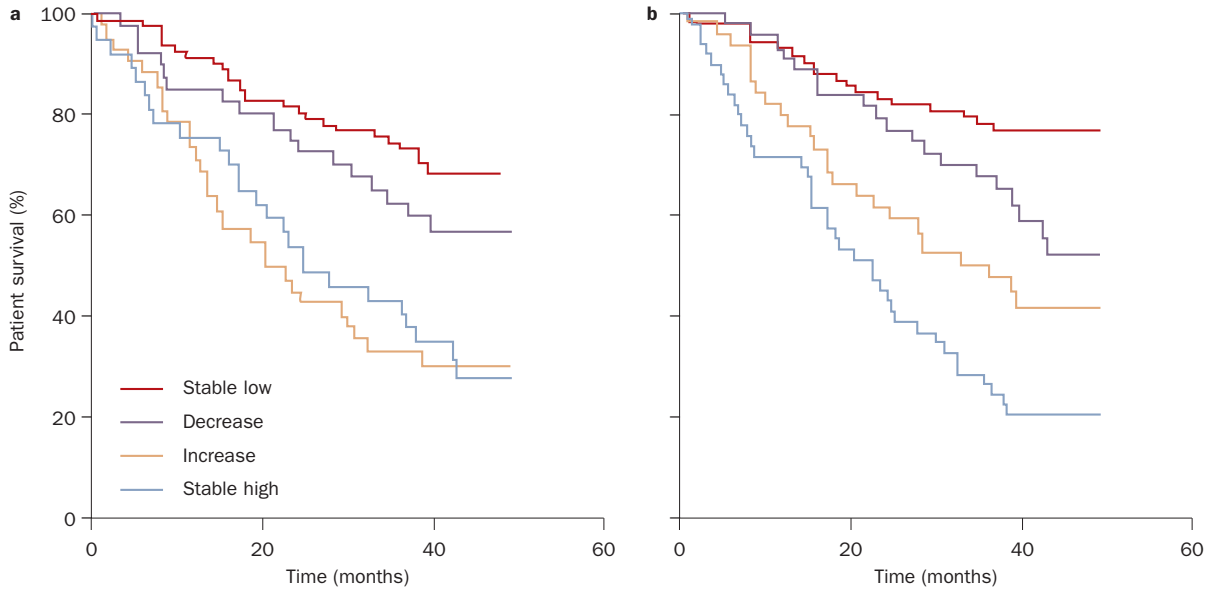

Figure 4. Kaplan–Meier survival curves according to trimestral variation patterns. a) CRP and b) IL-6 variations. Variation groups were created according to the tertile distribution at each time point. Survival curves in four different variability patterns are highlighted: a 'decrease' group, which contained individuals having a decrease in CRP levels from the upper tertile to the middle or lower tertile or from the middle tertile to the lower tertile; an 'increase' group which contained patients in whom CRP levels increased from the lower tertile to the middle or upper tertile, or from the middle tertile to the upper tertile; a 'stable high' group containing patients in whom levels remained in the highest tertiles; and a 'stable low' group containing patients who had both values in the lower or middle tertile. Abbreviation: CRP, C-reactive protein.

Why should we assess CRP?

In dialysis units, monthly CRP estimation could help to monitor the presence of contaminated water or dialysis fluid, audit vascular access status, and ensure optimization of dialysis protocols and dialysis. From a preventive point of view, however, CRP screening should not be used as an alternative to screening for major risk factors in determining patient risk, but should complement clinical judgment. Additional reasons for performing CRP measurements could be to motivate individuals with persistently elevated CRP levels to improve their lifestyles (by smoking cessation, dietary modification, exercise, and/or weight loss) or to comply with drug therapies.

To date, no solid evidence exists demonstrating the advantage of regular CRP monitoring in dialysis units. However, in an analysis from the ecological Dialysis outcomes and Practice Patterns Study,[16] Kawaguchi et al. reported that cardiovascular mortality was lower in renal facilities that measured CRP levels in ≥50% of patients. These data suggest that regular CRP monitoring could aid physicians' judgment and decision making, positively affecting overall patient survival. However, the design of ecological studies calls for caution in their interpretation owing to their susceptibility to the ecological fallacy. In this case, it is possible that units with a higher occurrence of CRP testing exhibited systematic differences in the use of materials affecting vascular access, dialysis filters, dialysis regimes or medicines. These factors could confound the observed inverse association between increased monitoring of CRP and cardiovascular mortality.

