Mortality, malnutrition, and atherosclerosis in ESRD: What is the role of interleukin-6?

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Mortality, malnutrition, and atherosclerosis in ESRD: What is the role of interleukin-6? There is growing evidence that increased plasma concentrations of CRP strongly predict cardiovascular death in both non-renal and renal patient populations. The interleukin-6 (IL-6) system activity, which is the major mediator of the acute phase response, is often markedly up-regulated in uremic patients and has also been shown to predict outcome. This raises the issue of whether or not IL-6 per se may contribute to increased mortality from malnutrition and atherosclerotic cardiovascular disease in uremic patients. The causes of elevated IL-6 levels in the uremic circulation are not fully understood, although a number of factors prevalent in uremic patients, such as hypertension, adiposity, infections, and chronic heart failure may all contribute. However, factors associated with the dialysis procedure, such as bioincompatibility and non-sterile dialysate, may stimulate IL-6 production. Furthermore, available evidence suggests that genetic factors may also have an impact on circulating plasma IL-6 levels. We advance the hypothesis that IL-6 may play a central role in the genesis of inflammatory-driven malnutrition and that it may be regarded as a significant proatherogenic cytokine. This hypothesis may provide a rationale to test if targeted anti-cytokine therapy may be one way to combat the unacceptable high cardiovascular mortality rate among dialysis patients.

Chronic inflammation, as demonstrated by increased levels of various acute phase reactants such as C-reactive protein (CRP), has recently been shown to be a common feature and also to predict outcome and cardiovascular disease in end-stage renal disease (ESRD) patients [1]. Although it is evident that a number of pro- and anti-inflammatory cytokines such as interleukin (IL)-1, IL-10, and tumor necrosis factor-α (TNF-α) as well as soluble cytokine receptors orchestrate the inflammatory response [2], available data suggest that IL-6 plays a key role in these events. IL-6 belongs to a family of 20 kD polypeptide cytokines that are secreted from a number of different cells, including fibroblasts, adipocytes, monocytes and endothelial cells. It is notable that whereas most other cytokines function via paracrine/autocrine mechanisms, the major effects of IL-6 are a consequence of its concentration in the circulation and can take place at sites distinct and far from its origin [3]. As the hepatic mediator of the acute phase response, IL-6 is often markedly up-regulated in uremic patients and has also been shown to predict outcome. This raises the issue of whether or not IL-6 per se may contribute to increased mortality from malnutrition and atherosclerotic cardiovascular disease in uremic patients. The causes of elevated IL-6 levels in the uremic circulation are not fully understood, although a number of factors prevalent in uremic patients, such as hypertension, adiposity, infections, and chronic heart failure may all contribute. However, factors associated with the dialysis procedure, such as bioincompatibility and non-sterile dialysate, may stimulate IL-6 production. Furthermore, available evidence suggests that genetic factors may also have an impact on circulating plasma IL-6 levels. We advance the hypothesis that IL-6 may play a central role in the genesis of inflammatory-driven malnutrition and that it may be regarded as a significant proatherogenic cytokine. This hypothesis may provide a rationale to test if targeted anti-cytokine therapy may be one way to combat the unacceptable high cardiovascular mortality rate among dialysis patients.

Key words: interleukin-6, inflammation, atherosclerosis, malnutrition, mortality.

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CAUSES OF ELEVATED IL-6 LEVELS IN ESRD PATIENTS

The potential causes of elevated plasma IL-6 levels in ESRD patients are many. Kaizu et al [14] showed that...
IL-6 are increased in patients with CHF and that local and systemic effects of pro-inflammatory cytokines may have an important role in the pathogenesis of CHF [23]. It has been reported that changes in IL-6 and CRP are dynamic and that increased levels occur mainly with decompensated CHF [24]. Thus, it is important to distinguish between compensated and decompensated CHF when studying circulatory plasma levels of acute phase reactants and cytokines. As cardiac cachexia is a strong independent risk factor for mortality in non-renal patients with CHF [25], it seems conceivable that CHF may contribute to wasting, elevated levels of IL-6, and increased mortality also in ESRD patients.

