Incidence and risk factors of atherosclerotic cardiovascular accidents in predialysis chronic renal failure patients: a prospective study


Department of Nephrology, Department of Biochemistry and INSERM U90, Necker Hospital, Paris, France

Abstract

Background. Accelerated atherosclerosis resulting in an abnormally high incidence of coronary and cerebrovascular occlusive accidents has been repeatedly reported in dialysis patients, but incidence and risk factors of such complications in chronic renal failure (CRF) predialysis patients are debated.

Methods. We prospectively assessed the incidence of first myocardial and cerebral infarction episodes in a cohort of 147 CRF patients (99 male) followed from January 1985 to December 1994. Relevant clinical and laboratory risk factors for atherogenesis were determined at yearly intervals. They included blood pressure, smoking, blood lipids, fibrinogen, and homocysteine which were compared in patients with (CVA+) or without (CVA−) occurrence of cardiovascular (CV) atherosclerotic accidents.

Results. Incidence of CV accidents was nearly three times higher in CRF patients than in the French general population in both genders. In particular, incidence of myocardial infarction in male patients aged 45–55, 55–65 and >65 years was 7.6, 18.2, and 27.8/1000 patient-years, respectively, compared to 3.4, 8.9, and 10.4/1000 subject-years in the general population. Although age and degree of renal failure at onset of CV events or at end of follow-up did not differ between CVA+ and CVA− groups, cigarette smoking (24.5 [SD 24.3] vs 8.2 [14.7] pack-years, P<0.0001) and systolic blood pressure (159 [19] vs 148 [19] mmHg, P<0.001) were markedly higher in CVA+ patients. Similarly, mean plasma HDL-cholesterol was lower, whereas LDL-cholesterol, triglycerides, apoB, Lp(a), fibrinogen, and homocysteine levels all were significantly higher in CVA+ than in CVA− patients. Multivariate Cox analysis identified cigarette smoking, systolic pressure, HDL cholesterol, and fibrinogen as independent risk factors for developing CV accidents.

Conclusions. Incidence of atherosclerotic CV complications is abnormally high in predialysis CRF patients, suggesting that the uraemic state per se is associated with atherogenesis. As several of the identified clinical and metabolic risk factors for such accidents are potentially remediable by specific therapeutic interventions, prophylactic measures should be initiated long before start of renal replacement therapy.

Key words: accelerated atherosclerosis; atherogenic risk factors; cardiovascular accidents; cerebral infarction; chronic renal failure; myocardial infarction

Introduction

Cardiovascular (CV) complications account for ~50% of deaths in patients on renal replacement therapy (RRT), a much higher proportion than in the general population, and atherosclerotic arterial occlusive accidents in the form of myocardial or cerebral infarction represent nearly half of these CV deaths [1–4]. Whether atherogenesis is related to the dialysis procedure itself or to the uraemic state per se is still debated [5]. If the latter is true, one should anticipate an abnormally high incidence of atherosclerotic CV complications to occur also in predialysis patients. Indeed, chronic renal failure (CRF) patients combine common atherogenic risk factors such as age, diabetes mellitus, hypertension, smoking, and dyslipidaemia with factors more specifically related to the uraemic state such as dyslipoproteinaemia, hyperfibrinogenemia and hyperhomocysteinaemia, all of which develop early in the course of CRF [3,6,7]. Relationships between such factors and the occurrence of atherosclerotic complications have been evaluated in patients on maintenance haemodialysis [6,8] or peritoneal dialysis [9] and in renal transplant patients [10] but not so far in predialysis patients with progressive CRF.

Therefore, we prospectively determined clinical and laboratory parameters relevant to atherogenesis in a cohort of predialysis CRF patients and evaluated the incidence of CV atherosclerotic events over a 10-year period by reference to that observed in the French population [11]. As laboratory parameters were deter-
minded prior to onset of atherosclerotic CV events, we were able to analyse their influence on atherogenesis by comparing affected patients with those who remained free of such complications.

Materials and methods

Patients

Between January 1985 and December 1994, 223 patients (147 male, 99 female) with progressive CRF defined by a creatinine clearance between 20 and 50 ml/min/1.73 m² were referred to our Nephrology clinic. Of these, 147 (99 male, 48 female) gave informed consent to participate in a study of risk factors of atherosclerosis. All were ambulatory and managed as outpatients. None had a history of previous CV arterial occlusive accident. Only nine were already on lipid-lowering therapy, and none received folic acid supplementation at start of follow-up. Primary renal disease was chronic glomerulonephritis in 19, chronic interstitial nephritis in 48, hypertensive angionephrosclerosis in 45, polycystic kidney disease in 26, diabetic nephropathy in seven, and was undetermined in two.

