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Impact of pre-transplant dialysis modality on post-transplant diabetes mellitus after kidney transplantation

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Abstract: Post-transplant diabetes mellitus (PTDM) is a well-known complication in renal transplant recipients (RTRs). While a number of risk factors for PTDM have been identified, the potential impact of pre-transplant dialysis modality on subsequent development of PTDM has not yet been explored.
We performed a multicenter retrospective study on 2010 consecutive RTRs who did not have a history of diabetes prior to renal transplantation. PTDM was defined as a need for anti-diabetic therapy in an RTR without a history of diabetes prior to transplantation. Analysis of the risk factors for development of PTDM was performed with respect to pre-transplant dialysis modality.
A total of 137 (6.8%) patients developed PTDM; 7% in the hemodialysis group and 6.5% in the peritoneal dialysis (PD) group ($p = 0.85$). In the multivariate analysis, age ($p < 0.001$), body mass index (BMI) ($p < 0.001$), use of tacrolimus ($p = 0.002$), and rejection episodes ($p < 0.001$) were identified as independent risk factors for development of PTDM. Patients in the PD group were younger ($p = 0.004$), had lower BMI ($p = 0.07$), and were less likely to have a history of hepatitis C ($p = 0.007$) and autosomal dominant polycystic kidney disease ($p = 0.07$). Adjustment for these variables did not modify the results.
The results of this study suggest that pre-transplant dialysis modality does not have an impact on the subsequent development of PTDM in RTRs.

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Post-transplant diabetes mellitus (PTDM) is a common complication of kidney transplantation and is associated with an increased risk of cardiovascular morbidity and mortality (1, 2). It has been shown that PTDM is also associated with an increase in the risk of graft failure and death (2–5). Relative insulin deficiency, caused by increased insulin resistance and impaired insulin production, is thought to be the underlying pathophysiologic mechanism for PTDM (1).

Several risk factors for development of PTDM have been identified: age, body mass index (BMI), ethnicity, hepatitis C infection, and certain immunosuppressive medications such as steroids and calcineurin inhibitors (CNIs) (6). Steroids and reversal of the uremic state stimulate the appetite

and increase food intake leading to post-transplant weight gain, which in turn results in relative insulin deficiency due to hepatic and peripheral insulin resistance. A significant subset of renal transplant recipients (RTRs) experiences weight gain during the first year after transplantation, potentially predisposing them to an abnormal glucose metabolism (7).

Based on a number of clinical observations, it is conceivable to hypothesize that pre-transplant renal replacement modality might affect the risk of PTDM. Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor, is a peptide hormone that is predominantly produced in the stomach and can significantly increase food intake (8). A 2.8-fold higher ghrelin levels have been reported in patients with renal failure, suggesting that the kidney plays an important role in the clearance and/or degradation of this hormone (9). In a report by Ayala et al., one yr of peritoneal dialysis (PD) was associated with a significant reduction in plasma ghrelin levels, while no changes were observed in hemodialysis (HD) patients (10). As previously reported by our group, higher levels of ghrelin in HD patients could be associated with a greater weight gain (7) and therefore a potential increase in the risk of PTDM. Inflammation is also considered a risk factor for PTDM (11). A number of studies have shown a significant increase in inflammatory mediators in HD patients compared with PD patients (12, 13). The pro-inflammatory effect of HD can therefore increase the risk of subsequent PTDM compared with those treated with PD.

Therefore, pre-transplant renal replacement modalities are associated with distinct metabolic profiles that can potentially affect the risk of subsequent development of PTDM. In this retrospective multicenter study, we evaluated the hypothesis that patients treated with HD are at higher risk for PTDM compared with those managed with PD.

Materials and methods

Study design

This study is a retrospective chart review of 2010 patients who received a renal allograft between January 1995 and December 2005 in five renal transplant centers in France. This study was designed to evaluate the impact of pre-transplant dialysis modality on the subsequent development of PTDM with respect to other known risk factors. The data were reviewed and recorded until six months after transplantation.

Demographic and clinical characteristics

We included all patients with end-stage renal disease who received a renal allograft between January 1995 and December 2005 in university-affiliated medical centers in Nancy (n = 754), Reims (n = 372), Besançon (n = 327), Strasbourg (n = 299), and Caen (n = 258). Patients with a history of pre-transplant diabetes mellitus were excluded. Clinical parameters such as age, gender, year of transplant, BMI, hepatitis C status, CNI agent (cyclosporine A [CsA] or tacrolimus), and dialysis modality (HD or PD) were recorded upon inclusion. Rejection episodes (either biopsy-proven or clinically suspected and treated), cytomegalovirus (CMV) disease (identified through treatment by gancyclovir), and a history of autosomal dominant polycystic kidney disease (ADPKD) were also considered as separate variables. The cumulative dose of steroids could not be compared because some centers had used steroid-withdrawal protocols in some patients with PTDM.