When should we assess CRP?

At the patient level, regular CRP screening could lead to further investigations into the underlying causes of inflammation and the assignment of appropriate treatment. During short-term monitoring, the most clinically interesting patients are those presenting a 'smoldering', chronically elevated CRP level in the range of 48–476 nmol/l (5–50 mg/l) (**Box 1**). Possible causes of these smoldering elevations include graft-related or catheter-related infections, peripheral arterial disease, silent coronary ischemia, ulcers, inflammatory bowel disease, malignancies, periodontitis, or hepatitis. According to the AHA/CDC recommendations, a second CRP measurement taken 2 weeks after the first might be useful in identifying transient processes while reducing biological variation in usual clinical practice.[90] Patients with elevated CRP levels within this smoldering range should undergo an extensive clinical work-up, whether or not they exert clinical symptoms. This scenario, in our view, is the most important and justified use for CRP screening at present. What has not been established, however, is how a clinical work-up should be performed in patients undergoing hemodialysis who have elevated CRP levels but no clinical signs of inflammation. In patients with rapidly rising CRP levels or levels consistently >476 nmol/l (>50 mg/l), the clinician should undertake all measures to detect overt infection, as well as other conditions associated with elevated CRP levels, such

Box 1. Possible causes of inflammation according to CRP ranges in patients undergoing dialysis*

CRP 47.6–476 nmol/L (smoldering or chronically raised)

- Failed kidney transplant in situ
- Biofilm (grafts, catheters, hemodialysis machine)
- Silent (encapsulated) infection of AV or arterial grafts
- Chronic obstructive uropathies
- Calciphylaxis
- Cholesterol emboli
- Peripheral arterial disease
- Silent cardiac ischaemia (myocardial ischaemia, stroke)
- Congestive heart failure
- Ischaemic ulcers, neuropathic and venous ulcers
- Chronic obstructive pulmonary disease
- Inflammatory bowel disease
- Periodontal inflammation
- Arthritis
- Hepatitis
- Major surgery

CRP >476 nmol/l (acute infection)

- Underlying renal diagnosis (infected cysts in autosomal dominant polycystic kidney disease)
- Vasculitis relapse, sinusitis, otitis
- Discitis, osteomyelitis, endocarditis
- Urinary tract infection/urosepsis, biliary sepsis
- Septicaemia, any cause (foreign material)
- Malignancy, de-novo and recurrent

* Normal CRP <47.6 nmol/l. Abbreviation: CRP, C-reactive protein. Adapted with permission from Oxford University Press © Wanner, C. et al. Nephrol. Dial. Transplant. 22 (Suppl 3), iii7–iii12 (2007).

as malignancy or relapse of vasculitis.[94] These diagnoses clearly show dynamic changes in the individual CRP distribution curve over time.[94] The studies addressing longitudinal changes in inflammatory status discussed above could assist clinicians in their interpretation of the outcomes of monitoring the inflammatory status. Clearly, persistent CRP elevations or increasing trends in CRP levels indicate patients at high risk of dying, and efforts should be made to address the causes of such elevations.

CRP measurements for mortality prediction

The evidence for a correlation between elevated CRP levels and an increased mortality risk among patients undergoing dialysis (even with multivariate adjustment for traditional risk factors) is abundant.[76,97] However, whether CRP measurements add prognostic value beyond traditional risk factor algorithms (such as the Framingham risk factor score) is not clear. Mallamaci et al. studied the predictive value of a composite of CRP and brain natriuretic peptide (BNP) levels in 246 patients undergoing dialysis.[98] The investigators observed that, by adding these two biomarkers to a basic score that was estimated using factors such as age, sex, smoking status, presence of diabetes mellitus and cardiovascular disease, and level of albumin, the explained variance increased by 9.9% for all-cause mortality and by 10.5% for cardiovascular mortality.[98] To our knowledge, no study has assessed the predictive gain that CRP measurements alone offer in addition to risk stratification by traditional risk factors in patients undergoing dialysis.

