Reducing cardiovascular disease in patients on peritoneal dialysis—is it possible?

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Introduction

Patients with end-stage renal disease (ESRD) have a vastly increased risk of death. This increase in mortality ranges from a 5- to 500-fold increase in risk, depending on the age of the patient. The major culprit of this increase in mortality rate is the high incidence of cardiovascular disease. The high prevalence of classical risk factors among ESRD population, such as hypertension, dyslipidaemia, smoking and diabetes, may in part explain this increased cardiovascular risk. However, other emerging cardiovascular risk factors may be involved such as hyperhomocysteinaemia, inflammation and oxidative stress. The uraemic condition per se also increases the risk of cardiovascular events through anaemia, calcium–phosphorus depositions and hypervolaemia. Treatment of cardiovascular disease in dialysis patients has been hampered by the multitude of factors that contribute to dialysis-related mortality and patients starting dialysis have a high level of comorbidity. In contrast to the general, non-nephrological, population, congestive heart failure is especially common in dialysis patients. This may be the cause of the reverse epidemiology of blood pressure in renal failure patients although this may be partly due to insensitive analytical approaches [1–4].

The purpose of this review is to: outline emerging markers of cardiovascular disease in peritoneal dialysis (PD) patients; identify potentially treatable cardiovascular risk factors and ultimately to define an optimal treatment strategy for patients on PD.

Markers of cardiovascular disease in PD

Among the vast number of different markers that have been implicated in cardiovascular damage in dialysis patients, it is important to point out some.

C-reactive protein

C-Reactive Protein (CRP) is an inflammation-marker, strongly associated with the onset and progression of cardiovascular disease in ESRD [5] and non-ESRD patients [6]. The CRP levels are also related to the progression of type II diabetes mellitus and the metabolic syndrome [7].

Several mechanisms have been implicated in this higher risk of inflammation in ESRD: A decrease in pro-inflammatory cytokine clearance, the uraemic state, oxidative stress and the presence of comorbidities, such as heart failure, hypervolaemic states, the presence of inflammatory diseases and chronic infections. In PD patients, the occurrence of peritonitis episodes or the peritoneal membrane exposure to biocompatible solutions has been related to an increased inflammatory state. However, it is not well-established whether the chronic inflammatory state is the cause or the consequence of cardiovascular disease. In PD patients, CRP is an independent predictor of all-cause mortality [8], and appears to be correlated with residual renal function (RRF).

Troponin T

Cardiac troponins are subunits of the cardiac actin–myosin complex, which leak into the circulation during myocardial damage. Detection in the circulation is considered as a specific marker of myocardial cell necrosis, hence infarction. In patients on dialysis, troponin levels are generally elevated, which hampers ischaemia detection [9]. However, increased troponin levels seem to be of predictive value especially when an increase from the baseline level is detected indicating myocardial necrosis [10]. Duman et al. [11] recently described a similar value for cardiac troponin T (cTnT) in patients on continuous ambulatory peritoneal dialysis (CAPD). In this study, cTnT predicted total and cardiovascular mortality and was associated with left ventricular hypertrophy (Figure 1).
Natriuretic peptides

Extracellular volume expansion and left ventricular hypertrophy are mainly responsible for high-plasma concentrations of atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP) in patients on dialysis [12]. Some studies have shown that ANP levels in PD patients were not increased. This indicates, that intravascular filling was not elevated, despite the fact that in the patients on PD total body water was increased to similar or even greater levels than in haemodialysis (HD) patients [13].

Fibrinogen

There is a positive correlation between fibrinogen and cardiovascular risk in normal and renal populations [14]. It is conceivable that fibrinogen is not only a cardiovascular risk marker, but it could also be involved in a common pathway for the onset and development of cardiovascular damage, through inflammation and coagulation.

PD-related risk factors for cardiovascular disease

Volume overload

There is abundant evidence to suggest that many patients on PD are volume-overloaded [14]. Fluid over-load itself is also believed to be a causative factor in the development of left ventricular hypertrophy and left ventricular dysfunction independent of blood pressure. Disturbed left ventricular function is highly prevalent in the dialysis population [2], but its diagnosis is made difficult by the volume dependence of generally employed measures of both systolic and diastolic function [14]. However, it is difficult to assess fluid state in individual patients. Inferior vena cava (IVC) diameter has been used to estimate volume status in HD and PD patients [15], but although an increase in IVC index appears to predict left ventricular hypertrophy, it remains a measure with a high variability, and it is quite impractical to perform on a day-to-day basis. Therefore, an accurate measurement of volume status is needed to monitor volume overload, as to date, only methods based on tracer dilution can be considered appropriate [16]. Although the short-term changes in volume in PD are less dramatic than in HD, volume status must be taken into account when interpreting echocardiographic measurements of left ventricular function.

Residual renal function

The absence of RRF appears to be important in the incidence of left ventricular hypertrophy and heart failure in PD patients (Figure 2) [17–18]. Maintenance of RRF has a clear impact on patient survival as peritoneal and renal clearances are not equivalent [19]. The NECOSAD study demonstrated a survival benefit when glomerular filtration rate remains stable [20]. Anuric patients show a higher mortality risk [21]. Numerous factors have been implicated in the deterioration of RRF such as ACE inhibitors, non-steroidal anti-inflammatory drugs, amino-glycosides.
and contrast agents. Nephrologists should be aware of these factors to preserve RRF in daily renal practice [22]. The benefits of preserving RRF are multiple, including facilitating volume control, preserving renal endocrine functions, increasing quality of life and reducing mortality. Several studies confirmed the evidence that RRF was better preserved in PD than in HD [23–24], even though there have been certain limitations in these reports [25] Amongst the potential causes for a better RRF preservation in PD are the avoidance of dehydration and hypotensive episodes and the more physiological rate of fluid removal [26].

