Netherlands
The Journal of Medicine

EDITORIAL

Reverse epidemiology of blood pressure in dialysis patients: implications for treatment?

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KEYWORDS

End-stage renal disease, reverse epidemiology

The number of patients with chronic renal insufficiency (CRI) is still growing, as is the number of patients with end-stage renal disease (ESRD).[1] Many of these patients have diabetes mellitus or generalised vascular disease. Dialysis patients experience a relatively low quality of life, high rates of hospitalisation, and a high mortality rate of almost 20% annually. Although dialysis treatments and techniques have improved, approximately 50% of all dialysis patients die within five years of starting dialysis treatment.[2-4] Sudden cardiac death, ischaemic heart disease, cardiac failure and cerebrovascular disease are the main causes of mortality and morbidity in dialysis patients.[5] The pathogenesis of cardiovascular abnormalities in uraemia is multifactorial.[6] Recently, abnormalities in calcium phosphate metabolism have emerged as an important risk factor.[7]

Hypertension is also highly prevalent in dialysis patients; it is a common finding and at initiation of dialysis, almost 80% of patients are hypertensive.[8] Blood pressure seems to be generally poorly controlled in dialysis patients.[9,10] The reasons for this are multifactorial, with persistent volume overload due to the combination of excessive interdialytic weight gain and an inability to achieve dry-weight due to short dialysis times being the most important factor.[11-13] In a recent study from the United States, the prevalence, treatment, and control of hypertension was investigated in a cohort of 2535 haemodialysis patients.[14] Hypertension was present in 86% of patients, but was treated adequately in only 30% of them. In the remaining patients, hypertension was either untreated (12%) or poorly controlled (58%). Thus, the control of particularly systolic hypertension in chronic haemodialysis patients in the United States is inadequate, despite recognition of its prevalence and the frequent use of antihypertensive drugs. The papers by Nurmohamed *et al.*[15] and Borsboom *et al.*,[16] published in this issue of the *Netherlands Journal of Medicine*, address the existence of what is known as reversed epidemiology in haemodialysis patients. Several large longitudinal cohort studies have shown a paradoxical inverse association between blood pressure and death in haemodialysis patients, i.e. a higher mortality rate in patients with a low blood pressure and a lower mortality rate in patients with a high blood pressure.[17,18] On the other hand, in dialysis patients a clear relation exists between hypertension and concentric as well as dilated left ventricular hypertrophy, which are both related to mortality in this population.[6] Moreover, in other studies, a relation between hypertension and mortality was observed.[19,20] In a recent cohort study of 11,142 dialysis patients, also high systolic blood pressure values were associated with increased mortality.[21]

In a cohort of 432 incident dialysis patients, systolic dysfunction was observed in 16%, with ischaemic heart disease being the most important risk factor.[6] Low blood pressure levels may be a consequence of systolic cardiac dysfunction. Hence, it has been suggested that the reversed epidemiology of hypertension in dialysis patients can be attributed to systolic dysfunction.[22] This would be in agreement with the reversed epidemiology of cholesterol levels in dialysis patients, which appears to be explained by the effects of inflammation and mal-

nutrition.[23] Indeed, also the relation between low blood pressure and mortality in dialysis patients appears to be influenced by comorbidity.[21]

The study by Borsboom *et al.*[16] was performed to obtain further insight into the pathophysiological background of the reversed epidemiology in dialysis patients. The authors studied 50 chronic dialysis patients for whom echocardiography was available. Twenty-eight of these patients had been on dialysis for more than three years. Echocardiographic findings were related to data on previous blood pressure control throughout the entire dialysis period that were retrieved from a computerised database. In agreement with the findings of Parfrey *et al.*, higher time-averaged values for mean arterial blood pressure and pulse pressure were related to left ventricular hypertrophy and left ventricular dilatation.[24] Fifteen patients had signs of systolic dysfunction on echocardiography. Interestingly, no difference in blood pressure parameters was observed in the last three months before the echocardiographic measurement between patients with or without systolic dysfunction. Therefore, from the data from Borsboom *et al.*,[16] it is not clear whether the relation between low blood pressure levels and mortality found in the literature can be fully explained by cardiac dysfunction. However, the inverse relation between pulse pressure at the start of dialysis and left ventricular fractional shortening might suggest a role for hypertension in the development of left ventricular systolic dysfunction, although strong conclusions are precluded by the small number of studied patients. Larger studies are needed to assess the potential relation between low blood pressure levels and cardiac dysfunction in dialysis patients.

The availability of all previous blood pressure levels throughout the entire dialysis history of the patient is a clear advantage of the study by Borsboom *et al.*[16] Drawbacks, however, are the small sample size and the fact that only single echocardiographic measurements are available. Moreover, patients were measured at different times of their 'dialysis vintage' (time on dialysis). It is also not clear in which percentage of the entire dialysis population and for which reason echocardiography was performed. Also the use of antihypertensive agents was not considered in the analysis. Nevertheless, the study by Borsboom *et al.* clearly confirms the relation between hypertension and left ventricular hypertrophy in dialysis patients.[16]

What implications does the existence of reverse epidemiology for hypertension have for the treatment of the dialysis patients? In recent literature, the consistent finding of an inverse relation between blood pressure and mortality has resulted in discussions on whether treatment goals for hypertension control in dialysis patients should be different from the general population.[25,26]

Because of the clear relation between hypertension and cardiovascular abnormalities in dialysis patients, it would appear counterintuitive to accept uncontrolled hypertension in dialysis patients. In cohorts of dialysis patients with well-controlled blood pressure, very high survival rates have been reported.[20] Moreover, treatment of hypertension in dialysis patients by sodium restriction and gradual lowering of dry weight has resulted in dramatic improvements in hypertension control and cardiac dilatation.[27] In a study in 153 dialysis patients, improvement of blood pressure control by dry weight reduction and antihypertensive agents, together with treatment of renal anaemia, resulted in a reduction in left ventricular mass. The hazard ratio for mortality was 0.78 for each 10% reduction in left ventricular mass.[28] Gradual fluid removal also improved blood pressure control, left ventricular diameter, mitral and triscuspid regurgitation as well as systolic function in dialysis patients with dilated cardiomyopathy.[29] In addition, increasing dialysis time and/or frequency results in improvements in both blood pressure control and cardiac structure.[30] Also the use of different classes of antihypertensive agents in dialysis patients has been associated with an increased survival.[23,31]

In conclusion, despite findings of a reverse epidemiology for blood pressure in dialysis patients, we do not believe that it is justified to leave hypertension untreated or insufficiently treated in dialysis patients. Treatment should, of course, be individualised. Also in patients with chronic renal failure, adequate blood pressure control may not only lead to preservation of renal function,[32] but may also prevent deterioration in cardiac function.[33]

In general, it would appear dangerous to adjust treatment goals based on observational studies only, certainly if the change is in contrast to clinical intuition. However, the optimal blood pressure target in this vulnerable population is not yet known. Prospective randomised studies are needed to compare the effect of different blood pressure targets on outcome in patients with end-stage renal disease.

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