Consequences of Chronic Inflammation in Peritoneal Dialysis

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Summary: The mortality of end-stage renal disease (ESRD) patients, including those receiving long-term peritoneal dialysis (PD), has remained unacceptably high owing to the prevalence of cardiovascular disease. It is well recognized that both traditional Framingham risk factors and kidney disease–related risk factors may contribute to the high prevalence of cardiovascular disease in these patients. Of the different risk factors, chronic inflammation frequently is observed in long-term PD patients. The causes of inflammation are usually complex and multifactorial, involving both dialysis-related and dialysis-unrelated factors. Inflammation is strongly associated with cardiovascular disease and malnutrition, and has been shown consistently to be a powerful predictor of mortality and adverse cardiovascular outcomes in PD patients. In this article we review the prevalence and potential causes of chronic inflammation in PD patients. More importantly, we provide emerging evidence that shows the serious consequences of chronic systemic inflammation in PD patients and the important contribution of inflammation to adverse clinical outcomes.
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Cardiovascular disease is the leading cause of death in end-stage renal disease (ESRD) patients, accounting for more than 40% of all deaths on maintenance dialysis. According to the most recent data from the United States Renal Data System, the adjusted rates of all-cause mortality are 6.7 to 8.5 times higher for dialysis patients compared with their age-, race-, and sex-matched counterparts in the general population.[1] Even though traditional Framingham risk factors such as hypertension and diabetes are highly prevalent in dialysis patients, these factors do not entirely explain the excessive cardiovascular mortality observed in these patients. A whole host of kidney disease–related risk factors contribute to the excessive cardiovascular disease burden in dialysis patients, one of which is chronic inflammation. Inflammation is well recognized to play a pivotal role in atherogenesis in the general population, and has been implicated in the accelerated atherosclerosis in the ESRD population. In this article, the prevalence and potential causes of chronic inflammation in long-term peritoneal dialysis (PD) patients are reviewed. More importantly, potential consequences of chronic inflammation in PD patients are addressed. Whether controlling the inflammatory response will improve clinical outcomes of PD patients warrants further investigation.

PREVALENCE OF INFLAMMATION IN PD PATIENTS

Inflammation is highly prevalent in the PD population. By using levels of C-reactive protein (CRP) as an estimate, the prevalence varies between 12% and 65%, depending on the sensitivity of the assay used and the cut-off value used to define inflammation.[2] The reported prevalence of an activated inflammatory response is generally lower in PD compared with hemodialysis patients.[3]

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Table 1. Causes of Chronic Inflammation in PD Patients

Dialysis-Related Causes	Dialysis-Unrelated Causes
Peritoneal catheters	Loss of residual kidney function
High-glucose, high-GDP dialysis solutions	Accumulation of uremic toxins
Complement activation	Atherosclerosis per se
Peritonitis and exit site infections	Chronic heart failure or fluid overload
Exposure to endotoxins and other cytokine-inducing substances from dialysate	Dental and gingival infections
High peritoneal membrane transport	Other infections
	Malnutrition
	Adiposity
	Genetic factors

Abbreviation: GDP, glucose degradation product.

CAUSES OF INFLAMMATION IN PD PATIENTS

The causes of inflammation in PD patients may be related to a multitude of factors including both dialysis-related and dialysis-unrelated factors as outlined in Table 1. The bioincompatibility of conventional glucose-based PD solutions containing glucose degradation products generated during sterilization and that in turn enhance advanced glycation end-product generation,[4] peritonitis, and exit site infections, are some common dialysis-related factors in PD patients. Persistent infections such as *Chlamydia pneumoniae*[5,6] or dental infections[7] also have been recognized to cause inflammation in dialysis patients. Genetic factors partly may contribute to an increased inflammatory response in PD patients. For instance, the interleukin-6 (IL-6) gene has functional variants such as the −174G/C single nucleotide polymorphism that affect inflammation response and risk of cardiovascular disease in dialysis patients.[8] The chemokine receptor 5 (CCR5) is a receptor for various proinflammatory chemokines, and a deletion variant of the CCR5 gene (CCR5 delta 32) leads to deficiency of the receptor and has been shown to attenuate the adverse effects of inflammation on overall and cardiovascular mortality in ESRD.[9]

Residual kidney function also may play an important role in regulating the inflammatory activity of PD patients. Decline in residual kidney function has been associated with a significant increase in serum CRP, IL-6, vascular cell adhesion molecule-1, and myeloperoxidase levels in PD patients.[10-13] Change in residual kidney function also has been associated with an increase in CRP in PD patients.[14] In fact, even before initiation of dialysis, patients with chronic kidney disease (CKD) show signs of inflammation. Various studies have reported an inverse relation between renal function and different inflammatory proteins such as CRP, IL-6, and tumor necrosis-factor-α (TNF-α) in predialysis patients.[15,16] The demonstration of decreased clearance of TNF-α and IL-1 in nephrectomized rats[17,18] was important evidence to suggest that the kidneys may be involved in the clearance of various inflammatory cytokines.

Apart from decreased clearance, increased cytokine generation also may contribute to an increased inflammatory profile in PD patients. Uremia or CKD per se may act as a potent stimulus of inflammation.[19,20] The adipose tissues express various cytokines and adipokines that modulate both systemic inflammatory response and insulin action.[21] It has been suggested that insulin resistance may be associated with inflammation in PD patients[22] and that the adipose tissue may account for as much as 20% of circulating IL-6.[23] The diseased myocardium and vasculature with progressive heart failure and atherosclerotic vascular disease also may be an important cause of inflammation and immune activation.[24,25]