Inflammatory Syndrome in Patients on Hemodialysis

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Mortality is markedly elevated in hemodialysis (HD) patients. Between 30 and 50% of prevalent patients have elevated serum levels of inflammatory markers such as C-reactive protein and IL-6. The presence of inflammation, chronic or episodic, has been found to be associated with increased mortality risk. The causes of inflammation are multifactorial and include patient-related factors, such as underlying disease, comorbidity, oxidative stress, infections, obesity, and genetic or immunologic factors, or on the other side, HD-related factors, mainly depending on the membrane biocompatibility and dialysate quality. The adequate knowledge of these causes and their prevention or treatment if possible may contribute to improving the inflammatory state of patients who are on HD and possibly their mortality.

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Between 30 and 50% of prevalent patients who are on hemodialysis (HD) have elevated serum levels of inflammatory markers. In some patients, this elevation is chronic, and in some, it is intermittent and generally is associated with breakthrough processes. Furthermore, on many occasions, HD sessions trigger inflammation in a way that is not always identifiable with the conventional markers. Inflammatory markers are powerful predictors of mortality after adjustment for other risk factors (1–7). Inflammation also is responsible for other mortality risk factors, such as anemia, malnutrition, vascular disease, and left ventricular hypertrophy. For lowering the high morbidity/mortality rate in patients who are on HD, inflammation must be tackled. How? First, by identifying the causes, then preventing or treating them. This review examines the causes of inflammation in HD (Table 1) and how to approach them.

Inflammatory Markers

The gold standard among the microinflammatory markers in HD is C-reactive protein (CRP) (1–5). It is easy to measure and a good predictor of short-term (1 to 2 yr) mortality and has become a routine test in HD units to warn of inflammation. IL-6 probably is more related to mortality and is associated with more causes of inflammation than CRP (6,7); however, it is more difficult to measure, and it is of little use in clinical practice. All acute- phase reactants are inflammation markers. At the present, new markers that are more sensitive to specific situations are being sought, such as procalcitonin (8).

Underlying Disease and Comorbidity

Underlying disease *per se* can result in a chronic inflammatory state, as in the cases of autoimmune diseases and amyloidosis. Moreover, comorbidity, mainly as a result of ischemic cardiopathy, peripheral vascular disease, or diabetes, can be a risk factor for inflammation and oxidative stress (9,10).

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Oxidative Stress

Among the nonconventional cardiovascular risk factors, oxidative stress and vascular calcification gradually are gaining importance. Glycoxidation products and advanced oxidation protein products show a close relationship with inflammatory markers such as CRP and IL-6 (11–13). Therefore, the end products of these processes could act as inflammatory markers.

The generalized use of intravenous iron to treat anemia in HD units is noteworthy. Intravenous iron administration may release free iron that could react with hydrogen peroxide and generate free radicals. This results in an increase in advanced oxidation protein product levels, which are related to CRP levels (14), and in common carotid artery intima-media thickness (15). Therefore, treatment with intravenous iron could be considered as an additional inflammatory factor, as well as a risk factor for atherosclerosis in HD patients.

Vascular Calcification

Vascular calcification is more frequent and more severe in HD patients than in the general population. Both artery intimal and artery medial calcifications occur and constitute a significant morbidity/mortality marker that is associated with coronary atherosclerosis and arterial stiffness. Its cause is multifactorial. On the one hand, mineral metabolism alterations plays an important role, especially when there is an increase in serum phosphate or calcium-phosphorus product (16,17). On the other hand, there are certain vascular calcification inhibitors, such as fetuin-A and matrix Gla protein, that are inversely correlated with inflammation markers (18–20) and with coronary calcifications (21).

