ORIGINAL ARTICLE

Mortality risk in post-transplantation diabetes mellitus based on glucose and HbA1c diagnostic criteria

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SUMMARY

Current diagnostic criteria for post-transplantation diabetes mellitus (PTDM) are either fasting plasma glucose ≥7.0 mmol/l (≥126 mg/dl) or postchallenge plasma glucose ≥11.1 mmol/l (≥200 mg/dl) 2 h after glucose administration [oral glucose tolerance test (OGTT) criterion]. In this retrospective cohort study of 1632 renal transplant recipients (RTRs) without known diabetes mellitus at the time of transplantation, we estimated mortality hazard ratios for patients diagnosed with PTDM by either conventional glucose criteria or the proposed glycated haemoglobin (HbA1c) criterion [HbA1c ≥6.5% (≥48 mmol/mol)]. During a median follow-up of 7.0 years, 311 patients died. Compared with nondiabetic patients and after adjustment for confounders, patients diagnosed with PTDM based on chronic hyperglycaemia early after transplantation (manifest PTDM) or by the OGTT criterion at 10 weeks post-transplant suffered a higher mortality risk (HR 1.59, 95% CI 1.06–2.38, $P = 0.02$ and HR 1.56, 95% CI 1.04–2.38, $P = 0.03$, respectively). In contrast, patients diagnosed with PTDM by the HbA1c criterion at 10 weeks or between 10 weeks and 1 year post-transplant were not associated with mortality (HR 0.96, 95% CI 0.61–1.51, $P = 0.86$ and 1.58, 95% CI 0.74–3.36, $P = 0.24$ respectively). After adjustment for confounders and competing risks, only patients with manifest PTDM had a significantly higher cardiovascular mortality risk (subdistributional HR 2.31, 95% CI 1.19–4.47, $P < 0.001$). Since many cases with PTDM were only identified by the OGTT, we recommend monitoring fasting plasma glucose early after renal transplantation followed by an OGTT at 2–3 months post-transplant in patients without overt diabetes mellitus.

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Introduction

Post-transplantation diabetes mellitus (PTDM) is recognized as a separate entity of type 2 diabetes [1,2] and is associated with a reduced life expectancy [3,4]. Transient hyperglycaemia is very common the first month after transplantation [5,6]. Therefore, the diagnosis of PTDM should not be made early after transplantation,

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and is currently diagnosed routinely at our centre 10 weeks after renal transplantation. Patients with chronic hyperglycaemia (manifest PTDM), identified by repeatedly elevated measurements of fasting plasma glucose (fPG) ≥7.0 mmol/l (≥126 mg/dl) that fails to normalize during the first 10 weeks after transplantation are diagnosed with PTDM without a confirmatory oral glucose tolerance test (OGTT) [7]. Additional cases of PTDM are identified by either fPG ≥7.0 mmol/l (≥126 mg/dl) and/or two hours postchallenge plasma glucose (2hPG) ≥11.1 mmol/l (≥200 mg/dl) during an OGTT at 10 weeks post-transplant (OGTT criterion) [1,7,8]. Glycated haemoglobin (HbA1c) ≥6.5% (≥48 mmol/mol) has been implemented internationally for the diagnosis of type 2 diabetes mellitus [9] and it has recently been proposed as a diagnostic criterion for PTDM (HbA1c criterion) [10]. However, use of HbA1c must be made with caution in the early phase after renal transplantation, as a normal HbA1c will not exclude PTDM in the presence of anaemia or reduced allograft function [10,11]. Although anaemia is usually resolved within a few weeks after transplantation, HbA1c is not a reliable diagnostic criteria before new haemoglobin has been synthesized and subjected to glycation following major surgery [12]. Therefore, an anaemic period may influence HbA1c measured several weeks later [1,10]. Furthermore, impaired renal function may reduce erythrocyte life span, which in turn leads to increased haemoglobin turnover and consequently lower HbA1c levels [13].

Oral glucose tolerance test is acknowledged as the gold standard for the diagnosis of PTDM. On the other hand, HbA1c would be a more convenient diagnostic method in daily practice than the OGTT. In the present study, we assessed associations with mortality for both glucose and HbA1c based diagnostic criteria for PTDM.

Materials and methods

Study participants

From a total of 2749 consecutive adult patients (≥16 years) who received a renal transplant at our centre between 30th of September 1999 and 13th of October 2011, we were able to retrieve data from 1632 patients without an established diagnosis of diabetes mellitus prior to transplantation (Fig. 1). Patients were in general followed at our centre the first 3 months after transplantation. The diagnostic screening strategy for PTDM includes fPG measurements twice a week the first month and thereafter once a week for 2–3 months post-transplantation, followed by an OGTT and HbA1c measurement at 10 weeks post-transplant (hereafter 10 weeks). Some RTRs were not included in the present study because of death or graft loss within the first 10 weeks (n = 53), diabetes prior to transplantation (n = 499), transferred early to other hospitals or had missing blood samples at 10 weeks (n = 551) or ongoing high-dose steroid therapy for acute rejection at 10 weeks (n = 14). With exception of patients with manifest PTDM (n = 75) HbA1c was measured and an OGTT was performed as standard routine in nearly all remaining patients who met at a scheduled clinical visit at 10 weeks (three patients had missing HbA1c measurements and 14 patients missing OGTT).