Post-transplant diabetes mellitus

PTDM was identified based on the need for insulin or oral anti-diabetic therapy for normalization of blood sugar levels. As the goal was to evaluate the potential effect of pre-transplant dialysis modality, we only included cases of PTDM that were diagnosed over the first six months after renal transplantation.

Statistical analysis

The results were expressed as mean ± standard deviation.

Pre-transplant dialysis modality and PTDM

Univariate analyses were first carried out to examine the relationship between PTDM and a number of potential independent variables. Covariates to enter multivariate analyses were the following: (i) continuous variables were tested using Student's *t*-test or Mann–Whitney's non-parametric test (ii) categorical variables were tested using Pearson's chi-square, or Fisher's exact test. The alpha threshold for covariate selection was 0.20. Those variables linked to PTDM with p-values of less than 0.20 were retained for multivariate analyses. Selected covariates were entered into logistic regression analysis. Results are expressed as relative risk (RR) and 95% confidence interval, with a p value testing the null hypothesis:

RR = 1. Therefore, when p value is less than 0.05, RR is significantly different from 1.

Results

Baseline data

This study included 2010 RTRs. All patients were Caucasians. Mean age was 46 ± 14 yr, and 62.3% were male. Mean BMI was 23.1 ± 4.2 kg/m^2. Sixteen percent had ADPKD and 3.6% showed positive hepatitis C serology. CsA was used in 68.3% patients and tacrolimus in 27.5%. Acute rejection and CMV disease were identified in 24% and 20.8%, respectively. Most episodes of acute rejection took place before PTDM (56%), whereas most cases of CMV disease occurred after PTDM (60.5%).

Pre-transplant dialysis modality

There were significant differences in the distribution of dialysis modality between centers. Prior to transplantation, 1564 patients (77.8%) were on HD and 332 (16.5%) on PD. One hundred and fourteen patients (5.7%) had undergone pre-emptive transplant. PD patients were significantly younger (p = 0.004), less likely to have a history of hepatitis C infection (p = 0.007) or ADPKD (p = 0.07), and had a lower BMI (p = 0.07). Other characteristics were not significantly different between the two groups (see Table 1).

Post-transplant diabetes mellitus

PTDM was identified in 137 patients (6.8%); 7% in the HD group and 6.5% in the PD group (p = 0.85). The mean time of onset was 30 ± 42.5 d after transplantation. Demographic and clinical characteristics of these patients are summarized in Table 2.

Risk factors

In univariate analysis, older age (p < 0.0001), higher BMI (p < 0.0001), tacrolimus use (p < 0.0001), CMV disease (p = 0.006), acute rejection (p < 0.001), and transplant center (p = 0.0002) were associated with development of PTDM (Table 2). Pre-transplant dialysis modality did not alter the risk of PTDM (RR 1.08 [0.45–2.6], p = 0.86). To explore more precisely the potential interactions between dialysis modality and the subsequent risk of PTDM, we calculated RR estimates for PTDM derived from proportional hazards modelling with dialysis modality adjusted for age, BMI, ADPKD, hepatitis C infection, and transplant center. Adjustment for this variables did not modify the RR of PD for PTDM (RR 0.96 [0.6–1.6], p = 0.86) (Table 3).

Table 1. Demographic and clinical characteristics of the study population

Variable	HD (n = 1564)	PD (n = 332)	No dialysis (n = 114)
Transplant centers[a]			
1 (n = 754) (%)	79.3	11.8	8.9
2 (n = 372) (%)	84.4	12.4	3.2
3 (n = 327) (%)	66.3	27	6.7
4 (n = 299) (%)	86	12	2
5 (n = 258) (%)	69	28.3	2.7
Age (yr)[a]	47 ± 13	44 ± 14	44 ± 14
Male gender (%)	63	62.3	54.4
BMI (kg/m^2)	23 ± 4	22.7 ± 3.8	23 ± 4
APKD (%)	16.7	12.7	14
HCV+ (%)	4.4	0.3	1.75
Tacrolimus (%)	27.1	27	33.3
Cyclosporine (%)	68.5	69.3	64
CMV disease (%)[b]	20.6 (n = 1307)	22 (n = 296)	21.3 (n = 108)
Acute rejection episode (%)	23.6	23.8	29.8

