Continuous glucose monitoring after kidney transplantation in non-diabetic patients: Early hyperglycaemia is frequent and may herald post-transplantation diabetes mellitus and graft failure

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Abstract

Objectives. – New onset of diabetes after transplantation (NODAT) is a known complication of renal transplantation, but early glycaemic status after transplantation has not been described prospectively. This study aimed to assess blood glucose (BG) levels immediately following kidney transplantation in non-diabetic subjects and to explore their relationship to later graft outcomes and NODAT occurrence.

Patients and methods. – Over a 9-month period, 43 consecutive non-diabetic patients who received a kidney transplant were prospectively investigated. During the first 4 days after transplantation, fasting BG was measured and the 24-h BG profile assessed by continuous glucose monitoring (CGM). Capillary BG was measured on hospital admittance and at least four times a day for CGM calibration thereafter. All adverse events were recorded, and fasting BG and HbA1c were assessed at 3, 6 and 12 months and at the last visit to our centre.

Results. – Immediately following renal transplantation, capillary BG was 12.2 ± 3.8 mmol/L. On day 1 (D1), fasting BG was 9.9 ± 4.3 mmol/L and decreased to 6.0 ± 1.5 mmol/L on D3. The CGM-reported mean 24-h BG (mmol/L) was 10.2 ± 2.4 on D1, 7.7 ± 1.3 on D2 and 7.5 ± 1.1 on D3. From D1 to D4, 43% of patients spent >12 h/day with BG levels >7.7 mmol/L. While morbidity during the 3 months following transplantation appeared unrelated to BG, the first post-transplantation capillary BG measurement and fasting BG on D1 tended to be higher in patients who developed diabetes 3 months later. Tacrolimus treatment was associated with a higher incidence of dysglycaemia at 3 and 6 months. After a mean follow-up of 72 months, NODAT was frequently seen (18.6%), and was associated with tacrolimus medication (P < 0.01) and a higher rate of renal transplantation failure (RR: 3.6, P < 0.02).

Conclusion. – Hyperglycaemia appears to be a nearly constant characteristic immediately following transplantation in non-diabetic kidney recipients. Higher BG values could identify patients at risk for later post-transplant diabetes and graft failure.

Keywords: New onset of diabetes after transplantation; Kidney transplantation; Continuous glucose monitoring; Hyperglycaemia

Résumé

Mesure continue du glucose après transplantation rénale chez des patients non diabétiques : l’hyperglycémie précoce est fréquente et peut annoncer un diabète post-transplantation et un échec de la greffe.

Objectifs. – L’évolution glycémique dans les suites immédiates de la greffe rénale n’a pas été évaluée de façon systématique et prospective, alors que le diabète post-transplantation est reconnu comme une de ses complications secondaires. Le but de notre étude était de décrire de façon prospective le statut glycémique de patients non diabétiques dans les suites immédiates d’une greffe rénale et d’en étudier les conséquences sur le risque de complications et de survenue d’un diabète post-transplantation.

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Patients et méthodes. – Pendant une période de neuf mois, 43 patients non diabétiques consécutivement hospitalisés pour transplantation rénale ont été évalués au cours des quatre premiers jours suivant la greffe par mesure quotidienne de la glycémie plasmatique à jeun et mesures continue du glucose par CGMS®. La glycémie capillaire était mesurée au retour du bloc puis quatre fois par jour pour étalonnage de l’enregistrement CGMS®. Les complications présentées par les patients ont été notées et la glycémie à jeun ainsi que l’HbA1c ont été mesurées à trois, six et 12 mois post-transplantation et lors de la dernière visite du patient dans notre centre.

