Prevalence and risk factors of pre-diabetes after renal transplantation: a single-centre cohort study in 200 consecutive patients

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Abstract

Background. After renal transplantation, patients are prone to develop impairments in glucose metabolism. In 2005, the American Diabetes Association published new guidelines on the diagnosis of pre-diabetes [plasma glucose levels from 100 to 125 mg/dL fasting or from 140 to 199 mg/dL 2 h after an oral glucose tolerance test (OGTT)]. This study sought to evaluate the prevalence and the potentially associated factors of pre-diabetes in a cohort of renal transplant patients on maintenance immunosuppressive medication. Furthermore, the diagnostic value of HbA1c measurements in predicting pre-diabetes in transplant patients is undetermined.

Methods. Two hundred consecutive renal transplant patients of our outpatient transplant clinic were evaluated using a standard OGTT. On the day of testing, multiple factors presumably associated with pre-diabetes were assessed via a standardized questionnaire: daily steroid dosage, triglyceride levels, cholesterol levels, estimated glomerular filtration rate (eGFR) [abbreviated Modification of Diet in Renal Disease (MDRD) formula], systolic and diastolic blood pressure, pulse pressure, age, gender, body mass index (BMI), BMI <30 and >25, number of renal transplants, number of rejection episodes prior to testing, source of renal transplant, cause of renal failure and medications as related to the prescription of cyclosporine, tacrolimus, mycophenolate mophetil, angiotensin-converting enzyme inhibitors, AT1-blockers, statins, β-blockers and thiazide diuretics. Patients diagnosed with pre-diabetes were compared to subjects with normal test results. Fishers exact test and the Wilcoxon rank-sum test were applied to compare the two study populations, whereas multivariate logistic regression was used to seek potential risk factors as related to other covariates. Risk ratios (RRs) to develop pre-diabetes were calculated for significant variables.

Results. Ten patients had results indicative of post-transplant diabetes whereas data sets of three other patients were incomplete and were thus not included in the analysis. From the remaining 187 patients, 130 (69.5%) displayed normal test results whereas 57 (30.5%) had results indicative of pre-diabetes. On multivariate regression analysis, patients with pre-diabetes were significantly older {55.3 ± 12.1 versus 47.7 ± 12.6 years, P = 0.0007, RRs per 5 years increase 1.28 [95% confidence interval (95% CI) 1.11–1.47]}, had more rejection episodes [0.26 ± 0.48 versus 0.12 ± 0.37, P = 0.0024, RRs per rejection episode 3.99 (95% CI 1.63–9.77)] and showed lower diastolic blood pressure readings [77 ± 10 mmHg versus 81 ± 10 mmHg, P = 0.0362, RR per 5 mmHg decrease 1.14 (95% CI 1.04–1.49)].

Conclusions. There is a high incidence of latent pre-diabetes among renal transplant recipients. Increasing age, rejection episodes and lower diastolic blood pressure proved to be associated with pre-diabetes. In contrast to post-transplant diabetes, tacrolimus use and HbA1c levels were not prognostic of pre-diabetes.