Infections

Several studies have demonstrated that infection by some microorganisms may participate in the development of inflammation and vascular damage in the general population (22–24). Infection with *Chlamydia pneumoniae* or *Helicobacter pylori* and periodontal disease are the most frequent. In HD patients, the presence of IgG or IgA antibodies to *C. pneumoniae* is associated

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Table 1. Causes of inflammation in HD[a]

Patient related
underlying disease
comorbidity, peripheral vascular disease
oxidative stress
Ca × P metabolism (calcification, fetuin-A)
infection (apparent and non-apparent)
Helicobacter pylori
Chlamydia pneumoniae
periodontitis
tuberculosis and others
vascular access
immunologic
genetic
nonfunctioning kidney transplants
encapsulating peritoneal sclerosis
anemia (hepcidin)
heart failure
obesity
tumors
physical exercise: sedentary lifestyle
Dialysis technique related
retention of inflammatory mediators
oxidative imbalance
acetate
pyrogenic substances of the dialysate
complement activation; membranes and other bioincompatible material

[a]HD, hemodialysis.

with a greater risk for cardiovascular events, and mortality is significantly higher (25,26). Furthermore, the carotid artery intima-media thickness has been reported to be greater in patients with IgA antibodies compared with patients without antibodies (27), and the number of atherosclerotic plaques is related to the titer of IgG antibodies in smokers but there is no such relationship in nonsmokers (28). In contrast, other authors found no differences in atherosclerosis scores between patients with and without antibodies (29), and the association with atherosclerotic disease was found to be very weak (30). Therefore, the relationship between infection with *C. pneumoniae* and atherosclerosis has not been established clearly. There is no clear connection between inflammation and *H. pylori* infection in HD patients either, as recently demonstrated (30). Consequently, further studies to establish the possible relationship between these infections and atherosclerosis are needed.

Periodontal disease is frequent in HD patients and is related to age, diabetes, smoking, HD duration, malnutrition, and inflammation (31). IgG antibodies to some periodontal bacilli are related to higher CRP levels (32). Moreover, CRP levels and erythrocyte sedimentation rate significantly decrease after periodontal treatment (33). Periodontitis, therefore, is a frequent occult source of chronic inflammation that could contribute to the atherosclerosis process and resistance to erythropoietic agents.

The prevalence of tuberculosis, mainly extrapulmonary, is increased among dialysis patients as a consequence of the depression of cellular immunity (34). Although the relationship with the inflammatory state has not been evaluated yet, it probably can be a contributory factor.

The type of HD vascular access is of prime importance for the evolution of HD patients. Patients with an indwelling catheter have higher comorbidity and a poorer survival on HD (35). However, its relationship with the inflammatory state has not been assessed sufficiently. It was demonstrated recently that patients with an indwelling tunnelled catheter have higher CRP levels and greater resistance to erythropoietin than those with arteriovenous grafts (AVG) or an arteriovenous fistula, who have the lowest values (36). Furthermore, patients with clotted AVG have elevated CRP, advanced glycation end products, and endothelial adhesion molecule levels (37–39). This demonstrates that clotted vascular access may play an important role in the inflammatory process. The elimination of these clotted grafts may result in a significant improvement in inflammation parameters (37). These findings suggest the need to monitor inflammation markers in patients with old clotted AVG, so they must be removed when in doubt.

Genetic and Immunologic Factors

Genetic factors such as single-nucleotide polymorphisms may influence significantly the immune response, the levels of inflammatory markers, and body composition, as well as the prevalence of vascular calcification in patients with chronic renal failure. Although genetic variations in the TNF-α–308 and IL-10–1082 single-nucleotide polymorphisms seem to be associated consistently with adverse clinical outcome in patients with ESRD, the results regarding genetic variations in the IL-6 gene have been conflicting (40).

Returning to HD after kidney transplant failure is becoming more frequent, especially in countries with high transplantation rates. It is standard practice to leave the nonfunctioning kidney transplant in place, even with low dosages of immunosuppressors, to maintain a minimum residual function. However, recent studies have demonstrated that, at least in some cases, the nonfunctioning kidney graft could act as a potent mediator of inflammation and erythropoietin resistance. In some cases, this situation may be completely asymptomatic but with the only evidence of elevated inflammatory markers. Only surgical removal of the graft can reverse the inflammatory state in these patients (41).