Some patients with transient hyperglycaemia received insulin therapy the first few weeks after transplantation, which often resulted in normalized glucose metabolism and the insulin therapy could therefore be stopped. These patients were not recognized as having PTDM and had their HbA1c levels measured and OGTT performed at 10 weeks. Follow-up beyond 3 months after transplantation was conducted by the patients′ local nephrologist. Further monitoring of the glycaemic status, usually by HbA1c measurements, have been performed on the discretion of the local nephrologist and was not available in our records for most patients included in this study.

Study design, data collection and procedures

Clinical data were extracted from medical records and endpoint data from The Norwegian Renal Registry. The registry is based upon annual reports from all Norwegian Nephrology Units and includes all patients on renal replacement therapy living in Norway. Mortality endpoints were defined according to the European Renal Association – European Dialysis and Transplant Association causes of death codes [14].

Renal transplant recipients (RTRs) without an established diagnosis of diabetes underwent an OGTT before they were wait-listed for transplantation. Diabetes mellitus prior to transplantation therefore included cases with known diabetes from medical records as well as cases identified by an OGTT before the time of transplantation. Since patients with pre transplantation diabetes were excluded, patients with PTDM in the current study had new onset diabetes after transplantation. The glucose measurements performed in this study have previously been described in detail [7]. In short, fPG was measured after a minimum of eight hours overnight fasting. An OGTT was performed by oral administration