The study by Danesh et al. addressed the question of whether CRP level adds prognostic gain to traditional risk factors in patients with cardiovascular disease.[32] The investigators compared 2,459 patients who had a nonfatal myocardial infarction, or died as a result of coronary heart disease, with 3,989 healthy controls, all of whom were followed for 12 years. Danesh et al. reported that CRP measurements provided limited predictive value for mortality over and above established risk factors such as hypertension, cholesterol, and smoking. This study was acknowledged by the AHA/CDC as being indicative that insufficient evidence existed to support the use of CRP as a clinical tool in the prediction of cardiovascular events.[90] Modern epidemiological approaches have, however, helped us to gain further insight into the potential of such a clinical tool through the discrimination of deceased patients and the reclassification of risk by introducing novel biomarkers into a model based on traditional risk factors.[99,100] The study by Blankenberg et al., published in 2010, added CRP, n-terminal pro-BNP, and troponin I to a conventional risk model in three independent cohorts.[101] Adding any single biomarker separately to the established risk model did not improve risk estimation. By contrast, incorporation of all three biomarkers effectively reclassified the true mortality risk in 11% of the patients.[101] Such a risk model could have important implications in common risk algorithms for the general population; however, whether and how such a model would help patients undergoing dialysis who are already at high risk of mortality is unclear.

Managing increased CRP levels

No clinical trials targeting a decrease in inflammation as a means of improving outcome in patients undergoing dialysis have been performed. Therefore, current recommendations for treating inflammation in patients with CKD are patient-specific and mainly include identifying and treating the cause of the inflammatory response. The first step in dealing with increased CRP levels in this patient group is the treatment of intercurrent events and comorbidities that might cause inflammation. The next step would be to evaluate and, if possible, handle potential dialysis-related causes of inflammation. Various nonpharmacological anti-inflammatory treatment strategies, such as physical training and nutritional interventions,[91] could be considered at this stage. Another consideration is that inflammation does not occur alone and clearly impinges upon many other metabolic manifestations of uremia, perhaps acting as a catalyst and magnifying the risk of other concurrent risk factors.[102] For instance, higher doses of erythropoietin-stimulating agents are needed to maintain target hemoglobin levels in patients experiencing inflammation.[103,104] Thus, the best treatment for patients undergoing hemodialysis who have elevated biomarkers of inflammation would probably be multifaceted. Interventional studies reported since 2008 have suggested that a variety of drugs, such as cholecalciferol,[105] sevelamer,[106] angiotensin- convertingenzyme inhibitors,[107] pentoxifylline[108] and statins[109] have anti-inflammatory effects. Finally, on the basis of the observation that chemokine receptor type 5 (*CCR5*) polymorphisms influence the outcome of patients undergoing dialysis who are experiencing inflammation,[110] blockade of CCR5 could provide a novel therapeutic approach in some individuals.[111] Randomized, placebo controlled trials that specifically target inflammation in patients with CKD are eagerly awaited.

Anticytokine therapies are gaining importance in treating diseases with an elevated inflammatory component, such as rheumatoid arthritis.[112] However, some concerns have been raised about the use of such therapies, as they are usually mediated through the blockade of cellular and/or molecular functions that presumably have an important role in host defense. For instance, because TNF, IL-1 and IL-6 are key factors in both the innate and adaptive host defense system, increased rates of infections with the use of these therapies have been reported.[113] Additionally, since TNF plays an important role in granuloma formation and the defense against intracellular pathogens, reactivation of tuberculosis has been observed with TNF inhibitors in patients with diseases other than CKD.[113] In patients undergoing dialysis, the safety of TNF blockers (specifically etanercept) has been assessed in two small, but important, reports. Don et al. initially designed a 3-month intervention trial with subcutaneous etanercept (25 mg twice weekly) in six patients undergoing hemodialysis who had normal albumin (>42.0 g/l) or CRP levels (<48 nmol/l [<5 mg/l]).[114] The investigators reported no adverse effects during the treatment phase or subsequent 6-month follow-up. The pharmacokinetics of etanercept in patients undergoing hemodialysis were similar to those in individuals with normal renal function and, therefore, administration of etanercept to patients on hemodialysis was deemed feasible without dose adjustment. Following on from this research, in 2010 the same group reported the results of an intervention trial where 10 patients

undergoing hemodialysis were randomly assigned to receive etanercept or placebo over a 44-week period.[115] Risk of infection was a major exclusion criterion, and patients were allowed to participate if both hypoalbuminemia (>38.0 g/l) and inflammation (CRP >48 nmol/l [>5 mg/l]) were present. Unfortunately, <6% of the screened patients met the inclusion criteria and the study was therefore not sufficiently powered to detect potential changes in the primary outcome (an increase in albumin and prealbumin levels).[115] However, an important message from this report is that, again, administration of etanercept for more than 7 months seems to be safe and is not associated with the occurrence of adverse events.

