PART IV

HAEMODIALYSIS

Chairmen: J L Funck-Brentano
           N Alwall

Page 149

PART V

HAEMOFILTRATION

Chairmen: V Cambi
          J Erben

Page 186

PART VI

ALUMINIUM

Chairmen: V Parsons
          M Mydlik

Page 213

PART VII

LIPID METABOLISM

Chairmen: B H B Robinson
          R Dzúrik

Page 240

PART VIII

CONTINUOUS AMBULATORY PERITONEAL DIALYSIS

Chairmen: S T Boen
           J Jirka

Page 266

PART IX

POSTERS ON DIALYSIS

Page 297
RISK FACTORS IN CHRONIC HAEMODIALYSIS

P Degoulet, I Reach, F Aimé, P Rioux, C Jacobs, M Legrain
Dialyse Informatique, Hôpital de La Pitié, Paris, France

Summary

A survival analysis was performed in 1,453 patients treated by chronic haemodialysis and prospectively followed up in the computerised French Diaphane Dialysis Registry. Risk factors found for overall and cardiovascular mortality are age, male sex, high systolic or diastolic blood pressure, low body mass index and low predialysis values of cholesterol, triglycerides, haematocrit, urea, creatinine and potassium. These results confirm the importance of optimal blood pressure control. They indicate that the nutritional state may play a more vital role than certain cardio-vascular risk factors found in the general population.

Introduction

Overall mortality (OM) and more specifically cardiovascular mortality (CVM) is much higher in patients treated by chronic haemodialysis than in the general population [1]. The annual death rate for the 2,518 patients registered in the Diaphane Dialysis Registry between 1972 and 1978 was 78/1000, which is 12 times higher than the death rate of the French population adjusted for sex and age [2]. During the same six-year period, death rate for cardiovascular complications (CVM) was 34/1000 and for strokes (SM) 12/1000 in dialysed patients, respectively 19 and 20 times higher than the National death rates for these two causes. The search for mortality risk factors, especially cardiac and cerebrovascular, is therefore an epidemiological priority in a population of dialysed patients.

Patients and methods

The study concerns 1,453 patients treated by chronic haemodialysis since June 1st, 1972 in 33 dialysis centres throughout France. Overall follow-up time up to December 31st, 1978 represents 2,053 patient-years. Mean age at start of haemodialysis was 45.9 ± 15.2 (± SD) (range 15–84). Main causes of primary renal
diseases were chronic and primitive glomerulonephritis (CGN) (30.0%), chronic pyelonephritis (PN) (20.9%), nephroangiosclerosis (NAS) (12.4%), polycystic kidney disease (PKD) (8.5%) and diabetic nephropathy (DN) (5.7%).

From the start of haemodialysis all patients were followed up in the computerised Diaphane Dialysis Registry of the Société de Néphrologie [3].

Fourteen parameters liable to influence mortality were analysed: age at start of dialysis, sex, primary renal disease, weekly dialysis schedule (WDS) and mean values during dialysis for systolic and diastolic blood pressure (SBP and DBP), body mass index (BMI) and blood values for total cholesterol, triglycerides, uric acid, urea, creatinine, potassium and haematocrit. Blood pressure is measured in the supine position before dialysis sessions. BMI is calculated as weight/height². All blood values are pre-dialysis values. Quantitative values are divided into three tertiles and survival curves calculated for each tertile. The Logrank test is used to calculate the ratio of observed/expected deaths (O/E) in each tertile and to compare mortality rates [4]. All calculations for significance are given after adjustment for age, sex and WDS.

Results

One hundred and ninety eight deaths (OM) were observed during the follow-up period (1972–1978): they comprised 87 cardiovascular deaths (CVM), including 35 strokes (SM) and 22 myocardial infarctions, but excluding 3 cases of haemorrhagic pericarditis, and 111 non-cardiovascular deaths (NCVM). Both OM and CVM rise significantly with age (p < 0.001 and p < 0.001); they are higher in males than in females (p < 0.01 and p < 0.05) (Figure 1), and in patients dialysed twice a week than in those dialysed three times a week (p < 0.002 and p < 0.05). OM and CVM do not differ significantly for patients with CGN, PN or PKD but are significantly increased in patients with NAS and DN. However differences between these five groups are no longer significant when results are adjusted for SBP or DBP.

