Interleukin/cytokine profiles in haemodialysis and in continuous peritoneal dialysis

Peter Jacobs, Griet Glorieux and Raymond Vanholder
Renal Division, Department of Internal Medicine, University Hospital, Ghent, Belgium

Abstract
The uraemic syndrome is a complex condition that results from the retention of ‘waste’ compounds that normally would be excreted into the urine or catabolized by the kidneys. In addition, inflammation has been implicated in symptoms associated with uraemia, including its role in the malnutrition–inflammation–atherosclerosis syndrome. Regarding vascular disease, traditional risk factors such as hypertension and gender do not seem to have the same significance in the uraemic population compared with patients without renal failure, and so the possibility has been raised that the uraemic toxins that result in the uraemic syndrome could play a role in this process. In this review, various questions are addressed regarding the involvement of cytokines in uraemia and the effects of dialysis membranes and fluids in patients receiving haemodialysis or peritoneal dialysis on cytokine levels. The effects of non-dialysis-related factors on levels of cytokines, mortality rates and other uraemic disorders are also discussed. It is concluded that cytokines are undoubtedly retained in uraemia, and that the loss of renal excretion almost certainly plays a key role in this process. Many cytokines have a pro-inflammatory role, probably resulting in a number of clinical events that are related to the increased morbidity and mortality of uraemic and haemodialysis patients. Any adjustment of the subtle balance between pro- and anti-inflammatory cytokines should be conducted carefully because of an enhanced risk of serious infectious episodes. Bioincompatibility of dialysis techniques probably enhances the generation of cytokines as well as other uraemic toxins.

Keywords: chronic renal failure; cytokines; dialysis; inflammation; interleukins; uraemia

Introduction
The uraemic syndrome is a complex condition that results from the retention of ‘waste’ compounds that normally would be excreted into the urine by the kidneys. These retention compounds are called ‘uraemic solutes’ [1]. Once retained, these compounds have a deleterious effect on physiological pathways and functions, and are called ‘uraemic toxins’. Many systems and functions are affected by these compounds [2].

Recent circumstantial evidence implicates inflammation in several of the symptoms experienced by a substantial proportion of patients with uraemia. Inflammation probably contributes to accelerated uraemic atherogenesis, and the association between malnutrition, inflammation and atherosclerosis in this population has been well recognized and is known as the malnutrition–inflammation–atherosclerosis (MIA) syndrome [3].

Atheroma formation in uraemia recently has raised many concerns. In dialysis patients, cardiovascular mortality is higher than in corresponding matched patients without renal failure, irrespective of age, sex and ethnicity [4]. The difference is ~40 times more pronounced in younger patients (<30 years of age) than in the older age strata (>85 years of age) [4].

During the last decade, there has been a shift in the perception of the pathogenesis of vascular disease [5]. Originally perceived as a degenerative disease, vascular disease recently has been classified as being at least partially inflammatory, with a pathophysiological role attributed to the adherence of activated leukocytes to the vascular endothelium, especially in the initiating stage [1]. Traditional risk factors such as hypertension and sex do not seem to have the same significance in the uraemic population compared with patients without renal failure [6], and so the possibility has been raised that uraemic toxins could play a role in this process [7]. The process itself almost certainly starts long before the patient reaches the stage of needing dialysis [8]. It is likely that several uraemic retention solutes are involved in the pathogenesis of atheroma, including a
number of cytokines which are known to have a pro-inflammatory role.

Unanswered questions

In this review, the aim is to answer the following questions:

- Are cytokines retained in uraemia?
- Do dialysis strategies affect the levels of cytokines?
  - Is there a role for dialysis membranes?
  - Is there a role for dialysis fluids in both haemodialysis (HD) and peritoneal dialysis?
- Do non-dialysis-related factors affect levels of cytokines?
- Is there a link between cytokines and mortality?
- Do cytokines play a role in other uraemic disorders?

The abundance of data in this area may make it difficult to formulate a consistent view. A recent Medline search with the keywords ‘cytokines’ and ‘haemodialysis’ resulted in 3405 hits, and 216 of these publications had been published in 2002. Although less prolific, an extensive literature on cytokines could also be collected in the areas of ‘peritoneal dialysis’ and ‘uraemia’ (Table 1).

Many issues relevant to this article are discussed in the European Best Practice Guidelines (EBPG) for Haemodialysis (Part 1) [9]. The EBPG are produced by working groups installed by the European Renal Association–European Dialysis and Transplantation Association (ERA–EDTA). The specific guideline issue devoted to HD is constructed around several topics which are of interest for the questions raised above, such as: (i) biocompatibility; (ii) quality of dialysis water; (iii) dialysis adequacy; (iv) infection; and (v) cardiovascular risk.

