Diabetic patients on renal replacement therapy: analysis of Catalan Registry data

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Abstract

Purpose of study. In recent years, a progressive increase in the need of renal replacement therapy has been noted for patients with diabetes mellitus. The present report is based on an analysis of the data of the ‘Registre de Malats Renals de Catalunya’ (RMRC). It was the aim to identify (i) the incidence and prevalence of diabetic patients on renal replacement therapy, (ii) associated diseases, (iii) the relative risk of different modes of treatment, and (iv) the rate of death compared to non-diabetic patients on renal replacement therapy and in the general population.

Results. Of the 936 diabetic patients starting renal replacement therapy during the period 1984–1994, 24.8% were classified as DN and IDDM, 65.7% as DN and NIDDM, and in 9.5%, diabetes accompanied renal failure from standard primary renal disease. The incidence of diabetic patients has increased from 3 per million population (pmp) in 1984 to 26.6 pmp in 1994. At any given age the risk of requiring renal replacement therapy with diabetes was 1.5-fold higher in males than in females. Of diabetic patients who were <45 years of age, 55% received a renal transplant and >50% lived with a simultaneous kidney/pancreas graft. For diabetic patients above this age, haemodialysis was the most prevalent form of treatment. Morbidity in diabetic patients was higher than in the overall RMRC population. Cardiac and vascular disease were the most prominent complications. Mortality of diabetic patients on renal replacement therapy was twice that of the overall population of RMRC and 16-fold higher than in the general population of Catalunya. The risk of death increased with age and was higher in patients with reduced functional autonomy. Transplanted patients had a smaller risk than patients on haemodialysis or CAPD. Survival has increased for patients starting treatment after 1990 compared to the period 1984–1989.

Conclusion. In conclusion, diabetes mellitus is one of the main causes leading to renal replacement therapy in Catalunya. Diabetic patients are more multimorbid than the rest of the population of the Registre de Malats Renals de Catalunya. These observations call for the institution of primary or secondary prevention.

Key words: diabetes mellitus; multivariate analysis; renal registry; renal replacement therapy

Introduction

Diabetic nephropathy (DN) is a microangiopathic complication which has a major impact on the health system and which afflicts more than one-third of patients with insulin-dependent diabetes (IDDM) [1] and a less well defined proportion (~20%) of diabetic patients with non-insulin-dependent diabetes (NIDDM) [2]. Once DN has set in, it will inexorably progress to end-stage renal failure [3], at least without treatment. Its very presence is a major risk factor for cardiovascular death [4]. This fact explains why morbidity and mortality in patients with DN is higher than in non-diabetic patients with renal replacement therapy (RRT) [5].

The proportion of the types of diabetes varies according to genetic background and geography [6]. In Northern Europe and in the UK, DN in patients with IDDM is more frequent than in other countries [7]. In contrast, in Central and Southern Europe, the overwhelming majority of uraemic patients reaching end-stage renal failure suffer from NIDDM which appears to predominate particularly in Mediterranean countries [8].

In the recent past, the majority of registries documented a progressive increase of diabetic patients on RRT. The magnitude of this increase varies, being highest in USA, Japan and Scandinavia, where DN has become the most frequent cause of end-stage renal failure [9–10]. The aetiology of end-stage renal failure in diabetes is not uniform. The diagnosis of DN is a diagnosis of exclusion and systematic renal biopsy is not practiced. DN is a most frequent cause of end-stage renal failure in diabetes mellitus and in >80% of IDDM patients this is the correct diagnosis. It must be admitted, however, that 30–50% of NIDDM...
patients reach end-stage renal failure for causes other than DN [8,11]. A certain proportion of patients is misclassified and the proportion of IDDM overestimated in many reports, since >60% of diabetic patients having reached end-stage renal failure are on insulin treatment [12].

It was the purpose of the present analysis of the Registre de Malats Renals de Catalunya (RVRC) to identify (i) the incidence and prevalence of diabetic patients on RRT, (ii) associated diseases, (iii) risk factors related to the modalities of treatment, and (iv) the rate of death compared to non-diabetic patients of the RMRC and of the general population.