Keywords: pre-diabetes; PTDM; risk factors; transplantation

Introduction

Historically, the prevalence of post-transplant diabetes mellitus (PTDM) ranged from 3 to 25% due to inconsistent definitions of diabetes mellitus as e.g. use of insulin or other oral agents to treat hyperglycaemia over 30 days [1]. In 2003, a consensus conference on PTDM agreed to adopt the definitions of diabetes mellitus set for the normal population by the American Diabetes Association (ADA) [2]. The development of PTDM has been recognized to contribute to the high cardiovascular burden of kidney transplant recipients during follow-up [3, 4, 5]. Major cardiovascular events are one of the leading causes of death in renal transplant recipients with a functioning graft. Validation of risk factors has revealed traditional as well as non-traditional risk factors contributing to this excessive cardiovascular risk profile. Although the total risk to develop PTDM has probably been markedly reduced over the last decade [6], it is still recognized as playing a major role in this increased cardiovascular burden. Various drugs such as steroids, tacrolimus as well as older recipient age and genetic aspects in different study populations have been reported to increase the incidence of PTDM [7, 8, 9]. Recently, particular emphasis has been placed on the diagnosis of pre-diabetes as a potential risk
factor of cardiovascular events [10, 11]. Pre-diabetes as defined by the ADA is composed of at least one of two different entities: impaired fasting glucose (IFG, plasma glucose levels 100–125 mg/dL) and/or impaired glucose tolerance (IGT, plasma glucose levels 140–199 mg/dL) 2 h after oral glucose tolerance test (OGTT)). It is generally thought to represent a stage preceding overt diabetes and thus deemed to be an ideal point of time for preventive measures. IGT can only be diagnosed with a standard OGTT and shows a higher correlation to cardiovascular events and the subsequent development of diabetes than IFG, at least in the non-transplant population [10, 11]. A negative impact of pre-diabetes on cardiovascular end points in renal transplant patients has been reported also [12, 13]. Importantly, early intervention has been shown to be effective in renal transplant patients as well as in non-transplant populations [14]. So far, pre-diabetes and its related risk factors in renal transplant populations have not yet been investigated as thoroughly as PTDM. The aim of this study was to assess the prevalence and the potentially associated factors for the development of pre-diabetes in renal transplant recipients on a calcineurin inhibitor (CNI)-based immunosuppressive maintenance protocol in combination with mycophenolate mofetil and/or low-dose steroids. In addition, we aimed at defining the value of different HbA1-c levels in screening for pre-diabetes after renal transplantation.

Materials and methods

Study approval

The study was approved by the local ethics committee and data were coded in such a manner that subjects could not be identified either directly or through linked identifiers. Patients were required to give their verbal consent to participate in the study and have their data collected and analysed according to the study protocol. The study reported herein adheres to the principles of the Declaration of Istanbul [15].

Table 1. Major characteristics of the whole patient cohort

<table>
<thead>
<tr>
<th>Variable</th>
<th>Whole patient cohort (n = 187)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time lag Ntx-OGTT (mo)</td>
<td>59.4 ± 61.7</td>
</tr>
<tr>
<td>Steroids (mg/day)</td>
<td>4.2 ± 2.6</td>
</tr>
<tr>
<td>Cyclosporine (ng/mL)*</td>
<td>141 ± 40</td>
</tr>
<tr>
<td>Tacrolimus (ng/mL)*</td>
<td>8.4 ± 2.7</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.15 ± 1.13</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.15 ± 1.16</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>166 ± 61</td>
</tr>
<tr>
<td>eGFR (MDRD formula)</td>
<td>39.7 ± 15.0</td>
</tr>
<tr>
<td>HbA1-c (%)</td>
<td>5.7 ± 0.5</td>
</tr>
<tr>
<td>BMI</td>
<td>25.3 ± 3.8</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>55 ± 15</td>
</tr>
<tr>
<td>RR systolic (mmHg)</td>
<td>134 ± 15</td>
</tr>
<tr>
<td>RR diastolic (mmHg)</td>
<td>80 ± 10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>50.0 ± 12.9</td>
</tr>
<tr>
<td>Number of renal transplants</td>
<td>1.17 ± 0.45</td>
</tr>
<tr>
<td>Rejection episodes</td>
<td>0.16 ± 0.41</td>
</tr>
</tbody>
</table>

*Cyclosporine (n = 129), tacrolimus (n = 53).
immunoturbidimetric method using the Tina-quant® II test (Roche). Normal values were defined as being between 4.8 and 6.0%.

**Interpretation of test results**

Results were classified following current ADA guidelines using the following categories: normal, IFG, IGT, combination of IFG and IGT and diabetes (PTDM). As opposed to the classification of impaired glucose metabolism used in the 2003 consensus conference on PTDM [1], we classified test results according to the current ADA criteria. The current classification system is effective as of 2005 and defines plasma glucose levels for the diagnosis of IFG (100–125 mg/dL), IGT (≥140–199 mg/dL) and PTDM (≥200 mg/dL) or IGT ≥200 mg/dL at 2 h as an OGTT or on random testing). For statistical analysis, the results were categorized as ‘normal’ or ‘pre-diabetic’ (IFG, IGT or combination of IFG and IGT).

