Huge Progression of Diabetes Prevalence and Incidence Among Dialysed Patients in Mainland France and Overseas French Territories. A Second National Survey Six Years Apart. (UREMIDIAB 2 Study)

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Summary - In 1989, we conducted a survey (UREMIDIAB) on the prevalence of diabetes among the population on Renal Replacement Therapy (RRT) in Mainland France (MF), the lowest of the developed countries (6.9%) with a North-South gradient (higher prevalence in the North). This highlighted a possible (genetical or nutritional) "new french paradox" in mainland France populations. In 1992 we conducted a similar study in the French (mainly non caucasian) overseas territories (OT) hosting 3.2% of the total French population, and observed a prevalence of diabetes in RRT of 22.9%. The frequency of diabetes mellitus as a cause of ESRD increasing worldwide, we conducted a second survey in year 1995, in MF and the OT. This study, UREMIDIAB 2, included all of the 244 french dialysis centers. A "Center file" allowed us to determine the prevalence and incidence of diabetes in the French RRT population, (response rate 73%). Then a "Patient medical file" (response rate 64.8% for MF and 91% for the OT) provided detailed informations: type of diabetes (type 1 or 2), etiology of nephropathy, status of diabetic complications, family's geographic origin of the patient. In MF the prevalence of diabetics in RRT doubled within 6 years: 13.04% vs 6.9%, the incidence reached 13.7%. In the OT the prevalence and the incidence reached 23.7% and 36.5%, respectively. Type 2 diabetes represented 87% and 93% of the RRT diabetics in MF and the OT, respectively. Diabetic nephropathy was considered as the cause of renal failure in 91.3% of type 1 and 57.5% of type 2 diabetics under dialysis. We found: 14.7% of myocardial infarction, 12.7% of cerebral strokes, 17.6% of amputations (extreme 37% in some OT centers) among this diabetic RRT population. A North-East (higher prevalence) South-West (lower) gradient was confirmed. We conclude that, while an unusual low prevalence (≤ 13%) of diabetics under dialysis persists in some parts of Mainland France, the total prevalence has been doubled within 6 years (1989/95) and that in Overseas Territories, hosting similar mixed blood populations than USA (afro-caribbeans, asians, indians, micronessians and melits), the high incidence of diabetes in RRT has reached the US levels during the same period.