Recently, a significant graded relationship between blood pressure and plasma levels of ICAM-1 [26] and IL-6 [26, 27] were observed in apparently healthy subjects. Based on these observations and the documented high prevalence of hypertension in ESRD, it could be speculated that poor blood pressure control might be another factor causing elevated IL-6 levels. Also increased total fat mass may be a cause of elevated IL-6 levels in ESRD patients because production of IL-6 occurs in adipose tissue [28]. As obesity is commonly associated with insulin resistance, it is not surprising that an inverse association between insulin sensitivity and IL-6 has been found [27]. Although accumulating data suggest that various persistent infections, such as Chlamydia pneumoniae, are associated with atherosclerosis, the mechanisms behind this association remain unclear. However, as it recently was demonstrated that the acellular components of Chlamydia pneumoniae are potent stimuli for IL-6 production [29], this may be one mechanism by which chlamydial infection causes atherosclerosis. This hypothesis is supported by two recent clinical studies, which showed an association between serological evidence of persistent chlamydial infection, carotid atherosclerosis, and elevated IL-6 levels in ESRD patients, (abstract; Kato et al, J Am Soc Nephrol 12:389A, 2001) [30].

Non-dialysis related factors that may cause elevated IL-6 levels

Because some studies have shown no difference in the circulatory levels of IL-1, IL-6, and TNF-α between long-term and not yet dialyzed patients, this suggests that the uremic syndrome per se may be a more important cause of elevated cytokine levels than the dialysis procedure [16, 17]. This may partly be caused by the fact that ESRD patients have a lower urinary IL-6 receptor excretion than controls [18]. Indeed, the deterioration of renal function has been shown to be associated with a significant increase in serum cytokine levels [19], and a strong positive correlation between creatinine clearance and various cytokines and their soluble receptors has been found in undialyzed patients with varying degree of renal failure [20]. Bolton et al [21] found in a multiple regression analysis that serum creatinine was the sole determinant of IL-6 levels in a group of predialysis and dialysis patients. Similarly, Panichi et al [22] recently demonstrated that both CRP and IL-6 levels are related to renal function in predialysis patients.

Clinical studies have shown that circulating levels of multiple factors, such as long-term HD, age, and the use of regenerated cellulose membrane dialyzer were associated with elevated IL-6. However, as a recent study showed that IL-6 production does not increase with age per se [15], it could be postulated that co-morbid factors associated with age are the main cause of elevated IL-6 levels. Indeed, a number of factors prevalent in ESRD patients, such as chronic heart failure (CHF), high blood pressure, increased body fat mass, insulin resistance, and chronic infections, have recently been shown to be associated with increased IL-6 levels.

Dialysis-related factors that may cause elevated IL-6 levels

Although Herbelin et al [5] found no difference in IL-6 activity between long-term and not yet dialyzed patients, others have found elevated IL-6 levels in dialysis patients compared with ESRD patients not yet on dialysis [4, 31]. This suggests that the dialysis procedure per se induces an acute inflammatory reaction and generation of IL-6. Indeed, Takahashi et al [32] demonstrated that both HD and PD generate an increase in blood mononuclear cell IL-6 mRNA expression and plasma IL-6 levels. Kaul et al [33] has demonstrated that the initiation of HD leads to a significant improvement of in vitro T-cell function. However, in this study it was notable that the expected normalization of IL-6 production did not occur, which may be the result of cytokine
Table 1. Possible causes of elevated interleukin-6 levels in ESRD patients