OM and CVM mortality significantly increase with SPB (p < 0.05 and p < 0.05) and DBP (p < 0.01 and p < 0.001). DBP seems a better predictive cardiovascular death risk factor than systolic blood pressure (Figure 1). The relationship between SM and blood pressure is particularly striking (p < 0.001) (Figure 1). NCVM is not significantly related to blood pressure. OM (p < 0.001), CVM (p < 0.01) and NCVM (p < 0.05) significantly decrease with BMI.

Contrary to what could be expected for general population surveys, OM (p < 0.01) and CVM (p < 0.01) are inversely correlated with total serum cholesterol and to a lesser extent with serum triglycerides. Concomitantly low mean predialysis urea and creatinine are associated with significantly increased OM (p < 0.001 and p < 0.001) and CVM (p < 0.01 and p < 0.01). Despite the relatively small number of fatal strokes involved in the present calculations (n = 35), low triglycerides (p < 0.05), low blood urea (p < 0.05) and low creatinine (p < 0.10) are associated with increased SM (Figure 1).

OM (p < 0.01) as well as CVM (p < 0.05) are inversely correlated with mean predialysis haematocrit. Patients with low predialysis potassium values (≤ 4.6 mmol/L) and high values (> 5.1mmol/L) have a higher OM than those with
Figure 1. Mortality risk factors. Cardiovascular mortality, non-cardiovascular mortality, stroke mortality. O/E = ratio of observed/expected deaths calculated by the Logrank test [4]. NS = not significant, *= p < 0.05, **= p < 0.01, ***= p < 0.001
intermediate values (respectively O/E = 1.47, 0.96 and 0.78, p < 0.01). High uric acid (≥ 550μmol/L) is not associated with significantly increased OM or CVM.

Discussion

The strong evidence for a high CVM in patients treated by chronic haemodialysis and well-documented observations of marked occlusive arterial disease even in young dialysed patients, led Linder et al to propose in 1974 the concept of accelerated atherosclerosis in prolonged maintenance haemodialysis [5]. In the following years, many authors considered that this high CVM might be due to the great prevalence in dialysed patients of some risk factors found in the general population (e.g. high blood pressure, hyperuricaemia, hyperlipidaemia, glucose intolerance) [6, 7]. However epidemiological evidence for such explanation is still lacking and even the ‘accelerated atherosclerosis concept’ has recently been criticised [8, 9]. In fact, the physician in charge of dialysed patients needs more precise information to take CVM risk factors into account:

1. The proof of a statistically significant association in dialysed patients between the supposed risk factors and CVM;

2. The demonstration for each risk factor that increased CVM is associated with increased OM; and

3. The demonstration of the preventive effect upon OM and CVM of risk factor normalisation by appropriate regimens or medical treatments.

The data in this study clearly confirm the highly significant association between elevation of blood pressure and CVM or OM already reported by Eliahou et al [10], Chester and Schreiner [11], Deschamps et al [12] and Vincenti et al [13]. Variations in OM and CVM among the five groups of PRD compared are significant after adjustment for age, sex and WDS, but not after adjustment for SBP or DBP. It may therefore be postulated that the difference in blood pressure levels among PRD cases is the predominant factor explaining differences in OM or CVM. The prognostic value of DBP is particularly obvious for strokes. Thus, 21 fatal strokes were observed in patients belonging to the third tertile of DBP (DBP ≥ 89mmHg), 11 in the second tertile (78 ≤ DBP < 89) and only 3 in the first tertile (DBP < 78). Since it has been clearly demonstrated for the general population that medical control of blood pressure reduces the incidence of strokes and cardiac insufficiency, better blood pressure control in dialysed patients is likely to improve their vital prognosis.

