Patients on renal replacement therapy for 20 or more years: a clinical profile

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Abstract

Background. Long-term survivors are living evidence of the goals and limits of renal replacement therapy (RRT).

Methods. A cross-sectional study was performed on all cases (188 patients) with RRT follow-up ≥ 20 years in Piemonte, northern Italy (4.350.000 inhabitants, 22 dialysis centres). Study included revision of clinical charts and assessment of functional (Karnofsky scale, KS) and nutritional status (subjective global assessment, SGA). According to treatment history, patients were sorted into three groups: group 1, 56 patients always on dialysis; group 2, 40 patients on dialysis with previous graft; group 3, 92 grafted patients.

Results. Age differed between group 1 and groups 2 and 3 (59.5 ± 11.5 vs 51.5 ± 7.9 and 51.0 ± 9.0 years; P < 0.001). Prevalence of comorbidity was higher in groups 1 and 2 (94.6% and 95%) compared with group 3 (81.5%), reflecting selection during follow-up. Twenty-two cases (11.7%) had no comorbidity; these patients were younger (44.3 ± 8.5 years) and 17 out of 22 had a functioning graft. The most common comorbidities were vasculopathy (73.4%), bone disease (72.9%) and cardiopathy (33.5%). Severe visual impairment was a common problem (18%), with a higher prevalence in patients with cardiovascular comorbidity (32%). Severe depression was found in 13.3% of cases. Despite comorbidity, functional scores (KS) were good (higher in group 3 (88.1 ± 15) than in groups 1 and 2 (67.9 ± 21.9 and 75.5 ± 18, respectively; P = 0.000) and 64% of patients were well nourished. The combination of cardiovascular comorbidity, bone disease and visual impairment may reflect the premature ageing of RRT patients.

Conclusion. Despite the high prevalence of comorbidity, long-term follow-up may promote good clinical conditions at least in some patients, highlighting the therapeutic potentials of dialysis in an era of reconsideration of open acceptance of RRT.

Keywords: comorbidity; long-term results; renal replacement therapy

Introduction

In March 1960 in Seattle, Claude Shields became the first uraemic patient to start chronic renal replacement therapy (RRT). Now, 40 years after one of the most extraordinary life-saving medical discoveries of the century [1], there are several good reasons to look at the cohort of patients with long-term RRT follow-up.

At present, every year approximately 130–150 patients per population million start dialysis in Europe and in Japan, and > 200 do so in the USA [2]. The incidence of end-stage renal disease (ESRD) is rising steadily in western countries and, while the increase is limited to the older age groups, the incidence in young patients is not decreasing [2]. These changes have focused attention on elderly patients with a relatively short life expectancy, and in the last decade the problems of younger patients, with a longer life expectancy, have sometimes been neglected. Furthermore, improvements in RRT lead to an increase in survival and, as a side effect, in long-term problems related to uraemia and its therapies [3–4].

Since some of the patients who started dialysis in the early 1960s in Seattle are still living active lives, the real limits of uraemia therapy are yet unknown [5]. Large epidemiological registries are able to evaluate long-term survival on dialysis and post-transplant, and can give generic definitions of comorbid factors [2]. However, crucial aspects such as functional status are seldom included in large surveys due to the difficulty in obtaining uniform definitions. Focusing on functional status was one of the suggestions of a recent paper...
examining length of time on dialysis and survival in haemodialysis patients [6]. Detailed clinical studies of large, unselected cohorts of patients treated with dialysis and transplantation for ≥20 years are lacking, and our knowledge relies mostly on common sense clinical opinions or on single-centre series [3–5,7–10]. Furthermore, complete registry data on the cohort of patients starting dialysis before the early 1980s are lacking; therefore analysis of the baseline case-mix and of the effects of the different therapies performed over time is feasible only in selected single centre series and not in larger populations.

The aim of this cross-sectional study was to clinically evaluate a patient cohort comprising all cases treated for ≥20 years in the 22 nephrology and dialysis centres in Piemonte (northern Italy), a region with ~4 350 000 inhabitants and open acceptance of dialysis since the mid-1970s. Also, the first continuous Regional Registry of Dialysis and Transplantation (Registro Piemontese di Dialisi e Trapianto; RPDT) in Europe was started in this region in 1981 [11]. Since the lack of baseline data does not allow evaluation of the complex events and multiple selections occurring over time, a very simple descriptive study design was chosen, including revision of clinical charts and direct assessment of clinical performance and nutritional status.

**Subjects and methods**

**Patient selection and study design**

The study was performed in Piemonte, northern Italy; in this area, all patients needing dialysis have been treated since 1975. Twenty-two nephrology dialysis centres (all public) in this region are active, and since 1981 the RPDT has been collecting information on all patients on chronic RRT [11]. All 22 regional dialysis centres and the transplant centre agreed to participate in the study.

Patient identification was achieved using RPDT archives, collecting ~80 items of information on all RRT patients [11]. Two referees in each centre ensured quality control of data. Two hundred and sixteen patients who started dialysis before 1978 were identified. At the time of clinical control, 120 patients were on dialysis and 96 had a functioning graft. Under the direct control of the centre referees, 192 cases were confirmed as alive at June 15th 1997. At the time of inquiry, 97 patients were on dialysis and 95 had a functioning graft. Twenty-three patients died in the period December 1995 to June 1997 and one moved out of region.