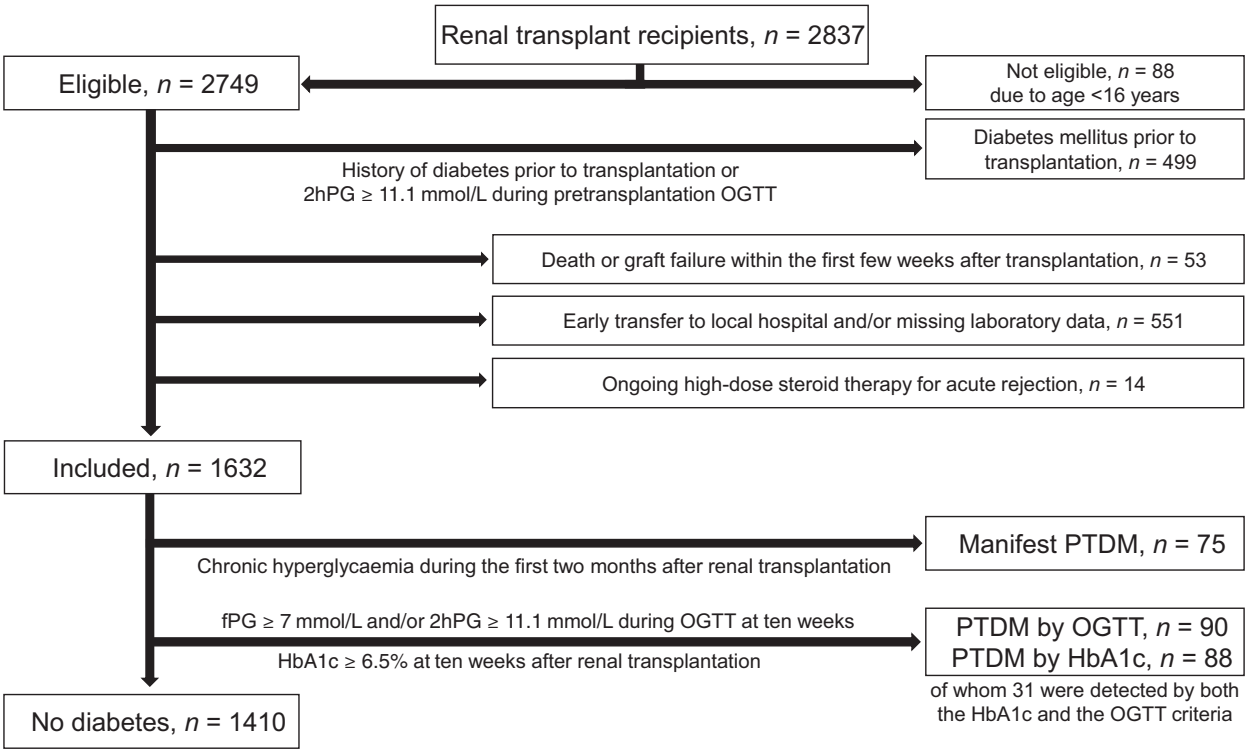

Figure 1 Flowchart for inclusion of patients in the study. Flowchart for inclusion of study participants and selection of patients subjected to an OGTT and measurement of HbA1c. Patients were categorized according to the American Diabetes Association guidelines: Manifest PTDM was defined as persistent hyperglycaemia during the first 2 months after transplantation and was identified by consecutive measurements of fPG ≥7.0 mmol/l (≥126 mg/dl) and random plasma glucose ≥11.1 mmol/l (≥200 mg/dl). PTDM diagnosed by the OGTT criterion was defined as fPG ≥7.0 mmol/l (≥126 mg/dl) and/or 2hPG ≥11.1 mmol/l (≥200 mg/dl) during an OGTT performed 10 weeks after transplantation. PTDM diagnosed by the HbA1c criterion was defined as HbA1c ≥6.5% (≥48 mmol/mol) at 10 weeks post-transplant. fPG, Fasting plasma glucose; HbA1c, Glycated haemoglobin; OGTT, Oral glucose tolerance test; PTDM, Post-transplantation diabetes mellitus; 2hPG, Two hours postchallenge plasma glucose.

of a standard dose of 75 g anhydrous glucose dissolved in 300 ml of water. Plasma glucose measurements were performed in the fasting state before glucose administration and again two hours after administration. Impaired glucose tolerance (IGT) was defined as 2hPG 7.8–11.0 mmol/l (140–199 mg/dl), impaired fasting glucose as fPG 5.6–6.9 mmol/l (100–125 mg/dl) and 2hPG <7.8 mmol/l (<140 mg/dl) and normal glucose tolerance as fPG <5.6 mmol/l (<100 mg/dl) and 2hPG <7.8 mmol/l (<140 mg/dl) during an OGTT. The HbA1c results were obtained from whole blood samples using a standardized immunoassay [7].

Patients diagnosed with PTDM by conventional glucose criteria (manifest PTDM or OGTT criterion) were either started on insulin or oral glucose lowering therapy and/or received dietary advice. We have no information on glucose lowering therapy beyond 10 weeks in the majority of patients identified with PTDM in the present study. No specific recommendations for treatment or glycaemic surveillance have been made for patients with isolated elevated HbA1c levels at 10 weeks. New cases of PTDM during the first year after transplantation were reported to the Norwegian Renal Registry and some additional cases were identified by inspection of medical records. Patients with repeated elevated HbA1c levels beyond 10 weeks post-transplant were considered having PTDM and received treatment accordingly. Thirty-three patients were identified with PTDM by the HbA1c criterion between 10 weeks and 1 year post-transplant. According to medical records, a confirmatory OGTT was performed in most cases, as this has been the method of choice in Norway.

The standard immunosuppressive treatment protocol has been based on a combination of a calcineurin inhibitor, prednisolone and a cell proliferation inhibitor with some variations of what drugs have been used during the present study period (Table 1). At the time of measurements 10 weeks after transplantation, prednisolone dose had been tapered to 7.5 mg per day according to the standard treatment protocol. The

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prednisolone dose was further reduced to a maintenance dose of 5 mg per day three to 4 months after transplantation in most patients. The calcineurin inhibitor was cyclosporine A in all patients until 2007, followed by a period where about half of the patients received tacrolimus and the other half cyclosporine A. Prior to 2001 the patients were treated with azathioprine, after which mycophenolate was used as a cell proliferation inhibitor. Induction therapy with basiliximab was given to all patients transplanted in the year 2000, followed by a period without induction therapy. Then from 2007 all patients have again received basiliximab induction. Rejections were treated with intravenous methylprednisolone followed by an increased dose of oral prednisolone. Steroid-resistant rejections were treated with anti-thymocyte globulin or anti-CD3 monoclonal antibodies.

Statins were discontinued during the first 3 months after transplantation. Calcium channel antagonists were the antihypertensive drugs of choice for RTRs at our centre.

The study was approved by the Regional Committees for Medical and Health Research Ethics in Norway and was performed in accordance with the Declaration of Helsinki.

Statistical analysis

Differences in patient characteristics between patients identified with PTDM by various diagnostic criteria and nondiabetic patients were evaluated by a Chi-square test for categorical data, Mann–Whitney *U*-test for dialysis vintage and *t*-test for other continuous data.

