

Original Article

Diabetes mellitus after kidney transplantation: a French multicentre observational study

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Abstract

Background. New-onset diabetes mellitus (NODM)—a common complication of kidney transplantation—is associated with increases in graft loss, morbidity and mortality.

Methods. This is a purely observational study of 527 patients taking a calcineurin inhibitor (CNI), based on data collected at a single routine visit 6–24 months after kidney transplantation. Diabetes was defined according to ADA/WHO guidelines.

Results. The mean age of the patients was 47.2 years and 61.1% were men; 49.5% were receiving cyclosporine microemulsion (CsA-ME) and 50.5% tacrolimus (Tac). NODM developed in 7.0% after a median interval of 1.6 months. In CsA-ME-treated patients, the unadjusted cumulative risks of NODM were 5.5% and 8.4% at 1- and 2-year post-transplantation, while in Tac-treated patients, the risks were respectively 17.4% and 21%. Four independent risk factors (RFs) were identified by multivariate analysis: maximum lifetime body mass index >25 [odds ratio (OR)=5.1], pre-transplantation impaired fasting glucose (OR=4.7), hepatitis C status (OR=4.7) and Tac vs CsA-ME treatment (OR=3.0).

Conclusions. NODM is associated with certain RFs present prior to kidney transplantation, and with treatment with Tac as opposed to CsA-ME.

Keywords: calcineurin inhibitors; hepatitis C virus; renal transplantation; new onset diabetes mellitus; pre-transplantation impaired fasting glucose

Introduction

New-onset diabetes mellitus (NODM) is a common complication of kidney transplantation. Apart from the well-characterized pathological processes of the diabetes itself (keto-acidosis, coma, atherosclerosis, angiopathy and susceptibility to infection) and its effects on quality of life in general, NODM has specific adverse effects on transplantation outcome. In controlled studies, post-transplant NODM has been shown to be associated with an increased incidence of infectious [1] and cardiovascular complications [2,3] as well as, most pertinently, impaired long-term graft function and reduced survival [4,5]; one large-scale study reported that the relative risk of graft loss 12 years after kidney transplantation was 3.72 times higher in patients who had developed NODM than in those with normal glucose metabolism [6]. Numerous studies have shown reduced long-term survival of recipients [4,7–9] as would be expected given, on the one hand, that cardiovascular complications are the leading cause of mortality in kidney recipients in general [10] coupled with, on the other hand, the well-established exacerbatory role of diabetes in the aetiology of cardiovascular disease [11].

Establishing the exact incidence of NODM from published data is difficult for a number of reasons. First, many of the published studies use unreliable markers for diabetes, e.g. for most of the clinical trial data, diabetes was defined as the need for a course of insulin therapy lasting 30 days or more, a definition which excludes all those who develop the disease and are managed with oral antidiabetic drugs. Secondly, blood glucose monitoring modalities have been very diverse and far from systematic, certainly leading to

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underestimation. Thirdly, follow-up times are not always adequate: the onset of post-transplantation diabetes is biphasic with a high rate in the immediate post-operative period followed by a gradual but sustained rise in prevalence for many years; in consequence, too short a follow-up time will give a misleading picture. Fourthly, diabetes and impaired glucose metabolism are by no means permanent in all cases, often resolving spontaneously even without treatment. Finally, there are both temporal and geographical variations: not only has the incidence of NODM been greatly reduced since the early days of transplantation (largely due to the availability of equally effective but less diabetogenic immunosuppressive modalities) but it also seems to vary from one part of the world to another. All these factors have led to highly divergent estimates of the incidence of NODM after renal transplantation [12]. A large-scale American study covering 11 659 patients transplanted between 1996 and 2000 reported that the incidence of NODM rose from 9.1% after 3 months to 24% after 3 years [4]. However, the prevalence of type 2 diabetes in the United States is already more than double that in Europe (7.9% [13] vs 3.5%) where the incidence of NODM (with which it shares risk factors) also appears to be lower; indeed, two specific risk factors identified in many studies—non-Caucasian ethnic origin and excess body weight—may account for the discrepancy between Europe and the USA. In consequence, the data obtained by meta-analytic approaches ought to be treated with caution, e.g. a European transplant specialist may not be entitled to be encouraged by a rate of NODM below that of the 13.4% reported in the broadest meta-analysis published to date [14] as this is largely based on North American data.