The study was performed on two levels: first, revision of the clinical charts; and second, direct evaluation of nutritional status (subjective global assessment, SGA) [12] and functional status (Karnofsky scale, Ks) [13]. The first step was completed in 188 of 192 cases (of the four patients for whom clinical charts were unavailable, two were living out of the region for >6 months every year and two were hospitalized out of the region for >2 months). One hundred and eighty-two out of 188 patients were asked to participate in the second part of the study; the interview was not proposed to six patients, in one case due to severe clinical impairment, in another due to a language barrier, and in four cases due to severe psychosis. One hundred and seventy-one out of 182 patients (94%) agreed and completed the second step of the study. Patients were divided according to treatment history into three main groups: group 1, 56 patients always treated by dialysis; group 2, 40 patients with previous grafts but currently on dialysis; and group 3, 92 grafted patients.

**Data collection**

The study was based upon the available clinical and biochemical data, obtained during routine clinical care. No additional laboratory or imaging tests were performed, except when clinically necessary. To minimize arbitrary definitions of comorbid conditions, all patients were interviewed and clinical charts were reviewed by a team of three trained operators; in case of discrepancies between definitions given on the basis of the clinical charts and the opinions of caregivers, a group of experts, nominated at the start of the study, was consulted. The presence of comorbid factors was determined according to the broad categories employed in the clinical work-up, based upon both clinical history and imaging data. The definitions chosen were the ones usually employed in epidemiological registries [2,11]. The following comorbid conditions were considered: severe cardiac, vascular and bone disease, neoplasia, liver cirrhosis, diabetes mellitus, clinical signs of cachexia, severe immunodepression, visual impairment (blindness), mental impairment (dementia), severe depression and severe psychosis.

The conditions of neoplasm, liver cirrhosis, diabetes mellitus, severe immunodepression and severe psychosis were recorded as determined by the caregivers or by each centre’s consultant(s), and discussed with the usual caregivers where doubt arose. To minimize subjective definitions in the other cases, the following criteria were used. Severe cardiac disease was defined according to the presence of one or more of the following elements: cardiac failure, previous cardiac events (infarction or revascularization procedures), severe valvular disease and severe hypokinetic heart disease; whenever possible, cardiologists were consulted. Severe bone disease was defined as the presence of one or more of the following: pathological fractures (present and previous), and permanent deformities or diffuse signs of bone disease, as defined by radiologists and caregivers. All available radiological material was reviewed by the same operators and in case of discrepancies, data were discussed with selected experts. Diffuse vascular disease was broadly defined: (i) on the basis of history of vascular events [including transitory ischemic attack (TIA) or stroke], (ii) on the need to perform any type of revascularization procedure, and (iii) on the presence of aortic aneurysm or diffuse vascular calcifications at X-ray (in the latter case, diffuse calcifications had to be empirically present in at least three different settings, scored by our radiologists as 2–3 on a 0–3 scale). As in the case of severe bone disease, all available material was reviewed and discussed by the same operators. Normotension was strictly defined in dialysis patients as pre-dialysis systolic blood pressure <140 mmHg and diastolic blood pressure <90 mmHg (mean of the last week) in the absence of anti-hypertensive drugs. In peritoneal dialysis and transplant patients, the definition was based upon the same criteria, on usual blood pressure as recorded in the clinical charts. Severe visual impairment was clinically defined as a condition seriously affecting daily life (inability to read or watch television, etc.). Severe depression was defined by the
usual caregivers (also according to the centres’ usual consultants); as a common criterion, severe depression was defined as a condition lasting for at least 1 year, needing at least occasional pharmacological treatment.

With respect to comorbidity, besides categorization into the three main groups, a further categorization of subgroups was performed by sorting patients according to absence of cardiovascular comorbidity, presence of cardiac or vascular comorbidity, or both.

With respect to functional status, the Karnofsky scale was selected because of its widespread use in internal medicine [13]. For nutritional evaluation, subjective global assessment was chosen due to the relative ease with which it may be used, its widespread use and the fact it provides a single, simple final score (well nourished, moderately malnourished, severely malnourished) [12].

Biochemical data were gathered, if available, within 3 months of clinical control (for albumin, cholesterol, tryglycerides, total proteins, haematocrit, creatinine, pre-and post-dialysis blood urea nitrogen, calcium, phosphate) or 6 months [for intact parathyroid hormone, HIV, hepatitis C virus-antibodies, hepatitis B antigen (HBsAg)]. With respect to dialysis efficiency, kinetic data were gathered in patients on treatment three times per week; the Lowrie formula was chosen because of its simplicity and widespread use [14]. Data on vascular access were also gathered in patients on dialysis at the time of study. Biochemical markers were analysed in relation to SGA scores and patients were categorized further according to SGA scores.