We estimated unadjusted and multivariable adjusted mortality hazard ratios (HR) for PTDM identified by various diagnostic criteria at 10 weeks (manifest PTDM, PTDM by the OGTT criterion and PTDM by the HbA1c criterion) compared with no diabetes mellitus at 10 weeks (Table 2), using Cox proportional hazard regression. In addition to PTDM diagnostic criteria, variables were selected to the final model in a stepwise forward manner ($P < 0.05$ for inclusion in the final model) from a set of predefined candidate variables: Recipient age, donor age, gender, biopsy proven acute rejection episodes (BPARs) during the first 10 weeks according to the Banff criteria, transplant era (year 1999 through 2006 vs. year 2007 through 2011), smoking status at the time of transplantation (former smoker, current smoker or life-long nonsmoker), atherosclerotic disease (coronary artery disease, peripheral vascular disease and/or cerebrovascular disease prior to transplantation), living or deceased donor, first or previous transplantation, dialysis vintage (time in dialysis prior to renal transplantation), preemptive renal transplantation, total number of human leukocyte antigen A, B and DR mismatches and use of cyclosporine A, use of tacrolimus, estimated glomerular filtration rate according to the Modification of Diet in Renal Disease equation (eGFR) and plasma haemoglobin level at 10 weeks. The observational time started at 10 weeks. Surviving patients were censored at the 1st of January 2015.

We estimated unadjusted and multivariable adjusted cause-specific subdistributional mortality hazard ratios (SHR) for various PTDM diagnostic criteria early after transplantation compared with nondiabetic patients (Table 3), using a proportional hazard regression model for the subdistribution of competing risks as described by Fine and Grey [15]. We used the same candidate variables and observational time as previously described.

We also performed a second Cox regression analysis, including PTDM identified by the HbA1c criterion between 10 weeks and 1 year after renal transplantation (Table 4). In this analysis, patients who died within the first year after transplantation were excluded and the observational time started at 1 year post-transplant. We used the same candidate variables as previously described with some exceptions: Plasma haemoglobin and eGFR was excluded from the model. BPARs during the first 10 weeks were replaced with BPARs during the first year after transplantation. Patients who had not developed diabetes mellitus during the first year after renal transplantation were used as the reference group. Surviving patients were censored at the 1st of January 2015.

Since a study conducted at our centre between 1995 and 2006 assessed associations between PTDM by glucose based criteria (combination of manifest PTDM and the OGTT criteria) and mortality risk [3], we compared associations between PTDM by conventional glucose criteria and mortality in the previous and recent transplant era. Finally, we assessed associations with mortality for IGT and diabetes mellitus prior to transplantation.

Proportional hazard assumptions were checked by inspection of the log-log survival time plots and by a formal hypothesis test (Schoenfeld residuals). A two-sided *P*-value of <0.05 was considered statistically significant. PASW Statistics® version 21.0 (IBM, New York, NY, USA) and STATA® version 14.0 (Stata Corp, College Station, TX, USA) were used for the statistical analysis.

Table 1. Patient characteristics according to post-transplantation diabetes mellitus diagnostic category.

Diagnostic category	No diabetes	Manifest PTDM		PTDM by OGTT		PTDM by HbA1c	
Number of patients	1410	75	*P*	90	*P*	88	*P*
Recipient age, years	50.3 (15.0)	59.1 (12.5)	<0.001	58.9 (12.4)	<0.001	61.1 (9.7)	<0.001
Donor age, years	48.0 (15.5)	47.7 (17.3)	0.86	50.3 (16.3)	0.16	48.5 (17.0)	0.77
Gender (Male), %	65.9	57.3	0.13	74.4	0.27	76.1	0.14
Tacrolimus, %	20.5	18.7	0.70	20.0	0.55	8.0	0.01
Cyclosporine A, %	78.7	80.0	0.79	73.3	0.09	86.4	0.05
mTOR inhibitor, %	16.2	17.3	0.79	22.2	0.85	27.3	0.19
Transplant era							
1999–2006, %	57.1	60.0		44.4		72.7	
2007–2011, %	42.9	40.0	0.62	55.6	0.003	27.3	<0.001
Coronary artery disease, %	10.7	12.0	0.72	18.9	0.49	21.6	0.10
Cerebrovascular disease, %	4.0	6.7	0.26	8.9	0.09	8.0	0.11
Peripheral vascular disease, %	6.0	6.7	0.81	14.4	0.01	13.6	0.05
Smoking status							
Current smoker, %	14.4	18.7		12.2		12.5	
Former smoker, %	37.1	36.0	0.59	50.0	0.16	47.7	0.40
Antihypertensive drugs							
None or one, %	54.2	58.7		54.4		54.5	
Two or three, %	41.7	38.7		43.3		40.9	
Four or more, %	4.1	2.7	0.67	2.2	0.96	4.5	0.55
Dialysis vintage, months	8 (0–18)	12 (1–23)	0.02	11 (0–21)	0.08	9 (1–18)	0.57
Preemptive transplantation, %	25.6	22.7	0.57	25.6	0.97	21.6	0.41
First renal transplantation, %	89.2	77.3	0.01	88.9	0.57	86.4	0.51
Living donor, %	44.0	20.0	<0.001	27.8	0.01	27.3	0.01
Number of HLA mismatches							
None or one, %	17.2	9.3		16.7		12.5	
Two, %	24.1	18.7		21.1		23.8	
Three, %	32.6	26.7		35.6		32.5	
Four or more, %	26.1	45.3	0.02	26.6	0.49	23.8	0.62
Body mass index, kg/m^2	24.6 (3.7)	24.7 (3.4)	0.74	25.2 (3.8)	0.11	24.6 (3.2)	0.95
Total cholesterol, mmol/l	6.37 (1.50)	6.41 (1.40)	0.79	6.46 (1.78)	0.57	6.97 (1.82)	0.003
LDL cholesterol, mmol/l	4.12 (1.69)	4.09 (1.19)	0.87	4.19 (1.58)	0.70	4.31 (1.55)	<0.001
HDL cholesterol, mmol/l	1.55 (0.49)	1.51 (0.59)	0.60	1.45 (0.46)	0.07	1.57 (0.54)	0.89
Triglycerides, mmol/l	2.06 (1.34)	2.34 (1.72)	0.01	2.36 (1.26)	0.01	2.37 (1.22)	0.01
Albumin, g/l	40.3 (3.7)	38.7 (3.7)	<0.001	40.3 (4.0)	0.99	38.1 (3.5)	<0.001