Résultats. – La glycémie capillaire était de 12,2 ± 3,8 mmol/L au retour du bloc opérateur. La glycémie à jeun était de 9,9 ± 4,3 mmol/L à j1 et 6,0 ± 1,5 mmol/L à j3. Les données CGMS® indiquaient une moyenne glycémique (mmol/L) sur 24 h de 10,2 ± 2,4 à j1; 7,7 ± 1,3 à j2; 7,5 ± 1,1 à j3. Au cours de l’enregistrement CGMS®, 43 % des patients passaient plus de 12 heures par jour avec une glycémie > 7,7 mmol/L. À trois mois, la morbidité de la transplantation n’était pas liée aux niveaux glycémiques initiaux. La première glycémie capillaire postopératoire et la glycémie à jeun à j1 tendaient à être plus élevées chez les patients qui présentaient un diabète à trois mois. L’immunosuppression par tacrolimus était associée à une fréquence plus élevée d’anomalies de la glycémie à trois et six mois. Après un suivi moyen de 72 mois, le diabète post-transplantation était fréquent (18,6 %), particulièrement chez les patients traités par tacrolimus (P < 0,01) et associé à un taux d’échec de transplantation plus important (RR = 3,6 ; P < 0,02).

Conclusion. – Nos résultats démontrent la quasi-constance de l’hyperglycémie en période post-greffe rénale immédiate chez des patients non diabétiques. Les valeurs les plus élevées de la glycémie dans cette période pourraient signaler un risque plus tardif de diabète et d’échec de transplantation.

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Mots clés : Diabète post-transplantation ; Transplantation rénale ; Mesure continue du glucose ; Hyperglycémie

1. Introduction

New onset of diabetes after transplantation (NODAT) is now a recognized common complication of kidney transplantation and associated with poorer outcomes in terms of graft and patient survival [1–3]. Among other deleterious effects, NODAT can amplify the already increased risk of cardiovascular events among kidney transplant recipients [4–8]. Transplant-associated hyperglycaemia (TAH) includes patients with newly diagnosed diabetes mellitus (DM) and patients with impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) after transplantation [9]. Various risk factors for NODAT and TAH development have been identified, including age, ethnicity, family history of diabetes, abnormal glucose regulation prior to transplantation, hepatitis C virus infection and type of immune suppression [2,10,11]. In addition, hyperglycaemia early after kidney transplantation has been reported in retrospective studies as a frequent occurrence [12,13] that is possibly predictive of acute rejection or infection in diabetic kidney recipients [14]. In a more recent study, TAH was described as frequent (66%) in the first week post-transplantation and possibly predictive of NODAT at 1 year but, as the study was retrospective, most of the data were not available for patients during this very early post-transplantation period [15].

These observations have raised specific interest in a more systematic, prospective assessment of blood glucose levels immediately following kidney transplantation. Some of the questions raised concern the actual occurrence of TAH and whether early post-transplant blood glucose levels might be associated with early complications and be predictive of the later development of NODAT. Our present study focused on the prospective assessment of blood glucose levels immediately following kidney transplantation in non-diabetic patients using several glucose-monitoring methods, including a continuous glucose monitoring system (CGMS®, Medtronic MiniMed, Northridge, CA, USA). The relationship between blood glucose profiles during this period and early post-transplant morbidity and secondary incidence of NODAT was also investigated.

2. Research design and methods

2.1. Patients

All patients admitted after kidney transplantation to the intensive care unit of the department of nephrology between November 2003 and July 2004 were eligible for the present study, which was designed in agreement with our institutional ethics committee. Patients were informed of the aims of the study and all but one gave their consent to participate. Adverse events were recorded, and fasting blood glucose (FBG) and HbA1c were assessed at 3, 6 and 12 months prospectively. Morbidity following transplantation (infections, cardiovascular and thrombotic events, acute rejection events and graft loss) was also prospectively recorded. In July 2011 after a mean follow-up of 72 months, graft survival and glycaemic status were assessed.