Encapsulating Peritoneal Sclerosis

This is a rare complication in peritoneal dialysis patients, and it means that they have to be placed on HD. These patients have elevated levels of biochemical inflammatory markers and a very poor prognosis (42). The best treatment is prophylaxis, with early detection of the disease in the peritoneal effluent in high-solute transporters. This disease currently is treated with pentoxifylline or tamoxifen with encouraging results (43,44).

Anemia

Although relative erythropoietin deficiency is a major factor in the anemia that is associated with chronic kidney disease, the chronic inflammatory state of uremic patients is an important associated factor. Stimulated mononuclear cells release numerous inflammatory cytokines such as IL-1, IL-6, TNF-α, and IFN-γ that may contribute to erythropoiesis suppression. Although the exact mechanism for this effect is not yet clear, the induction of apoptosis in erythroid progenitor cells is an important factor (45). Then, anemia mainly is a consequence of the inflammatory state instead of a cause. However, in recent years, hepcidin has been implicated as a complementary mechanism. This antimicrobial peptide, synthesized in the liver, inhibits intestinal iron absorption and is released into the circulation from the macrophages. It is stimulated by iron overload, hypoxia, and inflammation. The transcription of hepcidin is induced by IL-6 (46,47). In view of all this, hepcidin may be the link between inflammation and anemia (48,49), acting as an indicator of functional iron deficiency (50).

Heart Failure

Patients who are on HD and have a history of heart failure may have higher CRP levels (51). Furthermore, left ventricular hypertrophy has been associated with chronic inflammation states and oxidative stress (50,52–54). Recent studies have demonstrated that high-sensitivity CRP levels correlate positively with left ventricle mass and negatively with ejection fraction, and the multivariant analysis revealed that the chronic inflammatory state may be considered an independent risk factor for the development of cardiac hypertrophy and ventricular dysfunction in HD patients (52). However, whether control of the inflammatory state is accompanied by an improvement in cardiac size and function is not so clear.

Obesity

Obesity is part of the inverse epidemiology described for HD patients. In contrast to what occurs in the general population, HD patients with lower body mass index have a greater risk for mortality (55,56), and patients with excess weight have improved survival (57,58). Loss of adipose tissue may be the result of an inflammatory state, in which the release of proinflammatory cytokines may give rise to anorexia, predisposition to malnutrition, and weight loss (59–61). However, adipocytes are an important source of proinflammatory cytokines such as IL-6 and TNF-α, usually produced by monocytes, but they also are capable of producing other, more specific proteins, such as leptin and adiponectin. The latter is produced in a larger quantity than leptin and is inversely related with body mass index and resistance to insulin. Therefore, low adiponectin levels are associated with inflammatory markers and act as a predictor of cardiovascular events and mortality (61,62).

HD Technique

HD technique may contribute to maintaining the inflammatory state in many HD patients. Several theoretical mechanisms may be implicated: (*1*) The retention or nonelimination of proinflammatory molecules usually eliminated by the kidney; (*2*) potentiation of oxidative stress; and (*3*) stimulation of antigen-presenting cells, mainly monocytes, either directly or through contaminants. These cells in HD patients usually are preactivated, expressing CD-14 and CD-16 phenotypes in a greater proportion than in the general population (63).

Among the molecules that may be eliminated by convective transport using hemodiafiltration techniques are complement components (64), asymmetric dimethylarginine (65), and cytokines (66). It would be through this mechanism, by elimination of proinflammatory substances, that the preservation of renal function correlates inversely with inflammatory markers (67). HD regimens with greater depuration of all kinds of substances, such as nocturnal HD, also would have this effect (68). Techniques with a high middle molecule clearance, such as on-line hemodiafiltration, may contribute to decreasing inflammation in HD patients. Some protein-leaking dialyzers can improve chronic inflammation in HD patients (69).

Oxidative stress forms part of the inflammation mechanism. HD often is associated with an oxidative imbalance, in which oxidation of different lipids and proteins are predominant (68). Loss of some antioxidants, such as carnitine, during HD may contribute to this disorder (70). There is a clear interconnection between inflammation and oxidative stress in HD (71,72).

Several current HD components may provoke inflammation in patients. There is an intermittent, multiple stimulation during each HD session. Among these components are acetate, pyrogenic substances, and activation of the complement mainly as a result of dialysis membranes.

