Incidence of atherosclerotic arterial occlusive accidents in predialysis and dialysis patients: a multicentric study in the Ile de France district

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Abstract

Background. An abnormally high mortality from atherosclerotic cardiovascular (CV) accidents has long been reported in patients on maintenance haemodialysis (HD). However, incidence of atherosclerotic CV accidents had not been so far assessed in predialysis patients. In order to evaluate the respective influence of uraemia and the dialysis procedure, we compared incidence of atherosclerotic accidents before and after initiation of HD in a large population of patients.

Study design. A total of 748 patients (411 male) were included in a retrospective study based on anamnestic data of patients living on maintenance haemodialysis in March 1993 in nine dialysis units of the Paris area. Incidence of first myocardial infarction (MI) or cerebral infarction (CI) was calculated by reference to the number of years of exposure to the risk both before and after initiation of HD in the various age groups.

Results. Overall, 103 first atherosclerotic accidents were recorded, including 10 CI (7 in males) and 93 MI (68 in males). Of the latter, 39 occurred before and 54 after start of HD, at a mean (±SD) age of 62.4 ± 9.9 and 63.7 ± 11.1 years respectively. The annual incidence of MI in males was 8.0, 19.5 and 28.3/1000 patient-years, before and 18.8, 21.6 and 29.9 patient-years after start of HD in the age groups 45–54.9, 55–64.9 and ≥65 years respectively, compared to figures of 3.4, 7.5 and 10.4/1000 subject-years in the corresponding age groups in the general French population.

Conclusion. Incidence of atherosclerotic CV accidents is nearly three times higher in uraemic patients than in the general population in the same age range in both genders. The fact that incidence and age at onset of first MI was similar in predialysis and in dialysed patients suggests that the uraemic state per se is a main determinant of such accelerated atherosclerosis.

Key words: accelerated atherosclerosis; cardiovascular accidents; cerebral infarction; chronic renal failure; maintenance haemodialysis; myocardial infarction

Introduction

An increased mortality from cardiovascular (CV) disease has been consistently reported in patients on maintenance haemodialysis (HD) since the initial study of Lindner et al. [1]. Registries of patients on renal replacement therapy (RRT) indicate that nearly 50% of deaths in dialysis patients are related to CV complications, a proportion much higher than in the general population [2–5]. Occlusive arterial accidents involving either coronary, peripheral, or cerebrovascular arteries account for at least half of such CV deaths [2,3,5]. Thus, even if atherosclerosis is not the unique cause of CV morbidity and mortality [6], it represents a major risk factor for CV complications in patients with end-stage renal disease (ESRD).

In the early 70s, the term ‘accelerated’ atherosclerosis was proposed to stress the abnormally high incidence of deaths from myocardial infarction in middle-aged patients treated by maintenance haemodialysis [1]. Subsequently this concept was disputed because incidence of atherosclerotic complications does not seem to accelerate with time in dialysis patients [7]. However, a higher incidence of deaths from atherosclerotic accidents in dialysis patients compared to the general population in the same age range is universally observed, even if the reported incidence of fatal CV accidents widely varies between authors [2,7,8]. Indeed, frequency of CV atherosclerotic accidents has been reported to vary between three and 45 times that observed in the general population, depending on the age of patients and countries [2,7]. Notably, only dialysed or transplanted patients were studied, and only mortality was considered, whereas no study prospectively assessed the morbidity related to atherosclerotic CV accidents in the predialysis state.

To evaluate reliably the incidence of both fatal and non fatal occlusive arterial accidents in uraemic
patients, we performed a study based on anamnestic data obtained in a large population of ESRD patients on maintenance haemodialysis (HD) in the Ile de France district. Atherosclerotic events were analysed separately according whether they had occurred before or after start of HD. Incidence of coronary occlusive accidents in uraemic patients was compared with the incidence of myocardial infarction in the French general population, according to data provided by epidemiologic studies in France [9]. By comparing the incidence in the predialysis period and after start of dialysis in the same cohort of patients, we could delineate the respective influence of uraemia (or uraemia-related factors) per se and of the haemodialysis procedure on the development of atherosclerotic complications.

