Gülhane Tıp Dergisi 2007; 49: 271-276

DERLEME/REVIEW ARTICLE

The causes of the inflammation and possible therapeutic options in dialysis patients

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Summary

Cardiovascular morbidity and mortality are increased in patients with chronic kidney disease and especially dialysis. In patients with uremia, inflammation starts long before renal replacement therapy. Besides the other important parameters such as malnutrition and atherosclerosis, inflammation is one of the most important causes of morbidity and mortality in uremic patients. An association between cardiovascular mortality and morbidity and inflammation in both chronic kidney disease and dialysis patients has been demonstrated by a lot of studies in the past. Inflammation in patients with renal failure who have not yet begun dialysis and in patients receiving dialysis has shown increased levels of inflammatory markers, such as C-reactive protein, interleukin-6, tumor necrosis factor-alpha. In this review, it is tried to discuss both possible causes of inflammation and possible therapeutic strategies in dialysis patients.

Key words: Hemodialysis, inflammation, peritoneal dialysis, therapeutic options

Özet

Diyaliz hastalarında inflamasyon nedenleri ve muhtemel tedavi seçenekleri

Kronik böbrek hastaları ve özellikle diyaliz hastalarında kardiyovasküler morbidite ve mortalite artmıştır. Üremili hastalarda inflamasyon, renal replasman tedavisinden uzun süre önce başlamaktadır. Malnütrisyon ve ateroskleroz gibi önemli parametrelerin yanında inflamasyon, üremik hastalardaki mortalite ve morbiditenin en önemli nedenlerinden birisidir. Kardiyovasküler mortalite ve morbidite ile inflamasyon arasındaki ilişki, hem kronik böbrek hastaları hem de diyaliz hastalarında geçmişte yapılan pek çok çalışma ile gösterilmiştir. Henüz diyalize başlamamış olanlar ve halen diyalize girmekte olan böbrek yetmezliklilerde C-reaktif protein, interlökin-6 ve tümör nekrozis faktör-alfa gibi inflamasyon belirteçlerinde artışlar gösterilmiştir. Bu derlemede diyaliz hastalarındaki inflamasyonun hem muhtemel nedenleri, hem de muhtemel tedavi stratejileri tartışılmaya çalışılmıştır.

Anahtar kelimeler: Hemodiyaliz, inflamasyon, periton diyalizi, terapötik seçenekler

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Date submitted: April 11, 2007
Accepted: May 24, 2007

Introduction

Inflammation may contribute to the progressive loss of kidney function by promoting endothelial dysfunction and glomerular damage. Low-grade inflammation is indeed present at early stages of chronic kidney disease (CKD), and it is believed that the reduction of renal function per se runs parallel with an increase in the inflammatory response (1,2) also after starting renal replacement therapy (3-5). Patients with CKD stage 3-5 are at risk for progression of kidney disease and development of ESRD. In one study it has been suggested that most patients with stage 3-5 will die of cardiovascular complications prior to the development of end-stage renal disease (ESRD) (2). Chronic inflammation may indeed be one of the causes of the increased mortality and morbidity observed in this population (6-8), especially because of its association to atherogenesis and cardiovascular events, which account for approximately 50% of the deaths among patients undergoing dialysis therapy. Recent epidemiologic data show that upon commencement of dialysis therapy, 40% to 75% of patients already have manifestations of cardiovascular disease (CVD) (9). Some studies have shown that there is a high prevalence of acute-phase inflammation

including CRP and IL-6 and oxidative stress, both of which are associated with the high rate of cardiovascular mortality and morbidity (2,10). Several studies have shown that IL-6 levels may be the most reliable predictor of CVD and mortality (11,12). However, because CRP is cheaper to analyze, this more readily available inflammatory biomarker may be used in clinical practice to evaluate the presence and degree of inflammation. The present review aims to summarize our present understanding of the factors of this chronic inflammatory state in the dialysis population.

Multiple causes of chronic inflammation in ESRD

The reasons for the increased risk of persistent low-grade inflammation in ESRD patients appear to be complex and include a variety of both non-dialysis related and dialysis related factors that stimulate the inflammatory response by activating the production of interleukin 1 (IL-1), IL-6, TNF-α and interferon-γ (IFN-γ) by macrophages (13). In addition, the impaired immune response characterized by hyporesponsive neutrophils and T-cells present in CKD patients also contributes to the low-grade inflammation seen in ESRD. The combination of an impaired immune response coupled with a persistent immune stimulation might have an important role in low-grade inflammation and altered cytokine balance which are present in ESRD (13).