Statistical tests

Data were collected in the Access database (Microsoft Corp., Redmond, WA, USA). Statistical analysis was performed using SPSS-WIN. Comparison between continuous variables was performed using a two-tailed Student’s t-test or ANOVA (analysis of variance). In the case of the latter, significant differences were analysed using Sheffe’s test (at significance level $P=0.05$). Pearson’s $\chi^2$ test was performed for discrete variables.

Three logistic regressions were performed to investigate correlations between dependent variables and covariates (relative risk): the goodness of fit was tested by the likelihood test with a significance level $P=0.05$. Pearson’s $\chi^2$ test was performed for discrete variables.

A first logistic regression was performed considering the presence of either cardiac or vascular comorbidity or both (vs either or none) as a dependent variable (all were dichotomized into present/absent). Age at start (continuous), sex (dichotomous) and duration of a renal graft expressed by percentage of overall follow-up (continuous) were used as covariates. A second logistic regression employed the presence of severe visual impairment (vs absence) as a dependent variable and the above mentioned factors as covariates. A third regression was performed considering having received a renal graft, either previously or at the time of the study, vs having been treated all the time by dialysis (groups 2 or 3 vs group 1) as a dependent variable. The following covariates were tested: primary renal disease (dichotomized into glomerular/non-glomerular), sex (dichotomous) and age at the start of study (continuous).

Gross mortality was calculated as the number of deaths recorded divided by the number of years of observation, expressed as deaths per 100 years of observation. The periods analysed were from the updating of the archives to the start of the study, and from the beginning to the end of the study.

Results

Overall

The male/female ratio (113 males (60.1%), 75 females (39.9%)) in our study did not differ significantly from that recorded at the 1997 RPDT update (3916 males (60%), 2618 females (40%)) and is in keeping with 1995 European data [15].

Age was significantly lower in patients who had received a renal graft (age in years at start of study: $37.2 \pm 11.3$ in patients always on dialysis, $28.5 \pm 8.9$ in patients grafted at the time of study, and $29.3 \pm 7.9$ in patients previously grafted but presently on dialysis; $P=0.05$, Sheffe test). The age range was wide in each group (Table 1) and spanned from 2.2 to 53.4 years at the start of study; 19 patients who started dialysis at age $<18$ years were included in the present study, and eight patients were $>50$ years of age at the time of start of RRT. As a consequence, the age range of the study was 22.9–76.1 years and at the time of study 12 patients were $>70$ years old (Table 1).

RRT follow-up ranged from 19.25 to 29.17 years in group 1 (patients were selected when in at least their 20th year of treatment), to 26.25 years in group 2 and to 28.67 years in group 3. Median follow-up on renal transplantation was 59.12 months (range 0.23–227.99 months) in patients presently on dialysis who had received a previous graft (in five out of 40 cases, follow-up with a renal graft was $>50\%$ of the overall RRT follow-up). In patients presently grafted, median follow-up with the renal graft was 48.22 months (range 0.6–185.26 months); follow-up with a renal graft accounted for $>50\%$ of the overall follow-up in 47 out of 92 cases.

Gross mortality was calculated for the period 1996–1997, from updating of the archives to the start of the study, and for the period 1997–1999, from the start to the end of the study. Gross mortality was 8 per 100 years of observation in 1996–1997 and 7.1 per 100 years of observation in 1997–1999 (overall 7.7 per 100 years of observation).

Causes of ESRD

Glomerulonephritis was the main cause of ESRD (109 patients, 58%), followed by pyelonephritis (23 patients, 12.2%) and polycystic kidney disease (eight patients, 4.3%). Other nephropathies accounted for 12.2%, and 25 patients with ESRD of unknown origin (13.3%) were also recorded. Since only 25 out of 109 patients with a diagnosis of glomerulonephritis had had a renal biopsy performed, definitions may also reflect diagnostic criteria in the 1970s. A few patients with diagnoses of nephropathies, usually considered as having a poor prognosis, are present in this cohort (one lupus erythematosus systemicus, six nephroangiosclerosis). No diabetic patient was present in this cohort.
Long survivors on RRT

Table 1. Stratification of long-term RRT patients into three main groups according to treatment history

<table>
<thead>
<tr>
<th></th>
<th>All cases (188 long-term RRT patients)</th>
<th>Group 1 (56 patients always on dialysis)</th>
<th>Group 2 (40 patients on dialysis, previously grafted)</th>
<th>Group 3 (92 patients presently grafted)</th>
<th>Significance</th>
<th>Sheffe´</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age at start of study (years)</td>
<td>31.3±10.3</td>
<td>37.2±11.3</td>
<td>29.3±7.9</td>
<td>28.5±8.9</td>
<td>P=0.001</td>
<td>1–2, 1–3</td>
</tr>
<tr>
<td>Age at study (years)</td>
<td>53.7±10.3</td>
<td>59.5±11.5</td>
<td>51.5±7.9</td>
<td>51.0±9.0</td>
<td>P=0.002</td>
<td>1–2, 1–3</td>
</tr>
<tr>
<td>Follow-up (years)</td>
<td>22.4±2.3</td>
<td>22.2±2.2</td>
<td>22.4±2.4</td>
<td>22.4±2.4</td>
<td>P=NS</td>
<td></td>
</tr>
<tr>
<td>Male/female (%)</td>
<td>113.75 (60.1/39.9)</td>
<td>30/26 (53.6/46.4)</td>
<td>29/11 (72.5/27.5)</td>
<td>54/38 (58.7/41.3)</td>
<td>P=NS</td>
<td></td>
</tr>
</tbody>
</table>