HD, hemodialysis; PD, peritoneal dialysis; BMI, body mass index; APKD, adult polycystic kidney disease; HCV, hepatitis C virus; CMV, cytomegalovirus.
[a]Significant differences between dialysis modality (univariate analysis): age, p = 0.004; HCV, p = 0.007; transplant centers (3 and 5 vs. 1, 2, and 4), p < 0.0001.
[b]CMV disease: data not unavailable in one center

Table 2. Factors predicting post-transplant diabetes mellitus (univariate analysis)

Variable	NODAT− (n = 1873)	NODAT+ (n = 137)	p Value
Transplant centers			
1 (n = 754) (%)		9	–
2 (n = 372) (%)		2.7	0.0002
3 (n = 327) (%)		12.5	0.08
4 (n = 299) (%)		3	0.009
5 (n = 258) (%)		3.5	0.005
Age (yr)	45 ± 13	52.5 ± 11	<0.0001
Male gender (%)	62.3	63.5	–
BMI (kg/m^2)	22.9 ± 4	25.4 ± 5.7	<0.0001
HD (%)	77.7	78.8	0.76
PD (%)	16.6	16	0.86
ADPKD (%)	15.9	16	0.9
HCV+ (%)	2.9	5.1	0.3
Tacrolimus (%)	26.1	46	<0.0001
CMV disease (%)[a]	20 (n = 1589)	30.5 (n = 128)	0.006
Acute rejection episode (%)	22.2	48.2	<0.0001

BMI, body mass index; HD, hemodialysis; PD, peritoneal dialysis; ADPKD, autosomal dominant polycystic kidney disease; HCV, hepatitis C virus; CMV, cytomegalovirus.
[a]CMV disease: data not unavailable in one center.

Table 3. Relative risk (RR) estimate for post-transplant diabetes mellitus (proportional hazard modelling with dialysis modality and with multivariate-adjustment for potential confounding variables)

Category	RR estimate (95% confidence interval)	p Value
Dialysis modality (PD vs. HD) unadjusted	0.96 (0.6–1.54)	0.86
Dialysis modality (PD vs. HD) adjusted for		
Age	1.04 (0.64–1.68)	0.88
BMI	1.03 (0.6–1.67)	0.9
ADPKD	0.96 (0.6–1.54)	0.86
HCV	0.97 (0.6–1.56)	0.9
Transplant centres	0.85 (0.52–1.39)	0.512
Dialysis modality (PD vs. HD) final multivariate-adjusted model	0.96 (0.6–1.6)	0.86

HD, hemodialysis; PD, peritoneal dialysis; BMI, body mass index; ADPKD, autosomal dominant polycystic kidney disease; HCV, hepatitis C virus.

In the multivariate model, no difference in statistical analysis was observed irrespective of whether CMV disease was considered or not (data unavailable in one center). Therefore, the data presented herein are from statistical analysis without considering CMV disease. Age (RR 1.04 [1.03–1.06] for each one yr increase, $p < 0.0001$), BMI (RR 1.14 [1.09–1.18] for each 1 kg/m^2 increase, $p < 0.0001$), use of tacrolimus (RR 1.8 [1.25–2.75], $p < 0.002$), and acute rejection (RR 2.95 [1.96–4.44], $p < 0.0001$) were found to be independent risk factors for development of PTDM. Transplant center was independently associated with the risk of PTDM and there was a significant interaction between transplant centers and the association between dialysis modality and PTDM (Table 4). Although, the difference in the incidence of PTDM between the dialysis modalities was not statistically significant in any of the centers, p values showed notable variations ($p = 0.3$ [center 1], $p = 0.8$ [center 2], $p = 0.1$ [center 3], $p = 0.5$ [center 4], and $p = 0.9$ [center 5]). This might suggest that factors associated with the choice of PD or HD in some centers could have affected the incidence of PTDM.

Table 4. Factors predicting post-tansplant diabetes mellitus (multivariate analysis not considering cytomegalovirus disease)

Variable	RR	95% CI	p Value
Age	1.04	1.03–1.06	<0.0001
BMI	1.14	1.09–1.18	<0.0001
Tacrolimus	1.8	1.25–2.75	0.002
Acute rejection episode	2.95	1.96–4.44	<0.0001
Transplant centers			
1	1	–	–
2	0.48	0.23–0.98	0.04
3	1.8	1.15–2.86	0.01
4	0.48	0.2–1.12	0.09
5	0.6	0.3–1.36	0.24

BMI, body mass index; CI, confidence interval; RR, relative risk.