Table 1. continued.

Diagnostic category	No diabetes	Manifest PTDM		PTDM by OGTT		PTDM by HbA1c	
Haemoglobin, g/dl	12.1 (3.8)	11.8 (1.4)	0.56	12.1 (1.5)	0.87	11.4 (1.5)	0.12
eGFR, ml/min × 1.73 m^2	59.0 (19.3)	59.7 (21.8)	0.77	57.0 (20.3)	0.06	59.9 (17.8)	0.73

eGFR, Estimated glomerular filtration rate; HbA1c, Glycated haemoglobin; HDL, High-density lipoprotein; HLA, Human leukocyte antigen; mTOR, Mammalian target of rapamycin; LDL, Low-density lipoprotein; OGTT, Oral glucose tolerance test; PTDM, Posttransplantation diabetes mellitus.

No diabetes, defined as HbA1c <6.5% (<48 mmol/mol), fasting plasma glucose (fPG) <7.0 mmol/l (<126 mg/dl) and 2-hour postchallenge plasma glucose (2hPG) <11.1 mmol/l (<200 mg/dl) during an OGTT at 10 weeks. Manifest PTDM:PTDM diagnosed by persistent hyperglycaemia during the first 2 months after renal transplantation. PTDM by OGTT:PTDM diagnosed at 10 weeks by fPG ≥7.0 mmol/l (≥126 mg/dl) and/or 2hPG ≥11.1 mmol/l (≥200 mg/dl) during an OGTT. PTDM by HbA1c:PTDM diagnosed by HbA1c ≥6.5% (≥48 mmol/mol) at 10 weeks. Results are presented as proportions for categorical data, median and interquartile range for dialysis vintage and mean and standard deviations for other continuous data. Differences in patient characteristics between PTDM diagnostic categories and no diabetes at 10 weeks were evaluated by a Chi-square test for categorical data, Mann–Whitney *U*-test for time in dialysis and *t*-test for other continuous data.

Results

Demographic and clinical characteristics of study participants according to PTDM categories are presented in Table 1. Patients with PTDM were older, had less often a living donor and also slightly more cardiovascular comorbidity and dyslipidaemia than nondiabetic patients (Table 1).

The OGTT ($n = 90$) and HbA1c ($n = 88$) criteria identified different patients with PTDM at 10 weeks with a limited overlap ($n = 31$). In patients with HbA1c ≥6.5% (≥48 mmol/mol) at 10 weeks, 23 had normal glucose tolerance (26%), 22 had IGT (25%) and 12 had impaired fasting glucose (14%).

During a median follow-up of 7.0 years, 311 patients died (19%). The cause of death was cardiovascular disease in 117 patients (38% of deaths), infectious disease in 79 patients (25%) and 77 deaths were caused by cancer (25%).

In multivariable Cox regression analysis with baseline 10 weeks (Table 2), patients with manifest PTDM and patients with PTDM by the OGTT criterion suffered a higher mortality risk than nondiabetic patients [Manifest PTDM: HR 1.59, 95% confidence interval (CI) 1.06–2.38, $P = 0.02$ and OGTT criterion: HR 1.56, 95% CI 1.04–2.38, $P = 0.03$]. In contrast, there was no association between PTDM identified by the HbA1c criterion 10 weeks after transplantation and mortality after adjustment for confounders (HR 0.96, 95% CI 0.61–1.51, $P = 0.86$).

Manifest PTDM was positively associated with cardiovascular mortality risk after adjustment for confounders and competing risks (SHR 2.31, 95% CI 1.19–4.47, $P < 0.001$). Although not statistically significant, an effect size of probable importance was found for PTDM by the OGTT criterion and cardiovascular mortality (SHR 1.81, 95% CI 0.98–3.36, $P = 0.06$). In contrast, there were no associations between PTDM by either diagnostic criteria and infectious disease mortality after adjustment for competing risks (Table 3). No associations were found between PTDM and cancer mortality.

