Influence of uraemia and haemodialysis on host defence and infection

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Introduction

Dysfunction of the host defence is one of the major functional disturbances in end-stage renal disease (ESRD) with substantial clinical and socioeconomic implications. The resulting higher susceptibility to infection may lead to life-threatening complications such as sepsis, septic shock, and abscess formation.

The immune system defends against infection via a cascade of finely tuned mechanisms, which include (1) the functional involvement of immunocompetent cells, (2) the release of humoral substances upgrading immunocompetence, and (3) the attraction of cells towards regions of infection. All these elements cooperate to achieve ingestion and destruction of infectious agents by phagocytic cells. The effect of uraemia (and its treatment by dialysis) on the immune system will be considered in depth, to formulate therapeutic approaches and preventive measures.

Responsible factors

Opsonization defects

The uraemic status may affect both the quality and the quantity of opsonins of which fibronectin is one of the important components. A decrease in fibronectin may be responsible for defective immunological mechanisms [1]. A defect in opsonization may be significant in the peritoneal cavity of chronic ambulatory peritoneal dialysis (CAPD) patients, where a depletion of opsonins has been detected [2,3]. With the exception of gravely ill patients, it is debatable whether the cost–benefit ratio is sufficient to advocate systematic parenteral or intraperitoneal administration of expensive, concentrated solutions.

Haemodialysis (HD) patients develop inadequate and delayed antibody formation after hepatitis B vaccination with rapid disappearance of these antibodies from the circulation [4,5]. Success may be improved by increasing the number of vaccinations, the dose of antigen [6,7], and possibly by measures which improve immune function such as rHuEpo administration [8] or use of haemodiafiltration [9]. Thymopentin, a biologically active synthetic pentapeptide, that corresponds to the active sequence of the thymic hormone thymopoietin, of which it retains all the impressive immunoregulatory properties, has been used with variable success [10,11]. However, alternative methods should be considered to improve antibody response, since most of these are immunopotentiating and can result in fever and inflammatory response, and can enhance the risk of rejection after transplantation.

Uraemic toxicity

Uraemic serum and/or ultrafiltrate have repeatedly been demonstrated to alter aspects of immune function [12,13]. Knowledge concerning the factors that are responsible remain, in part, speculative. Phosphate, potassium, phenols, phenolic acids, indoles, uric acid, parathormone, spermine, spermidine, endorphins, and guanidino compounds have been incriminated [14]. Interestingly, Hörl et al. recently described a 28 000 Dalton polypeptide and another moiety with a molecular weight of 9500 D, with granulocyte inhibitory properties [15,16]. The latter is structurally homologous with β2-microglobulin. Results from the authors’ group suggest that the lipophilic and protein bound phenolic compound, p-cresol, negatively impacts granulocyte glucose break-down and chemiluminescence production [17], while urea and creatinine had no such effect. These data indicate that at least some of the compounds that inhibit immune function in uraemia have physical and chemical characteristics that profoundly differ from those compounds currently used for monitoring and optimizing dialysis therapy, such as urea and creatinine.

It should be noted that free radicals, produced by immunocompetent cells, may also exert toxic side-effects. The production of hypochlorite may result in the synthesis of organic chloramines via its reaction with organic retention compounds [18]. The penetration of organic chloramines into the cell may be facilitated by the lipophilic properties or affinity for cells or intracellular organic structures of the reagents (e.g. spermine, spermidine, taurine) [19]. In addition, organic chloramines may persist longer, and/or be
metabolized more slowly than their inorganic counterparts, extending the duration of tissue toxicity.

Two studies evaluating the role of nitric oxide (NO), an extremely toxic free radical, resulted in contradictory conclusions. One group found depressed [20], while another observed enhanced [21] NO production. Uraemia may depress NO production by the accumulation of endogenous inhibitors of NO synthesis, such as asymmetrical dimethylarginine [20], whereas dialysis, especially with complement-activating membranes, may enhance NO production.

The nature and characteristics of the toxins depressing immune function in uraemia, as well as the metabolic and functional processes that are affected, need to be thoroughly investigated.

Iron overload
Iron overload, the most frequent form of disturbed iron metabolism in chronic uraemia, is due to excessive iron administration, blood haemolysis, and overt transfusion, especially in haemodialysis patients.