Each patient had two visits per year, or at more frequent intervals according to the degree of renal failure, with assessment of blood pressure, body weight, and serum creatinine at each visit. All acute atherosclerotic CV events that occurred for the first time during the 10-year follow-up period were recorded. Coronary occlusive complications considered were myocardial infarction, defined as a typical clinical history together with characteristic ECG changes and rise in enzyme levels, evidence of coronary artery stenosis on coronary angiography, or coronary revascularisation procedure. Cerebral infarction (ischaemic stroke) was defined as a non-fatal accident with focal neurological deficit in the absence of arterial embolism, and with evidence of infarction on computerized tomodensitometry or magnetic resonance imaging. Although present in eight patients, peripheral arteritis or aortic aneurysm were not taken into account because the time of onset could not be determined. Angina and ECG ischaemic changes without necrosis also were not considered because ischaemic heart disease may occur in uraemics without evidence of significant coronary artery narrowing on angiography [12].

Variables

Plasma lipids (total cholesterol, HDL-cholesterol and triglycerides), apolipoproteins A1 and B, lipoprotein (a) (Lp(a)), fibrinogen, and total homocysteine were determined at yearly intervals, according to previously described methods [13–15]. However Lp(a) determinations were obtained after 1988 in 130 patients and homocysteine determination was available after 1989 and was obtained in 93 patients only. LDL-cholesterol was calculated according to the Friedewald formula which has been shown to be reliable in ESRD patients [16]. Laboratory parameters taken into account for correlation analysis were the initial values of plasma lipids, lipoproteins, and fibrinogen, while blood pressure value was the average of measurements of systolic and diastolic blood pressure made during the observation period.

Blood lipids, apolipoproteins, homocysteine, and fibrinogen were determined in 36 healthy adults who constituted the control group.

Statistical analysis

Incidence of CV atherosclerotic accidents was expressed in number of events per 1000 patients per year (n/1000 patient-years). Values are presented as mean [SD] unless otherwise specified. Comparisons used the χ² test and the Fisher’s exact test. Possible risk factors for CV accidents were examined using univariate Cox proportional hazard analysis. Covariates that tended to correlate with endpoints on univariate analysis (P<0.15) but age were also examined using multivariate Cox analysis. Since only two out of three patients had plasma total homocysteine determinations, we did not include plasma total homocysteine in the final Cox proportional hazard models. However because of its potential role in influencing atherosclerosis, plasma total homocysteine was analysed separately in the previous subgroup of patients. Statistical analysis was performed using SAS statistical software (SAS Institute Inc., Cary NC, USA).

Results

Incidence of atherosclerotic accidents

Among the 147 patients, a total number of 50 (41 males, 9 females) suffered a first atherosclerotic CV event. Myocardial infarction occurred in 40 patients (34 male, six female) and cerebral infarction in 10 (six male, four female). Overall, CV accidents occurred in 41% of men (41/99) and in 19% of women (9/48, P<0.001). The mean age of patients was 62.9 (SD 7.6) years (63.1 [SD 8.1] in males, 66 [SD 3.2] in females) at onset of the first myocardial infarction and 65.7 (SD 5.7) years (64.2 [SD 5.6] in males, 69.8 [SD 4.2] in females) at onset of the first cerebral infarction. Myocardial infarction accounted for 80% of the total number of CV events and was fatal in three cases.

Incidence of myocardial infarction in CRF patients compared to the incidence in the French general population in the various age groups is given in Table 1 for both genders. Incidence was 2.5–3 times higher in male CRF patients than in the general male population in all age groups. The same was true for female CRF patients until 65 years of age, whereas the difference was less marked beyond 65 years because of the sharply rising incidence in menopausal women. There was a marked gender effect, with incidence of myocardial infarction being about 2.5 times higher in male than

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>CRF Males</th>
<th>ENIM Males</th>
<th>CRF Females</th>
<th>ENIM Females</th>
</tr>
</thead>
<tbody>
<tr>
<td>45–50</td>
<td>6.2b</td>
<td>2.8</td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>50–55</td>
<td>9.1b</td>
<td>4.1</td>
<td>4.1b</td>
<td>0.8</td>
</tr>
<tr>
<td>55–60</td>
<td>15.8b</td>
<td>6.3</td>
<td>6.3b</td>
<td>1.5</td>
</tr>
<tr>
<td>60–65</td>
<td>20.8b</td>
<td>8.9</td>
<td>8.9b</td>
<td>2.7</td>
</tr>
<tr>
<td>≥65</td>
<td>27.8b</td>
<td>10.4</td>
<td>12.7b</td>
<td>8.1</td>
</tr>
</tbody>
</table>

CRF vs general population (ENIM) bP<0.05, bP<0.01, bP<0.001.
in female CRF patients, as also observed in the general population.