A number of risk factors for NODM have been identified including advanced age at transplantation, a family history of diabetes [7], pre-existing impaired glucose metabolism [15] and hepatitis C infection [16]. In addition to these factors which are all shared with Type 2 diabetes, certain factors are specific to transplantation, especially the immunosuppressive drugs used. Both corticosteroids [17] and the two calcineurin inhibitors (CNIs) commonly prescribed are now recognized as possessing diabetogenic activity, although it is reported that tacrolimus (Tac) is up to five times more diabetogenic than ciclosporin A [4,18]. Bringing down the incidence of NODM following kidney transplantation is going to depend on being able to effectively balance risk factors, the most obviously modifiable of which is the choice of immunosuppressive drugs. This will demand a clear understanding of all the various risk factors and their relative weight in the specific patient population concerned. This study was conducted in order to estimate the incidence and risk factors for NODM [according to the American Diabetes Association/World Health Organization (ADA/WHO) definition] in kidney recipients, including the impact of calcineurin inhibitors, in a European population.

Materials and methods

Study design

The principal objectives of this retrospective study conducted in a series of consecutive patients were to estimate the incidence of NODM following kidney transplantation in France, and to identify the most important risk factors, including the role of CNIs in this population. A secondary objective was to evaluate how well patients with NODM are being managed. All data—both on current status and retrospective data from before transplantation to the day of the study—were gathered in the course of a single visit scheduled in the context of each patient's routine post-transplantation monitoring program. Fasting blood glucose levels were collected retrospectively for each clinic visit (according to each patient's post-transplantation follow-up duration).

Centre selection

Seventeen centres—randomly picked from the 37 establishments in France that perform more than 30 renal transplantation procedures per annum in adults—were invited to participate and enrolled patients. In each centre, a fixed number of investigators was determined before the start of the study.

Patients

Each investigator participating in the study was asked to include all patients seen consecutively in the out-patients clinic, and meeting the inclusion criteria. All patients were seen in the context of a routine visit. Eligible for inclusion were all adults (over 18) who had received a first transplanted kidney at least 6 and no more than 24 months beforehand, and who were being treated with either ciclosporin A microemulsion (CsA-ME) (Neoral®, Novartis Pharma France) or Tac on the day of the study visit. Excluded were those who had been diabetic [a blood glucose reading of ≥ 7 mmol/l (126 mg/dl)] prior to transplantation or whose pre-transplantation glycaemic status was unknown; those who had undergone multiple organ transplantation; and those who had experienced an episode of acute rejection (AR) in the 3 months preceding inclusion. Additional exclusion criteria were serious intercurrent disease, HIV infection, and participation in a Phase I or II clinical trial since transplantation. Pre-transplantation impaired fasting glucose (IFG) (6.10–7.00 mmol/l) was not an exclusion criterion.

All patients were provided with written information about the study and signed an informed consent form prior to participation.

Study assessments

On the basis of an interview with the patient and an examination of his/her medical records, details on the following items were collected: demographic characteristics [gender, age, ethnic origin, current and maximum lifetime body mass index (BMI)], transplantation history (nature of kidney disease, donor and recipient information, episodes of

AR and comprehensive details of the immunosuppressive regimen including dosages and blood concentrations), diabetes-related factors (pre-transplantation fasting blood glucose levels, family history of diabetes and any significant obstetrical history), hepatitis B and C status, cardiovascular risk factors (CVRFs) (hypertension, dyslipidemia and current smoking status) and, for those with NODM, details on diabetes care (notably treatment). Blood glucose levels and changes in immunosuppressive therapy were recorded for the following time points (depending on the interval since transplantation): as close as possible to 3 months after transplantation (M3), M6, M12 and M18, and finally on the day of the study visit. Diabetes was diagnosed in accordance with ADA/WHO guidelines, i.e. on the basis of at least two consistent blood glucose measurements (taking into account all the blood glucose results available for the evaluation period): it was defined as either a fasting blood glucose level of ≥ 7.00 mmol/l (126 mg/dl) or alternatively, current treatment with an oral antidiabetic drug or insulin. With respect to the definition of IFG, in 1999 the ADA/WHO recommended that a fasting blood glucose between 6.10 and 7.00 mmol/l (110–126 mg/dl) without insulin or oral antidiabetic treatment should be used to define IFG. In 2003 the ADA recommended that the threshold for diagnosing IFG should be lowered to 5.6 mmol/l (100 mg/dl) [19]. However, in absence of convincing evidence that the attribution of the label of IFG will achieve better health outcomes, the European Diabetes Epidemiology group suggested that the initial ADA/WHO definition should not be altered [20]. Therefore, in the current study, IFG was defined according to the 1999 ADA/WHO definition.