Subjects and methods

The cooperative study involved nine dialysis units in the Ile de France district, the total population of which is 10.7 million inhabitants. They provided care to 802 patients treated with maintenance HD. Patients recruited in the study were all patients living on maintenance dialysis on file in March 1993. Excluded from the study were 54 patients aged less than 35 years or more than 75 years at start of dialysis. The 748 patients included in the study were 411 males and 337 females; 96% were Caucasian. Their age at start of HD was 52.4 ± 16.2 (mean ± SEM) years in males and 54.6 ± 15.5 years in females.

For each patient were recorded: date of birth, date of the first haemodialysis session and date of all coronary or cerebrovascular occlusive accidents. Age of patients at onset of the first event was used to assess the incidence of atherosclerotic accidents in relation with age. All recurrent occlusive CV events were also recorded and analysed separately. Only acute, indisputable CV occlusive accidents, defined as follows, were taken into account.

Coronary occlusive complications were myocardial infarction defined as a typical clinical history and characteristic ECG changes with rise in enzyme levels, significant coronary artery stenosis on coronary angiography, or need for coronary artery revascularization procedure. Cerebral infarction was defined as a cerebrovascular accident with neurological deficit in the absence of arterial embolism, and with evidence of cerebral infarction on tomodensitometry or magnetic resonance imaging. Although present in several patients, peripheral arteriopathy and aortic aneurysm were not considered because their time of occurrence could not be ascertained. By definition, fatal accidents that occurred prior to start of dialysis could not be taken into account whereas both fatal and non-fatal events that occurred after start of dialysis were recorded.

For each patient we determined the duration of exposure to the risk in the predialysis and in the dialysis state. In the predialysis state, we recorded the number of months elapsed in the age ranges 35–39.9, 40–44.9, 45–49.9 years etc., during the 7.5 years preceding start of dialysis, because a previous study had shown the average time elapsed from a creatinine clearance of about 50 ml/min/1.73 m² until ESRD to be 7.5 years [10]. In the dialysis state this recording was made from the first day on HD until March 1993 for patients who remained free of CV events, or until occurrence of the first myocardial or cerebral infarction in patients who suffered such accidents. The average duration of follow-up in dialysis patients was 7.3 ± 0.2 years. The total number of patient-years of exposure to the risk in the various age strata, both in the predialysis and in the dialysis state, was thus determined and the incidence of CV events, referred to the exposed population in all age groups, was expressed in events per 1000 patient-years.

Incidence of coronary occlusive events in uraemic patients was compared to the overall incidence of myocardial infarction in the general population in France, as evaluated in the ENIM study, a nation-wide survey conducted in year 1984 [9]. Because specific data on the incidence of cerebral infarction in the general population in France were not available, comparative analysis focused on myocardial infarction.

The observed number of myocardial infarction per 1000 patient-years before and after start of dialysis was compared with the expected number (E) per 1000 person-years calculated from the figures of the ENIM study. The ratio O/E thus defines the standardized event ratio, homologous of the standardized mortality ratio (SMR) as described elsewhere [8], with confidence intervals calculated by the Poisson distribution and standardized by age in both genders.

Results

As a whole, 103 first CV occlusive accidents occurred among the 748 patients at some time of their life. There were 93 myocardial infarctions (68 in males, 25 in females) and 10 cerebral infarctions (7 in males, 3 in females). Myocardial infarction accounted for 90% of first CV events, with a marked male predominance (16.5% in males vs 7.4% in females, P = 0.01). Of the 103 first CV events, 47 occurred before start of HD and 56 while on HD. Thirty-nine of the 93 myocardial infarctions occurred before and 54 after start of HD, whereas of the 10 cerebrovascular events, eight occurred before and two after start of HD. Distribution of CV events with respect to gender and time of occurrence before or after start of HD is given in Table 1. In 10 patients (6 males, 4 females), myocardial infarction occurred within 15 days prior to dialysis, and acted as a precipitating factor resulting in rapid worsening of renal failure and need for start of dialysis.