Hyperlipidaemia and hyperhomocysteinaemia
Accumulating data indicate that PD patients have strong atherogenic lipid abnormalities [27]. Patients who undergo PD have a more atherogenic lipid profile than patients on HD, with increased LDL-C, apolipoprotein B, oxidized LDL-C, triglycerides, Lp(a) and decreased HDL-C [27]. Furthermore, the LDL particles of PD patients are small and dense.
A strong association between homocysteine and cardiovascular disease has been well-documented for the general population. High homocysteine levels can be found right from the early stages of renal insufficiency, although the involved mechanisms have not been clarified. There is a broad controversy about the potential harm of these increased levels [28,29].

Treatment options
At present, the question remains whether either HD or PD leads to an advantage in mortality in patients with cardiovascular disease [30]. The PD may offer improved blood pressure control and the avoidance of peaks and troughs in the concentration of uraemic toxins. On the other hand, PD is associated with more unfavourable lipid profiles, elevated serum glucose and the appearance of advanced glycation end-products. Patients with coronary artery disease appear to have a slightly poor survival when treated by PD [31]. In this study by Ganesh et al. [31], clinical characteristics were studied in a large patient population. However, this study was observational in nature and its results must be viewed with caution due to the possibility of selection bias. Therefore, at present, the optimal treatment modality for patients with cardiovascular disease is open to debate.

Volume overload
As volume overload is highly prevalent in the PD population, and since it is related to both adverse cardiac geometry and outcome, an effort must be made to prevent and treat hypervolaemia. It was initially thought that PD, as a continuous mode of dialysis, would be characterized by effective removal of salt and water. However, after the initial period, usually when RRF declines, hypertension re-emerges as a major clinical problem. In these patients, it has been shown that vigorous sodium restriction can improve blood pressure regulation [32]. However, dietary sodium restriction is problematic as the majority of PD patients continue to consume more salt than required. In order to remove extra sodium, Medcalf et al. [33] have studied the use of furosemide in a prospective randomized trial. They observed an increase in the sodium excretion compared with the control group (Figure 3). However, diuretics had no effect on the loss of RRF and the doses required posed the risk of ototoxicity.

Konings et al. [34] have studied the effect of icodextrin on fluid status, blood pressure and cardiac geometry in 32 PD patients. A significant increase in ultrafiltration volume (by ~1l/day), and a decrease in the extracellular fluid volume was observed. Blood pressure control was not improved, but left ventricular mass was reduced in the icodextrin group (Figure 4). Davies et al. [35] reported similar findings. Treatment with icodextrin seems to be beneficial in relation to fluid status and sodium removal, but further long-term prospective studies are needed. Other promising approaches in PD could be the use of low sodium concentration solutions or mixtures of icodextrin and glucose to enhance ultrafiltration. But at present the clinical experience with these approaches is limited [36].
Residual renal function

As stated previously, the preservation of RRF offers a survival advantage in PD patients. All potential damage to RRF in PD patients should be avoided, and providing a steady volume control is mandatory, avoiding sudden changes in blood pressure and underhydration episodes [37]. The use of diuretics has not been effective in the preservation of RRF, but does increase urine volume and natriuresis, allowing improved volume control [33]. Other promising interventions that have been studied in randomized trials are using ACE inhibitors and angiotensin II receptor blockers [38,39].

In PD therapy, the prescription of icodextrin helps in achieving superior ultrafiltration rates, improved fluid balance and better maintenance of RRF, compared with glucose-based regimens [35]. The use of low-glucose regimes is also a promising strategy to preserve RRF [40].

Hyperlipidaemia and hyperhomocysteinaemia

In general, due to the lack of evidence from prospective trials, traditional risk factors have been under-treated in patients on dialysis [41]. This is especially true for lipid-lowering drugs. The use of statins is supported by the proven efficacy on LDL cholesterol, its favourable safety [42–43] and its anti-inflammatory properties [44]. However, the effect on cardiovascular–cerebrovascular events and mortality rates is still unclear [45]. At this point in time, there are four prospective ongoing randomized controlled trials studying the effect of statins on patient outcomes on dialysis. Unfortunately, the results from the 4D-study [46] are not as favourable as observational and registry data would have predicted. Caution is therefore in order before treatment can be recommended in the dialysis population [47,48]. Despite the dispute on the effectiveness of treating hyperhomocysteinaemia, it has been recommended to treat renal patients with folic acid and B6–B12 vitamins, although the mean standard dose has not been defined [49].

Conclusions

In summary, patients on PD have a vastly increased risk of cardiovascular disease. Volume overload plays a major role in its pathogenesis. Sodium restriction therefore must be advised in PD patients and supported by a patient education programme. Normovolaemia can be achieved through increased ultrafiltration rate using icodextrin or by increasing residual urine volume with loop-diuretics. Care must be taken to prevent underfilling and the preservation of RRF is crucial. Although it is tempting to assume that the survival benefit of non-dialysis patients on statin treatment will also translate to the PD population, the outcome of ongoing prospective trials is anxiously awaited. Finally, although PD may offer a survival advantage in patients initiating RRT [20,48], PD is currently under-utilized in many parts of the world [50].

Conflict of interest statement. None declared.

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