Thirty-three patients were diagnosed with PTDM based on repeated measurements of elevated HbA1c levels between 10 weeks and 1 year post-transplant. We failed to detect any statistically significant association between this group of PTDM patients and mortality risk (multivariable adjusted HR 1.58, 95% CI 0.74–3.36, $P = 0.24$, number of events = 7).

The mortality risk for patients diagnosed with PTDM by conventional glucose criteria was similar in the most

Table 2. Mortality risk according to post-transplantation diabetes mellitus diagnostic category.

Cox proportional hazard ratios			Unadjusted			Multivariable adjusted		
Diagnostic category	Number of patients	Number of events	HR	95% CI	*P*	HR	95% CI	*P*
No diabetes mellitus at 10 weeks	1410	231	1.0			1.0		
Manifest PTDM	75	27	2.68	1.80–4.00	<0.001	1.59	1.06–2.38	0.02
PTDM by OGTT at 10 weeks	90	26	1.96	1.28–3.01	0.002	1.56	1.04–2.38	0.03
PTDM by HbA1c at 10 weeks	88	27	1.42	0.93–2.16	0.10	0.96	0.61–1.51	0.86

CI, Confidence interval; HbA1c, Glycated haemoglobin; HR, Hazard ratio; OGTT, Oral glucose tolerance test; PTDM, Post-transplantation diabetes mellitus.

Associations between PTDM diagnostic categories and mortality risk. Presented are number of patients and events, unadjusted and multivariate adjusted estimated mortality hazard ratios using Cox proportional hazard regression analysis with no diabetes mellitus as reference. In addition to PTDM diagnostic categories, recipient age, donor age, smoking status, first renal transplant, atherosclerotic disease and dialysis vintage were also included as covariates in the final stepwise forward multivariable Cox regression model.

Table 3. Cause-specific mortality risk according to post-transplantation diabetes mellitus diagnostic category.

Subdistributional hazard ratios			Unadjusted			Multivariable adjusted		
Diagnostic category	Number of patients	Number of events	SHR	95% CI	*P*	SHR	95% CI	*P*
Cardiovascular mortality								
No diabetes mellitus at ten weeks	1410	81	1.0			1.0		
Manifest PTDM	75	13	3.27	1.79–5.96	<0.001	2.31	1.19–4.47	<0.001
PTDM by OGTT at ten weeks	90	12	2.24	1.20–4.17	0.01	1.81	0.98–3.36	0.06
PTDM by HbA1c at ten weeks	88	11	1.45	0.76–2.76	0.25	0.77	0.38–1.53	0.45
Infectious disease mortality								
No diabetes mellitus at ten weeks	1410	58	1.0			1.0		
Manifest PTDM	75	8	2.71	1.31–5.62	0.01	1.39	0.58–3.34	0.46
PTDM by OGTT at ten weeks	90	8	2.64	1.17–5.98	0.02	1.84	0.80–4.26	0.15
PTDM by HbA1c at ten weeks	88	5	0.82	0.30–2.22	0.70	0.44	0.16–1.20	0.11
Cancer mortality								
No diabetes mellitus at 10 weeks	1410	63	1.0			1.0		
Manifest PTDM	75	4	1.22	0.45–3.34	0.70	0.68	0.24–1.92	0.40
PTDM by OGTT at ten weeks	90	3	0.63	0.20–2.01	0.43	0.49	0.15–1.63	0.25
PTDM by HbA1c at ten weeks	88	7	1.84	0.83–4.07	0.13	1.02	0.42–2.48	0.97

CI, Confidence interval; HbA1c, Glycated haemoglobin; HR, Hazard ratio; OGTT, Oral glucose tolerance test; PTDM, Post-transplantation diabetes mellitus.

Associations between PTDM diagnostic categories and cause-specific mortality risk. Presented are number of patients and events, unadjusted and multivariate adjusted subdistributional mortality hazard ratio estimates (SHR) with corresponding 95% confidence intervals (CI), using a competing risk regression model with no diabetes mellitus at ten weeks post-transplant as reference.

recent transplant era (year 2007 through 2011: unadjusted HR 2.17, 95% CI 1.13–4.16) compared with the previous era (year 1999 through 2006: unadjusted HR 2.27, 95% CI 1.54–3.33).

Most patients who underwent an OGTT at 10 weeks after transplantation ($n = 1543$) had normal glucose tolerance, 6% had PTDM by the OGTT criterion, 12% had IGT and 11% had impaired fasting glucose. No association was found between IGT and mortality risk (unadjusted HR 1.10, 95% CI 0.80–1.53).

When we included patients with diabetes mellitus prior to transplantation ($n = 499$) in the Cox model, we found a strong positive association between pre-transplantation diabetes mellitus and mortality (unadjusted HR 2.25, 95% CI 1.85–2.75).