**Functional status**

Functional status was evaluated according to the Karnofsky scale [13] and the results are reported in Table 2. Only a minority of cases (6.3%) were not self-sufficient, and over half (51%) were in the 90–100 range (no, or only minor, signs of disease); 69.6% of grafted patients were scored 90–100. Also, patients on dialysis displayed good scores, even if they were lower than those of presently grafted patients (Ks 88.1±15 in patients grafted at time of study, 75.5±18 in patients previously grafted but on dialysis at time of study, and 67.9±21.9 in patients always on dialysis; P=0.000).

**Comorbidity**

The overall prevalence of major comorbid factors (severe cardiac, vascular, liver or bone disease, neoplasia) was high (88.3%) and was different in the three groups, being highest in patients always on dialysis and lowest in presently grafted patients (Table 3).

Twenty-two patients (11.7%) had no obvious comorbid factor. In this subset, age was significantly lower (mean age at study: 44.3±8.5 in patients without comorbidity vs 54.8±9.9 in patients with one or more comorbid factor; two-tailed t-test, P=0.000). An inversion of the male/female ratio was observed in the same two groups (9/13 vs 103/63, respectively; Pearson’s χ² test not significant (NS), P=0.057, odds ratio 2.36). As a consequence of clinical status, the Karnofsky index was significantly higher in patients without obvious comorbidity (97.3±4.7 vs 77±2.0 in patients with one or more comorbid condition; two-tailed t-test, P=0.000).

**Cardiovascular diseases**

Approximately one-third of patients (63 out of 188, 33.5%) displayed a cardiac comorbid condition; the most frequent diagnosis was ischaemic heart disease (43 cases) followed by valvular diseases (10 cases). Peripheral vascular disease was almost always diagnosed in the subset of patients with cardiac involvement (60 out of 63 patients). Overall, diffuse vascular disease was recorded in 138 out of 188 cases (73.4%), while major vascular events were relatively uncommon (eight amputations, eight TIA-ictus, one ‘other’).

The prevalence of cardiovascular comorbidity was higher in patients always treated using dialysis compared with grafted patients (Pearson’s χ² P=0.00086).

Diffuse cardiovascular disease is a major determinant of functional status (Table 2), therefore patients were stratified into three further subsets according to the presence of cardiac and/or vascular disease. The strict correlation among diffuse cardiovascular disease, functional status and, as will be discussed further, nutritional status confirms the coherence of the chosen clinical definitions.

**Hypertension**

The prevalence of hypertension was lower in this cohort compared with that usually reported in the RRT population [16]. One hundred and thirty (72%) patients were normotensive. No cases of severe hypertension were recorded. The prevalence of hypertension was higher in the grafted cohort (31%) than in patients always on dialysis (7.4%), while patients presently on dialysis but who previously received a graft(s) had an intermediate prevalence (15%; Pearson’s χ² P=0.007).

**Bone disease**

Severe bone disease was highly prevalent in this cohort (137 out of 188 patients, 72.9%). Osteopenia and/or amyloidosis were recorded in 111 and 77 patients (59% and 41%, respectively), permanent deformities were present in 16 patients (8.5%), and present or recollected pathological fractures were also found in 16 patients (in five of whom fractures were presumably related to corticosteroid therapy).

The prevalence of radiological signs of osteopenia and/or amyloidosis was higher in patients always treated using dialysis.

Overall, 65 patients (34.6%) received a parathyroidectomy (PTX), which correlated strictly with bone disease: only 15.4% of patients who received a PTX had no obvious radiological sign of severe bone disease at the time of the study, and the prevalence of cases free from severe bone disease was 33.4% in patients who did not receive a PTX (Pearson’s χ² P=0.0084).

Risk factors were interrelated. As expected, due to the greater length of time spent with uraemia, PTX was performed more frequently on patients always on dialysis (27 out of 56 cases, 48.2%; only two out of 27
were spared from severe bone disease) compared with patients presently grafted (prevalence of PTX 25% (23 out of 92 cases); five out of 25 patients were spared by severe bone disease; Pearson’s $\chi^2 P = 0.014$). Patients previously grafted had an intermediate prevalence of PTX (15 out of 40 cases, 37.5%; three out of 15 were spared by severe bone disease).

The presence of severe bone disease and of diffuse vascular disease were correlated: 24 out of 48 patients without obvious cardiovascular involvement were free from severe bone disease; prevalence dropped to 20 out of 80 in the presence of cardiac or vascular disease; and only seven out of 60 patients with both cardiac and vascular involvement were spared by severe bone disease (Pearson’s $\chi^2 P = 0.00004$).