Subjects and methods

The RMRC Registry was created by law in 1984 to assist the ‘Programa de Atenció a la Insuficiencia Renal’ as an aid to planning. It is an obligatory registry which receives information from all dialysis and transplant units in Catalonia. The 43 centres complete individual questionnaires for each patient (i) at the beginning of RRT, (ii) whenever the centre or treatment mode is changed, and (iii) regularly at the end of the year. RMRC receives information on treatment modality, associated diseases, and aspects related to RRT such as hospitalization, EPO treatment, functional autonomy, markers of viral disease, etc. In 1989, auditing confirmed the validity of the data for epidemiological studies. Since 1992, RMRC operates as a local registry, cooperating with the EDTA registry.

The EDTA codes were used to categorize the type of nephropathy. Standard nephropathy are primary nephropathies of glomerular, hereditary, interstitial or unknown origin. Patients were categorized as suffering from IDDM if diabetes began before age 30 and was treated with insulin during the first year of the disease. In such patients, the time interval between star of diabetes and beginning of RRT does not exceed 25 years [13]. The other patients with DN were categorized as NIDDM. We are well aware of the potential of misclassification when adopting this definition as patients with ‘associated diabetes’ were categorized patients in whom the cause of end-stage renal failure was some primary renal disease other than DN. This category was introduced in 1991 into the RMRC Registry.

With regression logistics, we analysed the influence of age and gender in the development of terminal renal failure due to diabetes. Univariate analysis of survival were calculated with the actuarial method and statistical significance was calculated with the long rank test. The figures on the population of Catalonia and the mortality in the Catalan population were taken from the 1992 census and populations statistics. The degree of functional autonomy was assessed using Karnofsky’s scale modified after Gutman [14].

Results

Of the 5875 patients starting RRT in Catalonia between 1984 and 1994, 936 (15.9%) had diabetes mellitus. The cause of end-stage renal failure was DN and IDDM in 233 (24.9%). DN and NIDDM in 615 (65.7%) and varied causes in the remaining 88 with ‘associated diabetes’. The overall incidence of end-stage renal failure increased from 68.2 pmp in 1984 to 111.1 pmp in 1994. In contrast, the incidence of patients with DN increased from 8 pmp to 19.8 pmp in the same period [15]. The number of cases with DN and IDDM remained 20–30 per year, while that of NIDDM increased from 30 in 1984 to 95 in 1994. Since 1992 the number of patients with ‘associated diabetes’ increased from 16 to 40 (Figure 1). As of December 31 1994, the prevalence of patients with diabetes on RRT was 590 (98.3 pmp), whereas that of non-diabetic patients was 4727 (780.1 pmp).

The aetiology of the renal insufficiency in patients classified as ‘associated diabetes’ was: ischaemic nephropathy in 31.4%, unknown in 24.4%, glomerular in 22.1%, interstitial in 14%, adult polycistic kidney disease in 3.5%, and other causes in 4.7%.

In all types of diabetes, the male gender predomin-
The male/female ratio was 1.9 in IDDM, 1.2 in NIDDM and 2.3 in ‘associated diabetes’. The risk of end-stage renal failure for the diabetic male was 1.5-fold greater and this risk increases with age (Figure 2). The mean age at the beginning of RRT is 43.6 years for IDDM, 66.4 for NIDDM and 66.9 for patients with ‘associated diabetes’. The greatest number of diabetic patients starting on RRT was found in the group of NIDDM between 65 and 74 years.