The mean age of patients at occurrence of the first

| Table 1. Incidence of atherosclerotic cardiovascular accidents (first events) before and after start of maintenance haemodialysis (HD) |
|------------------|----------------|----------------|------------------|
| CV events        | Gender | Total number | before HD | On HD |
| Myocardial infarction | Males | 68 | 29 | 39 |
|                   | Females | 25 | 10 | 15 |
|                   | Total   | 93 | 39* | 54 |
| Cerebral infarction | Males | 7 | 5 | 2 |
|                   | Females | 3 | 3 | 0 |
|                   | Total   | 10 | 8 | 2 |

*Ten myocardial infarctions (6 in male, 4 in female patients) occurred within 2 weeks before first dialysis.
myocardial infarction was 62.4 ± 9.9 years in pre-dialysis patients and 63.7 ± 11.1 years in dialysed patients, a not significant difference. The mean age at onset of myocardial infarction did not differ between males and females.

The course of coronary artery occlusive accidents in male and female patients, respectively, is given in Figure 1.

Of the 29 male patients who suffered a non-fatal first myocardial infarction in the predialysis period, a recurrent myocardial infarction was observed in one patient before and in seven after start of HD, with a fatal course in three of the latter (43%). Of the 39 male patients who suffered a first myocardial infarction while on HD, a fatal course was observed in seven cases (18%); a recurrent myocardial infarction was observed in eight of the surviving 32 patients (25%), which was responsible for death in three cases (37.5%). Overall, recurrent myocardial infarction was fatal in nearly 40% of cases in males. Of the 10 female patients who had a non-fatal first myocardial infarction predialysis, two had a non-fatal recurrent myocardial infarction. Of the 15 female patients who had a first myocardial infarction after start of dialysis (1 fatal case), two had recurrence, fatal in one case. In the whole series, the mean age of patients at onset of the second myocardial infarction was 69.2 ± 7.1 years.

The annual incidence of first myocardial infarction before and after start of HD, compared to the annual incidence in the general French population in the corresponding age groups, is given in Table 2. Incidence was about three times higher in male uraemic patients, either dialysed or not, than in the general population in virtually all age groups, whereas it was about two times greater in female uraemic patients than in women in the general population. Table 3 gives values of standardized event ratios (SER) for myocardial infarction in the same age groups for male and female patients.

The annual incidence grew with age at the same extent in uraemic patients as in the general population in both genders. Myocardial infarction incidence was three to five times higher in male than in female uraemic patients either predialysis or on dialysis under the age of 65 years. Beyond this age, incidence in males was only twice higher than in females, because of a marked rise in the incidence of myocardial infarction in menopausal women.

**Discussion**

The present study is the first to provide a direct evaluation of the incidence of fatal and non-fatal atherosclerotic arterial occlusive accidents, either coronary or cerebrovascular, in a large series of chronic renal failure patients studied sequentially before and after start of dialysis treatment. Our data afford undisputable evidence that such accidents, particularly myocardial infarction, are more frequent in uraemic patients than in the general population in the same age groups, thus confirming the concept of ‘accelerated’ atherosclerosis in the sense proposed twenty years ago by Lindner et al. [1].

The incidence of non-fatal myocardial infarction we found in dialysis patients is clearly higher than in the general population as evaluated in a nation-wide inquiry of the incidence of myocardial infarction in France (ENIM study) [9]. In all age groups, incidence of myocardial infarction was about three times greater in dialysis patients than in the general population, both in males and in females. In addition, incidence was about three to five times higher in males than in females up to 65 years, the difference attenuating beyond this age due to an increased incidence in menopausal women.

A higher incidence of deaths from myocardial infarction was reported by others [1,11]. In the Federal Republic of Germany in 1979 Ritz et al. [12] found the relative risk of death from CV atherosclerotic complications in dialysis patients aged more than 35 years to be 9.3 to 20 times greater than in the general population. Recent studies in Europe [2] also concluded that incidence of myocardial infarction is strikingly higher in dialysis patients than in the general population, but with marked geographic differences. Northern European countries such as Denmark and UK exhibit a three- to fourfold higher incidence of fatal myocardial infarction both in the general population and in dialysis patients than in Southern European countries such as Italy and France. However, in all of the studied countries, incidence of fatal myocardial infarction was 16–19 times higher in dialysis patients than in age- and sex-matched subjects in the general population.