**Neoplasia**

Overall, 24 neoplasias were recorded in 22 patients (12%). Cutaneous tumours in grafted patients were the most common (10 cases), as in most studies published so far [15]. Two Kaposi sarcomas were reported in grafted patients, and five neoplasias were recorded in four patients always on dialysis (two cutaneous tumours, two bowel carcinomas and one multiple hypernefroma of the native kidney). No

**Table 2. Prevalence and distribution of cardiovascular comorbidity in long-term RRT patients (distribution of patients according to group, gender, age, Ks and SGA scores)**

<table>
<thead>
<tr>
<th>All patients (n)</th>
<th>Patients (%)</th>
<th>M/F ratio (%)</th>
<th>Age at study (years)</th>
<th>Karnofsky index</th>
<th>SGA scores (%)*</th>
<th>Significance</th>
<th>Sheffe’s significance at 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vascular and cardiac disease (60)</td>
<td>31.9</td>
<td>58–42</td>
<td>59.1 ± 8.9</td>
<td>68.5 ± 20.7</td>
<td>(A) 41</td>
<td>$P = 0.0083$</td>
<td>1–2, 1–3, 2–3</td>
</tr>
<tr>
<td>Vascular or cardiac disease (80)</td>
<td>42.6</td>
<td>71–29</td>
<td>53.9 ± 9.2</td>
<td>79.0 ± 18.1</td>
<td>(B) 52</td>
<td>$P = 0.0000$</td>
<td>1–2, 1–3</td>
</tr>
<tr>
<td>No cardiovascular disease (48)</td>
<td>25.5</td>
<td>44–56</td>
<td>46.1 ± 9.3</td>
<td>93.7 ± 11.6</td>
<td>(C) 7</td>
<td>$P = 0.0000$</td>
<td>1–2, 1–3</td>
</tr>
</tbody>
</table>

**Table 3. Prevalence of major comorbid factors in long-term RRT patients**

<table>
<thead>
<tr>
<th>All cases (188 long-term RRT patients)</th>
<th>Group 1 (56 patients always on dialysis)</th>
<th>Group 2 (40 patients on dialysis, previously grafted)</th>
<th>Group 3 (92 patients presently grafted)</th>
<th>Chi square significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe vascular disease (n)</td>
<td>73.4% (138)</td>
<td>82.1% (46)</td>
<td>90.0% (36)</td>
<td>60.9% (56)</td>
</tr>
<tr>
<td>Severe cardiac disease (n)</td>
<td>33.5% (63)</td>
<td>46.4% (26)</td>
<td>40.0% (16)</td>
<td>22.8% (21)</td>
</tr>
<tr>
<td>Severe bone disease (n)</td>
<td>72.9% (137)</td>
<td>89.3% (50)</td>
<td>80.0% (32)</td>
<td>59.8% (55)</td>
</tr>
<tr>
<td>Severe liver disease (n)</td>
<td>5.9% (11)</td>
<td>3.6% (2)</td>
<td>10.0% (4)</td>
<td>5.4% (5)</td>
</tr>
<tr>
<td>Neoplasia (n)</td>
<td>11.7% (22)</td>
<td>7.1% (4)</td>
<td>10.0% (4)</td>
<td>15.2% (14)</td>
</tr>
<tr>
<td>No comorbidity (n)</td>
<td>11.7% (22)</td>
<td>5.4% (3)</td>
<td>5.0% (2)</td>
<td>18.5% (17)</td>
</tr>
</tbody>
</table>

*SGA scores were assessed in 179 patients (A, well nourished; B, moderately malnourished; C, severely malnourished).
lymphoma-leukaemia was present in this study, in keeping with the low risk in our population on a low immunodepressive regimen.

Chronic liver disease

The prevalence of HCV antibodies (134 out of 182 patients, 73.6%) and of HBsAg (19 patients, 10%) was high, but clinical liver disease was uncommon (11 cases, 6%). No difference in HCV positivity was found in grafted patients (68.5%) or in patients on dialysis (75%), while severe liver disease was more common in patients presently or previously grafted (nine out of 11; only two cases were recorded in patients always on dialysis, one due to Caroli’s syndrome in a patient with a polycystic kidney and liver who was also HCV positive). In 10 out of 11 cases with liver cirrhosis, HCV antibodies or HBsAg were positive, the exception being a grafted patient with a diagnosis of severe azathioprine toxicity.

Severe visual impairment

The prevalence of severe visual impairment was relatively high in this cohort (34 patients, 18%). Patients with severe visual impairment were significantly older (58.7 ± 11.2 compared with 52.4 ± 9.8 without visual impairment; two-tailed t-test \( P = 0.001 \)); the prevalence of visual impairment is higher in patients on dialysis but, when comparison was age adjusted, no difference was found in the three groups (treated by dialysis and/or grafted). Glaucoma was reported in four cases, two each of optic atrophy and retinitis, and bilateral cataract was the most frequent cause recorded (22 cases). However, since most patients (19 out of 22) with cataracts underwent surgery, this diagnosis offers only a partial explanation of the residual visual impairment. A strict relationship with diffuse cardiovascular impairment was found. Only three cases with severe visual impairment had no obvious cardiovascular risk factor (in two, visual impairment was related to a congenital disease). In 12 patients one comorbid factor (either vascular or cardiac) was present, and in 19 both comorbid conditions were present. Conversely, 19 out of 60 (31.7%) patients with both cardiac and vascular comorbidity were affected by severe visual impairment (Pearson’s \( \chi^2 \) \( P = 0.0019 \)). Ks confirmed the impact of this condition on functional status: 14 patients needed special care (41.2%) and 12 were not self-sufficient (35.3%).