<table>
<thead>
<tr>
<th>Factor</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-dialysis related factors</td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>[27]</td>
</tr>
<tr>
<td>Increased fat mass</td>
<td>[28]</td>
</tr>
<tr>
<td>Insulin resistance</td>
<td>[27]</td>
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<tr>
<td>Persistent infections (such as chlamydia pneumoniae)</td>
<td>[29]</td>
</tr>
<tr>
<td>Chronic heart failure</td>
<td>[24]</td>
</tr>
<tr>
<td>Decreased residual renal function</td>
<td>[21, 22]</td>
</tr>
<tr>
<td>Genetic factors</td>
<td>[7]</td>
</tr>
<tr>
<td>Dialysis related factors</td>
<td></td>
</tr>
<tr>
<td>Bioincompatibility</td>
<td>[18]</td>
</tr>
<tr>
<td>Unpure dialysate</td>
<td>[34]</td>
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<tr>
<td>Backfiltration</td>
<td>[35]</td>
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induction of the dialysis membrane [33]. Several factors related to HD have been proposed to contribute to the generation of IL-6 and/or enhance the inflammatory effect of IL-6, dialysis against bioincompatible membrane [18], the use of non-sterile dialysate [34], and backfiltration [35]. There is as yet little available evidence in the literature regarding the effects of PD on the generation of cytokines. However, the systemic inflammatory effects of PD may be similar to those observed in HD as Libetta et al [31] found that PD induces activation of monocytes with an enhanced release of IL-6. We (abstract; J Am Soc Nephrol 12:438A, 2001) have recently observed an association between peritoneal transport rate for small solutes and both plasma and intraperitoneal IL-6 levels, suggesting that systemic and intraperitoneal inflammation may be involved in the pathophysiology of high peritoneal transport status in PD patients.

HOW COULD IL-6 INCREASE RISK OF CARDIOVASCULAR DISEASE?

In the past couple of years, there has been a shift in the general view of the origin of atherosclerosis. The current understanding is that an inflammatory process involving the acute phase response, a biological response to various disturbances such as infection, tissue injury, or immune disturbance, is a primary event [36]. As a recent study has shown that injection of recombinant IL-6 exacerbates early atherosclerosis in apoE-deficient mice, the role of IL-6 in this process may be important [37]. Indeed, several lines of evidence suggest that IL-6 is a significant proatherogenic cytokine. First, elevated levels of IL-6 are a primary stimulant of soluble intercellular adhesion molecule-1 (sICAM-1), which mediates the attachment and migration of leukocytes across the endothelial surface [38]. We have found a strong positive association between IL-6 and sICAM-1 in ESRD patients supporting this hypothesis (Fig. 2). Second, IL-6 may contribute to the development of atherosclerosis through various metabolic, endothelial, and coagulant mechanisms recently reviewed by Yudkin et al [3]. In this respect, it is of interest that both TNF-α and IL-6 inhibit lipoprotein lipase production in adipocyte cell lines [39], thus mediating lipolysis and dyslipidemia [40]. Further support for the concept that IL-6 may be more than just a marker of atherosclerosis may be derived from a recent study showing that increased IL-6 expression is involved at the fibrous plaque stage of the atherosclerotic process [41]. Finally, a recent clinical study demonstrated that elevated circulating IL-6 levels were independently associated with progressive carotid atherosclerosis during the first 12 months of dialysis treatment [30].

OTHER CYTOKINES AND THE AHEROGENIC PROCESS

It should be pointed out that other pro-inflammatory cytokines also might affect the atherogenic process. For example, it has been shown that TNF-α may be the key cytokine mediating endothelial dysfunction [42] and in vitro vascular calcification [43]. The latter effect of TNF-α could be one possible link in the documented association between inflammation, malnutrition, and cardiac valve calcification recently documented in PD patients [44]. It should also be mentioned that various anti-inflammatory cytokines, such as IL-10, might have protective properties in the atherosclerotic process. Girndt et al [45] have postulated that the secretion of IL-10 might be regarded as a compensatory mechanism that controls monokine induction and that patients unable to enhance IL-10 synthesis are at risk. Indeed, Smith et al [46] recently demonstrated that the serum levels of IL-10 are decreased in patients with unstable angina pectoris, and Girndt et al (abstract; J Am Soc Nephrol 12:380A, 2001) have re-
ported that the IL-10 genotype influenced the risk of cardiovascular events in 300 HD patients.

