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The Pattern of Inflammation and a Potential New Clinical Meaning and Usefulness of C-Reactive Protein in End-Stage Renal Failure Patients

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Key Words

Microinflammation · Atherosclerosis · Cardiovascular disease · C-reactive protein · Hemodialysis · Risk factors, atherosclerosis · Risk index, atherosclerosis

Abstract

Inflammatory indexes are frequently elevated in end-stage renal failure (ESRF) patients. It seems that the pattern of inflammation is particular in this population. In the presence of a higher than normal microinflammatory background (CRP, C-reactive protein, values between 0.1 and 10–15 mg/l) that varies with time, waves of 'true' inflammation (CRP > 10–15 mg/l), mainly due to infections, are added periodically. To accurately assess the average microinflammation in these patients, multiple CRP measurements are required. As recent experimental studies showed that inflammation and particularly elevated CRP levels may be risk factors and not just a risk index for atherosclerosis, in this case, the characteristic inflammation pattern might be of importance in the evolution of this disease in ESRF patients. The causes of the inflammatory state in ESRF patients are multiple: renal insufficiency per se and its complications, coexisting diseases, established atherosclerosis, the consequences of renal replacement treatment, and frequent infections are potentially the main ones. The fluctuating inflammatory pattern is probably due to destabilization or changes in time of the above-mentioned parameters. Thus, the clinical meaning of the average microinflammation in these patients, as assessed by CRP measurements, seems to be that of an index indicative of the grade of their health aggravation by the multiple factors implicated in the inflammation formation. CRP is a sensitive, but not specific, risk index of the overall morbidity and mortality in these patients. The manipulation of the inflammation in ESRF patients should include follow-up and treatment of all the factors that contribute to this state and probably medications such as the statins. If inflammation and CRP in particular definitely prove to be risk factors for atherosclerosis, intensification of this treatment will be necessary.

Introduction

Inflammation is more frequent, and its level, as assessed by the serum inflammatory indexes, is correlated with cardiovascular disease (CVD) and overall morbidity and mortality in renal failure patients [1]. On the other hand, atherosclerosis is recognized as an inflammatory

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process, and, moreover, subtle C-reactive protein (CRP) increases seem to predict atherosclerosis complications in apparently healthy subjects [2].

The inflammation pattern observed in renal failure patients and the consequences of this particular pattern in the accurate estimation of microinflammation and possibly in the evolution of atherosclerosis in these patients have not been fully addressed until now. Furthermore, the exploration of the potential new clinical meaning and the usefulness of CRP measurements in end-stage renal failure (ESRF) patients based on recent findings seems possible nowadays and will be attempted to be addressed in this text.

This review will be focused on CRP, although other molecules (cytokines, chemokines, adhesion molecules, etc.) are also important in the inflammatory process, because this acute-phase protein is the marker more extensively investigated in clinical studies in patients with or without renal failure. It is a reliable index of inflammation (reflecting the intensity of inflammation rapidly and accurately), its serum level is dependent only on the hepatic synthesis rate [3], and it can be determined with high-sensitivity assays that are widely available, standardized [2], and relatively cheap; these data make CRP the most appropriate and well-studied (micro)inflammatory marker, for which a more solid proposal, applicable in clinical practice [2], can be formed at present.