Severe depression

Severe depression was recorded in 25 patients (13.3%), once again with a strong impact on functional status (Karnofsky index 67.2 ± 19.5 in patients with severe depression vs 81.3 ± 19.4 in patients without severe depression; two-tailed t-test \( P = 0.001 \)). Prevalence of severe depression was not related to a specific treatment (eight out of 56 in patients always treated with dialysis, eight out of 40 in patients presently on dialysis but with a previous graft(s), and nine out of 92 in grafted patients; Pearson’s \( \chi^2 \) \( P = \text{NS} \)). Prevalence of severe depression was higher in patients with diffuse cardiovascular disease: only four patients with severe depression were free from both cardiac and vascular disease (\( P = 0.01 \)).

Other comorbid factors

Severe psychosis was recorded in six cases, four of whom had features present prior to ESRD. Secondary diabetes was recorded in eight cases (seven presently and one previously grafted).

Logistic regressions

To describe in more detail the complex relationship between baseline data and the clinical situation recorded at the time of study, a series of logistic regressions was performed (Table 4), with the main clinical comorbidities as the dependent variables, and the age at start, sex and percentage of follow-up with renal transplantation as covariates. In all the correlations, the goodness of fit assessed by the likelihood test was statistically significant (\( P < 0.05 \)) and the applicability of the models ranged from 72.34% to 81.91% (Table 4).

On the other hand, the event ‘receiving a renal graft’ (presently or previously) was significantly correlated with age at start (\( P = 0.0000 \)) and not with sex or primary renal disease (\( P = 0.5395 \) and \( P = 0.2656 \), respectively), with a model applicability of 76.06% (Table 4).

Nutritional status

Nutritional status was assessed according to SGA (Table 2). Only 6% of patients had signs of severe malnutrition and 64% of long-term survivors were classified as well nourished. No difference was found when patients were divided according to sex. Prevalence of severe and moderate malnutrition was higher in patients always treated by dialysis, who were usually older and had a higher prevalence of comorbidity. Age was an obvious factor; severe malnutrition was recorded in one out of 68 patients aged <50 years, in three out of 57 aged 50–59 years and in six out of 46 aged ≥60 years (Pearson’s \( \chi^2 \) \( P = 0.00078 \)).

A strict correlation with functional status was found: the Karnofsky index was 87.2 ± 15.2 in cases with good nutritional status, 71.0 ± 18.8 in cases with moderate malnutrition, and only 55.0 ± 18.4 in the few severely malnourished patients (Sheffe test significant among all groups at \( P = 0.05 \)).

With respect to biochemical parameters, albumin and total protein levels were in the high-normal range in all subsets; accordingly, no correlation was found among SGA scores, albumin, total proteins and...
tryglyceride levels (the last two were analysed as a logarithm). However, a significant correlation was found with haemoglobin and cholesterol levels (Table 5).

**Dialysis adequacy**

The Lowrie formula was evaluated in patients on haemodialysis three times per week. Data within the last 3 months of treatment, excluding hospitalized patients, were available in 71 of 93 patients presently on haemodialysis. Three patients were on peritoneal dialysis at the time of study. Overall, $K_t/V$ levels were superimposable on bicarbonate dialysis ($K_t/V$: 1.2 ± 0.2) and on haemodiafiltration ($K_t/V$: 1.2 ± 0.2). Treatment time was similar for the two modes of treatment (3.8 ± 0.5 h on bicarbonate dialysis and 3.8 ± 0.4 h on haemodiafiltration), in keeping with a regional policy of choice of haemodiafiltration for tolerance purposes and not for shortening dialysis time [11].

At the time of study, the prevalence of the types of vascular access was as follows: in group 2 (patients previously grafted, presently on dialysis), two patients were on peritoneal dialysis, vascular access comprised a native arterio-venous fistula in 31 out of 38 cases (radio-cephalic in 15 patients, proximal fistula in 13, ‘snuffbox’ in three), six cases employed a prosthetic PTFE graft, and one employed a Tesio (central double lumen) catheter. In group 1 (patients always on dialysis), peritoneal dialysis was employed in one case, vascular access comprised a native arterio-venous fistula in 40 out of 55 cases (radio-cephalic in 20 patients, proximal fistula in 15, ‘snuffbox’ in five), a prosthetic PTFE graft was employed in 11 cases, and a Tesio catheter was employed in four.