**Statistics**

The main outcome of the study was a normal versus a pre-diabetic test result on OGTT and its relation to several covariates. These covariates were as follows:

**Continuous variables.** Body mass index (BMI), daily steroid dosage in milligram of prednisolone, tacrolimus and cyclosporine trough levels in nano gram per millilitre (available in 182 patients), triglyceride levels in milligram per decilitre, cholesterol levels in milligram per decilitre, estimated glomerular filtration rate (eGFR) (abbreviated MDRD formula), systolic blood pressure in millimetres of mercury, diastolic blood pressure in millimetres of mercury, pulse pressure in millimetres of mercury and age in years on the day of testing.

**Categorical variables.** Gender, BMI (<30), BMI (>35), organ source (living/cadaveric), cause of renal failure, rejection episodes (yes/no), number of transplants within each subject (1–2), use of CNIs (CsA/Tac) and use of pre-defined medications such as angiotensin-converting enzyme (ACE) inhibitors, ATI1-blockers, β-blockers, thiazide diuretics and statins (yes/no).

Data were collected from electronic patient records and using a patient questionnaire on the day of testing. Patients with normal results (Group A, n = 130) were compared to patients with abnormal results (Group B, n = 57). Descriptive statistics such as means, SDs, frequencies and proportions were provided for each variable of interest. Categorical variables were compared for inter-group differences using Fishers exact t-test and continuous variables using the Wilcoxon rank-sum test. Multivariate logistic regression was performed for continuous and categorical variables of interest in order to assess the combined effect on the outcome parameter after adjusting for other factors. Diagnostics to assess the model fit and to detect outliers were conducted. For each significant factor risk ratios (RRs), 95% confidence intervals (95% CIs) and P-values were provided. A P-value of ≤0.05 was considered significant.

To adjust for the effect of multiple testing, the Bonferroni-Holm method was applied. Several statistical parameters were calculated in order to analyse the predictive value of HbA1c measures on the outcome parameter (pre-diabetes). Statistical analysis was performed using SPSS 14.0 for Windows.

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**Table 2.** Overview immunosuppressive maintenance protocol of the whole patient cohort as well as Group A (normal results) and Group B (pre-diabetes) in numbers and percenta

<table>
<thead>
<tr>
<th>Immunosuppressive regimen</th>
<th>Whole cohort (n = 187)</th>
<th>Group A (n = 130)</th>
<th>Group B (n = 57)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
</tr>
<tr>
<td>Tac + MMF + ST</td>
<td>14</td>
<td>7.5</td>
<td>8</td>
</tr>
<tr>
<td>Tac + ST</td>
<td>31</td>
<td>16.6</td>
<td>23</td>
</tr>
<tr>
<td>Tac + MMF</td>
<td>12</td>
<td>5.9</td>
<td>8</td>
</tr>
<tr>
<td>CsA + MMF + ST</td>
<td>31</td>
<td>17.1</td>
<td>21</td>
</tr>
<tr>
<td>CsA + ST</td>
<td>69</td>
<td>36.9</td>
<td>51</td>
</tr>
<tr>
<td>CsA + MMF</td>
<td>30</td>
<td>16.0</td>
<td>19</td>
</tr>
</tbody>
</table>

*aCsA, cyclosporine; MMF, mycophenolate mophetil; ST, steroid and Tac, tacrolimus.

