Inflammation and Peritoneal Dialysis

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Summary: Inflammation is one of the well-recognized nontraditional risk factors that contributes to the excessive cardiovascular mortality in peritoneal dialysis (PD) patients. Serum C-reactive protein and interleukin-6 levels are common surrogate markers used to measure inflammatory burden and predict adverse clinical outcomes in PD patients. Causes of inflammation are complex and can be categorized into factors related to a decrease in renal function and factors related to dialysis. They interact with each other and finally result in systemic and intraperitoneal inflammation. This review discusses the various causes and clinical implications of inflammation in PD patients. More importantly, potential therapeutic options that target the underlying pathogenic mechanisms are explored.
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Peritoneal dialysis (PD) is an essential modality of renal-replacement therapy for patients with end-stage renal disease (ESRD). In 2008, there were approximately 196,000 PD patients worldwide, which contributed to 11% of the total dialysis population.[1] Nevertheless, the prevalence of PD patients was increasing in both developing and developed countries.[1] In the United States, although in-center hemodialysis (HD) remained the major treatment modality, home dialysis has gained popularity among ESRD patients in recent years. According to the US Renal Data System annual Data report for 2014, 95% of the 9,947 incident home dialysis patients chose to receive PD.[2] This remarkable difference confirmed the importance of PD even in developed countries.

PD has been the first choice of renal-replacement therapy in Hong Kong for more than 20 years. The PD-first policy has been implemented successfully in Hong Kong as a result of its lower infection risk, higher patient satisfaction, and better preserved residual renal function compared with HD.[3] Despite these advantages, the mortality of dialysis patients is still 6.1 to 7.8 times greater than the age-matched general population.[2] Cardiovascular disease remains the leading cause of death in dialysis patients. Observational study has speculated that PD may be associated with an increased hazard of cardiovascular disease compared with HD after 1 year of treatment.[4] However, this excessive cardiovascular mortality is unlikely to be fully accounted by traditional Framingham risk factors because advances in relevant treatment fail to improve cardiovascular risk significantly in ESRD patients. Therefore, focus has been shifted to nontraditional risk factors, including anemia, inflammation, and abnormal bone and mineral metabolism.[5] Importantly, systemic inflammation now is recognized as one of the key components in atherosclerosis in the general population and may accelerate atherosclerosis in ESRD patients. In this article, the causes and clinical implications of inflammation in PD patients are reviewed. In addition, potential therapeutic options to reduce inflammation are discussed.

PREVALENCE OF INFLAMMATION AND ITS PROGNOSTIC VALUES

The estimated prevalence of systemic inflammation in PD patients ranged between 12% and 65%, depending on the type and cut-off value of inflammatory markers, as well as the sensitivity of the assay used.[6] However, there is no convincing evidence to suggest a difference in the inflammatory burden between PD and HD patients.[6]

Various inflammatory mediators, such as C-reactive protein (CRP), interleukin (IL), and tumor necrosis factor (TNF), have been studied in dialysis patients. The most common surrogate markers used to measure inflammatory burden in PD patients are CRP and IL-6. Synthesized only in hepatocytes, CRP was the first described acute-phase protein and is a well-recognized sensitive marker of systemic inflammation and tissue damage.[7] Notably, the production of CRP is regulated predominantly by the transcriptional activities of IL-6. On the other hand, IL-6 is a pleotropic cytokine and exerts its effect not only on the immunologic system,

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but also the hematologic and endocrine systems. It activates the inflammatory response by engaging with its soluble IL-6 receptor, which results in the stimulation of proliferation and differentiation of T cells, production of immunoglobulin by B cells, and induction of hepatic synthesis of acute phase protein (including CRP, haptoglobin, and fibrinogen).[8]

Prognostic values of CRP, IL-6 and other inflammatory mediators

Systemic inflammation in PD patients is associated with adverse cardiovascular, metabolic, and nutritional consequences. These may manifest clinically as accelerated atherosclerosis, vascular calcification, muscle wasting, anorexia, and erythropoietin resistance.[9,10] Numerous studies have confirmed the prognostic value of inflammation (measured by CRP and IL-6) on mortality and cardiovascular outcomes in both HD and PD patients.[11]

