End-stage renal disease patients are at a heightened risk of developing cardiovascular disease, with contributions from both “traditional” and “nontraditional” cardiovascular risk factors. Some of the nontraditional risk factors, such as extracellular volume overload, inflammation, and hyperphosphatemia, have also been shown to be important predictors of mortality in the dialysis population. This article provides an in-depth review of the evidence that supports the substantial contributions of nontraditional risk factors to adverse cardiovascular outcomes in chronic peritoneal dialysis patients. In addition, it provides evidence to demonstrate how loss of residual renal function may be central to the development of cardiovascular disease in the peritoneal dialysis population.

KEY WORDS: Cardiovascular; residual renal function; inflammation; calcification; cardiac hypertrophy.

According to the U.S. Renal Data System and the European Renal Association–European Dialysis and Transplantation Association registry (1), mortality among end-stage renal disease (ESRD) patients is at least 10 to 20 times that of an age-, race-, and sex-matched general population. Moreover, at least half of all deaths in ESRD patients are attributable to cardiovascular causes. These facts are in keeping with data from the Hong Kong renal registry, which show that more than 50% of the mortality in chronic peritoneal dialysis (PD) patients is attributable to cardiovascular disease.

Although a greater prevalence of traditional Framingham risk factors such as hypertension, high blood cholesterol, and diabetes have been observed in chronic kidney disease patients and in patients on dialysis as compared with patients having normal kidney function (2), evidence is accumulating that a whole host of “nontraditional” risk factors—or, more correctly, kidney disease-related risk factors, including chronic inflammation, deranged calcium–phosphorus metabolism, extracellular volume overload, anemia, increased oxidative stress, hyperparathyroidism, hyperhomocysteinemia, insulin resistance, and sympathetic overactivity—also predispose those patients to an increased risk of cardiovascular events and mortality. This article reviews some of these highly prevalent cardiovascular risk factors that have been shown to predict cardiovascular outcome in PD patients.

EXTRACELLULAR VOLUME OVERLOAD

Chronic PD patients frequently exhibit the complication of extracellular volume overload. According to a study by Tzamaloukas et al. (3), symptomatic volume overload may manifest in various ways, including peripheral edema (100% of patients), pulmonary congestion (80%), pleural effusion (76%), systolic hypertension (83%), and diastolic hypertension (66%). A recent study showed that close to 40% of chronic PD patients developed one or more episodes of circulatory congestion during a 3-year prospective follow-up (4). The causes of extracellular volume overload are usually multifactorial, including noncompliance with fluid intake restrictions, low effluent drain volumes, and high membrane transport status. Diabetes is also associated with increased risk of extracellular volume overload (3).

As shown by Ates et al. (5), the degree of sodium and fluid removal significantly influences the survival of PD patients, in that patients with lower sodium and fluid removal have a higher mortality rate that may be attributable to extracellular volume overload with resulting greater left ventricular (LV) hypertrophy and dysfunction. That finding is in keeping with a study that showed more severe LV hypertrophy, dilatation, and ventricular dysfunction among patients with a previous history of
volume overload than in those with no such previous history (6).

The foregoing observations raise two possibilities. First, as compared with patients having with no previous history of volume overload, patients with such a history may remain persistently volume overloaded. Second, an episode of volume overload, though now in the past and presumably resolved, may continue to exert negative effects on the myocardium, resulting in more severe LV hypertrophy. In chronic PD patients, LV hypertrophy is an important predictor of mortality and cardiovascular death (7). A previous study showed that more than 90% of prevalent PD patients have LV hypertrophy (7).

The presence of congestive heart failure also predicts mortality in patients on dialysis (8). Furthermore, progression of LV hypertrophy provides important prognostic information (9). Controlling for baseline LV mass index and other clinical and demographic factors, patients with a >75th percentile increase in LV mass over a mean interval of 18 ± 2 months (standard deviation) had a mortality and cardiovascular event risk that was 3 times that of patients having minimal increases in LV mass. Thus, achieving strict volume control appears to be an important therapeutic strategy for inducing regression of LV hypertrophy and lowering cardiovascular event risk in chronic PD patients.

