

Inflammation in end-stage renal failure: could it be treated?

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Abstract

End-stage renal disease (ESRD) is characterized by an exceptional mortality rate, much of which is the result of cardiovascular disease (CVD). Although traditional risk factors are common in ESRD patients, they may not be sufficient alone to account for the high prevalence of CVD in this condition. Recent evidence demonstrates that chronic inflammation, a non-traditional risk factor which is observed commonly in ESRD patients, may cause malnutrition and progressive atherosclerotic CVD by several pathogenetic mechanisms. The causes of inflammation in ESRD are multifactorial and, while it may reflect underlying CVD, an acute-phase reaction may also be a direct cause of vascular injury by several pathogenetic mechanisms. Available data suggest that pro-inflammatory cytokines play a central role in the genesis of both malnutrition and CVD in ESRD. Thus, it could be speculated that suppression of the vicious cycle of malnutrition, inflammation and atherosclerosis (MIA) would improve survival in dialysis patients. Recent evidence has demonstrated strong associations between inflammation and both increased oxidative stress and endothelial dysfunction in ESRD patients. As there is as yet no recognized, or even proposed, treatment for ESRD patients with chronic inflammation, it would be of obvious interest to study the long-term effect of various anti-inflammatory treatment strategies on the nutritional and cardiovascular status as well as the outcome in these patients.

Keywords: atherosclerosis; chronic renal failure; cytokine; inflammation; malnutrition

Introduction

Cardiovascular disease (CVD) remains the main cause of morbidity and mortality in patients with end-stage

renal disease (ESRD). The annual mortality rate due to CVD is ~9%, which is 10- to 20-fold higher than in the general population, even when adjusted for age, gender, race and diabetes mellitus [1]. In fact, the death rate among ESRD patients with signs of inflammation, malnutrition and atherosclerosis are similar to what one finds in many patients with metastatic malignancy [2]. The causes of atherosclerotic CVD in ESRD patients are probably multifactorial. Classic risk factors such as dyslipidaemia, hypertension and smoking are prevalent in many patients with ESRD, but studies have shown that excess CVD is not explained adequately by traditional risk factors [3]. Thus, it has been postulated that non-traditional risk factors, such as oxidative stress and inflammation, may be more important [2,4]. Over the last years, the idea that inflammation plays a key role in atherosclerosis has received much attention [5] and, based on findings in non-renal patient groups, it is evident that inflammation may also be a contributor to cardiovascular morbidity and mortality in ESRD patients.

Markers of inflammation predict clinical outcome in dialysis patients

Since the first report by Bergström *et al.* [6] of an association between elevated C-reactive protein (CRP) and increased mortality, several groups have reported similar findings in both haemodialysis (HD) [7–9] and peritoneal dialysis (PD) [10,11] patients. Available evidence suggests that CRP is a precise objective index of the inflammatory activity and that it accurately reflects generation of pro-inflammatory cytokines, such as interleukin (IL)-6 and tumour necrosis factor- α (TNF- α). Accordingly, elevated serum levels of pro-inflammatory cytokines have also been demonstrated to be associated with increased mortality in dialysis patients [12,13]. As elevated CRP has been shown to be such a strong predictor of cardiovascular mortality [7,9], available data suggest that the association between inflammation and atherosclerosis is particularly strong in dialysis patients. Indeed, CRP has been shown to be an independent predictor of the

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number of atherosclerotic plaques in carotid arteries of dialysis patients [14], and a strong relationship between elevated CRP levels and atherosclerosis has also been documented in ESRD patients [15].

Strong relationships between inflammation, malnutrition and atherosclerosis

It may seem puzzling that whereas hypoalbuminaemia [16,17] and inflammation [7,9] have been shown to be important predictors of mortality in dialysis patients, complications from malnutrition and inflammation as such are not among the most common causes of mortality. In fact, malnutrition accounts for only 1–2% of deaths in renal patients [18], while atherosclerotic CVD is by far the most common cause of mortality in the dialysis population [1]. How can this paradox best be explained? One possible explanation may be the strong documented interactions between atherosclerotic CVD and inflammatory as well as nutritional parameters in ESRD patients [15]. Based on these findings, we have suggested the presence of a syndrome (MIA) consisting of malnutrition, inflammation and atherosclerosis [19]. This syndrome is present in a considerable proportion of patients who start dialysis treatment, and is associated with a high mortality rate [2]. Indeed, inflammation is more common in malnourished patients [20], and Ikizler *et al.* [21] have shown that the nutritional status and inflammatory response are independent predictors of hospitalization in HD patients. Moreover, malnutrition [22] and inflammation [7] are associated with a higher cardiovascular mortality rate in HD patients, and available evidence suggests that nutritional and inflammatory markers are closely linked to CVD in ESRD. Taken together, there seems to be a vicious circle of malnutrition, inflammation and atherosclerosis in ESRD patients and it is likely that pro-inflammatory cytokines may be important players in this scenario [19].