Patients with body iron overload show a markedly suppressed granulocyte response upon activation compared to patients with lower serum ferritin [22]. Episodes of bacteraemia per year are three times higher in patients with a serum ferritin above 1000 mg/l [23].

Body iron stores can be suppressed by the administration of rHuEpo. In a small group of patients with excessive body iron (average serum ferritin 1860 mg/l), Boelaert et al. found an improvement in phagocytosis and a decrease in serum ferritin after treatment with rHuEpo [24]. In a study by the authors' group, it was shown that erythropoietin tended to improve phagocyte metabolism, irrespective of the evolution of body iron [25].

Today, because of the availability of rHuEpo, patients with extreme iron overload are becoming rare. It should be noted that the administration of desferrioxamine, a method to reduce iron overload, may also lead to a diminished immune response [26].

Renal anaemia
In chronic haemodialysis patients, granulocyte CO₂ production in response to stimulation is correlated to the haematocrit [27]. Granulocyte response also improves with erythropoietin treatment [25]. A beneficial effect of rHuEpo has also been demonstrated for other aspects of the immune system, such as normalization of the composition of the subpopulation of lymphocytes, cytokine production, response upon vaccination and immunoglobulin production [8,28].

Trace elements
In renal failure, significant changes in concentration have been demonstrated for various trace elements. Among the factors that could interfere with immune function, we refer to cadmium, mercury, and copper accumulation, and to zinc depletion. Zinc therapy may improve impaired cell-mediated immunity in chronic uraemic patients [29].

Vitamin deficiency
Deficiencies of vitamin E, folic acid, and vitamin C may impair immune responses and cell immunity [30,31]. Supplementation of these water-soluble vitamins results in normal or greater than normal values of plasma vitamin levels [32]. Since this supplementation is common practice in many dialysis units, deficiencies of these vitamins will rarely play a role in immune dysfunction of uraemia.

Receptors for 1,25(OH)₂D₃ have been identified on human monocytes and T and B lymphocytes [33]. Vitamin D deficiency in chronic uraemia may affect the immune response, especially since 1,25(OH)₂D₃ acts as a cytokine for monocytes and macrophages [34].

Chronic renal failure results in a deficient renal 1,25(OH)₂D₃ production because of a decrease in renal mass with lack of 1-a-hydroxylase, and changes in calcitriol metabolism (both synthesis and degradation) also occur [35]. Hence vitamin D deficiency and resistance may have important consequences not only on the bone and calcium/phosphorus status, but also on other vitamin-D-dependent metabolic processes such as immunocompetent mononuclear cell function. Purines are among the potential inhibitors of vitamin-D-dependent metabolic activities [36], and a decrease in their concentrations may have a beneficial effect on calcitriol levels and biological activity [37].

Vitamin deficiency may interfere with immune response in renal failure. However, the current trend is to administer vitamin supplements, which generally results in normal and even too high levels of water-soluble vitamins. For vitamin D derivatives the problem may be more substantial in view of a relative end-organ resistance in uraemia. The mechanisms both of vitamin D resistance and of hypovitaminosis-D-dependent immune dysfunction need further elucidation.

Bio(in) compatibility of artificial organ treatment
The exposure of blood to cuprophane leads to repetitive activation of complement, degranulation of neutrophils, and release of oxygen free radicals [38]. Their unintended release results in decreased responsiveness to additional stimuli, e.g. infectious pathogens [39], in accordance with exhaustion of the immune system. In addition, the authors also described chronic, progressive inhibition of immune response during repeated contact with complement activating dialysis membranes [39]. Hence it is conceivable that membrane-related complement stimulation decreases the ability of the white blood cell to respond when it is really necessary. These findings parallel the poor response of granulocytes to various stimuli during other inflammatory states.

In addition to changes in direct parameters of poly-
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morphonuclear functional activity, more recent data point to marked differences in the expression of leukocytic surface molecules when cuprophane is compared to more compatible membranes, such as polysulphone [40,41]. Dialysis using cuprophane membranes results in activation of the baseline 'resting state', whereas upon stimulation (e.g. with phorbol myristate acetate) the response is blunted. The responsible mechanisms need to be further elucidated.