On the other hand, extracellular volume overload in PD patients may be partly attributable to decline of residual renal function (RRF), which itself is an important predictor of mortality (10). Long-term continuous ambulatory PD (CAPD) has been suggested to be disadvantageous in preserving cardiac performance (11). Evidence also suggests that long-term CAPD patients show greater volume expansion and LV hypertrophy than hemodialysis patients do (12). In the reanalysis of data from the CANUSA study (13), RRF was shown to be a more important contributor to the overall survival of PD patients than PD clearance was.

The importance of RRF in PD patients appears to be mediated partly by its influence on fluid removal: entering urine volume into the Cox regression model for mortality completely displaces residual glomerular filtration rate (GFR) from the model. That finding accords well with a study showing that volume expansion in PD patients is related not only to peritoneal transport characteristics but also to residual GFR (14). Taken together with the previous demonstration of the novel association between residual GFR and LV hypertrophy (15), this suggests that RRF may play an important role in extracellular volume control and that extracellular volume overload may in part explain the link between loss of RRF and development of LV hypertrophy in PD patients.

### INFLAMMATION

Dialysis patients are at an increased risk of accelerated atherosclerosis partly because of the presence of inflammation. The prototypic markers of inflammation, C-reactive protein (CRP) and interleukin-6 (IL-6), have been shown to play a role in atherosclerosis (16,17). Previous studies have demonstrated the importance of inflammation, as denoted by CRP, in predicting mortality and cardiovascular death in PD and hemodialysis patients (18). More recently, CRP was shown to predict the time to occurrence of cardiac events in dialysis patients (19).

The causes of inflammation in PD patients are usually multifactorial: infections, malnutrition, bioincompatible dialysis solution, and cardiovascular disease (20). Of note is the important inverse relationship observed between inflammation and RRF in PD patients (10). Anuric PD patients had higher serum levels of CRP than did patients with preserved RRF (21). In addition, CRP was positively linked with arterial stiffening, as denoted by arterial pulse pressure, LV hypertrophy, dilatation, and systolic dysfunction (7). Although the exact relationships between inflammation, RRF, and LV hypertrophy have yet to be determined, the previous study clearly demonstrated that inflammation, loss of RRF, and LV hypertrophy combined adversely to heighten risk of mortality and cardiovascular death in PD patients (7).

Vascular cell adhesion molecule 1 (VCAM-1) is involved in leukocyte–endothelial cell interactions and plays a pivotal role in inflammation. In PD patients, a strong inverse relationship was recently observed between RRF and circulating soluble VCAM-1 (22). In addition, there is evidence that the association between loss of RRF and increased mortality and cardiovascular events in PD patients may be partly mediated by an increased inflammatory profile as evidenced by elevated levels of the adhesion molecule in the circulation.

Data also suggest that IL-6 may serve as a better inflammatory biomarker than CRP in predicting mortality and cardiovascular outcomes in ESRD patients (23–25). Tripepi et al. showed that, in ESRD patients, IL-6 adds significant predictive power to estimates of mortality and cardiovascular death risk (26). In another study, Honda et al. found that, in comparison with other inflammatory markers including serum albumin, high-sensitivity CRP, and fetuin-A, IL-6 had the highest predictive value for cardiovascular disease and clinical outcome in ESRD patients (27). The importance of IL-6 in mediating cardiovascular disease is further reinforced by a recent study showing that functional variants of the IL-6 gene (~174C carriers in the absence of 162 Val allele) affect inflammation and risk of cardiovascular disease in dialysis patients (28).
HYPERPHOSPHATEMIA

Hyperphosphatemia and increased Ca×P product are well-established risk factors for mortality and cardiovascular death in hemodialysis patients and PD patients alike (29,30). They also contribute to an increased risk of vascular, valvular, and other tissue calcification. Although hyperphosphatemia was once considered to be a relatively infrequent complication in PD patients, increasing evidence suggests that it is highly prevalent in the PD population. The Netherlands Cooperative Study on the Adequacy of Dialysis and a study by Wang et al. (30,31) both showed that about 40% of chronic PD patients have a serum phosphorus level above the target 1.78 mmol/L recommended by the Kidney Disease Outcomes Quality Initiative.