**Discussion**

Patients with long-term follow-up on RRT ($\geq$ 20 years) constitute a relatively small portion of the cohort presently in the treatment setting, such as the one analysed here, where dialysis has received open acceptance since the mid-1970s [11]. The prevalence of patients treated for $\geq$ 20 years by RRT was 3% in our region, which was in the range reported by other investigators [2,7]. Since gross mortality among these veterans is relatively low (7.7 per 100 years of observation in the period 1996–1999) due to the continuous improvements in dialysis and transplantation, their prevalence is probably going to rise in the future.
future. The observations presented here stress the importance of focusing on this interesting cohort.

Over time, multiple selections occurred in this cohort: at the start of dialysis (when open acceptance to dialysis was not yet performed), at the enrollment onto the transplant waiting list and actually at transplantation. Other factors such as compliance or psychological attitude may have played a crucial role in the present clinical status [5,16–18]. The effect of these multiple selections and the lack of complete information on the baseline cohort, a problem shared by all the European settings until the early 1980s, prevented us from attempting comparisons among subgroups, since they should be corrected for case mix and for treatment features over time. Since, with these limitations, disentangling the results of treatments from other factors is almost impossible, a very simple cross-sectional analysis with a descriptive study design was chosen. For the sake of description, patients were sorted according to the three broad treatment groups corresponding to the macro-events in their clinical history (group 1, 56 patients always on dialysis; group 2, 40 patients always on dialysis at the time of study but with a previous graft; and group 3, 92 patients grafted at the time of study).

As suggested in previous clinical reports, the patient cohort with long RRT follow-up is characterized by a high prevalence of glomerulonephritis (58%) and by a relatively low age at start (31.3 ± 10.3 years) [7–10]. The low age at start reflects the selection policy that lasted in our region until 1975, because of lack of artificial kidneys, together with the progressive selection by mortality [11,17]. Therefore, the main clinical features at the start of dialysis mirror the policy and the referral criteria of the late 1970s [19]. Interestingly, heterogeneity is an important factor in this cohort and its extent was surprising, thus underlining the limits of long-term prognostic predictions in RRT patients. The first aspect concerns the wide age range, from 2.2 to 53.4 years at start and from 22.9 to 76.1 years at the time of study. Nineteen patients in this cohort started dialysis as children and eight patients were >50 years of age at start of dialysis. It should be noted that, in the 1970s, 50 years was the cut-off point for the definition of ‘elderly’ with respect to dialysis; at the time of study, however, 12 patients were in their 80s. The variety of clinical conditions in our cohort is reflected by the inclusion of some patients with ESRD that is usually considered to have a poor prognosis (such as one patient with systemic lupus erythematosus and six patients with nephroangiosclerosis). As a result of multiple selections, no diabetic patient was present in our cohort (as of December 1999, the longest follow-up recorded in the region for a diabetic patient was 19.7 years); this is in keeping with other reports [5,7–10,19].

The lower average age of group 3 (patients presently grafted) compared with groups 1 and 2 (patients presently on dialysis) is presumably a reflection of the selection occurring over time, allowing transplantation for the fittest and usually younger patients (Table 1). This is probably an important confounding factor and should be taken into account whenever clinical and outcome differences between patients on dialysis and with renal transplant are analysed, at least in settings such as ours where shortage of renal grafts has been a common problem [11]. The results of the logistic regression, performed to analyse in more detail the complex relationship between the different factors recorded in this cohort, confirm that age at start of treatment was significantly correlated with having received a renal graft, in keeping with the selection criteria of the 1970s and 1980s. On the other hand, the length of time for which patients have their graft is correlated with a lower risk of cardiovascular disease, while the risk of severe visual impairment is significantly correlated with age at the start of treatment (Table 4). While the study design does not allow determination of a causal relationship among these factors, this observation may lead to design of detailed data sets for prospective analysis of the time of development of comorbidities on the different treatments.

Overall, evaluation of functional status using the Karnofsky scale allows a relatively optimistic outlook. Only a minority of cases are not self-sufficient, and over half are in the 90–100 range (no or minor signs of disease). As expected, the prevalence of patients with high Karnofsky scores is greater (>60%) in the grafted cohort. This result, together with the differences developed progressively among the groups, further underlines the advantages of successful transplantation and may be considered proof of the coherence of the clinical definitions chosen [6–18,20].

Despite this good overall functional status, stressing the value of rehabilitation and quality of life in patients on long-term RRT treatment, there are several clinical problems. First, the presence of comorbidity is almost universal (88.3%); furthermore, comorbidity is present in these patients at a younger age and they are affected by a premature aging syndrome. Cardiac disease, diffuse vascular disease and bone disease are highly prevalent (33.5%, 73.4% and 72.9%, respectively) and their occurrence is usually concomitant (only seven of 60 patients with both cardiac and vascular comorbidity were spared from severe bone disease). Accelerated vascular disease, reported since 1974 as a major problem in patients on RRT and considered the bottleneck in the process for improving long-term results, may involve almost all body areas, from the heart (diffuse vascular disease is concomitant with severe cardiac disease in 60 out of 188 cases) to the retina [21–23]. Also of relevance in this cross-sectional study was the low prevalence of hypertension in all groups studied (ranging from 7.4% in patients always on dialysis to 31% in grafted patients), which was lower than the results usually reported on RRT. This result, confirming the pathogenetic role of commonly used immunosuppressors in RRT hypertension, may be seen as an indirect confirmation of the results obtained by the Tassin group on the importance of normotension as a positive prognostic factor [16].
The prevalence of anti-HCV antibodies in our study was high (73.6%), in keeping with the results found in patients with long RRT follow-up [24]. Although this may be alarming, clinical liver disease was uncommon (11 cases), possibly due to the relatively short follow-up. The high prevalence recorded, taking into account an overall regional prevalence of HCV antibodies on dialysis of 25.4%, is probably related to the long history of RRT, to frequent blood transfusion and to renal transplantation, frequently requiring further blood transfusions for immunological conditioning and for surgical reasons. The prevalence is also in keeping with other reports of increasing risk of HCV with dialysis duration [24].