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**Results**

Of the 200 patients initially enrolled in the study, 13 patients were excluded from the analysis (3 due to incomplete data sets and 10 due to unexpected diagnosis of PTDM). Of the remaining 187 patients, 130 patients (69.5%) had normal test results (Group A) whereas 57 patients (30.5%) had results diagnostic of pre-diabetes (Group B). Figure 1 gives an overview of the OGTT results. Compared to the current World Health Organization (WHO) classification system, the ADA classification led to a substantial increase in the diagnosis of IFG from 4 to 16% and the combination of IFG and IGT from 2 to 7%. Tables 3 and 4 depict major statistical results of each variable of interest of Groups A and B for continuous and categorical variables (mean, SD, median, range, 95% CI and range for continuous variables), numbers and proportions for categorical variables, P-values and RR if significant. Patients with pre-diabetes were significantly older [55.3 ± 12.1, 55.6, 44 years versus 47.7 ± 12.6, 46.5, 52 years, P = 0.0007, RR per 5 years increment 1.28 (95% CI 1.11–1.47)], had more rejection episodes [0.26 ± 0.48, 0.00, 2.00 versus 0.12 ± 0.37, 0.00, 2.00, P = 0.0024, RR per rejection episode 3.99 (95% CI 1.63–9.77)] and had lower diastolic blood pressure readings [77 ± 10, 76, 45 mmHg versus 81 ± 10, 80, 66 mmHg, P = 0.0362, RR per 5 mmHg decrement 1.14 (95% CI 1.04–1.49)]. With regard to all other test variables, there were no significant differences that could be found between the two study populations. Of special interest is the fact that use of tacrolimus, as compared to cyclosporine, did not result in an increased risk in the development
Prevalence and risk factors of pre-diabetes following transplantation

Table 3. Overview statistical results of continuous variables of Group A (normal test results) and Group B (pre-diabetic test results)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A (n = 130, 65.9%) normal results</th>
<th>Group B (n = 57, 30.5%) pre-diabetes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean ± SD</td>
<td>95% CI</td>
</tr>
<tr>
<td>Time lag Ntx-OGTT (mo)</td>
<td>60.9 ± 62.2</td>
<td>50.1–71.7</td>
</tr>
<tr>
<td>Steroids (mg/day)</td>
<td>4.2 ± 2.5</td>
<td>3.8–4.7</td>
</tr>
<tr>
<td>Cyclosporine (ng/mL)c</td>
<td>140 ± 35</td>
<td>133–147</td>
</tr>
<tr>
<td>Tacrolimus (ng/mL)c</td>
<td>8.2 ± 2.4</td>
<td>7.4–9.0</td>
</tr>
<tr>
<td>Triglycerides (mmol/L)</td>
<td>2.10 ± 1.09</td>
<td>1.91–2.29</td>
</tr>
<tr>
<td>Cholesterol (mmol/L)</td>
<td>5.09 ± 1.22</td>
<td>4.89–5.33</td>
</tr>
<tr>
<td>Creatinine (μmol/L)</td>
<td>172 ± 61</td>
<td>161–182</td>
</tr>
<tr>
<td>eGFR (MDRD formula)</td>
<td>38.5 ± 14.5</td>
<td>36.0–41.0</td>
</tr>
<tr>
<td>HbA1-c (%)</td>
<td>5.6 ± 0.4</td>
<td>5.6–5.7</td>
</tr>
<tr>
<td>BMI</td>
<td>25.1 ± 3.9</td>
<td>24.5–25.8</td>
</tr>
<tr>
<td>Number of renal transplants</td>
<td>1.20 ± 0.50</td>
<td>1.11–1.29</td>
</tr>
<tr>
<td>Pulse pressure (mmHg)</td>
<td>54 ± 14</td>
<td>51–56</td>
</tr>
<tr>
<td>RR systolic (mmHg)</td>
<td>135 ± 15</td>
<td>132–137</td>
</tr>
<tr>
<td>RR diastolic (mmHg)</td>
<td>81 ± 10</td>
<td>79–83</td>
</tr>
<tr>
<td>Age (years)</td>
<td>47.7 ± 12.6</td>
<td>45.5–49.9</td>
</tr>
<tr>
<td>Rejection episodes</td>
<td>0.12 ± 0.37</td>
<td>0.05–0.18</td>
</tr>
</tbody>
</table>

Note: The Wilcoxon rank-sum test was used to compare for inter-group differences of continuous variables (a P-value <0.05 was considered significant). Multivariate logistic regression was applied to calculate RR of variables of interest. Ntx, renal transplantation; mo, months; n.c., not calculated.