Résumé - Progression de la prévalence et de l'incidence du diabète parmi les dialysés en France métropolitaine et dans les DOM-TOM. UREMIDIAB 2. En 1989 nous avons conduit l'enquête UREMIDIAB sur la prévalence du diabète parmi les dialysés en France métropolitaine. Elle était alors la plus faible des pays développés (6.4 %) avec un gradient nord-sud (plus élevée dans le nord), constituant un autre "French paradox". En 1992 nous avons mené une étude similaire dans les DOM-TOM français (majoritairement non caucasiens) concluant à une prévalence de 22.9 % (presque 4 fois plus élevée) dont 92 % de diabétiques de type 2. Devant l'accroissement rapide et général du nombre des diabétiques en dialyse partout dans le monde, nous avons entrepris une seconde enquête épidémiologique sur l'année 1995 portant sur l'ensemble des territoires français, UREMIDIAB 2. Nous avons questionné l'ensemble des 244 centres de dialyse français (232 en métropole et 12 pour les DOM-TOM). Un « dossier centre » a permis de déterminer la prévalence et l'incidence du diabète (taux de réponse de 73 %). Le « dossier patient » précisant le type de diabète, le statut des autres complications liées au diabète, l'origine de la néphropathie, l'origine géographique des patients ; (taux de réponse de 64.8 % en métropole et de 91 % dans les DOM-TOM). Les résultats de 1995 montrent un doublement de cette prévalence, en 6 années, en France métropolitaine (13.04 %) et une incidence de 15.7 %, Dans les DOM-TOM la prévalence atteint 25.7 % et l'incidence 35.6 % soit plus d'un patient dialysé sur trois. La proportion de diabétiques de type 2 était de 87 % en métropole et 93 % aux DOM-TOM. La néphropathie était considérée comme due au diabète pour 91.3 % des diabétiques de type 1 et 57.5 % des diabétiques de type 2. On dénombre 14.7 % d'infarctus du myocarde, 12.7 % d'accidents vasculaires cérébraux, 17.6 % d'amputations (jusqu'à 37 % dans un des centres des DOM-TOM). Un gradient nord-est (haute prévalence)/sud-ouest (plus faible prévalence) est confirmé. Nous concluons que la France comporte encore dans certaines régions des zones de faible prévalence de diabétiques parmi les dialysés (≤ 13 %), mais en moyenne celle-ci s’est considérablement accrue en 6 années (X2) rejoignant dans plusieurs régions les niveaux des pays voisins (≥ 20 %). Dans les DOM-TOM l’incidence de plus de 35 % atteint les niveaux très élevés enregistrés aux USA pour des populations similaires (origine africaine, indienne, asiatique et européenne). Mots-clés : Diabète, insuffisance rénale terminale, dialyse, épidémiologie, DOM, TOM.
Diabetes mellitus has become the leading cause of end-stage renal disease (ESRD) and renal replacement therapy (RRT) in all developed countries [1-16]. Although incidence and prevalence of terminal renal failure in diabetic patients greatly vary from country to country, in the recent past, the majority of registries documented a progressive increase of diabetic patients on RRT. The proportion of the diabetics amongst the whole population in RRT is higher in Northern Europe and in the USA and lower in Central and Southern Europe. Moreover, the distribution of types of diabetes mellitus (i.e., type 1 and type 2 diabetes) varies with geographic and genetic background. In 1989, our group conducted a national epidemiological study in Mainland France to compare the situation in our country with international data. This survey concluded that the prevalence of end-stage renal disease in diabetic patients in France was the lowest, 6.9%, [18] of Western Europe [14] and four to five times lower compared to North America [15, 16], representing a new French paradox. In 1992, we performed an additional trial to measure the prevalence of RRT due to diabetes in the overseas French territories (OT). These territories, representing 3.2% of the total French population, are distributed across the world and their populations essentially are non-Caucasian (mixed blood population) with a higher prevalence of diabetes mellitus, mostly type 2. We found a prevalence of 22.9% [21] of diabetes amongst patients on dialysis in these populations, 3 times higher than the mainland prevalence.

Thus we decided to perform a new survey (1995) in mainland France aiming to see whether the huge increase of the prevalence of type 2 diabetes mellitus in RRT described in all other developed countries was also observed in our country or whether French “specific situation” remained unchanged. Additionally, our first survey described an influence of the geographical distribution of the patients in mainland France, i.e., a higher prevalence of RRT in diabetic patients in the northern part of the country and a lower one in the southern part [18]. Other additional studies were performed in this second trial, mainly to describe the usual management of diabetic patients in RRT in our country. This study was also conducted in the overseas French territories population.

**SUBJECTS AND METHODS**

The study population involved all the patients treated by dialysis of any kind in all the 244 public or private dialysis units listed in the 1993 AURA (Association for the Use of Artificial Kidneys) directory for mainland France (n = 232) and overseas territories (n = 12). There were two phases in the study. First, a prevalence and incidence study was performed. A form was mailed to heads of the units who were asked to record the total number of patients treated for dialysis during the last two days of year 1995, to identify those who were diabetic (prevalence) and to classify them according to the type of diabetes mellitus (type 1 or type 2). This classification was made by the nephrologist of each center according to an algorithm that had previously been established and validated by our group in the UREMIDIAB 1 study, based on age at diagnosis, body mass index and delay for insulin introduction (19). They were also asked to number the new dialysed patients (total and diabetics, including type of diabetes) for the year 1995, allowing to calculate the incidence of diabetes mellitus, amongst the total dialysed population. This constituted the “Center File”.

The second phase of the study provided detailed informations regarding the diabetic population under dialysis and constituted the “Patient File”. This second form contained the following informations:

- The clinical status of the patient and the history of diabetics were recorded, allowing to determine the type (type 1 or type 2) of diabetes according to the algorithm previously validated and published by our group [19].
- The family’s geographic origin of the diabetic patient and informations on the area where the family and/or the patient spent the last part of their life. These data were required to address the question of a genetic or environmental influence on RRT diabetic prevalence heterogeneity previously described in mainland France by our group [18].
- Also recorded was the presence of other diabetic subjects and nephropathies in the family of every diabetic dialysed patient.
- The status of diabetic complications was collected: retinopathy, cerebral stroke, amputations, coronary heart disease.
- In order to determine the etiology of nephropathy (diabetic glomerulosclerosis, other or both), each record was reviewed by one of us (DC) on the basis of a list proposed to each head of dialysis unit. Finally, type and duration of RRT were collected, as well as any history of previous kidney and/or pancreas transplantation.