Exposure to 2 to 4 mmol/L acetate, which is contained in the bicarbonate dialysate, produces in many patients pathologic increases in acetatemia that could initiate inflammation or intolerance to the dialysis technique (73–75). Techniques such as acetate-free biofiltration or acetate-free dialysate could prevent this increase (74,75).

It has been demonstrated that pyrogenic substances are transferred to the blood through the dialysis membrane (Table 2). This depends not only on the amount of pyrogenic substances but also on its quality, and although this transfer occurs mainly by backfiltration (76), low molecular weight substances also may enter by backdiffusion. Endotoxins can cross any type of HD membrane; however, it has been reported that this occurs more easily with highly permeable membranes, in which backfiltration is more common. Reactions to pyrogens are much more frequent with high-permeability membranes than with low-permeability ones (77). Dialysis membranes that are capable of absorbing/retaining endotoxins, such as polysulfone, polyamide, posidine, and polyethersulfone, may decrease endotoxin transfer (78). Once in the blood, endotoxins are capable of activating monocytes and inducing cytokine release (79). This monocyte activation is not linear, and several factors intervene to increase or decrease cytokine production. It is a multifactorial process that is influenced by the type and the level of toxin, the type of membrane, various plasma factors, and the concomitant action of other monocyte activation and inactivation systems (79). It is known that the presence of proteins or whole blood is a potentiating factor in this activation process. Currently, at least two proteins are known: LPS-

Table 2. Bacterium-derived pyrogens and their detection

Bacterium Cell Wall	Molecular Weight (Da)	Limulus Test	Mononuclear Cell Test
Components			
LPS	>100,000	+	+
lipid A	2000 to 4000	+	+
other LPS fragments	<8000	+/−	+
peptidoglycans	1000 to 20,000	−	+
muramilpeptides	400 to 1000	−	+
others		−	+
Other cellular components			
bacteria DNA	Variable	−	+
Secreted toxins			
exotoxin A	71,000	−	+
exotoxin A fragment	<1000	−	+
other exotoxins	20,000 to 50,000	−	+

binding protein, a transporter, and a bactericidal permeability-increasing protein. These two proteins are necessary for this process to be carried out (80). The concomitant presence of other stimuli or signs, such as the activation of the complement, is very important. Finally, to make this process even more complex, some cytokine downregulators come into play, such as IL-10 (81). All of the above emphasizes the importance of the patient's nutritional and immune system status in this field and explains the different patient responses to the same HD technique.

The dialysis membrane and its capacity to stimulate monocytes, either directly or through activation of the complement, increasing cytokine production, is another specific inflammatory factor in HD patients. The behavior of HD membranes varies greatly, and some of them clearly are more biocompatible than others.

Monocytes, as effector cells, respond to the various stimuli and produce a chronic release of cytokines. Knowing that monocytes express the endotoxin receptor antigen CD14 (82) confirms that endotoxins are their primary stimuli. Nevertheless, for cytokines to be secreted, other concomitant stimuli are needed, such as the complement CD16 (82).

To prevent this inflammatory state, several actions must be taken: prevent and treat bacteria contamination of the dialysate; eliminate endotoxins from the dialysate by using suitable filters in the HD equipment hydraulic circuit; prevent or treat chronic infections in HD patients; use ultrapure dialysate; use biocompatible materials to prevent concomitant stimuli of the monocytes; and eliminate acetate, even low levels, in the dialysate. Maintaining a good nutritional status in HD patients may contribute to an improved immune response. Acting on LPS-binding protein and bactericidal permeability-increasing protein or on monocyte or cytokine receptors still is in the preliminary stages. The elimination of some of these stimuli could decrease the inflammatory response in patients who are on HD and are identified by plasma levels of inflammatory markers (8).

Conclusion

HD patients with inflammation have a poorer prognosis. Biochemical inflammatory markers help us to identify these patients. In most cases, the cause of inflammation can be determined through clinical investigation, and some of them may be eliminated or corrected. The prevention and the treatment of inflammatory syndrome is of high priority in patients who are on HD.

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