**Risk factors**

Correlations between clinical and laboratory risk factors and occurrence of CV atherosclerotic accidents were analysed in the 138 patients not currently receiving hypolipaemic therapy at referral (mean follow-up 5.8 [SD 2.3] years). Of them, 31 (25 male) experienced a first myocardial infarction and 10 (seven male) an ischaemic stroke. All seven diabetic patients experienced CV accidents. Of the 138 patients, 31 reached end-stage renal disease and had to start supportive therapy during the observation period.

Demographic characteristics of patients who developed CV atherosclerotic accidents (CVA +) and those who remained free of such accidents (CVA −), together with clinical risk factors (cigarette smoking, systolic, diastolic and mean arterial blood pressure, and duration of hypertension) are given in Table 2.

There was no significant difference in age of patients, nor in serum creatinine or creatinine clearance (Ccr) concentration between the CVA + and CVA − groups. Serum creatinine at start of follow-up was 164 (80) vs 181 (81) μmol/l (NS) and 313 (266) vs 391 (290) μmol/l (NS) at end of follow-up or at onset of the CV accident, in CVA − and CVA + groups, respectively. Overall, the rate of decline in Ccr was 3.1 (3.4). It was <5 ml/min/year in 87% of patients and was faster than this value in only 13%. The mean rate of decline in Ccr was 2.6 (2.1) vs 3.3 (2.3) in CVA − and CVA + groups (NS).

By contrast, there were striking differences in tobacco smoking and blood pressure between the two groups. Cigarette smoking was considerably heavier in CVA + than in CVA − patients, the mean cumulative cigarette consumption being 3 times higher in the former than in the latter. Of note, smoking was much more prevalent in male CRF patients, 57% (51/90) of whom had a >5 pack-years consumption, vs only 6% (3/48) in females.

Similarly, systolic, diastolic and mean blood pressure levels all were higher in the CVA + group, the most marked difference being for systolic blood pressure, whereas duration of hypertension was of borderline significance. Mean systolic blood pressure was even higher in the subgroup of 10 patients with cerebrovascular accidents (167 (9) mmHg) than in the subgroup of 31 patients with myocardial infarction (157 (11) mmHg, P < 0.01).

Blood biochemistry parameters in the two patient groups are given in Table 3 compared to the control group. Both groups of CRF patients had significantly higher values of total and LDL-cholesterol, triglycerides, Apo-B, Lp(a), fibrinogen and homocysteine, and lower values of HDL-cholesterol than controls, whereas Apo-A1 level differed from controls in neither group. However, when compared with each other, CRF patients who developed CV accidents had significantly more elevated mean values of total and LDL-cholesterol, triglycerides, Apo-B, Lp(a), fibrinogen, and homocysteine, and lower values of HDL-cholesterol than CRF patients who remained free of such accidents. In particular, the proportion of CRF patients with an homocysteine level ≥14.1 μmol/l (the upper limit in our healthy controls) was 83% in the CVA + group, compared to 30% in the CVA − group.

