The association of early post-transplant glucose levels with long-term mortality

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Abstract

Aims/objective We aimed to assess the long-term effects of post-transplant glycaemia on long-term survival after renal transplantation.

Methods Study participants were 1,410 consecutive transplant recipients without known diabetes who underwent an OGTT 10 weeks post-transplant and were observed for a median of 6.7 years (range 0.3–13.8 years). The HRs adjusted for age, sex, traditional risk factors and transplant-related risk factors were estimated.

Results Each 1 mmol/l increase in fasting plasma glucose (fPG) or 2 h plasma glucose (2hPG) was associated with 11% (95% CI 1%, 24%) and 5% (1%, 9%) increments in all-cause mortality risk and 19% (1%, 39%) and 6% (1%, 12%) increments in cardiovascular (CV) mortality risk, respectively. Including both fPG and 2hPG in the multi-adjusted model the HR for 2hPG remained unchanged, while the HR for fPG was attenuated (1.05 [1.00, 1.11] and 0.97 [0.84, 1.14]). Compared with recipients with normal glucose tolerance, patients with post-transplant diabetes mellitus had higher all-cause and CV mortality (1.54 [1.09, 2.17] and 1.80 [1.10, 2.96]), while patients with impaired glucose tolerance (IGT) had higher all-cause, but not CV mortality (1.39 [1.01, 1.91] and 1.04 [0.62, 1.74]). Conversely, impaired fasting glucose was not associated with increased all-cause or CV mortality (0.79 [0.52, 1.23] and 0.76 [0.39, 1.49]). Post-challenge hyperglycaemia predicted death from any cause and infectious disease in the multivariable analyses (1.49 [1.15, 1.95] and 1.91 [1.09, 3.33]).

Conclusions/interpretation For predicting all-cause and CV mortality, 2hPG is superior to fPG after renal transplanta-
tion. Also, early post-transplant diabetes, IGT and post-challenge hyperglycaemia were significant predictors of death. Future studies should determine whether an OGTT helps identify renal transplant recipients at increased risk of premature death.

**Keywords** Mortality after renal transplantation · New-onset post-transplant diabetes mellitus · Oral glucose tolerance test · Post-transplant complications

**Abbreviations**

2hPG 2 h plasma glucose after an OGTT  
CV Cardiovascular  
CMV Cytomegalovirus  
fPG Plasma glucose after an overnight fast  
IFG Impaired fasting glucose  
IGT Impaired glucose tolerance  
NGT Normal glucose tolerance  
PTDM Post-transplant diabetes mellitus

**Introduction**

Renal transplant recipients have an increased risk of premature death, with cardiovascular disease (CVD), malignancy and infectious disease being the predominant causes of mortality [1]. Immunosuppressive therapy may potentiate traditional pre-transplant risk factors [2], but cannot fully explain the increased long-term mortality after renal transplantation [3].

Hyperglycaemia is reported to be a risk marker for CVD and cancer among healthy individuals without diabetes [4, 5]. Post-challenge hyperglycaemia is particularly associated with increased all-cause, cardiovascular (CV) and cancer mortality in the general population [5–7]. The impact of hyperglycaemia on patient survival after renal transplantation is, however, unknown. Some studies indicate an association between post-transplant diabetes mellitus (PTDM) and mortality [8–10], whereas others do not [11, 12]. Renal transplant recipients may have normal fasting plasma glucose (fPG) but at the same time elevated 2 h plasma glucose (2hPG). Only half of individuals with new-onset diabetes after renal transplantation are identified from an fPG ≥ 7.0 mmol/l [13], as compared with 70% in the general population [14] and 80% in morbidly obese persons [15]. In addition, approximately one out of five recipients has impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) 10 weeks after renal transplantation [16]. Thus, performing an OGTT in the early post-transplant period may be important for the identification of renal transplant patients with hyperglycaemia.

The aim of this study was to assess the long-term effects of early post-transplant glycaemia on overall and cause-specific mortality after renal transplantation.