Sample size in a hypothetical trials

At present, we await adequately powered, randomized controlled trials targeting inflammation as a treatment strategy in patients undergoing hemodialysis. However, on the basis of reported variability of the inflammatory response in patients with CKD, one would expect such studies to include, a priori, a large sample size. Intraindividual variability can be the result of measurement error and/or variability in the biomarker of interest (in this case CRP) or of patient-specific factors. In both cases, a practical solution to overcome the effects of such variability involves averaging consecutive measurements in each individual patient. To reduce variability due to measurement error, one solution would be to use the average of duplicate CRP measurements at each time point. However, given the reliable existing methodology for measuring CRP levels, variability caused by measurement error is not a major issue.[25] Intrapatient variability caused by patient-specific factors should be taken into account when a relatively longer period (for instance, weeks) is considered between successive measurements.

In practical terms, the primary outcome of a hypothetical study design can be defined as the average of two or more consecutive CRP levels measured some time apart. The following example illustrates that, by using the average of two or more consecutive CRP measurements taken 1 week apart, the minimum number of individuals needed in a hypothetical randomized controlled trial examining the CRP-lowering ability of a drug can be reduced. In this example, we use a cohort of 167 prevalent patients undergoing hemodialysis from the Stockholm region,[18] in whom CRP levels were measured weekly for 12 consecutive weeks. All CRP measurements were logarithmically transformed, because of non-normalcy in their distribution. Changes in the CRP levels, along with their standard deviations, were calculated over a 6-week period (during which a theoretical intervention could have taken place) on the basis of three different scenarios. In the first scenario, preintervention and postintervention values of CRP were both based on single measurements. In the second scenario, preintervention and postintervention values of CRP were both based on the average of two weekly measurements (two consecutive measurements 1 week apart). In the third scenario, preintervention and postintervention values of CRP were both based on the average of three weekly measurements (three consecutive measurements one week apart).

Table 2. Theoretical reduction in the sample size per arm of a hypothetical randomized controlled trial based on the use of average weekly CRP measurements to define end points[1]

	Δ CRP[2]	SD[3]	Reduction (%)[4]
End points based on single measurements	- 0.005	0.523	100
End points based on the average of two weekly measurements	0.016	0.442	71
End points based on the average of three weekly measurements	0.017	0.416	63

[1]The table illustrates a simulation of a hypothetical randomized controlled trial in which an increasing number of measurements causes a decrease in the standard deviation. This, in turn, effectively reduces the minimal number of subjects needed per arm. [2]Δ CRP; Changes in serum C-reactive protein levels over a 6-week period. Because of non-normality, CRP levels at both time points were logarithmically transformed. [3]SD, Standard deviation of the change in log-serum CRP levels. [4]Reduction in the minimum numbers of patients needed for a hypothetical trial. The squared ratios were multiplied by a hundred to obtain percentages. The scenario based on single measurements served as the reference category (100%).

From the logarithmic changes in CRP levels and their standard deviations, the reduction in the number of patients needed was calculated. This reduction equals the squared ratio of the standard deviation based on a single preobservation and postobservation, and on the standard deviation based on multiple measurements. As shown in **Table 2**, when the number of measurements is increased, the standard deviation of the change decreases gradually. Consequently, the minimum numbers of patients needed also decreases. This solution to high numbers of participants required would offer certain complexity in the accomplishment of the trial, but would provide a considerable reduction in the minimum numbers of individuals needed.

Conclusions

Inflammation is a prominent characteristic of patients undergoing dialysis. Although CRP is considered to be the prototypic inflammatory biomarker, its levels fluctuate substantially over time. Regular monitoring of CRP levels could provide us with important information on the existence of the processes behind this variability. Identifying and treating underlying proinflammatory processes is currently the only demonstrated way to tackle inflammation in this patient population. A number of studies in the dialysis setting pinpoint CRP levels as a powerful predictor of outcomes. Whether measurement of CRP levels adds predictive power beyond traditional risk factors is currently unclear. The available evidence suggests that regular monitoring of the inflammatory status could be an informative clinical tool for assessing disease progression and predicting outcomes. Finally, intraindividual CRP variability could be used to our advantage to reduce the number of patients necessary to adequately power future randomized controlled trials.

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