By univariate analysis, positive correlation was

### Table 2. Clinical characteristics of CVA + and CVA − patients (mean ± SD)

<table>
<thead>
<tr>
<th></th>
<th>CVA −</th>
<th>CVA +</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)</td>
<td>97</td>
<td>41</td>
<td></td>
</tr>
<tr>
<td>Males:females</td>
<td>58:39</td>
<td>32:9</td>
<td>P &lt; 0.001</td>
</tr>
<tr>
<td>Follow-up duration (years)</td>
<td>5.9 ± 2.3</td>
<td>5.4 ± 2.4</td>
<td>NS</td>
</tr>
<tr>
<td>Age (years)</td>
<td>65.1 ± 8.8</td>
<td>60.0 ± 8.3</td>
<td>NS</td>
</tr>
<tr>
<td>Per (μmol/l)</td>
<td>251 ± 206</td>
<td>277 ± 172</td>
<td>NS</td>
</tr>
<tr>
<td>Ccr (ml/min/1.73 m²)</td>
<td>35.9 ± 22.6</td>
<td>30.9 ± 17.9</td>
<td>NS</td>
</tr>
<tr>
<td>Cigarette smoking (pack-years)</td>
<td>8.2 ± 14.7</td>
<td>24.5 ± 24.3</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Systolic BP (mmHg)</td>
<td>148 ± 19</td>
<td>159 ± 19</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Diastolic BP (mmHg)</td>
<td>84 ± 9</td>
<td>88 ± 7</td>
<td>0.03</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>106 ± 10</td>
<td>112 ± 12</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Hypertension duration (years)</td>
<td>11.4 ± 8</td>
<td>14.4 ± 9</td>
<td>0.07</td>
</tr>
</tbody>
</table>

### Table 3. Laboratory parameters in CVA + and CVA − patients, compared to healthy adult controls

<table>
<thead>
<tr>
<th></th>
<th>Healthy controls (n = 36)</th>
<th>CVA − patients (n = 7)</th>
<th>CVA + patients (n = 41)</th>
<th>P values (CVA + vs CVA −)</th>
</tr>
</thead>
<tbody>
<tr>
<td>m ± SD</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.06 ± 0.78</td>
<td>5.98 ± 1.04</td>
<td>6.66 ± 1.51</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.39 ± 0.36</td>
<td>1.43 ± 0.38</td>
<td>1.20 ± 0.35</td>
<td>&lt;0.0002</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>3.26 ± 0.66</td>
<td>3.91 ± 0.89</td>
<td>4.43 ± 1.29</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>0.88 ± 0.30</td>
<td>1.41 ± 0.59</td>
<td>2.25 ± 1.05</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Apo-A1 (g/l)</td>
<td>1.47 ± 0.24</td>
<td>1.44 ± 0.22</td>
<td>1.40 ± 0.24</td>
<td>NS</td>
</tr>
<tr>
<td>Apo-B (g/l)</td>
<td>1.01 ± 0.18</td>
<td>1.33 ± 0.31</td>
<td>1.57 ± 0.39</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lp(a) (g/l)</td>
<td>0.12 ± 0.12</td>
<td>0.19 ± 0.16</td>
<td>0.44 ± 0.48</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fibrinogen (g/l)</td>
<td>2.42 ± 0.84</td>
<td>3.44 ± 1.40</td>
<td>6.08 ± 1.40</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Homocysteine (μmol/l)**</td>
<td>8.1 ± 2.4</td>
<td>12.4 ± 4.18</td>
<td>19.3 ± 7.1e</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Comparison controls vs CVA + and CVA − groups: *P < 0.05; **P < 0.01; **P < 0.001.
*In 130 patients, including 93 CVA − (median 0.15 g/l) and 37 CVA + (median 0.35 g/l).
**In 93 patients, including 69 CVA − and 24 CVA +.
found between cigarette smoking and plasma fibrinogen \( (r=0.24, P=0.005) \) as well as between cigarette smoking and homocysteine \( (r=0.33, P<0.001) \). Multivariate Cox analysis identified cigarette smoking, systolic blood pressure, HDL cholesterol and fibrinogen as independent risk factors for developing CV accidents (Table 4). It is noteworthy that the rate of decline of Cer did not selected as independent risk factor for developing CV accidents, and did not modify the final results of multivariate Cox analysis. It should be noted that HDL cholesterol was found to correlate with triglycerides \( (r=−0.55, P<0.001) \) and cholesterol \( (r=0.19, P=0.023) \). Plasma total homocysteine, although in a subgroup of patients was also an independent risk factor for developing CV accidents (relative risk for an increment of 1 μmol/1 [95% confidence interval] 1.17 [1.13–1.20], \( P<0.001 \)).

**Discussion**

Our study provides the first direct assessment of the incidence of atherosclerotic CV accidents, and of risk factors for atherogenesis in CRF patients not yet on RRT. In a prospective cohort study over a 10-year period, we observed an abnormally high incidence of atherosclerotic CV complications in predialysis CRF patients, in all age groups and in both genders, the overall incidence being nearly three times more frequent than in the French general population assessed by the nation-wide epidemiologic study ENIM (acronym for Enquête Nationale sur l’Infarctus du Myocarde) [11]. There was a clear gender effect with incidence of myocardial infarction being nearly 2.5 times more frequent in male than in female CRF patients in all age groups, and a prominent adverse effect of age in both genders.