In the population alive on December 31 1994, haemodialysis was the main form of treatment followed by renal transplantation and CAPD. Compared to the overall RMRC population [15], more diabetic patients were HD (72.8% vs 60%) and CAPD (5.5% vs 2%) and less were transplanted (21.6% vs 35%). Of all IDDM patients, 37% were alive with a functioning transplant. For those below age 45 years, this figure was 55% (of whom more than half had a simultaneous kidney/pancreas graft). Only 3% of NIDDM patients received a graft. The different types of treatment vary according to the time on RRT (Figure 3). The proportion treated by CAPD is higher initially and subsequently diminishes progressively. Beginning in the second year, the number of transplanted patients increases. The greatest proportion of patients with a simultaneous kidney and transplant is found between the first and the fifth year. In the seventh year of RRT, 60.4% of patients were on HD, 34.4% were alive with a transplant and 4.2% remained on CAPD.

At the beginning of RRT, diabetic patients had an average of 0.83 associated diseases (0.4 for IDDM and 1.0 for NIDDM). The proportion increased for all disease categories with duration of RRT. Amongst patients alive at December 31 1994, the mean number of associated diseases was 2.74 (vs 1.65 for non-diabetic patients with standard renal disease). Arterioocclusive disease was present in 18% of diabetic patients at the beginning of RRT and in 66% at the end of the study period. The prevalence of ischaemic heart disease increased from 16% to 35%, the prevalence of cerebrovascular disease and cardiomyopathy increased by a factor of 3. In contrast, the prevalence of hepatic and gastrointestinal disease increased more than 2-fold (Figure 4).

In 1994, 44.7% of diabetic patients required hospitalization (vs 26.7% of non-diabetic patients). IDDM patients on HD required a greater mean number of hospitalizations (13.1 days) compared to NIDDM on CAPD (12.1 days), whereas transplanted diabetics were hospitalized for a mean of 4.4 days.

Approximately 80% of diabetic patients were able to take care of themselves; normal or near normal functional autonomy was reported in 50% (vs 80% in non-diabetic patients). More than 90% of patients living with a transplant had normal or near normal functional autonomy. The proportion was only 50% in patients on HD or CAPD.

The survival in diabetic patients was poorer than in non-diabetic patients on RRT (Table 1, Figure 5). Survival was slightly better in haemodialysed than CAPD-treated patients (Table 1). Transplanted non-diabetic patients have 10–15% better survival (graft and patient survival) compared to diabetic patients (Table 1, Figure 6). With respect to transplantation of the kidney alone (TxR) and simultaneous kidney/pancreas transplantation (TxRP), patient survival was better for TxR and graft survival for TxRP (Table 1, Figure 7).

In the first year on RRT, mortality was higher by a factor of 2 in diabetic patients compared to the non-diabetic patient population on RRT and by a factor of 16 compared to the Catalonian general population [15]. Although mortality in diabetic patients above 75 years of age was highest (317 per 1000 patients), it was only 1.3-fold higher than in non-diabetic patients of the same age on RRT. In contrast, mortality of diabetic patients, age 25–34 years (118 per 1000 patients),...
patients) was 12.7-fold higher than that of non-diabetic patients of the same age on RRT (Figure 8).

The risk of death was 2.4-fold higher in patients with DN than in patients with glomerulonephropathy [15] adjusted for age, gender, functional autonomy, and comorbidity. Table 2 shows the result of multivariate analysis, using a proportional hazard model of Cox, for diabetic patients at the start of RRT. The risk of death increased with age, with loss of functional autonomy, was higher on dialysis than after transplantation, was higher for patients who started RRT before 1990, and showed no statistically significant differences between the genders.

**Discussion**

In the past decade, the number of diabetic patients entering renal replacement therapy has increased considerably in Catalunya as in other Western countries [10]. In Catalunya the admission of patients for renal replacement therapy has practically doubled in the period 1984–1994. Amongst these, the number of patients presenting with diabetic nephropathy has tripled, i.e. from 8 pmp to 18.9 pmp. Currently, diabetic nephropathy represents the second most frequent cause of renal failure in the population of RMRC, i.e. 18%. Although these figures are less than those observed in the USA, i.e. 77 pmp in 1992 [9], and in certain populations of Germany, i.e. 52 pmp in the Neckar region [16], they are comparable with the figures obtained in neighbouring countries such as Portugal, France, and Northern Italy [7,17]. Our data are further in good agreement with those reported from Badajoz, a community in the south of Spain, where the incidence of diabetic patients on renal replacement therapy was estimated to be 23.3 pmp [18]. The overall incidence of renal patients in the USA is virtually double than

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**Fig. 3.** Relative contribution of different treatments over time (Selwood Analysis). Period 1984–1994.