Although it is clear from the above-mentioned data that dialysis membrane structure may cause alterations in immune function which eventually result in infectious disease, the ultimate proof of the influence of bioincompatibility on infectious susceptibility will be the demonstration of differences in infectious incidence, morbidity, and mortality, dependent on the membrane used [42].

To date no prospective studies addressing this question have been performed. However, there are at least two retrospective clinical studies which suggest that membrane type influences susceptibility to infection [43,44]. Prospective data should be available in the near future, but susceptibility to infection in haemodialysis is so multifactorial that pure membrane effects may be hidden by numerous alternative factors.

In CAPD patients the need for hospitalization is at least in part caused by peritonitis [45]. This may be related to the instillation and/or the non-physiological composition of the peritoneal dialysate, or to the presence of a catheter entering the peritoneal cavity through the skin barrier. These can also be considered as a biocompatibility problem causing suppression of bactericidal activity by leukocytes [46]. Peritoneal effluent dialysis fluid has a negative impact on multiple functions of the phagocytic cell because of opsonin deficiency, uraemic toxins, and constituents such as glucose [47]. Haag-Weber et al. described at least two granulocyte inhibitory proteins, present in peritoneal fluid, which impair host defence [48]. Protracted intraperitoneal dwell-times inhibit IL-6 and TNF-α release by mononuclear leukocytes [49]. All these elements suggest the presence of toxic inhibitors in peritoneal dwell fluid.

Peritoneal macrophages of patients who suffer from a high incidence of peritonitis are insensitive to the cytokine effect of 1,25(OH)2D3 [50].

Fresh dialysate instilled in the peritoneal cavity also has a depressive effect on immunoreactive cells [51]. Low dialysate pH, lactate and dextrose content, and increased osmolality may all play a role. Alternatives in dialysate composition should be considered to minimize suppression of immune function.

To perform HD and CAPD it is necessary to perforate the skin by tubings, catheters, or needles, compromising the barrier function of the skin against invasion by bacteria, and enhancing the risk of infection [52]. Preventive measures against these events are still largely insufficient.

In dialysis patients a substantial risk of infection is associated with exogenous vascular access systems composed of foreign materials that are applied over long time periods, such as indwelling central vein catheters [52] or graft material as an alternative for arteriovenous fistulas [53]. Although the development of biomaterials rejecting bacteria would be useful, their manufacture has been hampered for reasons that are not always obvious.

Carriage

A specific risk for recurrent infection is caused by nasal carriage of Staphylococcus aureus [54]. Topical and/or oral administration of antistaphylococcal agents specifically decreases the incidence of S. aureus infections, [55], resulting in a substantial decrease in treatment costs.

The risk of infectious crises may equally be enhanced by the presence of chronic infectious disease (e.g. chronic urinary tract infection). Chronic low-dose prophylaxis may reduce the number of infectious episodes.

Malnutrition

In end-stage renal disease a substantial number of patients develop malnutrition [56], resulting in the inhibition of various aspects of immune function [57,58]. In the series reported by Churchill et al. low serum albumin as an index of undernourishment was associated with an increased risk of infection [59].

Protein-restricted diets, used to impede the progression of ESRD, induce undernourishment. The use of all-protein-restricted diets has been associated with non-specific decreases in circulating leukocyte numbers, and an ineffective in vitro response of mononuclear cells to various mitogens [60].

Drug treatment

A number of other causes of defective immune function that are not directly related to uraemia should not be overlooked. Immunosuppressive agents are administered to renal transplant patients and these with immune disorders. Treatment of infection by antibiotics may per se have a negative effect on the immune system [61], which counteracts their own anti-infective role. Indeed negative influences of any drug may be enhanced by altered pharmacokinetics and protein binding and increased retention of drug and drug metabolites due to renal failure.

Use of desferrioxamine as a chelating agent for iron and aluminium overload may induce immunodeficiency, especially depressing the fungistatic effect of serum against the yeast Rhizopus, resulting in a high incidence of fatal events due to mucormycosis [26]. This problem is especially acute in dialysis patients, which may be attributed to the altered pharmacokinetics of DFO in uraemia, resulting in its prolonged accumulation [62].
Conclusions

The immune defect in uraemia is multifactorial, mainly related to uraemic toxicity, various deficiencies, dialyser membrane bioincompatibility, anaemia, iron overload, and malnutrition. The changes of granulocyte function illustrate the pathophysiology associated with uraemic toxicity, and the strategies that should reduce this toxicity.