Of pre-diabetes as might be conferred from the more potent effect of tacrolimus to induce overt PTDM. Furthermore, as opposed to some reports on their effect to decrease the incidence of diabetes in the non-transplant population, ACE inhibitors and AT1-blockers did not show any protective effect with regard to the diagnosis of pre-diabetes in our study cohort. Table 5 depicts OGTT results in patients with normal results, IFG and IGT and the combination of IFG and IGT in detail combined with HbA1-c levels measured in percentage. Several statistical variables (sensitivity, specificity, positive predictive value, negative predictive value, per cent positive agreement, positive likelihood ratio and negative likelihood ratio) were calculated to test the value of HbA1-c measurements in predicting the outcome parameter pre-diabetes. In the first step, HbA1-c levels for statistical cut-off analysis were set at 5.7, 5.8, 5.9 and 6.0%, respectively. In the second step, we aimed to analyse HbA1-c values between 6.0 and 6.5% as a likely range for predicting pre-diabetes. In summary, no definite HbA1-c threshold level of clinical value could be defined in our cohort of long-term renal transplant recipients. In particular, the cut-off range of HbA1-c levels between 6.0 and 6.5% showed a low sensitivity of 0.26 and a high false negative rate of 0.73.

In a further step, multivariate logistic regression was applied to the same data set using the current WHO categorization of IFG (111–125 mg/dL). Here, logistic regression yielded the same variables as significant (age P = 0.009, rejection episodes P = 0.013 and diastolic
blood pressure $P < 0.001$, further data from this analysis are not shown).

Exclusion of patients with PTDM from the analysis may have affected the results; therefore, another analysis was performed including 10 patients with diabetes in the pre-diabetes group. Again, the same variables proved to be significant on multivariate as well as univariate logistic regression (age $P = 0.001$, rejection episodes $P = 0.001$ and diastolic blood pressure $P < 0.035$ on multivariate analysis and age $P = 0.005$, rejection episodes $P = 0.011$ and diastolic blood pressure $P < 0.012$ on univariate analysis).

To adjust for multiple testing, the Bonferroni-Holm analysis was performed using the following variables: age (years), RR diastolic (mmHg), RR systolic (mmHg), steroids (mg/day), tacrolimus (ng/mL), cyclosporine (ng/mL), rejection episodes, eGFR (MDRD formula), time lag Ntx-OGTT (months) and BMI. Here, age and diastolic blood pressure showed $P$-values lower than the calculated threshold: age $P = 0.0001$ versus 0.0050 and diastolic blood pressure $P = 0.0050$ versus 0.0056. The $P$-value of the variable ‘rejection episodes’ ($P = 0.0104$) fell above the Bonferroni-Holm threshold level of $P = 0.0063$.

Further studies with higher patient numbers are therefore necessary to prove the relevance of these parameters as putative risk or associated factors for pre-diabetes after kidney transplantation.

Discussion

Since 2003, publications on post-transplant hyperglycaemia have applied the current WHO and former consensus threshold levels of IFG of 111–125 mg/dL. In 2005, the ADA whole blood glucose criteria for the definition of IFG were lowered from 111–125 to 100–125 mg/dL [16]. Consequently, more patients are now being diagnosed with IFG. Particularly, renal transplant recipients treated with steroids or CNI may thus be more prone to be diagnosed with pre-diabetes. So far, it has not yet been fully investigated whether the current ADA classification system will yield the same results or rather conflicting data. Therefore, we investigated the prevalence and presumably associated factors of pre-diabetes, as defined by the ADA in 2005, in 200 consecutive patients of our outpatient transplant clinic, of whom 187 patients were eligible for final analysis.