Inflammation Pattern and Its Consequences in ESRF Patients

Inflammation Pattern

First Kaysen et al. [4] showed that inflammatory indexes vary with time in hemodialysis (HD) patients. Other investigators [5, 6] found that common inflammatory clinical events are in part responsible for this variability. In a longitudinal study [7], we examined this phenomenon in a group of 37 HD patients by measuring CRP, serum amyloid A, and interleukin-6 for 16 consecutive weeks and by recording every clinical event that usually induces inflammation during the same time period. We found that inflammation fluctuates in these patients. During periods (weeks) free from clinical events, microinflammation (CRP 3.70, 2.40, and 0.2–26.1 mg/l; mean, median, and range, respectively) predominated [7]. This level of low-grade inflammation was higher than that found in the general population – CRP 2.82, 1.42, and 0.1–16.1 mg/l (mean, median, and range, respectively) in a longitudinal study of 113 healthy subjects [8] – and showed a fluctuating pattern. From time to time, waves of 'real inflammation' – mean CRP 38.25 ± 39.35 mg/l during weeks positive for clinical events in our study [7] –, due mainly to infections, are added to this background microinflammation. Thus, the variability in time of the inflammatory indexes in HD patients seems to have a dual character: a microinflammatory background higher than in a healthy population that varies with time and a superimposed inflammation due to infections that is added periodically to the low-grade fluctuating inflammation.

It is worth noting that a similar pattern of inflammation is observed in patients with rheumatoid arthritis [9]. These differ from renal failure patients in that the superimposed inflammation is usually due to exacerbations of their disease rather than to infections. What both groups have in common, besides inflammation, is an increased morbidity and mortality due to atherosclerotic CVD [9].

Accurate Estimation of the Average Microinflammation in Renal Failure Patients

The characteristic fluctuating pattern of microinflammation in renal failure patients has to be taken into consideration, when an accurate estimation of the *usual microinflammatory background* is required. As we have previously shown, the average of two measurements of CRP with a high-sensitivity method, in weekly intervals free from clinical events, reflects with a relative accuracy the baseline level of microinflammation in HD patients [10]. The average value of three or four measurements may increase the reliability of this estimation [10]. Furthermore, we have calculated, applying receiver-operator characteristics, a cutoff point for CRP indicative of an inflammatory clinical event in these patients [7]. The cutoff point we have found for CRP was almost identical (10 mg/l) to that recently established [2] as indicative of inflammation not attributable to vessel wall damage in the general population. It is possible that this cutoff point is higher in other groups of HD patients, but, taking into consideration the majority of the studies where CRP was measured in ESRF patients, reporting values of between 8 and 15 mg/l [11], it seems improbable that the cutoff point will be >15 mg/l.

Thus, the estimation of the *average microinflammation* level in an ESRF patient seems to need two to four CRP measurements with a high-sensitivity method at weekly intervals free from clinical events. Every CRP value >10–15 mg/l has to be interpreted as being suspicious of a superimposed inflammatory event (usually infection) and, if confirmed by a repeated test, requires a complete

clinical and laboratory investigation of the patient for a possible inflammation focus [7].

Impact of the Inflammatory Pattern on the Evolution of Atherosclerosis in ESRF Patients

Although inflammatory markers are viewed nowadays more as risk indexes rather than risk factors for the atherosclerotic process, recent experimental studies constantly support the latter. Particularly for CRP, an increasing number of experimental studies showed that this acute-phase protein is potentially an active player in the atherosclerotic and innate immunity response processes [12–28] (table 1).

In case inflammation and specifically CRP have a pathogenic role in atherosclerosis, the characteristic inflammatory pattern of ESRF patients would be expected to influence the atherosclerotic process in this population; assuming that an increase of the CRP level precedes monocyte appearance – acting as chemoattractant for this cell – in the arterial intima [20], mediates low-density lipoprotein uptake by monocytes/macrophages [16], and activates endothelial cells to express adhesion molecules, chemokines [23, 24], etc., then every CRP increment – independent of its causes – is a potential initiating or aggravating atherosclerosis risk factor.

Finally, the similar pattern of inflammation probably also explains the common CVD morbidity and mortality profile observed in other chronically inflamed patients [9] (with collagen diseases, chronic pulmonary diseases, etc.).