Causes of inflammation in ESRD

It has been recognized that ~30–50% of pre-dialysis [15], HD [7,9,14,20,23] and PD [24] patients have serological evidence of an activated inflammatory response (Figure 1). The highly skewed distribution of CRP and IL-6, as reported in these studies, suggests that patient-specific processes, such as clotted access grafts [25], or persistent infections, such as *Chlamydia pneumoniae* [11,26] and dental infections [27], may cause inflammation in ESRD patients. However, decreased renal clearance of pro-inflammatory cytokines, co-morbidity (such as chronic heart failure), accumulation of advanced glycation end-products (AGEs) and various factors associated with the dialysis procedure may also contribute to inflammation in ESRD patients (Table 1).

All available evidence suggests an up-regulated pro-inflammatory cytokine system activity in ESRD patients, and markedly elevated levels of cytokines have been found both before and after the start of dialysis treatment [12,28–30]. The cause(s) of elevated serum levels of pro-inflammatory cytokines in ESRD patients are not well understood, although both decreased renal clearance and increased cytokine production are likely to contribute. In some studies, no difference in serum levels of IL-1, IL-6 and TNF- α was observed between long-term and as yet undialysed patients, suggesting that ESRD *per se* may be the most important cause of elevated serum levels of pro-inflammatory cytokines [28,29]. Indeed, the deterioration of renal function has been associated with significantly increased serum cytokine levels in ESRD patients, and strong positive correlation between creatinine clearance and various cytokines and their soluble receptors has been demonstrated in undialysed patients with various degrees of renal failure [31–33]. Moreover, lower urinary IL-6R excretion is found in ESRD patients compared with controls [34]. Finally, it has been demonstrated that reduced renal function may affect both TNF [35] and IL-1 [36] clearance in nephrectomized rats. However, as the half-life of various cytokines is short and local tissue degradation may be the most important pathway of cytokine degradation, more research is needed to determine the relative importance of the kidney in cytokine clearance. Other non-dialysis-related causes of elevated CRP in ESRD patients might include factors such as chronic heart failure with oedema [37] and the atherosclerotic process *per se*. In fact, by virtue of its acute-phase behaviour, CRP may be a marker for severity and progression of atherosclerotic processes in the vessels [38].

When aldehyde or ketone groups of carbohydrates react with amino acids, a variety of complex compounds called AGEs are formed which may promote atherosclerosis through interaction with endothelial receptors. In ESRD patients, it is possible that an accumulation of AGEs caused by decreased renal clearance might promote inflammation [39]. A correlation has been found between one AGE, pentosidine, and CRP [40], and several *in vitro* studies show that AGEs can trigger an inflammatory response [41–43]. Thus, the stimulation of the monocyte by AGEs could be an initial signal of an inflammatory cascade leading to CRP production [44].

As some studies have reported that increased levels of pro-inflammatory cytokines are found primarily in dialysis patients [45,46], this suggests that the dialysis procedure, with extracorporeal circulation of blood, may cause inflammation (Table 3). Indeed, Haubitz *et al.* [47] have reported that CRP levels 24 h after HD were significantly greater than pre-dialysis values, and exposure of mononuclear cells to the dialysis membrane is a potential source for increased cytokine levels [48]. Apart from dialysis against non-biocompatible membranes [34,49], the use of non-sterile dialysate [50] and back-leak of dialysate across the dialysis