We found a high prevalence of pre-diabetes in our cohort. Compared to the current WHO classification of IFG using higher threshold levels, the ADA criteria led to an increase of recognized pre-diabetes from 18 to 30% in our study population. Although a closer link of IGT over IFG to cardiovascular risks in the general population has been demonstrated [10, 11], a negative impact of IFG on graft and patient survival in renal transplant recipients has also been recently reported [17]. About 14% of our patients had results indicative of IGT. These patients could not have been diagnosed correctly when solely using plasma glucose levels during fasting. Patients with IGT displayed significantly higher HbA1-c levels than subjects with normal test results or IFG. Recently, the ADA supported measurements of HbA1-c levels alone to diagnose diabetes in the general population [18]. This could also be demonstrated in transplant patients where HbA1-c levels alone or in combination with fasting glucose levels had a significant association with PTDM [19, 20].

It is noteworthy that all of the 10 patients with PTDM in our initial cohort showed elevated HbA1-c levels [21]. As such, we tested the value of different HbA1-c levels and ranges with regard to the diagnosis of pre-diabetes. As opposed to the general population [18], our data do not support any value of HbA1-c measurements in the screening of IFG, IGT or the combined end point of both glucose impairments in renal transplant patients. Thus, whereas regular measurements of HbA1-c levels are useful in the screening of PTDM [19, 20], they do not seem to be of assistance with regard to the diagnosis of pre-diabetes. Nevertheless, it is worthwhile mentioning that owing to major test kit variability, these results may only apply to the HbA1-c test kit used in our study protocol. Despite its cumbersome nature, OGTT is thus a valuable tool in the armamentarium of regular risk assessment strategies after renal transplantation.

Bergrem et al. [22] reported rates of hyperglycaemia of IFG (0.7%), IGT (17.3%) and PTDM (13.0%), respectively, 10 weeks after renal transplantation; such results were markedly different to our findings. This was mainly attributed to a higher incidence of PTDM in relation to pre-diabetes as opposed to our findings. Compared to this study, our patients had lower daily steroid prescriptions and displayed a longer time interval from transplantation to OGTT. It has been demonstrated that normal glucose levels in the morning combined with rising levels during the day are typical features of transplant patients, most presumably due to metabolic effects of immunosuppressive medications [23], and that this distinct pattern differs from that in Type 2 diabetes patients [24]. We therefore attributed the overall low prevalence of PTDM (5.0%) in our cohort, as compared to other studies, to our strict study protocol whereby only patients on an immunosuppressive maintenance regimen were eligible.

Other main findings of our study are that older age, number of rejection episodes and lower diastolic blood pressure values were all recognized as associated factors for the development of pre-diabetes. In order to examine the effect of the new ADA IFG thresholds on the statistical analysis, multivariate logistic regression was applied to the same data set using the current WHO threshold levels of 110–125 mg/dL for the diagnosis of IFG. Nevertheless, statistical analysis resulted in the same variables as significant (age, rejection episodes and diastolic blood pressure).

Older age has long been identified in the general population, as well as in renal transplant patients, as a risk factor of diabetes [2, 25]. It predisposes to a variety of risk factors of impaired glucose metabolism such as, among others, reduced bodily activity, increased susceptibility to adverse drug reactions as steroids or CNI-inhibitors on insulin secretion and/or insulin sensitivity in peripheral muscle cells. Our data showed a 1.28-increased RR for the development of pre-diabetes per 5-year increment of age roughly equivalent to the calculated RR for...
the development of PTDM (although for an age increment of 10 years) in a large number of transplant patients reported by Shah et al. [4].