Table 1. CRP as a risk factor in atherosclerosis

Laboratory studies
CRP is deposited in human atherosclerotic lesions [13]
CRP binds to (oxidized or otherwise modified and probably also to native) low-density lipoprotein [14–16]
In vivo studies
Increased thrombosis after arterial injury (human CRP-transgenic mice) [17]
Accelerated atherosclerosis (human CRP-transgenic apolipoprotein-E-deficient mice) [18]
CRP participates actively in the innate immune response
Activates the complement system [19]
Binds to apoptotic cells (through phosphorylcholine of oxidized phospholipids) [14]
CRP interacts with cells involved in atherosclerosis (in vitro studies)
Monocytes/macrophages
Chemoattractant [20]
Mediates low-density lipoprotein uptake [16]
Induces tissue factor synthesis [21]
Stimulates matrix metalloproteinase-1 expression (plaque destabilization) [22]
Endothelial cells
Induces expression of adhesion molecules and chemokines [23, 24]
Attenuates nitric oxide production [25]
Induces plasminogen activator inhibitor-1 expression and activity [26]
Vascular smooth muscle cells
Inhibits nitric oxide production [27]
Relaxes human vessels independently of endothelium [28]

The Multiple Causes of CRP Increase and Fluctuation in ESRF Patients

The causes that prime low- or high-grade inflammatory activity in ESRF patients are multiple. They are most probably related to the renal failure per se and its complications, to the comorbidities, to an already established atherosclerosis, to the consequences of renal replacement treatment, and to the frequent infections. The reason why renal failure is a source of inflammation has not been fully elucidated [29], but recent studies [30, 31] have shown that even at initial stages of chronic renal failure (serum creatinine >1.3–1.5 mg/dl), the CRP level is elevated. Furthermore, a number of renal failure complications may participate in this inflammatory activity. Arterial calcification, a frequent finding in ESRF patients, seems to be correlated with inflammation rather than being an inert event, as shown by a recent study [32]. In a number of comorbid conditions that frequently appear in these patients, low-grade inflammatory activity was found to be present in clinical studies done in the general population [33–40] (table 2). A grade of already established atherosclerosis is a common feature in ESRF patients [41]. The low-grade inflammatory activity in the arterial wall, which has been proven by many experimental and clinical studies in the general population [2], possibly contributes to the microinflammation background of these patients. Also, the procedure of HD or other methods of renal replacement treatment prime, in diverse ways, the immune response and contribute to the formation of microinflammations [42] – although more longitudinal studies are needed to confirm this [43] – in ESRF patients. Finally, infections are among the main causes of morbidity and mortality in these patients and are potentially the main sources of the 'real inflammation' in this population. In particular, the unresolved problem of vascular access in HD patients is a specific cause of intermittent