Practical concerns

The relationship between cytokines and cardiovascular risk in uraemia is a subject skewed by a substantial number of factors with opposing effects and which are often overlooked:

- The concentration of several cytokines has been shown to be altered in uraemia. Some authors, however, examine the concentration of cytokines in the blood [10], whereas others monitor leukocyte secretion [11]. Thus, the net effect may not necessarily be the same, because the impact of secretion on serum concentration cannot be predicted precisely.
- When leukocyte secretion is considered as the marker to be measured, some authors examine unstimulated leukocytes [12], whereas others analyse stimulated leukocytes [13].
- Under some conditions, the cell supernatant is evaluated. In other studies, however, the focus is on the intracellular production of cytokines, which are not necessarily released from the cell.
- Some cytokines which are released are pro-inflammatory [14], but their effect might be counterbalanced by the simultaneous release of anti-inflammatory cytokines [15] or soluble cytokine receptors [16].
- Cytokines are bound to proteins [17] and the uraemic syndrome is characterized by changes in protein binding resulting in changes in the biologically active fraction [18,19].
- Uraemia is characterized further by a resistance to several hormonal systems [20,21], and a similar resistance may also modify the response to cytokines.

In summary, the global picture for the involvement of cytokines in cardiovascular risk in patients with uraemia is extremely complex. It would certainly be unwise to conclude that the release of cytokines in uraemia is a uniquely pro-inflammatory phenomenon, and that coping with this problem will result in the prevention of all subsequent complications, such as atherosclerosis, malnutrition and/or inflammation. It would perhaps be more correct to think of a disturbance in the balance between pro- and anti-inflammation in uraemia, which over the long term results in atherogenesis, but, in the short term, may also be related to infection. Changing this subtle balance in an effort to decrease atheroma formation might, as a counterbalance, enhance the risk for serious infectious complications.

Are cytokines retained in uraemia?

In studies by Descamps-Latscha et al., it was demonstrated that the concentrations of several cytokines are elevated in patients with uraemia, independently of the patient baseline status, whether it is the pre-dialysis stage, HD or peritoneal dialysis [22]. In addition, a significant correlation was demonstrated between the decline in renal function and cytokine concentration.

Similar changes in concentration have been demonstrated for a host of cytokines (Table 2). Marked differences (up to 8-fold) have been reported in the literature, which may depend upon methodological factors [23,24].

It should be noted that a change in concentration does not necessarily mean a rise in concentration. As most cytokine concentrations are increased, however,

<table>
<thead>
<tr>
<th>Keywords</th>
<th>No. of hits (total)</th>
<th>No. of hits (2002)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines and haemodialysis</td>
<td>3405</td>
<td>216</td>
</tr>
<tr>
<td>Cytokines and peritoneal dialysis</td>
<td>856</td>
<td>53</td>
</tr>
<tr>
<td>Cytokines and uraemia</td>
<td>952</td>
<td>52</td>
</tr>
</tbody>
</table>
The cytokines shown in this table are present in abnormal concentrations (increase or decrease) during renal failure. IL = interleukin; IFN-γ = interferon-γ; MC-SF = macrophage colony-stimulating factor; TGF-α = transforming growth factor-α; TGF-β = transforming growth factor-β; IL-1R = interleukin-1 receptor; IL-2R = interleukin-2 receptor; IL-6R = interleukin-6 receptor; sTNFR = soluble tumour necrosis factor receptor.

The question can be asked as to whether reduced renal clearance plays an important role in their retention. This appears to be the case in view of: (i) the apparent negative correlation between renal function and cytokine levels [22]; and (ii) the increased plasma half-life of cytokines in experimental animals after nephrectomy [25].

Over the last few years, changes in cytokine concentrations have been demonstrated, not only for the best known and most currently studied cytokines, but also for some of the more recently detected cytokines such as macrophage colony-stimulating factor (MC-SF) and interleukin-18 (IL-18) [26].

Do dialysis strategies affect cytokine levels?

Certain HD membranes induce a more significant release of cytokine than others. This has been especially demonstrated for complement-activating membranes, such as cuprophan [27]. According to Schindler et al., a direct correlation exists between the induction of IL-1β mRNA and the increase in complement factor 5a (C5a) [28]. Cuprophan and other unmodified cellulose dialyser membranes are well known for their capacity to activate the complement system [29], and cytokine generation and release is one of the epiphenomena of this leukocyte activation [30].

Dialyser membranes may affect the plasma concentration of cytokines, not only by activating leukocytes, but also by adsorbing these compounds on the membrane surface. This is especially characteristic of some of the biocompatible synthetic membranes, which are composed of artificially manufactured ‘synthetic’ polymers [31]. Although performed in patients with acute renal failure, a study by De Vriese et al. demonstrated, however, that this adsorptive capacity is rather limited in time, and that in parallel with the removal of pro-inflammatory cytokines, anti-inflammatory cytokines also disappeared to the same extent [32], resulting in a net balance of zero. This again points to the two-edged impact of dialytic cytokine removal. Dialyser membranes have, by definition, been designed to remove waste products through diffusion and/or convection, and adsorption is probably nothing more than a fortunate side effect. It is clear that this adsorption is of relatively minor importance, mainly because of the restrictive surface area [1]. Specific adsorptive devices with beads, resulting in a cumulative area which may be hundreds of times higher, may be the only solution to this problem [33].