**Statistical analysis** – The prevalence and the incidence rates of diabetes mellitus in the dialysed population were calculated for each type of diabetes. Standard statistical tests were used to compare subgroups of the study population (Chi square test, Student’s test). To assess the geographical distribution of diabetic nephropathy cases, we compared the mean prevalence and incidence rates of type 1 and type 2 diabetes mellitus among the 22 regions of mainland France and overseas territories using the 22 corresponding state official classification. The analysis was conducted with an IBM-PC computer using the SPSS/PC + statistical package (SPSS Inc., Chicago, 1988).

**RESULTS**

**Prevalence and Incidence** (Table I and II) – One hundred and eighty one unit files were returned to determine the prevalence and incidence of diabetic patients under dialysis. The mean response rate was 73%. The response rate ranged from 33% in one region in Mainland, with a large majority of mainland regions responding between 60% and 80%, to 91.7% in
overseas territories. No particular characteristics emerged from the units that did participate in the study. However, unit size and geographical location did not differ between responding and non-responding centers. Amongst the responders (178/244), twenty-three did not return the patient file. This allows to determine the diabetic patients characteristics for 64.8% of the dialysis unit and for 91% of them in the overseas territories. The unit characteristics did not differ between the centers that participated in the second (patient file) phase of the study, and those that did not. The number of patients (total dialysed and diabetic dialysed) per center was higher in the non-responding centers: n = 107.4 vs n = 87.7 (p = 0.11) and 14.7 vs 12.5 (p = 0.58), respectively, but these differences were not significant. The total population receiving dialysis in the participating units was 16,174 patients, 2,303 of whom were diabetic (14.24%). In mainland France, 1915 diabetics were found amongst 14,666 dialysed patients (13.05%) vs 388 diabetics amongst 1,508 in overseas territories (25.72%). Of these dialysed diabetic patients, 13.05% (n = 270) were classified as type 1 and 87% (n = 1,666) as type 2 in mainland France and 7.5% (n = 29) vs 92.5% (n = 359) in overseas territories (Table II). However, 70% of diabetics in RRT were treated with insulin.

The sex ratio M/F was 1.1 (52% male) for all diabetes types and geographic regions. The total incidence of diabetic patients admitted in dialysis for year 1995 was 17.15% (670/4500). This incidence was 15.7% (6.45 to 25%) in mainland and 35.61% in overseas territories. The mean age of type 1 or type 2 diabetics in RRT was 44.7 ± 10 years and 66.5 ± 9 years, respectively. Thus the total incidence of RRT in the French general population during 1995 can be 7.9 fold higher in diabetic patients. This corresponds to an RRT admission rate of 46 diabetic patients/million (ppm) vs 382 patients/million for all causes of RRT. When separately calculated for type 1 and type 2 diabetic patients, this ratio is 8- and 7.3-fold higher, respectively, when compared to the non-diabetic population.

Among the 1925 (83.5%) completely fulfilled patient forms, 827 diabetics in RRT (42.9%) reported a diabetic (first and second degree) parent in their family and 18.5% of them were known to suffer from some nephropathy.

The status of diabetes-linked complications was studied for retinopathy, coronaropathy, amputations and cerebral stroke. Among type 1 diabetics, 97% presented with one or more of these complications vs 84% among type 2 diabetics. The percentage of pa-