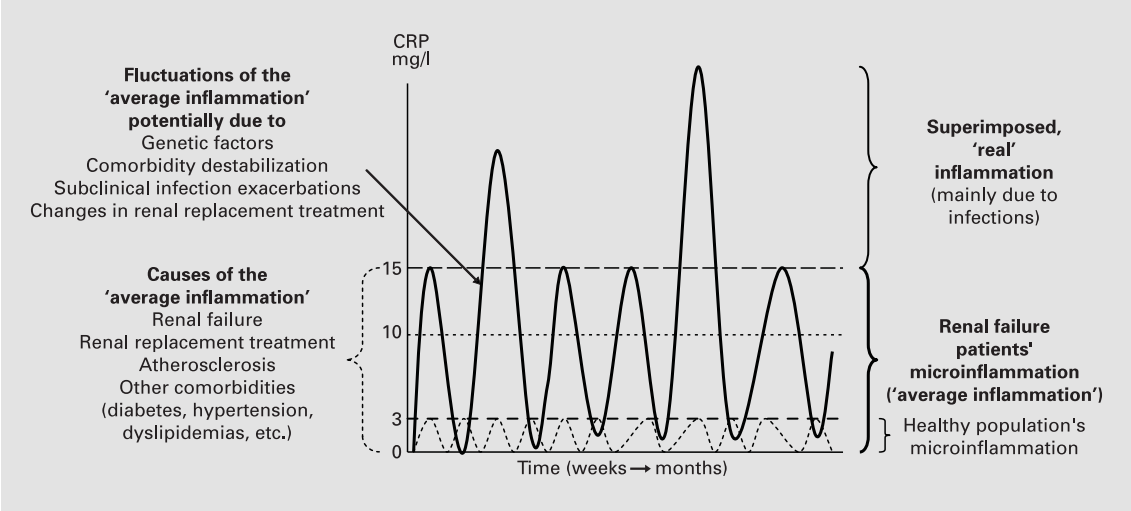

Fig. 1. The patterns of inflammation and their causes in ESRF patients. The cutoff point of CRP indicative of an infection is potentially between 10 [7] and 15 mg/l in these patients.

Table 2. Frequent – apart from atherosclerosis – comorbidities in renal failure patients that are associated (in clinical studies done in the general population) with CRP increases

Common
Diabetes [33]
Insulin resistance [34]
Dyslipidemias (hypertriglyceridemia, low high-density lipoprotein levels) [35, 36]
Hypertension [37]
Other
Periodontitis [38]
Obstructive sleep apnea [39]
Depression [40]

inflammation (infections clinically evident or subclinical, surgical procedures, every-other-day manipulation of the vascular access, etc.) or microinflammation in ESRF patients.

The average (usual) microinflammation (CRP level between 0.1 and 10–15 mg/l) in ESRF patients that is most probably due to the above-described causes varies with time. The potential causes of this waveform inflammation pattern are also multiple. A recent study [44] showed that a specific polymorphism of the CRP gene influences the intensity of the inflammatory response to diverse stimuli, and a similar finding is also valid for a genotype of the anti-inflammatory cytokine interleukin-10 in HD patients [45]; thus, the genetic background of the patient might determine, at least partially, inflammation fluctuations in renal failure patients. Also inadequately controlled diabetes [46] and/or hypertension (hypervolemia might be of importance in this setting), destabilized or new atherosclerotic injury of the arterial wall, or other destabilized comorbidities are potential causes of this 'renal failure average microinflammation fluctuation'. Changes in the material used in renal replacement treatment (more or less biocompatible blood lines and dialyzers, dialysis water, etc.) might be other causes of the inflammation variability with time. Several subclinical chronic inflammation stimuli (related to nonfunctioning vascular accesses or to chronic persistent infections, e.g., with *Chlamydia pneumoniae*) [47, 48] might, from time to time, exacerbate this inflammation. Malnutrition may also be related to inflammation and atherosclerosis (MIA syndrome) [49] in this population, but a cause-and-effect relationship is difficult to be clarified in this complex interrelation. Finally, to the average fluctuating microinflammation, 'real waves of inflammation' due mainly to infections are added periodically. The patterns of inflammation and their potential causes in these patients are presented schematically in figure 1.

A Potential New Clinical Meaning of CRP Measurements in ESRF Patients

In case the above-described causes of inflammation in ESRF patients are valid, and the list is complete, the average microinflammation level in these patients is the sum of many parameters. In this case, the new clinical meaning of CRP in ESRF patients – as opposed to the traditional one as a sensitive index of the activity of various collagen diseases, infections, traumatic conditions, tumors [3], etc. – is that of an index that reflects their overall health (or disease) state as determined by several conditions and potentially by their genetic background. In other words, it shows *the grade of their health aggravation* mainly by the renal insufficiency and its complications, by other severe diseases (atherosclerosis, diabetes, hypertension, etc.) that potentially coexist, as well as by the consequences of the mechanistic replacement of their renal function. This reflection is valid in case the average inflammation level is correctly measured and for the period of time during which all the above-described conditions remained essentially unchanged.