Another way by which the dialysis strategy might influence body cytokine load is by leukocyte induction caused by dialysate impurities, especially lipopolysaccharides (LPS) and LPS fragments [34]. Several studies point to such an impact, but these may not have been properly replicated in in vivo clinical conditions [35]. A number of other studies do not show such an inductive capacity of impure dialysate [36], but in these studies, the so-called ‘impure’ dialysate may already be of a sufficient quality that it does not induce leukocyte activation.

Enhanced serum cytokine concentrations have also been demonstrated in patients receiving peritoneal dialysis [22]. In these patients, dialysate bio(in)compatibility may also play a role. Patients treated with dialysate containing the less biocompatible lactate buffer had much higher levels of cytokines in the blood, compared with patients treated with dialysate with the more physiological bicarbonate buffer [37].

Involvement of non-dialysis related factors

In an in vitro study, Cohen et al. demonstrated that increasing the concentration of active vitamin D added to the medium could inhibit cytokine release by peritoneal macrophages from patients receiving chronic ambulatory peritoneal dialysis [38]. Uraemia is, however, characterized not only by a lack of active vitamin D, but also by a state of vitamin D resistance, which in turn is induced by uraemic retention solutes [20,21].

Genetic predisposition could affect the generation of cytokines. According to Girndt et al., the production of the cytokine IL-6 differed depending on the genotype of IL-10 receptor [39]. Infectious disease causes inflammation and hence might in turn induce cytokine release. Patients with chronic kidney disease, however, have a critical balance between pro-inflammatory factors, causing vascular damage and enhancing the risk for infection (which in turn causes inflammation). Inhibition of pro-inflammatory factors might allow anti-inflammatory factors to become more prominent, leading in turn to an increase in infections. In several recent studies, antibody development against the bacterium Chlamydia pneumoniae was correlated to vascular damage in uraemia [40–42]. In the general population, the atherogenic impact of C.pneumoniae remains a matter of debate [43] but, in a study by Stenvinkel et al., C.pneumoniae antibodies were found to be related to plasma concentrations of IL-6 [44].

Other uraemic toxins may also induce cytokine release. In a recent study by our group, guanidines were shown to enhance the production of tumour
necrosis factor-α by monocytes [45]. Similarly, advanced glycation end-products have been shown to provoke cytokine release [46].

The link between cytokines and mortality

In the seminal study by Kimmel et al., there was a highly significant correlation between cytokine concentration and mortality [24]. For some cytokines, the pro-inflammatory cytokines in particular, the correlation was positive, whereas for anti-inflammatory cytokines, a negative correlation was found [24]. It should be noted that the data from this study were based on relatively high cytokine concentrations, compared with the rest of the methodological literature [47], but the relationship between cytokine concentrations and mortality has been corroborated in a study by Bologna et al. [48].

What is the role of cytokines in other uraemic disorders?

Cytokines may play a role in a host of other symptoms and signs that are part of the uraemic syndrome. These include, but are not limited to, anaemia and erythropoietin resistance, osteopathy and bone disease, decline of residual renal function, malnutrition, susceptibility to infection, and carcinogenesis.

Although all of these items deserve extensive attention, special focus should be placed on the decline in renal function [49], which may have a specific impact on the final outcome. A residual renal clearance of 5 ml/min still removes more uraemic solutes per 48 h than an HD session of reasonable efficiency.

Conclusion

There is no doubt that cytokines are retained in uraemia, and that the loss of renal excretion almost certainly plays a key role in this process. Many cytokines have a pro-inflammatory role, probably resulting in a number of clinical events that are related to the increased morbidity and mortality of uraemic and HD patients. Some cytokines are anti-inflammatory, however, and it must be remembered that if pro-inflammatory cytokines were suppressed by medical interventions, the subtle balance between pro- and anti-inflammatory cytokines could be disturbed, resulting in an enhanced risk of serious infectious episodes. Bioincompatibility of dialysis techniques probably enhances the generation of cytokines as well as other uraemic toxins.

Conflict of interest statement. None declared.

References

13. Le Meur Y, Lorgeot V, Aldigier JC et al. Whole blood production of monocyte cytokines (IL-1β, IL-6, TNF-α, sIL-6R, IL-1Ra) in haemodialysed patients. Nephrol Dial Transplant 1999; 14: 2420–2426
33. Le Meur Y, Lorgeot V, Aldigier JC et al. Whole blood production of monocyte cytokines (IL-1β, IL-6, TNF-α, sIL-6R, IL-1Ra) in haemodialysed patients. Nephrol Dial Transplant 1999; 14: 2420–2426