**Fig. 4.** Concomitant diseases at start of renal replacement therapy and at 31 December 1994.
registered in Catalunya, i.e. 212 pmp in 1992 vs. 111.1 pmp in 1994 [9]. When one compares the rate in different registries, one must take into consideration whether all patients have been truly registered. Whereas the RMRC and the United States Renal Data System (USRDS) register virtually all patients admitted for renal replacement therapy (or in the case of the USA those beyond the third month of treatment), this is not the case for the EDTA Registry data from Portugal, France, or Italy. Their response rate to the EDTA registry was 63%, 61%, and 54%, respectively in 1994, suggesting major underestimation of the true incidence [19].

Another factor accounting for differences in the incidence of ESRF from diabetic nephropathy are differences in the prevalence of diabetes mellitus between countries. Friedman [20] reported that the proportion of diabetics on renal replacement therapy is a reflection of demography of diabetes mellitus in the general population. The present study documents that NIDDM is mainly responsible for the increment of the number of diabetic patients admitted for renal replacement therapy in Catalunya. The prevalence of NIDDM in Catalunya amongst citizens >64 years, is 8.95% [21], whereas in the USA for individuals >50 years it is 28% [22] and in Germany for individuals aged 60–69 years it is 13.5%, and individuals >70 years it is 23% [23]. Not unexpectedly, this will result in a greater proportion of diabetic patients amongst those admitted for renal replacement therapy. Finally, the difference between our results and those of the Lombardy Registry, i.e. in 1992 10.4 diabetic patients
pm patients admitted for renal replacement therapy, could be explained by the greater prevalence of diabetic patients in Catalunya [21] compared to Lombardy [17]. The respective incidence figures for IDDM in Catalunya (i.e. 11.5 per 100,000 inhabitants, aged 0–14 years vs 6.63 per 100,000 inhabitants in Lombardy) are higher as are those for NIDDM, i.e. known prevalence in Catalunya of 8.95% equivalent to ~15% of known plus non-diagnosed cases vs 10.6% of known plus non-diagnosed cases in Lombardy.

In Catalunya, haemodialysis is the main form of treatment administered to diabetic patients >45 years of age. CAPD is the most frequent modality of treatment in countries such as Australia, UK, or Canada [24]. In contrast, this modality of treatment has not caught on in Catalunya and is utilized in <3% of patients. However, a frequent indication are vascular access problems [15]. During the period 1985–1989 utilization of CAPD reached its peak, but it was not used in >8% of patients. Renal transplantation is the second most common form of renal replacement therapy in diabetic patients, although only 22% of patients survive with a functioning graft vs 43% of non-diabetic patients on renal replacement therapy. The proportion of diabetic patients on the waiting list does not exceed 30% and the proportion of patients excluded for medical reasons exceeds that of the rest of RMRC patient population. Nevertheless if one studies in more detail the group of patients who received a graft, one notes that transplantation is the
Fig. 8. Standard mortality ratio (SMR) during the first year on renal replacement therapy. Diabetic patients and non-diabetic patients. New cases 1984–1994.

principal form of treatment for those <45 years of age (of whom more than half live with a simultaneous kidney and pancreas graft) and that the percentage of transplanted patients amongst IDDM patients is 37%, the figure similar to the non-diabetic patients in RMRC. For the group aged 45–64 years, the proportion receiving a graft is 30%. In contrast, only 3% of NIDDM patients live with a graft and this figure is unlikely to increase in these population of elderly patients with high comorbidity.