Previous studies on the incidence of atherosclerotic CV complications in uraemic patients were mainly done in patients on maintenance dialysis, and used cardiac death as end-point, thus precluding accurate comparison with our data. According to the EDTA Registry, death rate from ischaemic cardiac disease was 16–19-fold more common in RRT patients than in age- and sex-matched population without renal disease [2]. In addition, there was indirect evidence that predialysis uraemic patients suffer an increased morbidity from atherosclerotic CV disease, as an history of myocardial infarction or need for coronary revascularization procedure is present in 12–18% of patients at start of RRT [6,17,18].

That an abnormally high incidence of atherosclerotic CV complications is already observed in the predialysis state highly suggests that uraemia per se is a major risk factor for accelerated atherosclerosis, although this does not preclude that dialysis procedure through bioincompatibility constitutes an additional risk factor [5].

The crucial problem, therefore, was to identify risk factors responsible for such uraemia-related accelerated atherosclerosis, inasmuch as most of clinical and metabolic derangements associated with the uraemic state are present from the early stage of CRF, long before start of RRT [19]. Our study provides evidence that the same factors that favor atherogenesis in the general population, i.e. hypertension, smoking, and dyslipidaemia are involved in CRF patients, but their effect is amplified because incidence and degree of such alterations are higher in uraemics. Moreover predialysis patients who developed CV atherosclerotic accidents had significantly more altered clinical and laboratory parameters than those who remained free of such accidents.

Hypertension appeared as a major factor of CV atherosclerotic accidents, especially high systolic blood pressure. An adverse role for systolic blood pressure was also reported in other studies both in RRT patients [18] and in the general population [20,21]. Conversely, a low incidence of CV death has been noted in dialysis patients with optimal blood pressure control [22].

Cigarette smoking revealed a very important, independent risk factor. In our patients, cumulated cigarette consumption, expressed in pack-years, was three times higher in the CVA+ than in the CVA− group. Cigarette smoking may be especially atherogenic in uraemic patients because it enhances free radical generation and subsequent lipid peroxidation [23] which is already increased in uraemic patients [24].

Uraemic dyslipidaemia, namely low HDL-cholesterol level, was also a major, independent risk factor, all the more deleterious that lipid disturbances develop early in the course of CRF [13,25,26]. Plasma total and LDL cholesterol, apoB and triglyceride levels all were significantly higher, and HDL cholesterol lower in CVA+ than in CVA− patients. All of these lipid parameters were closely correlated with each other. Of note, lipid parameters were significantly altered in CRF patients as a whole, compared to healthy controls, but to a significantly greater extent in the CVA+ than in the CVA− group. The degree of lipid abnormalities, as observed in our predialysis patients, is in agreement with findings of other authors in non-dialysed CRF patients [26] and in dialysis patients [27]. In kidney transplant recipients a relationship was similarly found between the degree of dyslipidaemia and occurrence of atherosclerotic events (10).

**Table 4. Independent risk factors for cardiovascular accidents in predialysis chronic renal failure patients**

<table>
<thead>
<tr>
<th>Independent risk factors</th>
<th>Relative risk (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cigarette smoking (5 pack-years)</td>
<td>1.11 (1.06–1.14)</td>
<td>0.008</td>
</tr>
<tr>
<td>Systolic blood pressure (10 mmHg)</td>
<td>1.25 (1.13–1.37)</td>
<td>0.026</td>
</tr>
<tr>
<td>HDL cholesterol (0.2 mmol/l)</td>
<td>0.79 (0.71–0.88)</td>
<td>0.032</td>
</tr>
<tr>
<td>Fibrinogen (0.5 g/l)</td>
<td>1.23 (1.18–1.30)</td>
<td>0.000</td>
</tr>
</tbody>
</table>

*Variables not predictive of cardiovascular accidents in chronic renal failure patients by multivariate analysis were age, gender, diabetes, diastolic blood pressure, total cholesterol, triglycerides, apolipoproteins A and B, lipoprotein (a), rate of decline in creatinine clearance.
A relationship between an increased level of lipoprotein Lp(a) and occurrence of atherosclerotic CV complications has been reported in dialysis patients as well as in kidney transplant recipients [14,28,29]. Although mean plasma concentration of Lp(a) in the CVA+ group was more than twice higher than in the CVA− group, the latter being itself nearly twice as high as in the control group, the Lp(a) concentration was not an independent risk factor in multivariate analysis. However, we did not analyse apolipoprotein (a) phenotype, which has been shown to be a better predictor than Lp(a) concentration in patients with ESRD [30]. Moreover, in view of the skewed distribution of serum Lp(a) concentrations the small number of control subjects in our study (<100 subjects) may preclude a definitive conclusion.