Whether our studied population, limited to nine dialysis centres, is representative of the whole population of dialysis patients in the Ile de France district is...
Table 2. Compared annual incidence (per 1000 patient-years) of myocardial infarction in uraemic patients before and after start of haemodialysis (HD) and in the general French population (GP) in the various age groups

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Males</th>
<th>Females</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>Before HD</td>
<td>On HD</td>
</tr>
<tr>
<td>45–55</td>
<td>8.0(a)</td>
<td>18.8(c)</td>
</tr>
<tr>
<td>55–65</td>
<td>19.6(c)</td>
<td>21.6(c)</td>
</tr>
<tr>
<td>(\geq 65)</td>
<td>25.0(c)</td>
<td>29.9(c)</td>
</tr>
</tbody>
</table>

Patients vs general population: \(aP<0.05; bP<0.01; cP<0.001\).

Table 3. Standardized event ratio (SER) for myocardial infarction by age group in male and female patients

<table>
<thead>
<tr>
<th>Age range (years)</th>
<th>Males</th>
<th>Females</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before HD SER (CI)</td>
<td>On HD SER (CI)</td>
</tr>
<tr>
<td>45–55</td>
<td>2.35 (1.02–4.63)</td>
<td>5.53 (3.37–8.64)</td>
</tr>
<tr>
<td>55–65</td>
<td>2.61 (1.59–4.04)</td>
<td>2.81 (1.81–4.43)</td>
</tr>
<tr>
<td>(\geq 65)</td>
<td>2.40 (1.58–3.57)</td>
<td>2.87 (1.95–4.13)</td>
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questionable. At the time of the study, there were nearly 50 dialysis units in the district, caring for approximatively 3000 in-centre patients. Cooperating centres did not differ from other units, except in willingness to participate in the study.

The validity of our control group may also be questioned. In the ENIM study, all myocardial infarctions (both first episodes and recurrent events) were taken into account, whereas in our study only first episodes were considered for incidence analysis. Therefore, the relative risk of suffering myocardial infarction in CRF patients compared to age-matched subjects in the general population is probably underestimated.

It should be noted that we did not include, by definition, patients with fatal CV accidents who died before starting dialysis, or who did not reach dialysis. As a result, the incidence of first myocardial infarction may be somewhat higher in predialysis patients than reported here.

Finally, our data provide evidence that the development of atherosclerosis in uraemic patients is in no case restricted to the dialysis state but starts from the early stage of CRF and relentlessly progresses while on dialysis. Thus, in view of the usually long duration of the predialysis period, and in view of the potential arterogenic role of factors such as hypertension [13,14] lipid disorders [15–17] hyperfibrinogenaemia [18] and hyperhomocysteinaemia [19,20] that develop early in the course of chronic renal failure, there is clearly a need for preventative measures aimed at limiting atherogenesis in uraemic patients long before initiation of RRT.

In conclusion, the present multicentre study involving a large number of patients longitudinally studied before and after initiation of maintenance haemodialysis affords evidence that incidence of atherosclerotic arterial occlusive accidents, especially myocardial infarction, is at least three times higher in uraemic patients than in subjects of similar age and gender in the general population. The fact that incidence and mean age at occurrence of first myocardial infarction episodes does not differ before and after start of dialysis strongly suggests that the uraemic state, rather than the haemodialysis procedure itself, is the main determinant of such accelerated atherosclerosis in uraemic patients. Because atherosclerotic complications develop in the predialysis state several years before start of dialysis, further studies aimed at identifying risk factors involved in the development of atherosclerosis in chronic renal failure patients are needed to provide rationale for prophylactic measures which should be instituted long before start of RRT, in order to reduce morbidity and mortality associated with atherosclerotic complications in uraemic patients.

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