Despite the results of general population surveys, high cholesterol (≥ 5.6mmol/L) and triglyceride levels (≥ 2.3mmol/L) are not associated with increased CVM. In fact, the high mortality observed in patients with low BMI, cholesterol, triglycerides, blood urea or serum creatinine seems to indicate that nutritional factors play a predominant role. Much more, when these parameters are low, CVM is more elevated than NCVM. Increased incidence of strokes is particularly marked in patients with low BMI, low triglycerides, low urea. The rise in CVM and SM in patients with low urea remains significant after adjustment for age, sex, WDS, BMI and blood pressure. On the contrary, the relationship between cholesterol
and SM or triglycerides and SM is not significant after adjustment for BMI. These results suggest that in dialysed patients, poor nutritional state and/or insufficient protein and perhaps lipid intake may diminish patient resistance to strokes. They support the results obtained by Yamori et al in rats showing the importance of protein and fat intake in preventing strokes in stroke-prone hypertensive rats [14, 15]; they are also in agreement with recent food consumption surveys in Japanese populations particularly exposed to cerebrovascular accidents [16].

Conclusion

In conclusion, this survey of 1,453 patients treated by chronic haemodialysis and prospectively followed-up confirm the predominant role of blood pressure in explaining high cardiovascular mortality. These results also draw attention to the role of the nutritional state and the possible benefit which could be derived from optimal weekly dialysis schedule and dietetic manipulations on proteins, lipids and glucids. However these parameters have to be considered among other possible risk factors such as vascular state at onset of treatment, smoking habits, disorders of calcium and phosphorus metabolism which are likely to be of importance in assessing CVM and OM but were not investigated in the present study.

Acknowledgments

We are indebted to all the medical and nursing staffs of the Dialysis centres participating in the Diaphane Dialysis Registry, without whose active cooperation this work would not have been possible.

References

1 Brunner FP, Brynger H, Chantler C, Donckerwolcke RA, Hathway RA, Jacobs C, Selwood NH, Wing AJ. *Proc EDTA 1979; 16:3*
5 Lindner A, Charra B, Sherrard DJ, Scribner BH. *New Engl J Med 1974; 290:697*
6 Lazarus JM, Lowrie EG, Hampers CL, Merrill JP. *Kidney Int 1975; 7:S167*
7 Bagdade JD. *Actualités néphrol Hop Necker 1979; 11. Paris: Flammarion*
9 Nicholls AJ, Catto GRD, Edward N, Engeset J, MacLeod M. *Lancet 1980; i:276*
11 Chester AC, Schreiner GE. *Trans ASAIO 1978; 24:36*
Open Discussion

KRAMER (Gottingen) Was the cause of death in your patients dying from ‘cardiovascular disease’ confirmed by autopsy? I ask because the diagnosis ‘cardiac circulatory failure’ is very common in patients dying in France.

DEGOULET Information is obtained from a specific questionnaire directly filled in by the nephrologist responsible for the dialysis unit and relating the exact conditions of death. I must add to your comment that 35 of the cardiovascular deaths were strokes, the most common cause of death among the patients we studied, and for which diagnosis is relatively easy.

GHAVAMIAN (Tehran) Does the presence of an internal fistula or shunt have an effect on cardiovascular complications in chronic haemodialysis patients?

DEGOULET Nearly all patients had an internal fistula. We cannot answer this question.

LINDENAU (Berlin) We can confirm your results with regard to the hazard of predialytic hypokalaemia. We observed cardiac disturbances due to hypokalaemia, especially in the elderly patient and we could prevent it by higher potassium bath concentration. Do you find any relationship between weekly dialysis schedule and body mass index?

DEGOULET Patients on three dialyses per week had a significantly higher body mass index than patients on twice weekly dialysis (22.6 ± 3.7Kg/m² versus 22.1 ± 3.8Kg/m², p < 0.02).