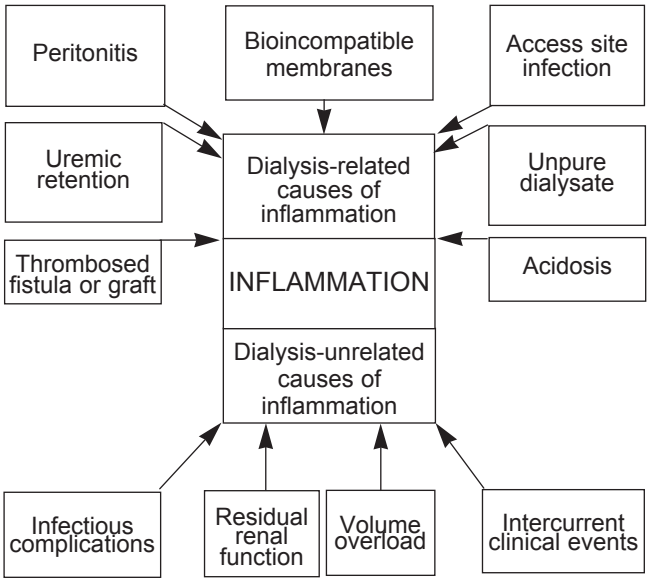

Figure 1. Possible non-dialysis and dialysis related causes of inflammation in ESRD patients

Dialysis-unrelated factors

Residual renal function

A reduction of kidney function per se is associated with an inflammatory response in both mild and advanced renal failure, suggesting that differences in residual renal function may contribute to this "uremic inflammation", perhaps through the retention of circulating cytokines (13). As the failing heart produces large quantities of pro-inflammatory cytokines, volume overload and/or congestive heart failure may also link inflammation to reduced residual renal function (13). Not surprisingly, strong interrelations between inflammation, residual renal function and cardiac hypertrophy are found in peritoneal dialysis (PD) patients (14).

Chronic inflammation can be related to uremic conditions and explained by reduced excretion of cytokines (10,15). The catabolic effects of hemodialysis procedure are well documented (16,17), indicating modest changes in selected cytokine concentration before and after the hemodialysis session, with the use of bioincompatible membranes (18,19). Caglar et al. have hypothesized that the hemodialysis procedure indeed induces an acute inflammatory reaction, which is further exacerbated during the 2-hour period following completion of the hemodialysis session (17). Carrero et al. have recently observed that during the first year of dialysis, CRP concentrations decreased significantly in hemodialysis (HD), but not in PD patients, suggesting that dialysis procedures might exert different effects on inflammation (20). The reason for this finding is still unclear, but it could be speculated that frequent heparinization may hamper pro-inflammatory status in HD patients (20).

Infectious complications

Infections are common in CKD and dialysis patients possibly as a consequence of impaired humoral and cellular immunity and vascular access (21). The prevalence of tuberculosis, for instance, is higher in dialysis patients, and wasting syndromes may be the result of *Mycobacterium tuberculosis* infection. Other inflammatory diseases, including systemic lupus, rheumatoid arthritis and other malignancies usually accompany CKD or dialysis patients. Dialysis patients who have diabetes with foot infection are also one of the other sources of infection (21,22). Periodontitis, a chronic bacterial infection of the oral cavity, has for instance been associated with renal insufficiency and related to elevated CRP values in HD populations (23,24).

Intercurrent clinical events

Intercurrent clinical events including infections, surgical interventions and inflammatory or injurious conditions may be related to inflammation. In one study neither the type of dialyzer nor bacterial quality of the

dialysate predicted CRP values in HD patients (25). Whether changes in CRP values, which are associated with intercurrent clinical events, influence the long term prognosis of chronic HD patients is unknown.

Volume overload

Overhydration is frequent in patients with renal failure and may contribute to inflammation. Extracellular volume control besides contributing to cardiovascular morbidity and hypertension is closely related to patient survival in PD patients. Extracellular fluid volume expansion is believed to increase inflammation (26,27), and adequate control of extracellular volume has prevented loss of residual renal function and reduced cardiovascular mortality and morbidity (28).