That the CRP – as an index of low-grade inflammation – has a high sensitivity but a low specificity is also obvious from results of studies that have used this acute-phase protein for correlations with morbidity and mortality in ESRF patients; in the majority of these studies CRP was correlated with CVD, but also with the overall morbidity and mortality in these patients [50]. It seems that the high sensitivity and the low specificity of the CRP in its traditional use [3] are similar also, in an extended sense, to its new clinical use. The CRP measurement was indicative of a disease or a condition's activity and was very useful in the monitoring of the treatment of this disease/condition, but was never helpful in establishing a specific diagnosis. In its new role, the microinflammation estimation in ESRF patients, its sensitivity is of value, because it can measure the aggravation of their health by a series of conditions, but its measurement is not helpful for the determination of a specific entity that might be responsible for this aggravation.

The Potential Usefulness of CRP Measurements in ESRF Patients

Could a CRP measurement be useful in clinical practice in case that its clinical meaning is the above described? It seems that the answer is positive. The accurate assessment of the average microinflammation level in ESRF patients, as assessed by CRP, could give us an estimation of their overall health status during the period of the measurement. A high value (in the range of 0.1–15 mg/l) should indicate an unfavorable condition – aggravated by renal insufficiency and its complications, eventually by atherosclerosis, diabetes, hypertension or other diseases, and by a less biocompatible renal replacement treatment – while a lower one should show a relatively good condition of their health, less aggravated by the above-mentioned parameters. It is useful to have an index that summarizes the harmful consequences of the most serious health problems that these patients may have. As recent clinical studies showed [1], the *CRP could be a sensitive risk index of the overall morbidity and mortality in ESRF patients*. On the other hand, the number of parameters that contribute to the microinflammatory state in ESRF patients is high, and determination of any specific association seems to be difficult. It seems improbable that the CRP measurement is useful for primary or secondary atherosclerosis prevention in these patients, as was recommended [2] – although before the publication of the results of the largest clinical study to date in this field that reconsidered the strength of this acute-phase protein for the prediction of CVD events [51] – for the general population.

Is it possible to manipulate a high average microinflammation level in ESRF patients? It does seem possible, but the complexity of such a manipulation has to be realized. As it is summarized in table 3, medications such as the statins, antioxidants, or the angiotensin-converting enzyme inhibitors could be helpful, but the therapeutic approach has to include an appropriate follow-up and manipulation of many parameters (keeping in mind that the genetic factor may play an important role, but it is not modifiable). Thus the role of some medications might be important, but probably is only subsidiary.

Table 3. Potential therapeutic interventions for manipulation of microinflammation in ESRF patients

Follow-up and treatment of renal insufficiency complications (Ca-P-vitamin D disturbances, anemia, etc.)
Follow-up and treatment of comorbidities (atherosclerosis, diabetes mellitus, hypertension, etc.)
Biocompatible renal replacement treatment (less immunostimulating dialyzers, high quality of the dialysis water, etc.) – vascular access follow-up and careful manipulation
Medications: statins, antioxidants, angiotensin-converting enzyme inhibitors

In case that inflammation is definitely proven to be a pathogenic risk factor and not only a risk index for atherosclerosis, the above-mentioned options have to be partially reconsidered. First, a satisfactory explanation for the high CVD morbidity and mortality in ESRF patients should be given. Second, an intensive manipulation of the average microinflammation level – and of the 'real' inflammation as well – in these patients will have to be considered as first-line treatment priority, but in this case as well, the therapeutic interventions have to include all the parameters listed in table 3.

Conclusions

The fluctuating pattern of inflammation in ESRF patients necessitates multiple measurements of the CRP for an accurate estimation of the average microinflammation level that is characteristic of every patient. This pattern of inflammation potentially contributes to the high CVD morbidity and mortality found in this population. The multiple causes that determine the level and the variability in time of this inflammation are related to the main medical problems these patients have and to the consequences of the renal replacement treatment and potentially show the degree of their health aggravation by these conditions. As a sensitive but not specific index of their overall morbidity, the CRP might be clinically useful as well. The interventions needed for the manipulation of inflammation have to take in consideration all the causes that contribute to its formation, and this therapeutic approach has to become more intensive in case that inflammation, and particularly CRP, will be definitely proven to be a pathogenic factor for atherosclerosis.

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