Steroids have been known for decades to induce impairments in blood glucose control due to different mechanisms. In transplant patients, steroid use or the cumulative prescribed steroid dosage are commonly associated with an increased risk of developing PTDM [4, 26]. We could identify the number of rejection episodes to be positively correlated to pre-diabetes, whereas steroid use alone at a dose of or below 7.5 mg/day was not. As part of our inclusion criteria, patients on daily steroids above 7.5 mg prednisolone or with steroid pulses due to rejection episodes within 3 months prior to OGTT were also not eligible unless they were on a low-dose steroid regimen, again for at least 4 weeks. Forty-three patients from our cohort (23%) were on a steroid-free immunosuppressive protocol and did not show a lower prevalence of pre-diabetes as compared to patients with low-dose steroids. Furthermore, as all patients were asked to postpone their complete morning medication after test completion, confounding of 2 h OGTT results, e.g. by rising CNI C2-levels over the test interval could be excluded. Thus, our data suggest that oral low-dose steroids might not substantially increase the risk of pre-diabetes and might therefore be given safely in this context, at least in Caucasian transplant recipients.

Although tacrolimus is known for its greater diabetogenic effect as compared to cyclosporine, we could not detect any inter-group difference in tacrolimus use as related to the diagnosis of pre-diabetes on univariate as well as multivariate testing. This differs from a multicentre study by Porrini et al. [27] in 154 renal transplant patients describing a positive association of tacrolimus on the development of new onset diabetes and pre-diabetes within the first year after transplantation. In contrast to this study, our patients were tested ~5.5–6.0 years after successful renal transplantation. Moreover, use of tacrolimus has been described to be associated with a higher rate of PTDM than cyclosporine only in the presence of pre-transplant insulin resistance [28]; therefore, our data are more in line with a report by Luan et al. [29] on a cohort of 704 renal transplant recipients in the late post-transplant period, although data on the effect of the immunosuppressive medication on the advent of IGT were not provided. In this study, tacrolimus and cyclosporine again carried a quantitatively similar risk of impaired glucose metabolism defined as new onset diabetes or IFG ~47 months after transplantation. Further studies with higher patient numbers and more patients on tacrolimus than in our study are indeed certainly necessary to evaluate the capacity of tacrolimus to induce pre-diabetes as compared to different other immunosuppressants as cyclosporine, low-dose steroids or mTOR inhibitors and to determine the dependency of this effect on trough levels of the specific immunosuppressant.

Recently, although controversially discussed, valsartan was reported to reduce the incidence of diabetes in a large cohort of non-transplant patients with IGT [30]. In our cohort, uni- and multivariate analysis of different medications did not indicate a harmful (β-blockers and thiazide diuretics) or protective effect (statins, ACE inhibitors and AT1-blockers). Further prospective long-term follow-up studies are needed to unravel any effect of non-immunosuppressive medication on prevalence and incidence of pre-diabetes in renal transplant patients.

Analysis of blood pressure readings on the day of OGTT showed a positive correlation of diastolic values to pre-diabetes with a calculated RR of 1.14 for every decrement of 5 mmHg in diastolic blood pressure. These data are of course preliminary and at most only suggestive as they were measured on the day of testing only and were neither adjusted by serial measurements on follow-up visits or 24-h automated blood pressure readings nor by anti-hypertensive drug dosages or cardiologic evaluations of the participants.

In contrast to other publications on PTDM [4, 7, 9, 31], BMI, as a continuous and a categorical variable, was not associated with deranged glucose metabolism in our study as well as in the study by Bergrem et al. [22]. A recent study of BMI data in a large population without substantial chronic kidney disease failed to demonstrate an association with stroke, coronary infarctions or overall risk of death in the non-transplant population [32]. Instead, waist-to-height ratio was proposed to present a better predictor of death or cardiovascular events. Therefore, BMI measurements in the context of post-transplant glucose metabolism or post-transplant cardiovascular risk profile assessment still await further clarification or might even be substituted by other parameters. Noteworthy is also that in a recent study by Hornum et al. [33], waist-to-hip ratios also failed to be associated with impaired insulin secretion and insulin resistance 1 year post-transplantation.