2.2. Study design and blood glucose measurement methods

Prior to kidney transplantation, at least two fasting blood glucose measurements were performed. Patients with one blood glucose value > 11.1 mmol/L or two FBG ≥ 7 mmol/L were diagnosed as having DM and not included in the study. If only one value was ≥ 7 mmol/L or two blood glucose values were between 6.1 and 6.9 mmol/L, then IFG was diagnosed. After kidney transplantation, FBG was measured on D1, D2 and D3 by enzymatic assay. Criteria for DM and IFG were the same as described above. Capillary blood glucose (CBG) was measured with a glucose meter, after checking its accuracy with control solutions, on admittance to the intensive care unit and then at least four times a day for CGM calibration. Hyperglycaemia was diagnosed when CBG was > 7.7 mmol/L, allowing for a potential 10% error. From D1 to D4, CGM was performed using CGMS® System Gold™ (Medtronic MiniMed). Recorded daily data
were considered interpretable when comparison of daily calibration and sensor values gave a correlation coefficient $>0.79$ and a mean absolute difference $<28\%$ for a minimum of three paired values within 24 h, as recommended by the manufacturer. The same threshold of 7.7 mmol/L was defined as the upper limit of normal glucose in the CGM data analysis.

2.3. Immune suppression regimen

The standard immunosuppressive regimen consisted of cyclosporine or tacrolimus, mycophenolate mofetil or azathioprine, and prednisone. Induction of immune suppression was made with thymoglobulin infusion on day 0 (D0). The infusions were renewed when T CD3 lymphocytes exceeded 20/mm$^3$. Intravenous (IV) methylprednisolone was administered at D0, D1 and D2 (500 mg, 125 mg and 20 mg, respectively), followed by oral prednisone at 20 mg once daily. Calcineurin inhibitors were introduced when blood creatinine levels decreased to $<250 \mu$mol/L.

2.4. Statistical analysis

Data were expressed as mean $\pm$ SD. Continuous variables were compared by Student’s $t$ test or by Mann–Whitney test if values were not normally distributed. For qualitative data, proportions were compared by Chi$^2$ test analysis. Results were considered statistically significant when $P$ was $<0.05$.

3. Results

3.1. Demographic data and baseline characteristics

Of the 51 patients who underwent transplantation within the 9-month inclusion period of the study, eight were excluded for the following reasons: one refusal; three had known DM prior to transplantation; and four for logistic reasons. All patients had been on dialysis for $43 \pm 35$ months except for four who had not required dialysis prior to transplantation. Thirty-four patients (79\%) were having their first kidney transplant, eight (19\%) a second one and one (2\%) a third transplant. Two patients received kidneys from living donors. As for metabolic data, body mass index (BMI) was $23.9 \pm 3.6$ kg/m$^2$, including three obese and 14 overweight patients. HbA1c values $>6\%$ were found in 16 patients (38\%) and IFG in six patients (14\%). Patients’ characteristics are summarized in Table 1.

3.2. Immediate post-transplant glucose levels: capillary, blood glucose and continuous glucose monitoring recordings

From D1 to D4, all patients but one (97\%) experienced hyperglycaemia according to at least one method of blood glucose assessment. CBG measured immediately after the surgical procedure was $12.2 \pm 3.8$ mmol/L (median: 11.1 mmol/L) and was $>11.0$ mmol/L in 50\% of the patients. On D1, average CBG was $10.0 \pm 2.5$ mmol/L and FBG was $9.9 \pm 4.3$ mmol/L, which fell gradually to reach $6.0 \pm 1.5$ mmol/L on D3 (Fig. 1, A) and $4.97 \pm 1.0$ mmol/L on D10. TAH was diagnosed in 83\% patients (including 71\% with DM criteria) on D1, 33\% (24\% DM) on D3 and 17\% (7\% DM) on D10 (Fig. 1B).