Neoplasias were recorded in 12% of patients; since aggressive tumours are unlikely to be disclosed in a cross-sectional analysis, the neoplasias recorded had a relatively good prognosis, the majority (10 cases) being skin tumours in grafted patients. The risk of skin neoplasia in grafted patients is therefore confirmed once again [25].

Malnutrition was rare in the whole cohort (6% were severely malnourished) and 64% of patients were well nourished according to SGA scores. However, subtle signs of malnutrition may escape such a test since the evaluation is sensible to rapid changes in clinical status and may underestimate a slow nutritional impairment, which is probably more common in long-term RRT patients. This may explain the apparent discrepancy between some recent data reporting a progressive impairment of nutrition with duration of treatment [6,26]; moreover, in a cross-sectional study, the low prevalence of severe malnutrition is in keeping with a short-term effect of severe malnutrition on survival. Vasculopathy, cardiac and bone disease and malnutrition are frequently comorbid and their prevalence increases with age, alongside a parallel reduction in functional status. This pattern, further confirming the coherence of the clinical definitions chosen, points to a common pathogenesis and may describe a general picture of an accelerated ageing process in uraemic patients.

Analysis of comorbidity identified the presence of two further relevant problems: (i) severe depression, only recently described in dialysis patients and so far not extensively studied in long-term survivors; and (ii) severe visual impairment, an important comorbid factor both because of its high prevalence (18% in the whole cohort) and because of its impact on quality of life (it was clinically defined as a condition severely impairing daily living activities such as reading, watching television, etc.) [27].

Severe depression, defined as a condition lasting for at least 6 months and needing at least occasional pharmacological treatment, was relatively common (24 cases, 12.8%), in keeping with a recent report on the overall dialysis population [27]. Once more, the prevalence of diffuse cardiovascular disease was high in this subset (21 out of 24 patients with severe depression had cardiac or vascular comorbidity, or both).

Severe visual impairment has not yet been reported as a common complication in non-diabetic uraemic patients with a long RRT follow-up. Even if the diagnosis most commonly reported in the clinical charts was a cataract, the vast majority of cases underwent surgical correction, without apparent benefit. In the search for an alternative explanation, a close relationship between severe visual impairment and diffuse vascular disease was found. A causal relationship with diffuse vascular impairment may be hypothesized on the basis of the high prevalence of severe visual impairment in patients with cardiac and vascular comorbidity (31.7% vs 7.3% in patients without cardiovascular comorbidity; \(P = 0.001\)).

Some further suggestions may arise from the analysis of the exceptions, represented by the patients without obvious comorbid factors. This subset of 22 patients accounted for 12% of the whole cohort and was characterized by younger age (44.3 ± 8.5 years at the time of study), by an inversion in the male/female ratio (9/13) and by a higher prevalence of grafted patients (17 out of 22). However, a few male patients aged >50 years or always treated using dialysis were also recorded in this subset, to underline once more how long-term predictions are not always wholly useful when assessing the long-term effects of uraemia and its treatments.

Study of the history and evolution of the most relevant clinical problems (cardiovascular, nutritional or bone disease) in patients who already display them, and in the few exceptions who find themselves without them, may be useful in preventing the onset of comorbid factors in new patients and in identifying useful prognostic indicators in the clinical work-up. The loose relationship between clinical conditions at study and some well known clinical predictors (ESRD, age at start) is interesting, since it highlights the difficulty of foreseeing outcome even in cases considered poor candidates for dialysis, such as a 2-year-old child, now turning 23, who plays the piano and sings in a chorus, or a relatively old patient with polycystic kidney disease who survived to become a 74-year-old grandfather.

In this context, the heterogeneity of the cohort of ‘survivors’ highlights the problems faced when trying to identify discriminating criteria. These observations may be of particular value now, at a time when the rationing of dialysis treatment is being discussed and when researchers are trying to identify the prognostic factors capable of identifying candidates for long-term clinical success [28].

The growing tide of elderly patients and patients affected by severe comorbidity at the start of dialysis is changing our approach to treating the RRT population, in particular concerning the need for a multidisciplinary team and for geriatric predialysis care. However, analysis of the survivors should remind us that the incidence of young people needing dialysis has not decreased since the first registry data, and that we should not forget to plan our interventions based also on long-term goals.
Long survivors on RRT

Investigators


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