Statistical analysis

All results are expressed as the percentage of responses to the relevant questionnaire item (rather than as a function of the overall population). Qualitative descriptive variables are expressed as percentages. Quantitative descriptive variables are expressed as the median (range) or mean (SD). Qualitative variables were compared using the Fisher's Exact test and for quantitative variables, the Wilcoxon test was used. Kaplan–Meier estimates tested for differences in the incidence of NODM between CsA-ME and Tac in patients transplanted since at least 1 year (log-rank test). Logistic regression was used for multivariate analysis of a combination of categorical and continuous variables: the result for any given parameter is presented as the odds ratio (OR). Statistical analyses were performed using SAS software, version 8.2 (SAS Institute Inc. Cary, NC, USA).

Ethics

This purely retrospective study did not involve any special examinations or treatment modalities above and beyond those scheduled in the patient's routine post-transplantation follow-up. All subjects gave written, informed consent to participate, having been judged able to understand and comply with the study's requirements. The Study was approved by the French National Order of Physicians and the National Information Technology and Privacy Commission.

Results

Study population

A total of 17 centres participating in the study included 527 patients who had been transplanted in mean 13.6 ± 5.7 months before inclusion (Table 1). The median age of the patients was 48.5 years old (18.8–75.5); 61.1% were men, 95.2% were Caucasian and 3.7% had a positive hepatitis C serology. Impaired fasting glucose was diagnosed in 18 (3.4%) patients before transplantation. Apart from glomerulonephritis, the main diseases which had lead to kidney transplantation were polycystic kidney, nephroangiosclerosis, and interstitial nephritis. More than one-quarter of all the subjects had some family member with diabetes, a first-degree relation in 66% of cases. The great majority of the transplanted kidneys had

Table 1. Overall population characteristics

| Parameter | Mean (SD) or Percentage of responses |
|---|--------------------------------------|
| Demographic details | |
| Age (at transplantation) (years) | 46.4 \pm 13.59 |
| Gender (males) | 61.1% |
| Caucasian ethnic origin | 95.2% |
| History of transplantation | |
| Interval between transplantation and inclusion (months) | 13.6 \pm 5.66 |
| Cadaveric graft | 93.4% |
| Donor age (years) | 43.3 \pm 14.25 |
| Donor sex (males) | 64.7% |
| Causal pathology | |
| Glomerular disease | 35.8% |
| Polycystic kidney | 17.0% |
| Other | 35.8% |
| Unknown | 11.4% |
| At least 1 AR treated with steroids since transplantation | 12.1% |
| At least 1 steroid resistant AR episode since transplantation | 1.8% |
| Diabetes-related factors | |
| Family history of diabetes | 27.1% |
| Significant obstetric history ^a | 14.5% |
| Newborn child weighing over 4 kg and gestational diabetes | 9.8% |
| Body mass index (at transplantation) (kg/m ²) | |
| mean | 23.4 \pm 3.95 |
| >25 | 31.3% |
| Body mass index (maximum lifetime) (kg/m ²) | |
| mean | 26.1 \pm 4.87 |
| >25 | 52.4% |
| Pre-transplantation fasting glycaemia (mmol/l) | 5.0 \pm 0.66 |
| Impaired fasting glycemia pre-transplantation | 3.4% |
| Cardiovascular risk factors | |
| Hypertension | 70.8% |
| Dyslipidemia | 25.8% |
| Smoking history | 13.3% |
| Viral infection | |
| Hepatitis B (surface antigen) | 0.6% |
| Hepatitis C (specific antibodies) | 3.7% |

^aFemale respondents only (*n* = 193).