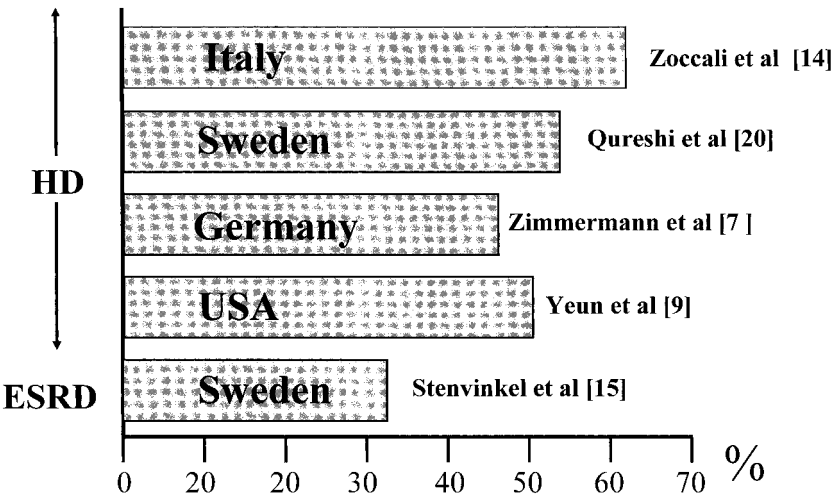


Fig. 1. Prevalence of elevated CRP (>5–10 mg/l) in studies conducted in HD and ESRD patients.

Table 1. Potential causes of inflammation in end-stage renal disease patients

End-stage renal disease	Additional causes in dialysis	Additional causes in peritoneal dialysis
Reduced renal clearance of cytokines	Graft and fistula infections	Peritonitis
Accumulation of AGEs	Bioincompatibility of dialysis membrane	Bioincompatibility of peritoneal dialysis solution
Chronic heart failure	Exposure to endotoxins and other cytokine-inducing substances from contaminated dialysate	Exposure to endotoxins and other cytokine-inducing substances from contaminated dialysate
Atherosclerosis <i>per se</i>		
Various inflammatory diseases		
Unrecognized persistent infections		

membrane [51] might also contribute to inflammation. However, it should be emphasized that although optimized HD therapy using ultrapure dialysate and biocompatible membranes reduces CRP, it does not normalize it [52], suggesting that dialysis-unrelated factors may be the most important cause of inflammation in ESRD.

Mechanisms by which chronic inflammation may cause atherosclerosis

Although the association between CVD and inflammation in the dialysis patient population is well documented, we do not know if the acute-phase response merely reflects an epiphenomenon accompanying established atherosclerotic disease or whether different acute-phase reactants themselves are involved in the initiation and/or progression of atherosclerosis (Table 2). However, several lines of evidence suggest that CRP actually may be directly involved as a causative factor in atherogenesis [53,54], and CRP recently has been shown to have direct pro-inflammatory effects on human endothelial cells [55]. Also other acute-phase reactants, such as Lp(a) [56] and fibrinogen [57], may have properties that accelerate atherogenesis. It should be emphasized that

Table 2. Direct and indirect effects by which cytokines and various acute-phase reactants may cause accelerated atherosclerosis

Direct	Indirect
CRP deposits in the arterial wall	Endothelial dysfunction
Serum amyloid A (SAA) affects lipoprotein structure	CRP
Lp(a) and fibrinogen promote athero- and thrombogenesis	TNF- α
TNF- α down-regulates apo E secretion and promotes calcification of vascular cells	Insulin resistance
IL-6 deposits in the arterial athero-sclerotic walls	Oxidative stress
	Persistent infections

pro-inflammatory cytokines may also have direct atherogenic effects *per se*. For an example, TNF- α has been shown to mediate endothelial dysfunction [58], down-regulate Apo E secretion [59] and promote *in vitro* calcification of vascular cells [60]. Also, IL-6 may have independent atherogenic properties, as a recent study has shown that injections of recombinant IL-6 exacerbate early atherosclerosis in mice [61]. Further support for the concept that IL-6 may be a cause of atherosclerosis comes from recent studies showing that elevated IL-6 predicts myocardial

Table 3. Various anti-inflammatory treatment strategies that could be considered in ESRD patients with MIA

Today	Tomorrow
Treat co-morbidity	Anti-cytokine therapy
Chronic heart failure	Anti-TNF- α antibodies
ACE inhibitors	Soluble TNF- α receptors
Ischaemic heart disease	IL-1 receptor antagonists
Acetylsalicylic acid	IL-6 receptor antagonists
Persistent infections	Thalidomide
Antibiotics	HMG-CoA reductase inhibitors
Optimal dialysis treatment	Immunonutrition
Biocompatible membranes	Vitamin E
Ultrapure dialysate	
Optimal nutrition	

infarction in healthy men [62] as well as cardiovascular mortality over a 5-year follow-up in elderly patients [63]. However, it should also be pointed out that the association between chronic inflammation and CVD may also be indirect, as chronic inflammation has been shown to be associated with endothelial dysfunction, insulin resistance and increased oxidative stress, all believed to cause atherosclerosis [64].