**NUTRITIONAL STATUS IS AFFECTED BY IL-6**

Disturbances in protein and energy metabolism, hormonal derangements, and a spontaneous reduction in dietary energy and protein intake may be responsible for the decline in nutritional status with progressive renal failure. Little is known about the specific mechanism(s) responsible for the altered appetite and metabolism in renal disease, although a role for pro-inflammatory cytokines has been proposed [47]. In elderly patients without renal disease, cachexia is usually associated with higher-than-normal concentrations of TNF-α, IL-1, and IL-6 [48]. An important role for IL-6 in this scenario could be proposed, as it stimulates the breakdown of muscle protein [49], activates cathepsin activity [50], and promotes cancer cachexia [51]. Moreover, IL-6 receptor antibody has been shown to inhibit muscle atrophy in IL-6 transgenic mice [52]. Also, clinical data suggest a significant role for IL-6 in mediating malnutrition in ESRD patients. Increased levels of IL-6 predict hypoalbuminemia [13, 30] and are associated with various markers of malnutrition in cross-sectional analyses [14, 30, 53]. Finally, Kaizu et al [14] showed that the body weight loss over 3 years was significantly higher, and serum albumin levels were significantly lower in dialysis patients with high IL-6 levels.

Although pro-inflammatory cytokines may predomi-
nantly cause malnutrition by increased protein catabo-
lism, they also affect appetite and eating behavior. The mechanism of cytokine-induced anorexia is not clear, although some studies have implicated a role of elevated leptin. Interestingly, both leptin and its receptor share structural and functional similarities with the IL-6 family of cytokines. Grunfeld et al [54] found that administration of cytokines increased leptin mRNA levels in hamsters and noted a strong inverse correlation between leptin mRNA level and subsequent food intake. Unfortunately, available data regarding the association between inflammation and leptin are conflicting in humans. Whereas Fouque et al [abstract; J Am Soc Nephrol 12:355A, 2001] have presented data showing a significant positive relation between IL-6 and serum leptin in HD patients, Don et al [55] demonstrated that leptin levels might actually be suppressed during inflammation. Thus, it is obvious that more studies are needed, especially in humans, to test if pro-inflammatory cytokines mediate anorexia directly at hypothalamic nuclei, indirectly through leptin, or by other mechanisms.

**TREATMENT STRATEGIES THAT MAY DECREASE IL-6 LEVELS**

As elevated IL-6 levels have a strong predictive power on outcome in ESRD patients and may have direct pro-
atherogenic properties, it could be speculated that various treatment strategies inhibiting IL-6 production could decrease cardiovascular morbidity and mortality. For example, Schouten et al [56] reported that, whereas the use of a bioincompatible dialyzer membrane (Cuprammonium) was associated with increased IL-6 levels, the use of a biocompatible membrane (Polysulfon) was not. Moreover, Schiffl et al [34] have shown that a change from conventional to ultrapure dialysis fluid reduced the levels of IL-6 and improved nutritional status in HD patients. In addition, other treatment regimens, such as ACE-inhibitors [57] and vitamin E [58], which have been shown to decrease IL-6 levels in plasma or monocytes in non-renal patient groups, should be considered in ESRD patients. Recently, cytokine-blocking agents, such as monoclonal antibodies, soluble receptors, and receptor antagonists, have been explored as therapeutic agents for patients with rheumatoid arthritis (RA). Injections of anti-IL-6 monoclonal antibodies have been associated with improvement in clinical variables as well as reduced acute-phase protein in RA patients [59]. It would therefore be of interest to study the effect of targeted anti-IL-6 treatment on inflammatory and nutritive parameters as well as outcome in ESRD patients. However, as the effects of IL-6 are complex and interrelated to local and systemic concentrations of other pro- and anti-inflammatory cytokines (e.g. TNF-α, IL-1, and IL-10), targeted anti-IL-6 therapy may turn out to have only minor clinical effects.

**CONCLUSION**

Interleukin-6, the major mediator of the acute phase response, is elevated in most, but not all, ESRD patients and predicts outcome. A number of factors prevalent in patients with ESRD, such as hypertension, adiposity, insulin resistance, CHF, and persistent infections could all be associated with elevated IL-6 levels. However, factors associated with the dialysis procedure, such as bioincompatibility and non-sterile dialysis fluids, also may stimulate IL-6 production. Although patterns of cytokines and their interactions may be more important than individual circulatory plasma levels, we advance the hypothesis that increased IL-6 levels may adversely affect nutritional status and have pro-atherogenic properties in ESRD patients.

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