Table 2. Median doses of steroids (mg/kg). Median doses (mg/kg) and blood concentrations (ng/ml) of calcineurin inhibitors

| Immunosuppressive drugs | NODM | Non-NODM | P |
|---|--------------|--------------|----|
| Corticosteroids | | | |
| Dose at M3 | 0.13 ± 0.17 | 0.14 ± 0.09 | NS |
| Dose across the study period | 0.12 ± 0.04 | 0.13 ± 0.06 | NS |
| At least 1 steroid-treated AR since transplantation | 21.6% | 11.4% | NS |
| Cyclosporine microemulsion | | | |
| Dose at M3 | 4.08 ± 0.78 | 3.99 ± 1.32 | NS |
| Dose across the study period | 3.12 ± 0.56 | 3.65 ± 1.24 | NS |
| C0 at M3 | 138.0 ± 88.4 | 151.5 ± 60.5 | NS |
| C0 at M6 | 154.5 ± 51.1 | 145.6 ± 50.7 | NS |
| C0 at M12 | 114.0 ± 29.1 | 131.0 ± 50.5 | NS |
| C0 at M18 | 149.0 ± 18.1 | 123.0 ± 63.2 | NS |
| Tacrolimus | | | |
| Dose at M3 | 0.11 ± 0.06 | 0.10 ± 0.05 | NS |
| Dose across the study period | 0.09 ± 0.06 | 0.08 ± 0.05 | NS |
| C0 at M3 | 10.6 ± 5.8 | 9.5 ± 2.9 | NS |
| C0 at M6 | 9.5 ± 2.8 | 8.5 ± 2.7 | NS |
| C0 at M12 | 9.4 ± 1.7 | 8.4 ± 3.3 | NS |
| C0 at M18 | 9.2 ± 1.3 | 7.7 ± 2.2 | NS |

been taken from cadavers (93.4%). The demographic details of this population are presented in Table 1.

Immunosuppressive regimen

For the analysis, the CNI prescribed at discharge was used if the patient's blood glucose status was normal but in patients with NODM, the CNI being taken on the day the NODM was diagnosed was input. When a sensitivity analysis was conducted according to the CNI being taken immediately following transplantation, there was no effect on the result (not shown) so it was decided to focus on the first approach. A total of 261 patients (49.5%) were receiving CsA-ME and 266 (50.5%) Tac. The mean treatment duration was similar for both groups (13.4 ± 5.9 months for CsA-ME, 13.0 ± 5.7 months for Tac). At the study visit, 74.5% of the patients were still receiving steroids, a majority of them received a mycophenolic acid drug (79.1%) and 3.6% were being treated with sirolimus. Median doses of calcineurin inhibitors and steroids and CNI trough blood levels are described in Table 2.

Incidence of NODM

A total of 37 patients (7.0%) had developed NODM by the time of the study visit, with a median time of onset of 1.6 months following transplantation. In other respects, 7.9% of the patients (without pre-transplantation IFG) developed *de novo* IFG. In the group that received Tac, the incidence of NODM was 10.2% compared with 3.8% among those who received CsA-ME ($P=0.006$) and the median onset time was shorter although not significantly [0.9 (0.0 – 16.1) months vs 2.9 (0.03 – 16.1) months: $P=0.087$] (Table 3). It is of interest to note that almost 80% of the cases of NODM in Tac-treated patients onset within 3 months

Table 3. Patient glucose status according to calcineurin inhibitor

| Glucose status | CsA-ME <i>n</i> = 261 | Tacrolimus <i>n</i> = 266 | P |
|--|--------------------------|------------------------------|-------|
| Median pre-transplantation glycemia (mmol/l) | 5 (2.7–6.8) | 5 (2.8–6.8) | NS |
| Pre-transplantation IFG (%) | 2.7 | 4.1 | NS |
| Mean duration of treatment (months) | 13.4 ± 5.93 | 13.0 ± 5.69 | NS |
| NODM incidence (%) (95% confidence interval) | 3.8 (1.5–6.16) | 10.2 (6.52–13.78) | 0.006 |
| Median interval between transplantation and diagnosis of NODM (months) | 2.9 (0.2–16.1) | 0.9 (0.03–16.1) | 0.087 |
| Diagnosis of NODM (% , <i>n</i>) | | | |
| Within the first 3 months after transplantation | 50.0 (5) | 77.8 (21) | NS |
| >3 months | 50.0 (5) | 22.2 (6) | |

of transplantation, compared with just 50% in CsA-ME-treated patients. No significant difference was detected in the percentage of each group with IFG prior to transplantation (4.1% of those on Tac vs 2.7% of those on CsA-ME: NS) nor in pre-transplantation blood glucose levels (5.0 ± 0.7 mmol/l in each group). A sensitivity analysis on the basis of the incidence of NODM in each treatment group ignoring all those patients who had presented IFG prior to transplantation did not affect the result (data not shown).