Hyperfibrinogenemia revealed a strong independent atherogenic risk factor in CRF patients, as already observed in the general population [31]. In our study, plasma fibrinogen level was markedly higher in CRF patients as a whole than in healthy controls, but was significantly higher in the CVA+ than in the CVA− group. An increased plasma fibrinogen level has been consistently reported in dialysis patients in association with evidence of endothelial dysfunction characterized by concomitant high plasma concentrations of proconvertin and type I plasminogen activator inhibitor (PAI-1) [32,33], all factors that contribute to the initial steps of aterogenesis. Fibrinogen and PAI-1 are acute phase proteins which rise in response to various stimuli including cytokines, especially IL-1 and TNFα, which indeed are released following monocyte activation, a process which has recently been shown to be part of the uraemia-associated immune dysregulation [34]. In addition, tobacco smoking may also contribute to hyperfibrinogenemia as nicotine has been shown to increase plasma fibrinogen level [23]. Interestingly, in our patients, there was a close relationship between plasma fibrinogen level and cigarette smoking.

Finally, hyperhomocysteinemia revealed a prominent risk factor of atherosclerotic CV accidents in our studied population. Mean total homocysteine plasma concentration was in the upper range of normal values in the CVA− group, whereas it was nearly two times higher in CVA+ patients, 83% of whom had plasma homocysteine concentrations above the upper limit of normal values. An increased homocysteine plasma level has been reported in non-dialysed and in dialysis patients [35], and a relationship between elevated plasma homocysteine concentration and occurrence of atherosclerotic CV accidents was evidenced in dialysis patients [36] and in kidney transplant recipients [15]. Our study provides first unequivocal evidence of the atherogenic effects of hyperhomocysteinaemia in predialysis uraemic patients, as age and degree of renal function impairment were similar in CVA+ and CVA− patients.

Such findings appear to be of relevance for the management of chronic CRF patients. Because clinical and biochemical atherogenic factors are present from the predialysis state, it will be of importance to implement preventive therapeutic measures against all potentially alterable factors. At the present time, hyperfibrinogenemia is poorly accessible to therapy, except by smoking discontinuation. By contrast, several other clinical and metabolic risk factors are already amendable by modifications in lifestyle or drug intervention. In this respect, every effort should be made to convince uraemic patients, especially males, to discontinue smoking [37], inasmuch as deleterious effects of smoking are amplified in uraemic patients due to nicotine accumulation resulting from impaired renal excretion [38]. Optimal blood pressure control should be achieved irrespective of its possible beneficial effects on the progression of renal failure [39]. Although there are no intervention trials to evaluate whether antilipaemic therapy should reduce incidence of atherosclerotic CV accidents in uraemic patients, it may be expected that reduction in LDL cholesterol and triglyceride concentration and/or increase in HDL cholesterol should reduce the risk of such accidents as already observed in the non uraemic population [19]. Pharmacologic agents that may be used in uraemic patients have been recently reviewed [40]. Lastly, prevention of hyperhomocysteinaemia should be considered an important goal to achieve. Recent studies provided evidence that pharmacologic supplementation with folic acid is able to substantially reduce plasma homocysteine level, by 40% as a mean, in predialysis and dialysis patients [41,42]. Thus, folic acid supplementation may become part of routine management in all uraemic patients, irrespective of any haematologic indication.

In conclusion, the present study provides evidence of a strikingly higher incidence of atherosclerotic CV accidents in predialysis chronic uraemic patients when compared to gender- and age-matched subjects in the general population. Heavier cigarette smoking, poorer blood pressure control, more marked dyslipidaemia including lower HDL-cholesterol level, and a higher degree of hyperfibrinogenemia and hyperhomocysteinaemia were found in CRF patients who subsequently developed atherosclerotic CV complications than in those who remained free of such accidents. Such findings are of potential relevance in the management of uraemic patients as several of these risk factors are presently amendable by specific therapeutic interventions. Because uraemia-related atherogenic metabolic alterations are present from the early stage of chronic renal failure, prophylactic measures aimed at reducing the risk of atherosclerotic complications should be considered long before the start of RRT.

References


Received for publication: 19.2.97

Accepted in revised form: 5.8.97