Of the 43 investigated patients, 36 (83\%) had usable CGM recordings. According to CGM, average glucose levels were $10.2 \pm 2.4$ mmol/L on D1 and 7.7 $\pm 1.3$ on D2, decreasing to 7.5 $\pm 1.1$ mmol/L on D3 and 7.32 $\pm 1.24$ mmol/L on D4. Mean daily glucose levels $>7.7$ mmol/L were observed in 86\% of patients on D1, 43\% on D2, 52\% on D3 and 38\% on D4. Considering the whole recording period, patients spent $11.5 \pm 7.0$ h/day with glucose levels $>7.7$ mmol/L. Average daily time spent in hyperglycaemia fell from $20.0 \pm 7.2$ h on D1 to $11.0 \pm 8.0$ h on D2, $10.3 \pm 7.5$ h on D3 and $9.2 \pm 7.5$ h on D4 (Fig. 1C). From D1 to D4, only 22.9\% of patients spent $<6$ h in hyperglycaemia.

These immediate post-transplantation glucose levels did not correlate with classical risk factors for NODAT such as age, hepatitis C virus infection, family history of diabetes or metabolic status before transplantation. However, the patients who experienced end-stage renal failure due to glomerular nephropathy had lower glucose levels after transplantation ($P<0.05$, data not shown).

In the first days of follow-up, vascular thrombosis was observed in five (11.6\%) patients, four of whom had undergone transplantectomy before anticalcineurin introduction. Acute rejection was seen in three (7\%) patients, but none led to graft loss. Cytomegalovirus (CMV) infection was observed in seven (16.3\%) patients, and at least one bacterial infection was noted in 21 (48.8\%) patients. No significant relationship was found between these adverse events and early blood glucose levels whatever the method of glucose monitoring used. Hospitalization duration also did not correlate to blood glucose levels.

3.3. Evolution of blood glucose status

Three months after transplantation, five patients had IFG and three presented with DM. Interestingly, the first CBG

| Table 1: Patients’ characteristics prior to kidney transplantation. |
|-----------------|------------|-----|
| n               | Mean $\pm$ SD | %   |
| Age (years)     | 45 $\pm$ 13 |     |
| HbA1c (g/dl)    | 11.8 $\pm$ 1.3 |   |
| BMI (kg/m$^2$)  | 23.9 $\pm$ 3.6 |   |
| FBG (mmol/l)    | 5.10 $\pm$ 0.78 |   |
| HbA1c (%)       | 5.95 $\pm$ 0.45 |   |
| Donor age       | 49 $\pm$ 3 |     |
| Age $>40$       | 29 67 |   |
| Male gender     | 28 65 |   |
| Glomerular nephropathy as former kidney disease | 27 63 |
| Obesity (BMI $>30$ kg/m$^2$) | 3 7 |
| Impaired FBG    | 6 14 |   |
| HbA1c $>6\%$    | 16 38 |   |
| Family history of diabetes | 10 23 |
| Hepatitis C virus infection | 2 5 |

n: number, SD: standard deviation, BMI: body mass index; FBG: fasting blood glucose.
measurement after transplantation tended to be higher in these eight patients who presented with TAH after 3 months (M3): 15.0 ± 6.5 mmol/L vs. 11.9 ± 2.8 mmol/L in patients without TAH ($P = 0.06$). Fasting blood glucose on D1 also tended to be higher among patients with TAH at M3: 12.1 ± 4.5 vs. 9.8 ± 4.2 mmol/L in patients without TAH ($P = 0.09$). No relationship was observed between TAH at M3 and time spent in hyperglycaemia or mean glucose levels according to CGM in the immediate post-transplantation period.

During the first year of follow-up, blood glucose disorders were not constant and fluctuations were noted: one DM patient at M3 showed IFG at M6, but no dysglycaemia at either M12 or at the end of follow-up. The single patient without TAH within the first 3 days of transplantation presented with IFG on D10 post-transplantation and at M6, in contrast to normoglycaemia at M3 and M12, and finally presented with NODAT at the end of the study. Five patients with IFG after 6 months were no longer dysglycaemic at the end of the study. Nevertheless, 40% of the
TAH patients at the end of the follow-up were already dysglycaemic at 3, 6 or 12 months. Glycaemic status at M3 correlated with TAH at the end of follow-up ($P < 0.05$) and HbA1c values at M3 were higher in patients with TAH at the end of the study ($6.2 \pm 0.6\%$ vs. $5.5 \pm 0.5\%$).