Dialysis-related causes of inflammation

Peritonitis

Peritonitis remains one of the most important complications of PD and contributes not only to the inflammatory status but also to the mortality of PD patients (29). Bacterial infections usually occur by inoculation through or around the catheter or by contamination of dialysate, providing an additional inflammatory stimuli (30).

Uremic retention

A number of compounds are retained in uremia and such compounds often interact with the proinflammatory milieu, resulting in their oxidative modification (31). A number of uremic retention solutes, such as guanidine compounds, have shown to exert both pro- and anti-inflammatory effects on monocyte/macrophage function, which could altogether contribute to CVD in this group of patients (32).

Unpure dialysate

The microbiological impurity of hemodialysis water and dialysate might constitute a cause of chronic inflammation in the dialysis population. Uremia and its metabolic complications, together with the bioincompatibility of the components of the dialytic procedure could contribute to higher cytokine concentrations. Inflammation mediated by the cytokine response to bacterial contamination of the dialysis fluid appears to be an independent factor affecting the nutritional status of HD patients (33).

Bioincompatible membranes

The type of membrane, its flux and the extent of convective transport are additional factors that may influence inflammation. Indeed, direct blood membrane specific interactions, the permeation of bacterial products from the dialysate and the activation of the complement because of these interactions have been shown to stimulate cytokine production in the blood stream, and high-flux membranes showed a better performance against cytokine-inducing substances from the dialysate (34).

Access site infection

Vascular access site-related infections can also increase inflammation in dialysis patients. Venous catheters are associated with increased rates of infections as compared to other forms of vascular access (35). Catheter related bacteremia may have various clinical presentations, and stringent monitoring in this regard can substantially minimize the global impact of vascular access-related infection (36).

Thrombosed fistula or graft

The incidence of infections caused by the HD vascular access have shown to be higher when a central venous catheter is used and lower when a native arterivenous fistula is implanted (37). It has also been shown that there is a higher infection rate when using a graft than when using a native arteriovenous fistula and that such infections are indeed contributors to the systemic inflammation (38). However, bacterial infections in thrombosed grafts and fistulas tend to be silent, which makes it difficult to diagnose (36), and further research is warranted with regards to the detection and management of infections derived from old thrombosed grafts.

Acidosis

Acidosis is a well known complication of uremia that also contributes to inflammation. Consumption of ammonium chloride in animal models increased the excretion of urea nitrogen (34,39), and acidosis augmented the in vitro production of IL-6 and chemokine (regulated upon activation, normal T cell expressed and secreted) RANTES from smooth muscle cells, suggesting a direct contribution to chronic inflammatory uremic state (18).

Adipose tissue and malnutrition as causative inflammatory factors

Recent discoveries, notably of the adipokines leptin and adiponectin, have revised the notion that adipocytes are simply a storage depot for body energy. Instead, hormones secreted by the adipocytes (adipokines) act as autogenic regulators of body fat depots, modulating

gastrointestinal activities, metabolic changes and central nervous mechanisms, and have been speculated to play a central role in the development of complications often observed in this group of patients, such as insulin resistance, CVD and sarcopenia (40). Furthermore, there are intimate links among adipokines and pro-inflammatory cytokines as well as between fat and muscle tissue (41). Considering the dramatic effect that loss of renal function has on the clearance of these substances (13), the systemic effects of adipokines in CKD patients may be greater than those in the general population. It has been estimated that about 20% of the circulating IL-6 originates from fat tissue and a significant amount of the circulating TNF-α comes from macrophages present in the adipose tissue (42). As visceral fat appears to produce adipokines more actively than subcutaneous adipose tissue, visceral abdominal fat may be the main producer of IL-6. In accordance, in ESRD patients evaluated shortly before the start of renal replacement therapy (RRT) Axelsson et al. found a significant association between serum IL-6 and truncal fat, but not between IL-6 and non-truncal fat (43).