Pre-diabetes is closely linked to insulin resistance and insulin resistance in turn is thought to represent a major pathogenic background mechanism for the development of metabolic syndrome or its components and inflammation [34]. As a consequence, insulin resistance (or pre-diabetes) increases the cardiovascular risk profile of transplant recipients [35]. Earlier diagnosis of pre-diabetes may therefore be a valuable tool to decrease the acknowledged high cardiovascular risk profile of transplant recipients with stable renal function on maintenance immunosuppressive medication. Clinically, a pathological test result in our patient cohort prompted us to recommend lifestyle modifications as well as dietary counselling. Both interventions have been reported to improve glycaemic control in renal transplant recipients [36]. We did not advocate a change of the immunosuppressive medication, but lowered CNI levels in patients with trough levels in the upper range of our routine protocol and a low immunological risk profile. Furthermore, patients with pre-diabetes were asked to have their HbA1c level checked every 3 months (all others once a year) in conjunction with fasting glucose levels for further early risk assessment and as a screening method for the development of overt PTDM. Nevertheless, in the future, it would be crucial to determine the effect of such interventions on glucose metabolism and outcome parameters in renal transplant patients.
Limitations

The strengths of our study are the pre-determined inclusion and exclusion criteria and a well-characterized patient population as well as stringent performance criteria of the OGTT to minimize any potential confounding. Nevertheless, there are several limitations. Firstly, our data clearly need further support in cohorts with higher patient numbers. Secondly, we did not perform a pre-transplant OGTT to rule out unexpected non-transplant-related hyperglycaemia. We tried to minimize possible bias by a thorough chart review for PTDM prior to testing and implementation of strict inclusion criteria. Thirdly, although all of our patients were on a maintenance immunosuppressive protocol, the point in time of testing was not pre-determined by the study protocol. This resulted in marked differences in the time-delay from transplantation to OGTT between patients. Nevertheless, there was no significant difference in this time-delay between the two study populations. Fourthly, we did not incorporate hepatitis C virus or cytomegalovirus status of our patients in our analysis. As chronic infection with both viruses has been reported to exert a negative impact on glucose metabolism in transplant patients [37, 38], non-adjusted chronic infection might thus be a source of potential confounding. This might also be the case in young transplanted women with undetected polycystic ovarian syndrome. It is known that the severity of insulin resistance is correlated to the degree of kidney function expressed as eGFR [39]; therefore, different allograft function levels might have confounded OGTT test results. Patients with normal test results in our study population displayed lower, although statistically non-significant, eGFR levels than patients with pre-diabetes. Therefore, although possible, confounding by eGFR levels seems to be at least unlikely. Finally, our patients were mainly of Caucasian genetic background; our results might thus not be valid for patients of African or Hispanic origin [40].

Conclusion

In conclusion, we could demonstrate that pre-diabetes is a common phenomenon among renal transplant recipients. Routine HbA1c testing is not useful in screening for pre-diabetes after renal transplantation. Age, rejection episodes and lower diastolic blood pressure were independently associated with pre-diabetes, whereas low-dose steroids as well as tacrolimus at maintenance levels were not. The role of other non-immunosuppressive drugs with regard to the induction of pre-diabetes needs further evaluation. The value of BMI or other measures of body mass index in transplant patients and its relation to pre-diabetes or other outcomes have to be determined in more detail in future studies. The long-term effects of follow-up measures as lifestyle changes, dietary counselling or frequent laboratory reassessments on the clinical course of kidney transplant recipients with pre-diabetes await further clarification.

Conflict of interest statement. None declared.
The risk of cancer in people with diabetes and chronic kidney disease

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Abstract

Background. Diabetes and chronic kidney disease (CKD) are both associated with an increased risk of cancer but it is unclear whether diabetes complicated by CKD further augments an individual’s cancer risk. The aim of our study was to determine the association of CKD [defined as an estimated glomerular filtration rate (eGFR) <60 mL/min] with the overall and site-specific risks of incident cancers among individuals with Type 2 diabetes.

Methods. Cox proportional hazard regression models and competing risk analyses were used to examine the univariate and multivariate adjusted associations between reduced kidney function and the overall and site-specific risks of cancer in participants enrolled in the Action in...