The patients were also divided into three cohorts depending on when their transplantation was performed: less than 1 year, 12–18 months, and 18–24 months before the study entry. The incidence of NODM in each cohort is presented in Figure 1 (see online addendum). A Kaplan–Meier estimate was performed in patients who were transplanted for at least 1 year ($n=290$, 146 patients on CsA-ME-based therapy and 144 on Tac-based therapy). The unadjusted cumulative risks for NODM at 1 and 2 years post-transplantation were 11.4% and 14.5%, respectively (Figure 2). In CsA-ME-treated patients, the unadjusted cumulative risks of NODM were 5.5% and 8.4% at 1- and 2-year post-transplantation, while in Tac-treated patients; the risks were, respectively, 17.4% and 21%. The overall difference between the two groups was statistically different ($P=0.003$, log-rank test) (Figure 2).

The mean steroid dose at M3 was 0.17 ± 0.17 mg/kg in the diabetics and 0.15 ± 0.09 mg/kg in the non-diabetics (NS). Nor was there any substantial difference between the groups in the mean corticosteroid dose administered between transplantation and the study visit (0.12 ± 0.04 vs 0.13 ± 0.06 mg/kg) (Table 2). The doses of steroids taken by the Tac patients did not significantly differ from those taken by the CsA-ME patients at any time point evaluated (M3, M6, M12 or the total taken between transplantation and the day of the study visit). Within the CsA-ME and

