Cardiovascular Risk Factors in End-Stage Renal Disease: Beyond Framingham

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Introduction

Cardiovascular disease is the leading cause of mortality in patients with end-stage renal disease (ESRD). According to the report from the National Kidney Foundation Task Force on Cardiovascular Disease in Chronic Kidney Disease, ESRD patients treated by dialysis had at least 10 to 30-fold higher risk of cardiovascular mortality compared to age, gender and race-matched control population. Data from the Hong Kong Renal Registry showed that over half of the mortality in ESRD patients was accounted by cardiovascular causes. Background atherosclerotic vascular disease increased mortality and cardiovascular death risk in ESRD patients by nearly three-fold and having a previous history of heart failure increased the subsequent cardiovascular mortality by at least three fold.

Apart from considering the traditional Framingham risk factors, there is an increasing recognition of 'non-traditional' risk factors in predisposing ESRD patients to cardiovascular complications. These include abnormalities in mineral metabolism with resulting hyperphosphatemia, secondary hyperparathyroidism, inflammation, extracellular volume overload, anaemia, increased asymmetric dimethylarginine, sympathetic overactivity, insulin resistance and increased oxidative stress. In this article, we will provide an overview on some of these risk factors.

Hyperphosphatemia

Hyperphosphatemia is highly prevalent in ESRD patients on maintenance dialysis. The United States Renal Data System showed that 70% of chronic haemodialysis patients had hyperphosphatemia. A local survey and a survey from Europe showed that around 40% of chronic peritoneal dialysis patients had serum phosphorus above the Kidney Disease Outcome Quality Initiative (KDOQI) recommended target of 1.78 mmol/L and the prevalence increased further with loss of residual renal function.

Hyperphosphatemia not only contributes to secondary hyperparathyroidism but is an important predictor of mortality in dialysis patients. Analysis from two large national databases from the United States revealed that hyperphosphatemia, elevated calcium*phosphorus product and elevated parathyroid hormone were specifically associated with death from coronary artery disease and sudden cardiac death in ESRD patients.

One of the major mechanisms whereby hyperphosphatemia contributes to an increased cardiovascular mortality relates to the development of vascular and valvular calcification. Hyperphosphatemia is capable of inducing a phenotypic change of vascular smooth muscle cells to 'osteoblast-like cells' which further lay down calcium and phosphorus loaded matrix vesicles, leading to calcium deposition. Vascular calcification that develops secondary to hyperphosphatemia classically occurs in the media and is also known as the 'Monckeberg's calcinosis'. It has a tram-line appearance on plain radiographs and is associated with generalised arterial stiffening which increases the afterload and results in left ventricular (LV) hypertrophy. This may reduce coronary flow reserve and increase risk of myocardial ischaemia. Hyperphosphatemia may also increase cardiac fibrosis, hypertrophy and aggravate microvascular disease and predispose to sudden cardiac death in dialysis patients. On the other hand, vascular calcification that occurs in the intima is typically atherosclerotic in nature and may lead to obstructive lesions with resulting ischaemia. ESRD patients frequently exhibit both intimal and medial type of calcification but the intimal calcification is usually more extensive and severe as compared to non-uraemic subjects.

Vascular and valvular calcification is an important predictor of mortality and cardiovascular death in ESRD. There is evidence that valvular calcification also represents a marker of generalised atherosclerosis as shown by its strong association with carotid intima-media thickness and plaque calcification and atherosclerotic vascular disease in ESRD. This suggests that calcification and atherosclerosis are indeed closely associated phenomena.

Coronary artery calcification (CAC) is a highly prevalent complication in ESRD with a prevalence ranging from 40% to almost 100% in different dialysis cohorts. The prevalence of valvular calcification ranged from 30% to over 50%. The degree of coronary artery calcification was at least 2.5 to 5-fold higher in dialysis patients compared to age and gender-matched non-dialysis controls with coronary artery disease. Coronary calcification was rapidly progressive in dialysis patients. A recent longitudinal study showed that serum phosphorus and calcium*phosphorus product predict the progression of coronary calcification in dialysis patients. Other factors that predisposed to coronary calcification included increasing age, increasing duration of dialysis and cumulated dose of calcium-based binders.
There is recent concern that calcium-based binders may increase risk of vascular calcification when mineral metabolism was not well controlled 22. However, the evidence regarding this issue has remained inconclusive. In the 'Treat to Goal' Study, sevelamer hydrochloride, a non-calcium based binder, has been shown to attenuate the progression of CAC 23 and is associated with better survival compared to calcium-based binder in haemodialysis patients 24. However, this observation is contrary to the recent 'Dialysis Clinical Outcome Revisited (DCOR)' Trial which showed no overall survival benefit with sevelamer hydrochloride compared to calcium-based binder 25.

Inflammation

Inflammation plays a pivotal role in the initiation and progression of atherosclerosis 26 and is considered one of the major non-traditional risk factors for accelerated atherosclerosis in dialysis patients. Using C-reactive protein (CRP) as the prototype marker of inflammation, inflammation was detected in 20 - 50% of ESRD patients 27. According to a previous local survey, around 35% of dialysis patients were inflamed as denoted by a CRP 5 mg/L 2. The prevalence was somewhat lower compared to that reported in Caucasian population 27. An elevated CRP was not only associated with greater prevalence of atherosclerotic vascular disease but also more severe cardiac hypertrophy and dilatation 2. CRP is a powerful predictor of all-cause mortality and cardiovascular death in ESRD patients 28, 29. The risk associated with an elevated CRP appears to be independent of other parameters including background cardiovascular disease, cardiac hypertrophy and residual renal function 2. CRP has also been shown to contribute to the progression of carotid atherosclerosis in dialysis patients 30. Cellular adhesion molecule which is involved in leukocyte-endothelial activation and plays a pivotal role in inflammation has also been shown to be associated with carotid atherosclerosis 30 and predicts mortality and cardiovascular events in ESRD 31. Recent study suggested that interleukin-6 may be a stronger predictor of mortality and cardiovascular death in ESRD patients as compared to CRP 32.

Extra-cellular Volume Overload

Left ventricular (LV) hypertrophy is one of the most prevalent cardiovascular complications and is a powerful predictor of mortality and cardiovascular death in ESRD patients 33. According to a cross-sectional survey in incident dialysis patients, the prevalence of LV hypertrophy was around 75% 34. Our previous survey showed that over 90% of the prevalent peritoneal dialysis patients had LV hypertrophy 35. There are numerous risk factors responsible for LV hypertrophy in ESRD patients. Hypertension and arteriosclerosis result in pressure overload and give rise to concentric LV hypertrophy. Anaemia, chronic volume expansion, hyperparathyroidism and arteriovenous fistula which result in volume overload state are associated with ventricular dilatation with LV hypertrophy or so-called eccentric LV hypertrophy. In a previous study, we observed greater LV hypertrophy and dilatation as well as more diastolic dysfunction among peritoneal dialysis patients who had previous history of volume overload 41, suggesting the importance of extra-cellular volume overload in predisposing ESRD patients to greater LV hypertrophy.

Conclusions

Mortality of ESRD patients has remained high due to an excessive cardiovascular risk burden resulting in a very high incidence of coronary artery disease, vascular and valvular calcification, LV hypertrophy and circulatory congestion. To improve the cardiovascular outcomes of these patients, we believe a more proactive approach is required and attention should be focused not only on modifying the traditional Framingham risk factors but more importantly the 'non-traditional' cardiovascular risk factors in ESRD.
References