Table 4. Mortality risk according to post-transplantation diabetes mellitus diagnostic category including patients diagnosed with post-transplantation diabetes mellitus between 10 weeks and 1 year after transplantation.

Cox proportional hazard ratios			Unadjusted			Multivariable adjusted		
Diagnostic category	Number of patients	Number of events	HR	95% CI	*P*	HR	95% CI	*P*
No diabetes mellitus at 1 year	1331	209	1.0			1.0		
Manifest PTDM	74	26	2.83	1.88–4.25	<0.001	1.65	1.09–2.50	0.02
PTDM by OGTT at 10 weeks	89	25	2.01	1.17–2.89	0.002	1.64	1.08–2.49	0.02
PTDM by HbA1c at 10 weeks	88	27	1.52	0.99–2.33	0.05	0.87	0.57–1.33	0.51
PTDM by HbA1c between 10 weeks and 1 year	33	7	1.45	0.69–3.08	0.33	1.58	0.74–3.36	0.24

CI, Confidence interval; HbA1c, Glycated haemoglobin; HR, Hazard ratio; OGTT, Oral glucose tolerance test; PTDM, Post-transplantation diabetes mellitus.

Associations between PTDM diagnostic categories and mortality risk. Presented are unadjusted and multivariate adjusted mortality hazard ratio estimates (HR) with corresponding 95% confidence intervals (CI), using Cox proportional hazard regression with no diabetes mellitus at 1 year after renal transplantation as reference.

Patients identified with PTDM by the HbA1c criterion had slightly lower eGFR and haemoglobin levels than the other study participants (Table 1). When patients with haemoglobin <10.0 g/dl and/or eGFR <30 ml/min × 1.73 m^2 at 10 weeks were excluded, associations between different PTDM diagnostic categories and mortality were not changed.

Discussion

The main finding of this study is that patients diagnosed with PTDM by glucose-based criteria (manifest PTDM or the OGTT criterion) early after transplantation suffered a higher mortality risk than nondiabetic patients. In contrast, no statistical significant association with mortality was found with PTDM by the HbA1c criterion at 10 weeks or PTDM by the HbA1c criterion between 10 weeks and 1 year after renal transplantation. Patients with manifest PTDM suffered a particularly high cardiovascular mortality risk.

In this cohort, we have previously reported that HbA1c have a low sensitivity for detection of PTDM early after transplantation [7]. Possibly, the lack of association between the HbA1c criterion and mortality risk in the present study mirrors the low sensitivity of the HbA1c criterion for detection of PTDM early after transplantation (Table 2).

The role of HbA1c for the diagnosis of type 2 diabetes is already established, while it is less clear for PTDM [2,10]. Implementation of the diagnostic HbA1c threshold value of 6.5% (≥48 mmol/mol) in type 2 diabetes was based on the relationship between HbA1c levels and the occurrence of retinopathy [16]. Since transplant recipients primarily suffer high cardiovascular morbidity and mortality rates, focus in patients with PTDM is on prediction and prevention of cardiovascular events and mortality rather than microvascular complications. There is also limited evidence for associations between PTDM and microvascular complications [17]. In contrast to the OGTT, HbA1c is a convenient test that can easily be performed several times after transplantation at a low cost. The utility of the proposed HbA1c criterion for detection of PTDM is likely to differ between the early phase after renal transplantation and later timepoints [18,19].

Although not statistically significant, the association between PTDM by the HbA1c criterion beyond 10 weeks could give a signal of a possibly true relationship given a larger number of cases and events (Table 4). Since these cases of PTDM were based on reports from local nephrologists, it is possible that some late debuting cases of PTDM in this cohort were missed. On the other hand, the low number of patients diagnosed with PTDM between 10 weeks and 1 year

might also partly reflect the diagnostic precision of the OGTT performed at 10 weeks and exclusion of overt diabetes mellitus by an OGTT prior to transplantation.

Transplant recipients are at increased risk of developing diabetes mellitus, mainly because of side effects of immunosuppressive drugs [1,10]. PTDM is characterized by a rapid progression from transient hyperglycaemia to diabetes, with reduced first phase insulin release, postprandial plasma glucose peaks and elevated afternoon and evening plasma glucose levels as predominant features [20,21]. It has long been acknowledged that HbA1c identifies a different population of diabetic patients than glucose based criteria in type 2 diabetes mellitus [22]. In our study population, several patients with elevated 2hPG had normal fPG and HbA1c levels, and were only identified with PTDM by an OGTT and some patients with elevated HbA1c levels had normal glucose tolerance. Because of future risk of events, the diagnosis of PTDM should be established and optimal treatment given as early as possible, preferably within the first few months after transplantation. Based on the results presented in this study, we therefore recommend a continued use of OGTT for the diagnosis of PTDM. More convenient glucose based diagnostic criteria, including postprandial, afternoon and evening plasma glucose, may possibly challenge the role of OGTT for detection of PTDM in the future [19].