The prevalence of TAH was 21% at M3, 30% at M6, 20% at M12 and 35% at the end of follow-up. DM was diagnosed in 8%, 9%, 6% and 19% of patients at the same time points, respectively (Fig. 1D). Overall, 50% of patients presented with glucose disorders during the follow-up.

### 3.4. Transplant-associated hyperglycaemia and immunosuppressive regimen

All patients but one received anticalcineurin-based immunosuppression with either cyclosporine (63%) or tacrolimus (34%). Corticosteroids were also used in all patients except two, and doses did not differ between tacrolimus- and cyclosporine-treated patients. Fasting blood glucose was higher in patients receiving tacrolimus, and the last recorded fasting glycaemia was higher in tacrolimus- vs. cyclosporine-treated patients ($4.99 \pm 0.78\ mmol/L$ vs. $6.65 \pm 1.47\ mmol/L; P < 0.01$), although blood glucose levels before anticalcineurin introduction were similar regardless of method of measurement. A tacrolimus-based regimen appeared to be the highest risk factor for post-transplantation glucose disorders: 38% of patients receiving tacrolimus had IFG or DM at M3 post-transplantation compared with only 12% with cyclosporine. At M6, M12 and at the end of the study, 42%, 36% and 62% of patients, respectively, receiving tacrolimus had TAH compared with only 19%, 5% and 17%, respectively, of those receiving cyclosporine. The relative risk of developing NODAT with tacrolimus was 4.62 (Fig. 1E).

### 3.5. Transplantation complications, graft failure and new onset of diabetes after transplantation

After a mean follow-up of 72 months, 33 (77%) patients had experienced complications leading to 15 (35%) graft failures. Eight patients had acute rejection (19%), in one case because of discontinuation of the immunosuppressive regimen, and four (9%) presented with chronic rejection, two (5%) had nephropathy recurrence, five (12%) had malignant diseases and 24 (56%) had infectious diseases. One death related to transplantation occurred on D4 post-transplantation. Glucose disorders were associated with a trend towards complications ($P = 0.06$), and glucose status was highly correlated with graft failure, as 73% of those who lost their graft had glucose disorders at some time during the study. At the end of the study, 67% of patients with graft failure had TAH ($P < 0.01$; Table 2). From M3 onwards, patients who later had graft loss had higher HbA1c levels ($6.17 \pm 0.71\%$ vs. $5.53 \pm 0.56\%; P < 0.05$). The relative risk for graft failure with either DM or IFG was 3.6. The type of immune suppression regimen did not appear to correlate with either complications or graft failure.

### Table 2

<table>
<thead>
<tr>
<th>%</th>
<th>TAH ($n = 15$)</th>
<th>Normoglycaemic ($n = 27$)</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>60.0</td>
<td>55.6</td>
<td>NS</td>
</tr>
<tr>
<td>Cancer</td>
<td>6.7</td>
<td>14.8</td>
<td>NS</td>
</tr>
<tr>
<td>Vascular disease</td>
<td>33.3</td>
<td>11.1</td>
<td>$&lt; 0.10$</td>
</tr>
<tr>
<td>Acute rejection</td>
<td>20</td>
<td>18.5</td>
<td>NS</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>20</td>
<td>3.7</td>
<td>$&lt; 0.10$</td>
</tr>
<tr>
<td>Recurrence of kidney disease</td>
<td>6.7</td>
<td>3.7</td>
<td>NS</td>
</tr>
<tr>
<td>Any complication</td>
<td>93.3</td>
<td>66.6</td>
<td>$&lt; 0.10$</td>
</tr>
<tr>
<td>Graft loss</td>
<td>66.6</td>
<td>29.4</td>
<td>$&lt; 0.01$</td>
</tr>
</tbody>
</table>

### 4. Discussion

The present study describes for the first time the glycaemic profile according to continuous monitoring in kidney-transplant patients during the very first days after transplantation. Thanks to CGM recordings, the high rate of occurrence and high level of early TAH in non-diabetic recipients have been highlighted. Furthermore, the level of early TAH can identify patients at risk of post-transplant DM after 3 months. As HbA1c at M3 correlated with transplant failure, our results suggest a link between early TAH and transplantation outcomes. Moreover, the high liability of TAH observed in individual follow-ups should prompt specific attention and response to glucose status and immune suppression regimens, especially corticosteroid and tacrolimus prescriptions.