Discussion

PTDM, a well-known complication of renal transplantation, has been shown to be associated with lower graft and patient survival. Our group recently reported that it can also increase the risk of atherosclerotic events in RTRs (14). Pre-transplant identification of patients at risk for PTDM and post-transplant monitoring are of utmost importance for timely implementation of preventive and therapeutic measures. Few European studies have so far focused on the incidence of PTDM in RTRs (15–19). Lack of a universally accepted definition for PTDM has likely contributed to a significant variation in the reported incident rates of this complication, ranging from 2% to 53% (20). Recently, international consensus guidelines were published on the diagnosis and management of PTDM (6). These recommendations are based on one of the common definitions of new-onset DM as well as the results of glucose tolerance test. However, most of the currently available studies on the impact of PTDM on transplant outcomes have used the ''need for treatment'' to identify these patients. Therefore, the clinical relevance of the consensus guidelines is yet to be established. Because of the design of our study, the recommended definition of the American Diabetes Association (ADA) could not be applied; we used ''the need for treatment'' to identify patients with PTDM. We limited our analysis to the first six months after transplantation as the distinction between PTDM and type 2 diabetes mellitus is difficult to make after this period. Our results are consistent with previous reports from other European centers (15–19).

In this study, the significant difference in the incidence of PTDM among transplant centers persisted even after adjustment for other relevant parameters. Variation in demographic characteristics is unlikely to explain these differences as the study population was relatively homogeneous. Practice patterns are likely to explain, in part, the observed difference in the incidence of PTDM among centers. In fact, the management of mild-to-moderate elevation in fasting blood glucose level during the post-transplant period of tapering the steroids can be quite variable, especially if steroid withdrawal protocols are implemented.

The lack of association between the pre-transplant dialysis modality and the risk of PTDM needs to be interpreted with caution. First, a type-I error cannot be excluded with certainty. Based on the incidence of PTDM and the proportion of the patients in each dialysis modality, our study had a power of 90% to detect a reduction of 40% in the incidence of PTDM in PD patients. To detect a more realistic difference of 20%, a study with more than 10 000 patients is needed. It is noteworthy that there was no trend observed towards a beneficial or deleterious impact for each of the dialysis modalities. Second, only the latest dialysis modality prior to transplantation was considered; the switch between PD and HD that was not taken into account might have led to a bias in analysis. Finally, the reasons for each patient being treated with HD or PD may have created an unwanted selection bias. PD patients in our study were younger, had lower BMI, and were less likely to have a history of ADPKD or hepatitis C infection. There were also large discrepancies in the repartition of PD and HD patients between centers. Even though these factors were taken into account in the logistic regression analysis, other unknown factors associated with the propensity of being on PD or HD could still have potentially affected the results.

We identified a number of clinical variables that are associated with PTDM. Higher BMI increased the risk of PTDM. This is consistent with the results of other studies that found an association between overweight and PTDM (21–23). Interestingly, the increased risk of PTDM in our study was not limited only to overweight or obese patients, but was also increased in patients with lower BMI compared with those with normal BMI (data not shown). Overweight is a potentially modifiable risk factor; and lifestyle changes might help reduce the risk of PTDM. Dietary advice, weight loss, and exercise should be an integral part of a comprehensive pre- and post-transplant program. Age is also identified as an important risk factor for PTDM. Previous studies have consistently found PTDM to be more common in older patients compared with younger individuals (21, 24); it has been reported in $< 3\%$ of children (25).

Our study confirms the results of previous observations on the association between tacrolimus and PTDM. In a meta-analysis by Webster et al., the RR of PTDM at six months, one yr, and three yr was found to be 2.56, 1.86, and 3.86, respectively (26). In a recently published study by Vincenti et al. (27), the authors observed an overall increased risk of PTDM or impaired fasting glycemia with CNI-based immunosuppression regimens; the risk was significantly lower for CsA compared with tacrolimus. Acute rejection is also a risk factor for PTDM, which is likely due to the use of high doses of steroids for its management.

This study has a number of limitations. Because of its retrospective design, the criteria for diagnosis and treatment of PTDM might have been different among centers, and the observed incidence of PTDM could hence be dependent on the practice patterns of physicians in each center. Moreover, the impact of cumulative dose of steroids, a known risk factor for PTDM, could not be evaluated in our study. Early steroid withdrawal (i.e., during the first month post-transplant) has been shown to decrease the risk of PTDM. As the steroid tapering protocols were very similar in the centers participating in this study, the potential difference in the cumulative dose of steroids would mostly be related to the episodes of rejection and their therapy.

In conclusion, our study does not find any relationship between pre-transplant dialysis modality and subsequent development of PTDM.

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