An earlier study in our center reported that in 246 prevalent continuous ambulatory peritoneal dialysis patients, increased high-sensitivity C-reactive protein (hs-CRP) level was associated with an increase in all-cause mortality and cardiovascular mortality.[12] A similar prospective study of 240 incident PD patients also suggested that CRP independently predicted cardiovascular events, after adjustment of traditional and nontraditional risk factors (albumin and homocysteine).[13] A more recent study showed that hs-CRP not only predicted patient survival, but also technique survival in prevalent PD patients.[14] This 2-year study also showed a significant inverse association between hs-CRP and albumin, which was another crucial predictor of mortality in the dialysis population. Interestingly, genetic polymorphism of CRP was found to have an additional contribution to clinical outcomes. Our group examined the effect of a single-nucleotide polymorphism, -717A→G substitution in the promoter of the CRP gene, on the cardiovascular events of 441 incident PD patients.[15] The A allele promoter has been shown to possess a greater transcriptional activity than the G allele.[16] Although CRP genotypes did not seem to affect event-free survival of the entire cohort, stratification according to plasma cholesterol level showed that the 5-year event-free survival rate in the AG/GG group was significantly better than that in the AA group when the plasma cholesterol level was 200 mg/dL or greater.[15] This study illustrated the complex interaction between cholesterol, CRP, and cardiovascular disease in PD patients. Furthermore, in a mouse model, we found that CRP transgenic mice have significantly more inflammation and fibrosis than wild-type mice after PD treatment.[17] Our results suggested that CRP plays a role in inflammation and fibrosis induced by PD.

Similarly, IL-6 also has been shown to be a strong predictor of clinical outcomes in PD patients. Pecoits-Filho et al[18] showed that both IL-6 and soluble IL-6 receptor (which determines the bioactivity of IL-6) were associated with the survival rate of 173 incident dialysis patients. A recent multicenter study with up to 8 years of follow-up evaluation suggested that systemic and intraperitoneal inflammation represented two distinct processes, and only plasma IL-6 concentration but not dialysate IL-6 predicted patient survival.[19] Similar to CRP, baseline serum IL-6 level has been shown to predict composite cardiovascular events independently in incident PD patients.[20] Table 1 summarizes the association of individual inflammatory markers with clinical outcomes in dialysis patients.

It also is worthwhile to note that increasing evidence has confirmed the prognostic roles of novel markers such as myeloid-related protein 8/14 (calcium-binding proteins released by cells of myeloid lineage upon immune activation) and tumor necrosis factor–related apoptosis-inducing ligand (a negative modulator of inflammation) on the clinical outcomes of PD patients.[21,22] This again acknowledges the importance of inflammation in ESRD patients.

CAUSES OF INFLAMMATION

The causes of inflammation in PD patients can be categorized broadly into factors related to a decrease in renal function and factors related to dialysis (Table 2).

Residual Renal Function and Uremic Toxins

Residual renal function (RRF) plays an important role in regulating inflammatory activity in patients with ESRD. Previous studies have reported a negative correlation between RRF and inflammatory burden in predialysis and dialysis patients.[23-28]

It is believed that such association in predialysis patients may be explained by impaired renal excretion of proinflammatory cytokines and increased generation of cytokines in the uremic milieu. It has been shown that a significantly negative correlation existed between glomerular filtration rate (GFR) and circulating inflammatory markers (IL-6 and hyaluronan) in 176 ESRD patients.[23] A lower GFR was associated with inflammation independent of age and the presence of cardiovascular disease. A similar cross-sectional study showed that plasma levels of TNF-α increased with the severity of renal failure.[24] In addition, a recent case-control study showed that serum IL-6 and TNF- α levels were related inversely to estimated GFR and related positively to urinary albumin excretion, which was independent of established risk factors of chronic