Few studies have described early hyperglycaemia following kidney transplantation. In the 1970s, Buckingham et al. [16] noticed that kidney-transplant patients in the urology department were more frequently hyperglycaemic. Early hyperglycaemia was also described as a frequent event by Thomas et al. [13] in a retrospective analysis of blood glucose on days 1 and 2 after allogenic kidney transplantation. In that report, the blood glucose threshold used to define hyperglycaemia was 8 mmol/L, and 73% of transplanted patients showed hyperglycaemia after surgery. Cosio et al. [15] retrospectively confirmed this high rate of TAH (66%) in the very first days post-transplantation according to the American Diabetes Association (ADA) definition of glucose disorders [1]. Nevertheless, one-third of the retrospective data was lacking.

In our present study, early hyperglycaemia was not only more frequent, but the level of hyperglycaemia was higher. All but one (97%) of the non-diabetic recipients experienced hyperglycaemia $> 7.0\ mmol/L$. This is higher than the prevalence observed in intensive care unit (ICU) studies where 76% of patients had glycaemia $> 6.1\ mmol/L$ [17,18]. In an early post-stroke follow-up, 20 to 40% of non-diabetic patients experienced mild hyperglycaemia [19]. Thanks to tight glucose monitoring, our first capillary glucose measurement reached $12.2 \pm 3.8\ mmol/L$ and 50% of patients had capillary glycaemia $> 11\ mmol/L$ immediately after transplant surgery. In contrast, in the Thomas et al. [13] and Van den Berghe
[17] studies, only 31% and 13%, respectively, of patients experienced hyperglycaemia > 11.0 mmol/L. The difference in the present study compared with the Thomas et al. [13] study may be explained by the tighter supervision of blood glucose levels in our study, and the differences compared with ICU studies may be related to the metabolic status of our ureaemic patients on dialysis prior to kidney transplantation [20,21]. Indeed, 38% of the patients in our study had HbA1c levels > 6% before transplantation, but no diabetes. High ureaemic levels have been associated with increased insulin resistance and may contribute to impaired glucose levels [20,22]. High initial CBG levels also reflect the effects of stress and corticosteroid induction treatment, which might reinforce defects in glucose homeostasis in the first days after transplantation [23,24]. It is also noteworthy that corticotherapy in healthy volunteers affects insulin sensitivity, but usually not glycaemic levels [25]. In our present study the presence of high pretransplantation insulin resistance, eventually combined with prevalent β-cell failure in prediabetic patients, may explain the huge glucose increase following the corticosteroid bolus [26].

The profile of early TAH over time can also be seen in our study. Glycaemia was maximum on D1, then gradually decreased during the first 4 days of transplantation. While 71% of patients had fasting glycaemia > 7.0 mmol/L on post-transplantation D1, only 7.1% were still hyperglycaemic on D10. Given the recovery of kidney function within the first few days of transplantation, the decrease in insulin resistance per se related to initial high ureaemic levels may explain this relatively short duration of post-surgical hyperglycaemia compared with that usually following major surgery. The rapid decrease in corticosteroid dosages may also have contributed to the rapid improvement. No correlation was found between glucose evolution and the resumption of meal or IV glucose intakes.

The uniqueness of the present study rests on the use of CGM recordings for the first time in recently kidney-transplanted patients. The feasibility of such continuous monitoring has been previously assessed in the ICU elsewhere [27,28]. As already assessed in non-diabetic patients with acute coronary syndromes [29], CGM highlights the underestimation of glycaemic excursions using the usual methods of glucose measurement. On D1 after transplantation, patients spent an average of 20 h in hyperglycaemia. On D3 post-transplantation, although FBG levels were close to normal, the patients still spent 10 h in hyperglycaemia.