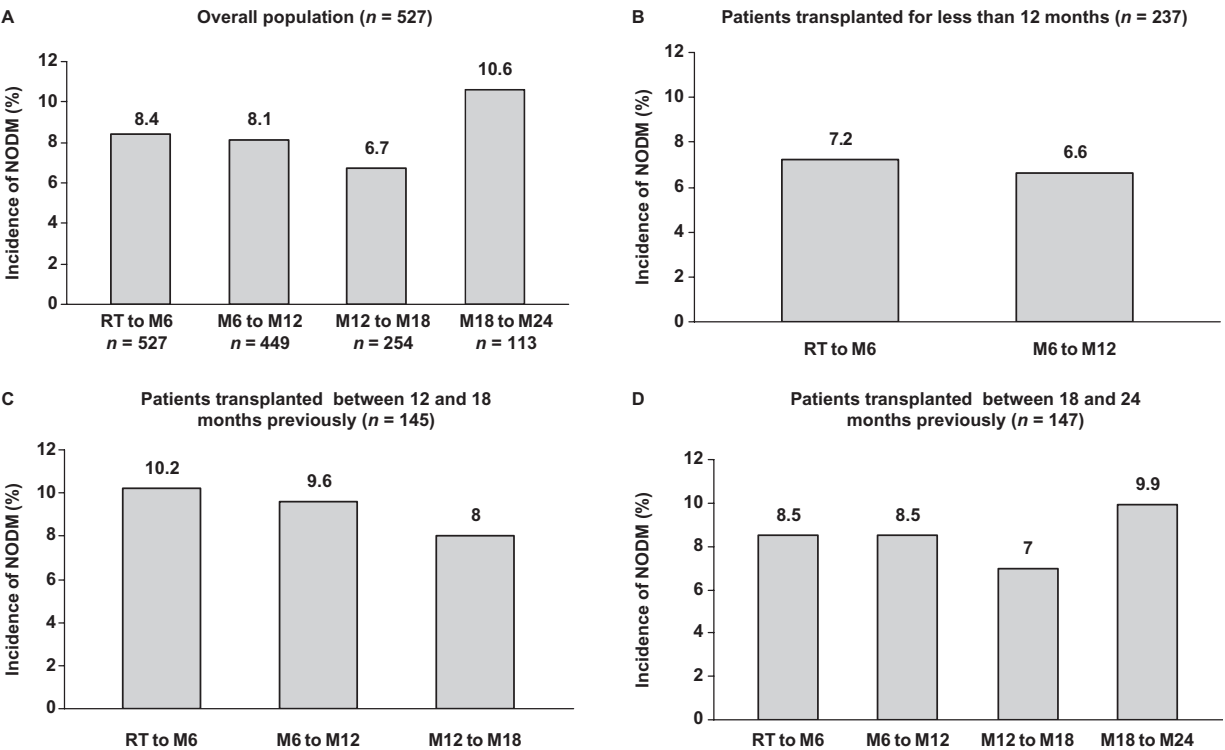


Fig. 1. Prevalence of NODM in the overall population and in three patient cohorts, i.e. <12 months, 12–18 months, and 18–24 months since the time of transplantation at inclusion. RT: renal transplantation.

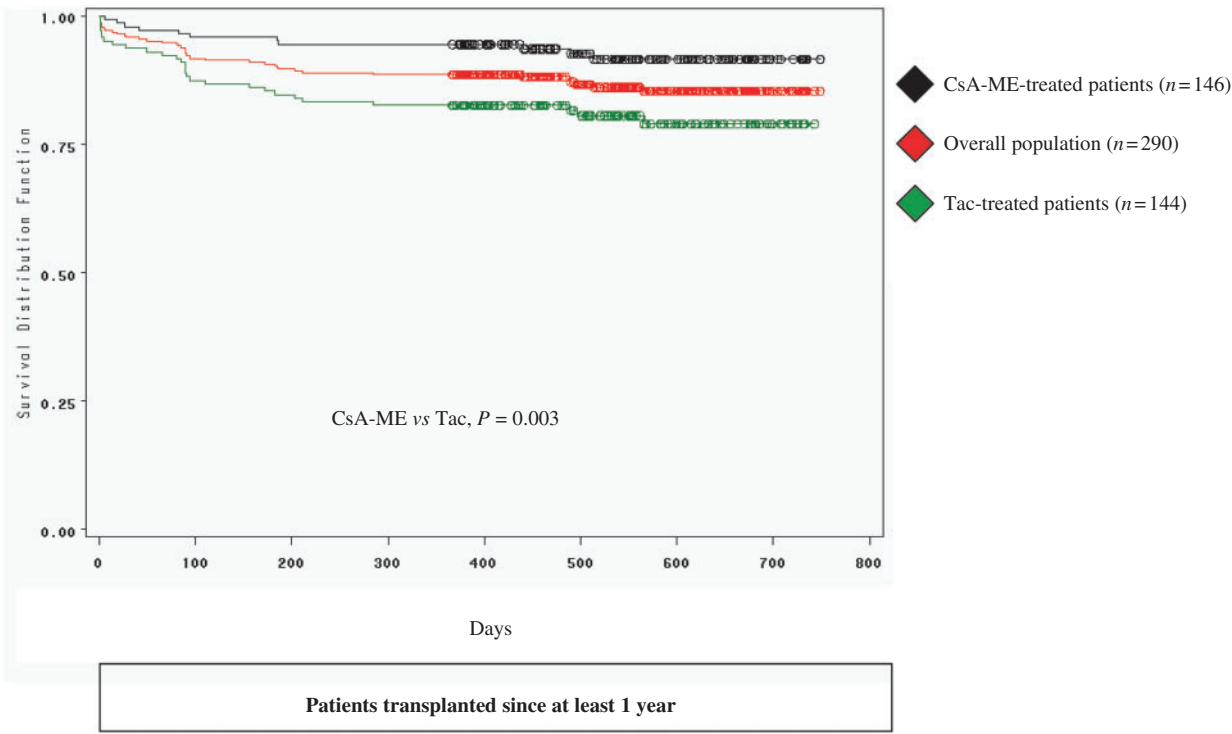


Fig. 2. Kaplan–Meier estimates: risk of NODM in the overall population and in patients stratified according to CsA- or Tac-based therapy.

Tac groups, mean steroid doses at M3 were also comparable between non-diabetics and diabetics (CsA-ME: 0.13 ± 0.05 vs 0.14 ± 0.04 mg/kg; Tac: 0.13 ± 0.06 vs 0.12 ± 0.05 mg/kg).