We need new treatment strategies of the inflamed ESRD patient

Although the prevalence of inflammation in ESRD patients is high, there are as yet no valid recommendations on how chronic inflammation should be handled (Table 3). Of course, if a persistent infection is found, it should be treated adequately by antibiotics. As various co-morbid conditions, such as chronic heart failure and coronary heart disease, may be a cause of inflammation, it is essential to optimize the treatment of these conditions. In this respect, it is of interest that it has been demonstrated that angiotensin-converting enzyme (ACE) inhibitors may suppress production of cytokines, such as TNF- α or IL-1 β , both *in vitro* [65] and *in vivo* [66], in mice. Moreover, the use of ACE inhibitors in pre-dialysis patients has been shown to be associated with lower TNF- α and CRP levels [67].

Aspirin has been shown to reduce both CRP and IL-6 levels in patients with angina pectoris [68]. Moreover, the reduction in the risk of myocardial infarction associated with use of aspirin seems to be directly related to the level of CRP [69]. Thus, treatment with aspirin could be a treatment of choice in ESRD patients with inflammation. However, in view of its significant side effects, such as bleeding [70], generalized use of aspirin could not be advocated in ESRD until prospective randomized studies have been performed. As available evidence suggests that the HD procedure *per se* may also cause an inflammatory response, it is important to optimize the HD treatment. The use of both biocompatible membranes [49,52]

and ultrapure dialysate [71] has been shown to reduce various inflammatory parameters, and HD patients with inflammation should thus be treated with biocompatible membranes and ultrapure dialysate.

As there is as yet not recognized, or even proposed, treatment for patients with MIA syndrome, it would be of obvious interest to find new specific treatment strategies that could improve the high mortality rate observed in this patient group. In view of the strong documented association between elevated levels of pro-inflammatory cytokines and mortality, it would be interesting to study the impact of various anti-cytokine treatment strategies in ESRD patients with MIA. Indeed, anti-cytokine therapy (e.g. anti-TNF- α antibodies, soluble TNF- α receptors and IL-1 receptor antagonists) in other patient groups with wasting disorders, such as rheumatoid arthritis [72] and chronic heart failure [73], has been found to be associated with a rapid improvement in not only clinical findings but also inflammatory parameters. It should also be noted that thalidomide (which selectively inhibits the production of TNF- α) reverses the wasting syndrome associated with HIV [74] and tuberculosis [75]. Prospective studies are therefore needed to investigate whether anti-cytokine therapies are safe and may have a beneficial effect on cardiovascular and nutritional status and mortality rate in ESRD patients with MIA. Moreover, as treatment with cerivastatin results in a significant reduction of CRP unrelated to the magnitude of lipid alteration [76], the anti-inflammatory effects of statins also need to be tested in ESRD patients.

Available recent evidence suggests that certain nutrients and/or antioxidants may have a significant modulatory role on cytokine biology [77], which is of interest as advanced oxidation products may be mediators of inflammation in ESRD patients [78]. Interestingly, supplementation with vitamin E decreases CRP [79,80] and monocyte IL-6 levels [79] in non-renal patient groups. Thus, as vitamin E has been shown to decrease the oxidative susceptibility of low-density lipoprotein [81] and to reduce cardiovascular end points in HD patients [82], it would be of interest to study the impact of vitamin E on inflammatory parameters in ESRD patients.

Conclusions

ESRD is characterized by an exceptional mortality rate, much of which is the result of CVD. Recent evidence demonstrates that chronic inflammation is a common feature in ESRD patients and it may cause malnutrition and progressive atherosclerotic CVD by several pathogenetic mechanisms. The cause(s) of inflammation is multifactorial and, while it may reflect underlying CVD, an acute-phase reaction may also be a direct cause of vascular injury. Available data suggest that pro-inflammatory cytokines play a central role in the genesis of both malnutrition and CVD. Thus, it

could be speculated that suppression of the vicious cycle of malnutrition, inflammation and atherosclerosis (MIA syndrome) would improve survival in dialysis patients. As there is as yet no recognized or proposed treatment for ESRD patients with chronic inflammation, it would be of obvious interest to study the long-term effect of various anti-inflammatory treatment strategies on the nutritional and cardiovascular status as well as the outcome in these patients.

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