The impact of blood glucose normalization in the ICU has been well documented by studies by Van den Berghe [18,30], although the disease conditions motivating the intensive care remain a subject of debate [31]. The relationship between glucose status and infectious complications has already been assessed in a diabetic population after kidney transplantation [14], but this was not significant in our present study, nor was any relationship found between TAH and cardiovascular outcomes or death in our population in contrast to Cosio et al. [15].

However, glucose disorders at the end of the study or at any time during follow-up were strongly associated with graft loss and early hyperglycaemia, and TAH and HbA1c at M3 were also associated with graft failure. NODAT is known to impair graft survival and may be associated with a 63% increase in kidney failure [32]. Roth et al. [33] demonstrated lower rates of graft survival in NODAT patients (54% vs. 82% without NODAT) after 4 years. At 12-years post-transplantation, DM has been found responsible for a relative risk of graft failure of 3.72 [7]. In our study, less graft survival in TAH patients was confirmed by a relative risk of 3.6 at 5 years. Whether early or later, hyperglycaemia is responsible for impaired graft outcomes or is only a symptom of conditions determining poor graft survival remains to be investigated. Interestingly, Revanur et al. [8] demonstrated that NODAT had almost the same impact as pretransplantation DM on kidney-recipient survival.

In the study by Cosio et al. [15], development of TAH in the first week post-transplantation was predictive of diabetes at 1-year post-transplantation. In our study, very early glucose levels tended to be predictive of post-transplant DM at 3 months, but did not correlate with glucose status at M6, M12 or at the end of the study. Individual FBG fluctuations around the threshold for diagnosis of DM or TAH during the first year of follow-up in our patients prevented a clear view of progression towards DM. However, glucose status at M3 appeared to be a good indicator for the later development of NODAT during follow-up.

The known deleterious impact of tacrolimus on NODAT and TAH occurrence was confirmed in our study. The connection between tacrolimus use and the development of TAH was evident from M3 post-transplantation. As glucose levels soon after transplantation can herald TAH occurrence, patients with higher glucose levels immediately after transplant surgery are likely to benefit from intensive glucose monitoring. Persistent TAH in the first months post-transplantation should also encourage nephrologists to consider avoiding either tacrolimus or rapid corticoid-tapering strategies. Also, although TAH and graft failure are closely linked, no correlation was noted between tacrolimus use and graft loss most likely because of other positive effects [32].

The main limitation of our present study was the small size of our patient sample that might prevent adequate analysis of the risks connected to early post-transplantation glucose levels especially for cardiovascular and infectious complications. Because of the high frequency of hyperglycaemia, no euglycaemic control group could be tested for comparison. Moreover, the glucose follow-up of our patients was based on FBG and HbA1c levels at distant time intervals and did not include postprandial glucose measurements that could have determined IGT. IGT and IFG are both (along with NODAT) part of the transplant-associated glucose disorders. This may have underestimated the true incidence of TAH in our study population and precluded a stronger assessment of the outcomes related to early post-graft glucose levels. Valderhaug et al. [34] also pointed out that FBG is not the optimal choice for TAH assessment in these patients. Furthermore, bias due to the uncommonly high incidence of graft failure in our patient sample compared with what is usually observed [35] may have led to overestimation of the link between TAH and graft loss.

Nevertheless, our present study emphasizes the importance of early repeated glucose monitoring in non-diabetic renal transplant patients. High blood glucose levels over this time period
tend to suggest a later risk of NODAT and impaired transplant outcomes. In addition to promoting investigations of larger patient groups to further elucidate the risks associated with early glucose deviations, this work raises the question of specific interventions, such as early insulin therapy and/or modulation of the immunosuppressive regimen, that may improve the outcomes of kidney transplantation.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

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