<table>
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<tr>
<th>Territories</th>
<th>Number of dialysed patients (measured)</th>
<th>Number of diabetic dialysed patients (measured)</th>
<th>Number of type 1 (measured)</th>
<th>Number of type 2 (measured)</th>
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<td>705</td>
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<tr>
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<td>1915</td>
<td>249</td>
<td>1666</td>
</tr>
<tr>
<td>(UREMIDIAB 2)</td>
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<td></td>
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<tr>
<td>Overseas Territories</td>
<td>934</td>
<td>214</td>
<td>22</td>
<td>192</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Overseas Territories</td>
<td>1508</td>
<td>388</td>
<td>29</td>
<td>359</td>
</tr>
<tr>
<td>Year 1995 (UREMIDIAB 2)</td>
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</table>
Patients with complications reached 91.4% in OT although the majority of them were type 2 diabetics. Retinopathy was present in 71.7% of the whole French diabetic RRT population and in 80 to 100% of patients in the OT dialysis centers. A recent (< 12 months) myocardial infarction (MI) was present in 2.7% of the patients, and a not recent (> 12 months) one in 14.7% of them. Cerebral stroke was present in 12.3% of the whole diabetic RRT population, without any influence of the geographic region (from 11.5 to 14.1%). The mean prevalence of amputations was 17.6% in the whole diabetic RRT population, from 5.9% in one mainland dialysis center to 37% of the patients in some others (overseas territories). A large majority (81.4%) of diabetics in RRT had 1 or 2 other diabetic complications.

The origin of the ESRD – was considered as a diabetic nephropathy in 91.3% of type 1 and in 57.5% of type 2 RRT diabetics. The main other causes supposedly responsible for ESRD in type 2 RRT diabetics were: chronic vascular nephropathy in 12.4%, interstitial and tubular nephropathy in 6.6%, and different other diseases (glomerulonephritis, polycystic kidney disease) in 13.2%.

Geographic distribution of the diabetics in RRT – in mainland France (Fig. 1). Among the 22 administrative regions of our country, a North-South gradient was observed in this study. In 80% of dialysis centers located in the north-east (N-E) of France, the prevalence of diabetics exceeded 16% (16.34 to 17.94%), in 75% located in the south-west (S-W) of France this prevalence was lower than 13% (8.22 to 12.78%). However there were some exceptions, as a low prevalence (11.8%) in Lorraine (N-E). This could be explained by a low survival rate in RRT, the incidence being 16.74% in this region. By contrast, a higher incidence (21.93%) in Midi-Pyrénées (S-W) was also found. No gradient was observed for the geographical distribution of type 1 diabetics in RRT. A North-South gradient was found for the type 2 diabetics in RRT that was mainly explained when the place of birth of the patients was taken into consideration. This was confirmed when the place of birth of the parents (the father, or the mother or both parents) was taken into account. Dialysis centers situated in Paris area showed a special distribution for the origin of the parents of the diabetic patients in RRT due to the large number of migrating patients coming from other regions, OT or foreign countries.

The duration on RRT — in the whole population ranged between 1 to 4 years for 72% of the prevalent diabetic patients, 5 to 7 years for 17.4% and over 7 years for 10.6%.

Modalities of Renal Replacement Therapy (RRT) – hemodialysis (HD) was used by 70.2% of type 1 and
of diabetics in RRT grew from 884 to 1915 patients (+116%, +20% per year). Thus, the increase of diabetics in RRT was higher than 2-fold, while the total number of RRT in mainland France increased by 25%. This huge increase mainly is due to the progression of type 2 diabetics in RRT: 80 to 87% of all dialyzed diabetics and 705 to 1,666 patients (+136%, +22.6% per year). Meanwhile, the absolute number of type 1 diabetics in RRT increased from 179 to 249 (+39%, +6% per year). The epidemiological value of this study is validated since the size and geographical location of responding and non responding dialysis centers were not significantly different. We can further extrapolate to a total general RRT population of 22,156 patients, amongst them 341 type 1 and 2,282 type 2 diabetics. The incidence for year 1995 showed a further increase: 15.7% in mainland France, ranging from 6.45 to 25% according to the studied region. The analysis of the geographical prevalence and incidence distribution confirmed the gradient previously described in UREMIDIAB 1 study: higher for the north-east part and lower in the west, south and south-east of the country. This gradient was due to type 2 diabetics and values recorded for the french regions were close to those of the adjacent countries [1-5, 7, 9, 12, 14]: Belgium incidence 21.5% (1997), Austria 18% (1996), Lombardy 11% (1992), Catalunya 16.6% (1997). The number of prevalent diabetics in RRT may be underestimated in Germany: 22% [1]. During the same period, for the Heidelberg region, this prevalence reached 59% in 1995 [7]. For the Hanover region, this prevalence was about 47% in 1997 [5, 23]. Thus, while the progression of diabetic patients in dialysis in mainland France was dramatic between 1989 and 1995, the ppm remained the lowest of the developed countries with Lombardy 46 and 59 ppm respectively (Table III). We tried to analyze geographical differences to determine whether they were due to ethnic or environmental origins. Our data showed that outside the Paris area, diabetic patients were mainly dialysed in their family’s original geographical location. This does not allow to explain the geographical differences confirmed by the present study. The high prevalence observed in the overseas territories in 1992 was confirmed 3 years later with a slow progression of the prevalence (25.72% vs 22%). However, the high level of incidence in 1995 (35.6%) in OT was comparable to that of the non-white US citizens [16]. This discrepancy between incidence and prevalence in OT probably is due to a rather short survival of diabetic patients in dialysis [22, 24], the majority of them being type 2, older and multicomplcated diabetics. This incidence of diabetes in RRT is comparable to that of African Americans [16] and to that of asian populations, Aborigenes in Australia (41%), Maories in New-Zealand (61%) and Pacific islanders (49%) [10, 11].