In the present study, only manifest PTDM was significantly associated with a higher cardiovascular mortality risk. This group of patients probably had a more aggressive type of diabetes than patients identified with PTDM at later time-points. PTDM by the OGTT criterion was significantly associated with overall but not cardiovascular mortality, possibly because of a lower event rate (Table 3). We also failed to detect significant associations between various PTDM diagnostic criteria and infectious disease mortality after adjustment for confounders and the impact of other causes of death. Future studies with a larger sample and more events could better assess associations between various PTDM diagnostic criteria and cause-specific mortality.

The low event rate also partly reflects the relatively low incidence of PTDM in this cohort (10% of nondiabetic RTRs at 10 weeks according to conventional glucose criteria for PTDM) [7]. The cumulative incidence of type 2 diabetes mellitus in the Norwegian general population is considerable lower than in most other European countries, which might be because of various dietary and life-style factors, including lower sugar consumption [23,24]. Interestingly, a low sensitivity of HbA1c for detection of PTDM early after renal transplantation [7] has also been found in other population of RTRs [25,26] with higher sugar consumption and PTDM incidence than in Norway [23–26]. Furthermore, relatively low doses of immunosuppressive drugs as standard treatment at our centre in recent years might have contributed to lower the incidence of PTDM in Norwegian RTRs [27,28].

In the most recent transplant era (year 2007 through 2011), the association between PTDM identified by conventional glucose criteria and mortality risk was in line with findings from a study conducted at our centre between 1995 and 2006 [3]. However, in contrast with the previous study, we did not find an association between IGT and mortality. Improved glycaemic surveillance and cardiovascular protection in patients with IGT in recent years could have improved their life expectancy. Current recommendations for patients identified with IGT at our centre include dietary advice and more frequent glycaemic measurements.

Strengths of this study include a relatively large number of events, a long follow-up period and a high inclusion rate of consecutively transplanted adult patients from a single centre that underwent uniform prospectively planned clinical investigations. The risk of diabetes diagnosis misclassification in the early phase after renal transplantation should be quite low in this cohort because of exclusion of overt diabetes mellitus by pretransplantation OGTT.

The study has several important limitations, some of which has been addressed in previous sections. We lack information on HbA1c and glucose measurements in patients who did not meet at the clinical visit at 10 weeks. We also have limited data on changes in glycaemic indices over time, including patients diagnosed with PTDM. The OGTT was performed once per patient, which is accepted by the World Health Organization for epidemiological studies. However, guidelines recommend a confirmatory test as the OGTT has a relatively poor reproducibility [29] and ideally OGTT should have been performed at several time-points after transplantation to increase diagnostic precision. For practical purposes a confirmatory OGTT was not possible in this cohort, illustrating the disadvantage of OGTT as a diagnostic test.

Lack of data on the use of antithrombotic drugs, use of statins and type and dose of glucose-lowering and antihypertensive drugs might all have influenced the results. At the time of measurements, the prednisolone

dose had been tapered down to 7.5 mg per day according to standard protocol, hence they were not yet on maintenance prednisolone dose of 5 mg per day. Less than one of four patients received treatment with tacrolimus, which is now the calcineurin inhibitor of choice in most transplant centres, including our centre.

The study population almost exclusively consisted of Caucasian patients and the results may therefore not apply to other ethnical groups. Since the observational time started at 10 weeks, the survival analyses were hampered by immortal time bias to some degree.

In summary, early diagnosis of PTDM based on conventional glucose criteria was associated with a higher mortality risk after renal transplantation compared with nondiabetic patients, while PTDM identified by HbA1c ≥6.5% (≥48 mmol/mol) at 10 weeks or between 10 weeks and 1 year after transplantation was not. Since many patients with PTDM were detected by an OGTT alone, we recommend monitoring fasting plasma glucose during the first 2 months after transplantation, combined with an OGTT at 2–3 months post-transplant in patients without overt diabetes mellitus. Future studies on utilizing the HbA1c criterion for detection of PTDM are necessitated to establish whether elevated HbA1c levels at a later time-point later than 10 weeks could be adequate for the diagnosis of PTDM in RTRs.

Authorship

TJ, TASH, IAE, AH, AVR, AÅ and DOD: designed the study. IAE and TASH: collected data from patient records for patients transplanted at our centre between 30th of September 1999 and 13th of October 2011. IAE, TASH and DOD: analysed the data. TASH, IAE and TJ: edited the manuscript. AÅ, AH, AVR and DOD: co-edited the manuscript. TASH, IAE, AH, AÅ, AVR, DOD and TJ: all approved the final version of the manuscript. IAE: submitted the manuscript.

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Conflicts of interest

The authors declare no disclosures or conflict of interest. All authors had access to the data for the present study and decided to submit for publication. The funding organizations had no role in the design of the study, data collection, data analysis, interpretation, manuscript preparation or the decision to submit.

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