Apart from the increase in the number of patients, another major component for the impact on the health system caused by diabetic patients results from their high rate of comorbidity. At the time when renal replacement therapy is started, practically half of the patients with IDDM and all patients with NIDDM have one or more associated diseases and this number increases considerably during the period they remain on renal replacement therapy. The diabetic patients are the group with the greatest number of comorbid conditions (average 2.74 vs. 1.65 in non-diabetic patients). Although all types of comorbid conditions increase in prevalence during replacement therapy, vascular disease plays a major role. In their pathogenesis, advanced glycation endproducts (AGE), a novel form of middlemolecules, appear to play a pathogenic role by interacting with endothelial cells [25,26]. Peripheral vascular disease progresses most markedly: it is present in <20% of patients at the beginning of treatment and affects >66% during renal replacement therapy. The prevalence is similar in both types of diabetes.

In view of such high comorbidity it is not surprising that patients with diabetes mellitus are the group with least functional autonomy in the RMRC: functional capacity is limited in 50% compared to 20% in non-diabetic patients. Similar figures have been reported from Minnesota [27]. Nevertheless the figures are less than those reported by others, where only 23% of diabetic patients were able to care for themselves [14]. The degree of functional autonomy is related to the type of treatment. It is normal or virtually normal in 95% of patients living with a functioning transplant, but is only normal in 45% of patients on haemodialysis of CAPD. It must not be forgotten, however, that the former group comprises younger patients with less comorbidity.

Survival of the diabetic patients is worse than for non-diabetic patients on renal replacement therapy and this is true for all treatment modalities. The figures noted in this study are similar to those reported from other European Registries [17,28] and better than those reported from the USA [9]. The survival curve is better for patients on haemodialysis than on CAPD. The difference is in 10% in the third and 5% in the fifth year of treatment. Analysis of the cases who have received a transplant shows worse results in diabetic patients compared to non-diabetic patients of RMRC. This is true for patient survival and for graft survival.

Simultaneous kidney and pancreas transplantation is a therapeutic modality which is on the increase, although it remains somewhat controversial, and some authors consider it still being in its experimental phase [29]. The results obtained in IDDM patients who received a double graft are comparable to those from other Registries [30]. If one compares the results of double transplantation with renal transplantation alone, it is obvious that in patients with simultaneous kidney and pancreas transplantation survival rates are less than in recipients of a renal graft alone, although graft survival is better.

Multivariate analysis using the Cox model documents that in patients with diabetic nephropathy mortality is three times higher compared to non-diabetic
patients [15]. The risk increases with age, as shown by others [9,17,28]. The Cox model analysis documents that patients on CAPD have a higher mortality than those on HD (RR = 1.35). This agrees with the observation of Held et al. [31] in the USRDS (RR = 1.26) and Catalane et al. [32] in Italy (RR = 1.6). Other authors e.g. Miorca et al. [33] and the Lombardy registry, in contrast, found no difference between HD and CAPD. In our study, diabetic patients who received a graft had a lesser risk than those on HD (RR = 0.43). A similar result has been reported by Port et al. [34]. Our result contrasts with those reported from Leicester [35] where the diabetic population treated from 1974 to 1985 was analysed; no significant difference of mortality was found between CAPD, HD, or renal transplantation.

In conclusion, the present study analysed the current state of renal replacement therapy in diabetic patients in Catalunya. The fact that the cohorts who started renal replacement therapy in the 1990s have better survival than those started in the preceding decade is encouraging. This may be due to the technological improvements, better medical treatment, or improved management of haemodinamic instability. In agreement with other authors, we feel that we are confronted with a disease which is preventable, at least in principle [36], if preventive measures are instituted in time. This includes organization of multidisciplinary services which offer integrated patient management including prevention, early diagnosis, and treatment of diabetes and its complications. Particular attention must be paid to the management of arterial hypertension [37] and dyslipidaemia [38] in an effort to delay the evolution of macroangiopathy, particularly ischaemic heart disease, which is the major hazard for diabetic patients on renal replacement therapy.

References

7. Raine AEG. Epidemiology, development and treatment of end-stage renal failure in non-insulin dependent diabetics in Europe. Diabetologia 1993; 36: 1099–1104