Among patients with preserved RRF, residual GFR was second to dietary protein intake in the list of the most important factors associated with hyperphosphatemia. Residual GFR was even more important than PD clearance. However, among anuric patients, the adequacy of PD clearance appeared to be the most important determinant of serum phosphorus control (31). Based on the data, it appears that total weekly urea and creatinine clearances of at least 2.0 and 60 L/1.73 m² respectively may be optimal targets for maintaining serum phosphorus below 5 mg/dL in Chinese CAPD patients. However, the data also suggest the inadequacy of PD alone in achieving adequate phosphorus control in anuric PD patients.

One major clinical consequence of hyperphosphatemia is the development of vascular, valvular, and other tissue calcification. The importance of vascular calcification in predicting mortality and cardiovascular death has been demonstrated in hemodialysis patients (32). Valvular calcification is also a powerful predictor of mortality and cardiovascular death in PD patients (33). Vascular calcification in ESRD patients commonly occurs in both the intimal and the medial layers. Vascular calcification secondary to hyperphosphatemia typically occurs in the media and is associated with generalized arterial stiffening that increases the afterload and results in LV hypertrophy (34,35), which may reduce coronary flow reserve and increase risk of myocardial ischemia. Further, data from animal studies show that hyperphosphatemia may increase cardiac fibrosis and hypertrophy, and aggravate microvascular disease (36). On the other hand, vascular calcification occurring in the intimal layer is typically atherosclerotic in nature and may lead to obstructive coronary lesions with resulting coronary ischemia. Interestingly, previous data suggest that valvular calcification also represents a marker of atherosclerosis in PD patients, as evidenced by its association with greater carotid intima media thickness and more plaque calcification (37).

The prevalence of coronary artery calcification (CAC) was reported to range from 40% to 100% in the dialysis population (38–41). To date, most of those surveys were conducted in hemodialysis populations, and only a few surveys in PD populations are available. In one of the latter surveys, the prevalence of CAC was reported to be 60% (42). Using echocardiography, one third of the Chinese PD population were noted to have valvular calcification. In addition, a much higher CAC score was observed in dialysis patients than in age- and sex-matched non-dialysis control subjects with coronary artery disease (38).

In dialysis patients, CAC is rapidly progressive (41). In a recent longitudinal study that included PD patients only, serum phosphorus and Ca×P product were found to be the most important factors predicting progression of CAC (43). Other factors that may predispose to cardiac calcification include increasing age, increasing dialysis duration, and cumulative dose of calcium-based binders (41). The use of calcium-based binders was most likely to be associated with progressive CAC when mineral metabolism was not well controlled (44). That finding is in keeping with a study showing that sevelamer hydrochloride, a non-calcium-based binder, attenuates the progression of CAC in hemodialysis patients (45).

Evidence that inflammation may be involved in the calcification process is also increasing, as shown by the important link between inflammation and valvular calcification (46). Reduced circulating levels of the calcification inhibitor fetuin-A, which is a negative acute-phase reactant, predicts mortality in dialysis patients (47) and is also associated with increased risk of valvular calcification (48). The recent finding that higher CRP is associated with more rapid annualized progression of CAC score in dialysis patients is further evidence to support the role of inflammation in mediating calcification (49). On the other hand, a recent unpublished observation by Wang and colleagues suggests that loss of RRF also predisposes PD patients to an increased risk of valvular calcification as a result of higher Ca×P product and increased inflammation. Of additional importance is the observation that inflammation, high Ca×P product, loss of RRF, and valvular calcification combine adversely to increase the severity of LV hypertrophy in PD patients.

CONCLUSIONS

Patients on PD are at a heightened risk of developing accelerated atherosclerosis, vascular and valvular calcification, and LV hypertrophy secondary to a
multitude of traditional and kidney disease–related risk factors. Previous studies suggest that the prevalence and severity of some of these risk factors may increase with decline in RRF. More attention should be paid to preserving RRF and improving cardiovascular outcomes in PD patients.

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REFERENCES