Our present knowledge indicates that the type of dialysis membrane used must be carefully considered. The cuprophane membrane apparently affects granulocyte response both acutely and chronically. However, direct evidence that increased rates of infection are associated with the use of certain membranes is not available. The fact that dialyser bioincompatibility could affect defence against infection could have important implications both for the treatment of acute and chronic renal failure. If the presently held hypotheses are confirmed, the use of cuprophane should be discontinued, even if only short periods of dialysis are foreseen, e.g. in acute events or for transplant candidates. This is especially the case in septicae mia intensive care patients with acute tubular necrosis, since recovery of renal function may also be delayed by the continued use of cuprophane [63].

Once the responsible toxin(s) for suppressing phagocytic function are identified, it might be suitable to develop specific adsorption systems. Until then, the only means to optimize phagocytic function in chronic dialysis patients is to pursue dialysis treatment that is as efficient as possible, with elimination of small water-soluble compounds, as well as larger and/or hydrophobic compounds.

Several pharmacological strategies are available to improve phagocytic function. Erythropoietin may be one of those. Whereas most antibiotics are suppressive or neutral in respect to immune function [61], the third-generation cephalosporin cefodizime clearly has a stimulatory effect on the immune system of uraemic patients [64,65]. The use of stimulants of immune function, such as cytokines or interferon, might improve immunological function [66], but we are not aware of any data that disclose their effect on infection risk in uraemia. In one single study the response towards hepatitis B vaccination was improved in long-term HD patients by the administration of recombinant human interferon [67]. At this moment virtually no information is available on the treatment of dialysis patients with HCV infection by interferon because renal failure is a relative contraindication to the use of this drug [68].

To our knowledge, no data is available about the effect of administration of colony-stimulating factors on immune function in uraemia. In one paper, spontaneously elevated levels of macrophage colony-stimulating factor were reported without any therapeutic intervention [69]. The question is whether these measures, if they were used in chronic renal failure patients, would not enhance bioincompatibility reactions and transplant rejection. Circulating and intracellular levels of cytokines appear to be already increased with exactly those treatment modalities (e.g. cuprophane dialysis), where decreased immune response has been suspected.

Iron and blood donations should be used with care. This can be realized more easily since the advent of proper methods to estimate body iron stores and the availability of rHuEpo. We feel strongly that iron overload will become more infrequent as rHuEpo treatment becomes routine. Treatment of iron overload with desferrioxamine may induce immune dysfunction by itself.

Care should be taken to avoid introduction of bacteria at insertion sites of dialysis catheters. Indwelling catheters for long-term use (either CAPD or HD) should be developed with materials of low affinity for bacteria.

Patients at risk of chronic infection might be treated with prophylactic long-term low-dose antibiotics. Antibiotic prophylaxis has been successfully administered to nasal carriers of S. aureus [54], resulting in a decrease in infection of access sites, skin, and soft tissue.

Malnutrition may be underestimated as a cause of immune deficiency and should be corrected by parenteral hyperalimentation, and/or the use of hormones stimulating tissue anabolism, e.g. growth hormone or erythropoietin. Although vitamin deficiency may cause immune dysfunction, incidence is low since most vitamins are adequately substituted or even over-substituted in uraemic dialysis patients. However, substitution of 1,25(OH)2D3, may be inadequate, since relative resistance occurs due to inadequate DNA response to receptor–vitamin complexes. Uraemic toxin accumulation, especially of purines, may play a role. Decrease of purine concentration, e.g. by allopurinol administration, may be corrective [37].

The main problem at the moment is that not all fundamental pathophysiological events in uraemic immune deficiency are exactly defined. This is especially true for complement activation and/or dialyser incompatibility-related events and for the toxic factors involved. Further study is necessary to formulate a more specific preventive and therapeutic approach.

Nevertheless, this paper summarizes our current knowledge of factors which contribute to infection of the continuously growing population with renal failure and/or on renal replacement therapy. Taking into account and countering these factors should decrease the number, severity, and mortality of these infections, improving the quality of life and survival of ESRD patients.

References

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