On the other hand, protein-energy malnutrition (PEM) is highly present in patients with CKD and is a strong predictor of morbidity and mortality (44). Indeed, PEM is reported to be present in as many as 37% to 48% of CKD patients, percentages that increase once RRT starts (44). Usually, this deterioration of the clinical nutritional status is characterized by a progressive weight loss, wasting of both fat and skeletal muscle tissues and a reduction of serum proteins, including albumin, pre-albumin and transferrin. Of these, muscle wasting (sarcopenia) is the one strongest and most consistently associated with poor outcome (44). Malnutrition and inflammation are often interrelated in the clinical setting and also have additive effects on outcome (44). Kaizu et al. demonstrated that muscle mass was inversely correlated to both IL-6 and CRP in HD patients, even after adjustment for age and gender (45). In a longitudinal study, the declining markers of muscle mass during a 1-year period in HD were also associated with higher IL-1β concentrations (46). Moreover, a study from our group reported that patients who lost lean body mass (LBM) after 1 year in PD had significantly elevated initial CRP levels than patients who gained LBM (47). Although the mechanisms connecting inflammation to muscle wasting are not fully understood, enhanced protein turnover seems to play a central role, and Carrero et al. have recently reviewed the ATP-ubiquitin-proteasome pathway, insulin resistance, resting energy expenditure and anorexia as plausible mechanisms supporting this connection to inflammatory biomarkers (20).

Polymorphonuclear leukocyte (PMNL) priming

When PMNL gets in contact with a stimulus/damage, it remains in a "primed" state. In the case of CKD patients undergoing continuous ambulatory peritoneal dialysis (CAPD) or HD these PMNL seem to be permanently "primed" (48,49). This PMNL priming is believed to be one of the contributing causes to the systemic oxidative stress and chronic low-grade inflammation associated with renal failure (49). In the elderly general population, absolute neutrophil and total white blood cell counts have been associated with atherosclerotic risk factors (50), adverse cardiovascular outcomes and all-cause mortality (51). This association has also been described in ESRD patients, where both higher neutrophil count and lower lymphocyte count were independently associated with increased risk of death (52,53). It is known that nutritional status can affect the levels of leukocytes and that lymphopenia is a common finding in malnourished patients (54). Thus, low lymphocyte count may reflect protein-calorie malnutrition and therefore has additive effects on its risk of death secondary to this co-morbid condition. Altogether, the PMNL priming might underline the intimate association between malnutrition, inflammation and atherosclerosis (MIA syndrome) present in uremia.

Strategies for reducing chronic low-grade uremic inflammation

At a rudimentary level, reducing complications is always about optimizing care. Thus, one obvious but unfortunately often neglected strategy is the optimization of dialysis prescription. Specifically, volume overload should be avoided, water purity should be monitored, peritonitis should be prevented by stringent hygienic regiments, and biocompatible dialysis solutions should be evaluated to see if they can contribute to reducing inflammation in this group of patients. Heparin has been shown to have anti-inflammatory properties in renal patients, and a recent study has shown decreasing systemic CRP when heparin is given intraperitoneally to PD patients (55).

As interventions directed towards traditional risk factors have so far not proven to be very effective, controlled studies are needed to evaluate if various novel pharmacological as well as non-pharmacological anti-inflammatory treatment strategies, alone or in combination, may be more effective than traditional strategies. To date, four classes of drugs; statins, angiotensin-con-

verting enzyme inhibitors, peroxisome proliferators-activated receptor agonists and natural antioxidants, have been proposed as promising in dialysis patients. Nutritional intervention may also be a potential strategy to reduce inflammation while ameliorating the CKD. The anti-inflammatory properties of fish oil (omega-3-fatty acids) show promise in preventing CVD in the general population, but have not been tried in ESRD. Also, vitamin E supplementation (using γ-tocopherol), genistein (antioxidant and anti-inflammatory soy isoflavones) and anthocyanins (antioxidant flavonoids from wine or berries) are currently in the process of being evaluated.

Conclusion

Taken together, the present review aimed to emphasize the following key messages:

1. Low-grade inflammation is a common feature of chronic kidney disease that is related to glomerular filtration rate.

2. Leukocyte priming may be a key mediator in inducing a vicious circle of inflammation in CKD.

3. The inflammatory characteristics of uremic retention solute compounds need to be further elucidated.

Acknowledgment

Mahmut Ilker Yilmaz is supported by the ERA-EDTA.

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