This progression of the diabetics in RRT partly is due to the rise of the prevalence of type 2 diabetes, linked to the the general population aging and, more importantly, to the continuous improvement of care and survival in type 2 diabetics during the last decade [17, 22]. One can predict this phenomenon to increase in the next

### Table III

<table>
<thead>
<tr>
<th>Country</th>
<th>Renal replacement therapy prevalence</th>
<th>Renal replacement therapy prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All patients</td>
<td>Patients with diabetes</td>
</tr>
<tr>
<td></td>
<td>Total number</td>
<td>ppm</td>
</tr>
<tr>
<td>Australia 1996 (11)</td>
<td>9,244</td>
<td>507</td>
</tr>
<tr>
<td>Belgium 1997 (with the courtesy of the A.S.B.L.)</td>
<td>3,357</td>
<td>763</td>
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<tr>
<td>Denmark 1997 (12)</td>
<td>2,861</td>
<td>535</td>
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<td>Catalunya 1997 (9)</td>
<td>5,445</td>
<td>908</td>
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<tr>
<td>Lombardy 1996 (in 17)</td>
<td>7,371</td>
<td>825</td>
</tr>
<tr>
<td>USA 1995 (15)</td>
<td>266,226</td>
<td>965</td>
</tr>
<tr>
<td>Mainland France 1995</td>
<td>22,156</td>
<td>382</td>
</tr>
<tr>
<td>French Overseas Territories 1995</td>
<td>1037</td>
<td>830</td>
</tr>
</tbody>
</table>

*A.S.B.L.: Groupement des néphrologues francophones de Belgique
ppm = per million population

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decade. This would emphasize a continuous improvement of survival of diabetic patients on dialysis treatment, which remains very short. The high mortality of these patients mainly is due to cardiovascular disease. The first cause of death is myocardial infarction (MI) (62% of deaths). Mortality is 4.8- in type 1 and 3-times higher in type 2 diabetics compared to non diabetic RRT patients. A majority of type 2 diabetics in RRT exhibits two or three severe complications. Although these diabetic patients in dialysis are type 2 elderly polymorbid patients, it is noteworthy that a few of them are listed for kidney transplantation when compared to other European countries [25]. Finally, it is remarkable to note that in our present study, the relative risk of RRT compared to the general population appeared similarly high in type 2 diabetes (7.3-fold) and type 1 diabetes (8-fold) [26].

In conclusion, this second French survey confirms the silent epidemic of ESRD in diabetic patients and mainly emphasizes the dramatic human and economical cost of type 2 multicomplicated diabetes, as it is worldwide. On the other hand, we confirm a relatively lower prevalence of diabetes among ESRD patients, mainly in the western and southern regions of mainland France, possibly linked to genetic or environmental factors.

Multiple efforts are needed in the treatment of diabetic patients and mainly type 2 diabetics, as recently suggested by the UKPDS trial [27-29], that showed the frequency of microangiopathic complications could be reduced by a tight glycemic control and, more impressively, by an intensified antihypertensive treatment. Moreover, kidney transplantation must be developed for ESRD diabetic patients and mainly for type 2 diabetics [25].

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