The mean dose of CsA-ME taken at M3 was similar in non-diabetic and diabetic patients (respectively, 4.07 ± 1.32 mg/kg and 3.74 ± 0.78 mg/kg) as was the mean dose of Tac at M3 (respectively,

Table 4. Risk factors: univariate and multivariate analysis

| Risk factors—univariate analysis | NODM | Non-NODM | P |
|---|------------|----------|--------|
| Age at transplantation (percentage over 45 years) | 81.1% | 53.5% | <0.01 |
| Pre-transplantation IFG | 13.5% | 2.7% | <0.01 |
| Tacrolimus treatment | 73.6% | 48.7% | <0.01 |
| Maximum lifetime BMI (percentage over 25 kg/m ²) | 80.0% | 50.3% | <0.01 |
| Hepatitis C (antibodies) | 12.8% | 2.9% | 0.01 |
| Composite cardiovascular risk factor (≥ 2 RFs ^a) | 70.3% | 49.0% | 0.02 |
| Risk factors—multivariate analysis | Odds ratio | CI 95% | P |
| Maximum lifetime BMI (≥ 25 kg/m ² vs <25 kg/m ²) | 5.1 | 2.0–12.9 | 0.0005 |
| Tacrolimus (as opposed to CsA-ME) | 3.0 | 1.4–6.7 | 0.007 |
| Pre-transplantation IFG | 4.7 | 1.4–15.3 | 0.01 |
| Positive hepatitis C serology | 4.7 | 1.2–17.4 | 0.02 |

^aAt least two of the following at the time of transplantation: male gender, BMI over 25, family history of diabetes, hypertension, dyslipidaemia, age of over 50, IFG.

0.10 \pm 0.05 mg/kg and 0.12 \pm 0.06 mg/kg), and the same is true of CNI dose (mg/kg) across the whole evaluation period (Table 2). At M3, trough blood levels (C0) were available in 215 patients for CsA-ME and in 225 patients for Tac; no difference in C0 was seen between non-diabetic and diabetic patients on either CsA-ME or Tac.

Risk factors

Univariate analysis detected six main discrete factors associated with the development of NODM: recipient age (over 45-years-old), IFG before transplantation, the presence of at least two CVRFs, positive hepatitis C serology, maximum lifetime BMI > 25 and Tac (Table 4). A BMI of over 25 kg/m² at the time of transplantation also emerged as a risk factor ($P = 0.01$) but the correlation was less strong than that with maximum lifetime BMI. A special cardiovascular risk composite (at least two of the following at the time of transplantation: male gender, BMI over 25, family history of diabetes, hypertension, dyslipidemia, age of over 50, pre-transplantation IFG) emerged as significant. Discrete factors which did not correlate with the development of NODM were: male gender, a family history of diabetes, significant obstetrical history (in particular a history of gravid diabetes or of delivery of a baby weighing over 4 kg), any of the donor characteristics analysed, acute or corticosteroid-resistant rejection since transplantation, steroid dosage at M3, cumulative dosage of steroids and certain CVRFs taken individually, namely hypertension, dyslipidaemia and smoking.

Four independent factors emerged in a multivariate analysis with very strong correlation (Table 4), i.e. a maximum lifetime BMI of over 25 kg/m²

(OR = 5.1, $P = 0.0005$), evidence of abnormal glucose metabolism prior to transplantation (OR = 4.7, $P = 0.01$), positive hepatitis C serology (OR = 4.7, $P = 0.02$) and Tac treatment (OR = 3.0, $P = 0.007$). Variables that were introduced into the model and rejected were recipient age, BMI at transplantation, the composite CVRF, a family history of diabetes, and the steroid dosage at M3.

Management and treatment of diabetic patients

Less than half (45.7%) of the patients diagnosed with NODM were being followed by a diabetes specialist and 26% had had no specific diabetes-related procedures. Monitoring of glycosylated haemoglobin levels was far from systematic in diabetic patients (only 32%).

Discussion

The incidence of NODM of 7% observed in this population is comparable to that published for another French population [21] but substantially lower than those commonly reported elsewhere, notably in the United States [4]. It is possibly under-estimated due to the study design (retrospective approach); and also because we do not collect any data on oral glucose tolerance test to identify impaired glucose tolerance. Moreover, another limitation of this study is the recruitment method. Nevertheless, the centres were randomly selected and in each centre only a few transplant physicians participated to the study. During the recruitment period, each investigator had to include all the consecutive patients seen in the out-patient clinic for a routine visit, and meeting the inclusion criteria. Therefore, this procedure probably reduced the selection bias. Nevertheless, NODM is a common complication of kidney transplantation in France and comparison with the prevalence of diabetes mellitus in the general population (about 3.5%) shows that transplantation is clearly a major risk factor.

All the risk factors identified in this French population have been previously incriminated in other studies [10] apart from the novel parameter of maximum lifetime BMI which emerged as a more reliable independent risk factor for NODM than the BMI at the time of transplantation. This parameter may be more suitable for the purposes of prediction and prevention because it may better represent a personal tendency to be overweight given that many patients have lost weight before transplantation. Abnormal glucose metabolism prior to transplantation was strongly predictive of NODM: this parameter does not systematically emerge as a risk factor in all the published studies and further investigation is indicated to establish whether this is due to real differences between populations. Interpreting abnormal glucose data is complicated in this type of patient since blood glucose levels are often relatively high in

subjects on dialysis [22]. In fact, one might have expected to see a higher percentage of patients with IFG than that observed here (3.4%); there may have been some skewing effect as a result of pre-existing diabetes (as defined by the ADA-WHO guidelines) being a formal exclusion criterion in this study. Despite the small number of patients infected with hepatitis C in this population ($n=19$ according to serological results), the correlation with NODM was strong. It has become quite clear that there is a link between hepatitis C infection and type 2 diabetes [23] and the data are accumulating to indicate as strong a link if not a stronger one with NODM [16]. This has implications for the post-transplantation follow-up of such patients, in whom close blood glucose monitoring and special preventive measures are indicated, and possibly antiviral therapy.

Since the numbers of subjects of African ($n=19$) and Asian ($n=6$) origin were so small, ethnicity was not addressed and similarly, with only three patients positive, hepatitis B status was not analysed. The age of the patient at transplantation did not emerge as a significant independent risk factor for NODM although it has been systematically observed in all other populations studied. ADA guidelines [24] stipulate a history of certain obstetric events as a risk factor for type 2 diabetes but no significant correlations with NODM were observed in this study whether the analysis focused on delivery of a child weighing over 4 kg ($n=18$) or gestational diabetes ($n=1$) only, or whether the less specific items of spontaneous miscarriage ($n=12$) and birth defects ($n=1$) were also taken into account. The proportion of patients with a family history of diabetes (27%) was markedly higher than the national average although this factor did not emerge as predictive of NODM in the analysis.

With greater experience, it might be possible to identify a more predictive set of pre-transplantation parameters: on the basis of the results presented here, such a 'NODM risk' composite might include the parameters of IFG at the time of transplantation, maximum lifetime BMI and Hepatitis C status, possibly together with age at transplantation.

Of course, the importance of being able to predict those patients who are at highest risk of NODM on the basis of parameters present before transplantation is related to the availability of immunosuppressive alternatives with differential diabetogenic activities. Corticosteroids are known to have strong diabetogenic activity although in this study, the corticosteroid dosage was the same in those who developed diabetes and those who did not. In parallel, the rate of rejection was identical in both groups so in this population, NODM was not due to the diabetogenic activity of the supplementary corticosteroids administered to treat AR. However, the risk associated with Tac as opposed to CsA-ME treatment was 3.0 which is consistent with the results of other studies conducted in diverse populations [14]. Thus, Tac is substantially more diabetogenic than CsA-ME, and this differential is unrelated to steroid dosage, or indeed to any other

difference between the Tac and CsA-ME sub-groups. Nevertheless, relatively high doses of steroids were used across the study. Steroids are known to increase insulin resistance while Tac reduces insulin secretion [25]. The combination of relatively high doses of both drugs might explain the high risk of NODM in Tac-treated patients. It would be useful to be able to identify those patients at particularly high risk of NODM in order to select the appropriate CNI. Given the necessary information and tools, such a strategy would enhance the safety profile of CNIs and generally improve outcomes in kidney transplantation.

Moreover, our study also highlighted that less than half of the patients were referred to a diabetes specialist. Therefore, it seems that there is still work to do on raising the awareness of physicians about the possibility of this serious complication, especially in the light of the data presented here which suggest that there is also great room for improvement in terms of management.

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