**Methods**

**Design and study population** A total of 2,458 consecutive patients received a renal transplant at our centre between 2 February 1995 and 19 October 2006. After the exclusion of 1,048 patients because of re-transplantation, age <18 years, early death, early graft loss, pre-existing diabetes mellitus or failure to perform an OGTT, 1,410 patients were included in this prospective cohort study (Fig. 1). The participants were observed until either the primary endpoint (death) was reached or 31 December 2008 (median [range] 6.7 [0.3–13.8] years). Patients who developed PTDM (manifest PTDM, n=58) before the scheduled OGTT did not complete the test, while the remaining 1,352 first-time renal transplant recipients underwent an OGTT 10 weeks (mean [SD] 71 [9] years).

**Fig. 1** The number of patients receiving their first kidney transplant without pre-existing diabetes mellitus at the time of transplantation (Tx). Re-transplant recipients were excluded. Failure to perform an OGTT denotes patients who were transferred to local hospitals before the scheduled OGTT at baseline 10 weeks after renal transplantation. Patients who developed manifest diabetes during the first 10 weeks after transplantation (Manifest PTDM) did not undergo an OGTT. A total of 1,410 patients were included in the prospective cohort study and 1,352 patients underwent an OGTT.
Glucocorticoids and immunosuppressive therapy

Our immunosuppressive protocol consisted of prednisolone, ciclosporin A, azathioprine, and mycophenolate. In most instances, tacrolimus was included: prednisolone, ciclosporin A, azathioprine, and mycophenolate. In most instances, tacrolimus was given if ciclosporin A was withdrawn because of rejection, toxicity or side effects.

Data registration and endpoints

The following baseline variables were used as predictors during the imputation process. The variables used for multiple imputation included: age, sex, donor age, donor status (living or deceased), height, weight, creatinine, use of ciclosporin A, early CMV infection, early hepatitis C virus infection, total cholesterol, fPG, 2hPG, HbA1c, early rejection, hypertension, primary diagnosis of renal disease (glomerulonephritis, pyelonephritis, polycystic kidney disease, nephrosclerosis, other diagnoses), pre-transplant renal status (haemodialysis, peritoneal dialysis, pre-emptive transplantation), human leucocyte antigen (HLA)-DR mismatch (none, one, two), smoking status (never, former or current), cause of death (CVD, malignancy, infection, other, unknown), survival time (months). Variables not normally distributed were logarithmically transformed (fPG, 2hPG and creatinine). Statistical analyses were first performed on each imputed data set, and thereafter pooled to achieve a single variable estimate.
Statistical analyses Non-imputed descriptive data are presented as mean (SD) or frequency (%). The 1,352 patients who underwent the OGTT were dichotomised to have post-challenge hyperglycaemia (2hPG ≥7.8 mmol/l) or normoglycaemia. Differences between groups were analysed using independent samples t test for continuous data and Fisher’s exact test for categorical data. Associations between fPG and 2hPG were analysed using non-parametric correlations (Spearman’s ρ). Kaplan–Meier plots and logrank test were used to analyse crude cumulative survival for the various ADA categories.

Hazard ratios and corresponding 95% CIs were estimated using Cox proportional hazard regression models. Glycaemia was included as either a continuous explanatory variable or a categorical variable. Continuous explanatory variables were fPG and 2hPG. Categorical variables were: NGT=reference; IFG; IGT; PTDM; and post-challenge hyperglycaemia, yes/no. Patients with manifest PTDM (n=58) before the scheduled OGTT were included only in the analyses with glucose categories as explanatory variables. Also, an interaction term between fPG and 2hPG was included.

We fitted three multiple Cox regression models. In model 1 we adjusted for age and sex. In model 2 we further adjusted for traditional risk factors: BMI; creatinine; pre-transplant CVD; total cholesterol; hypertension; and smoking status [1–3, 10]. In model 3 we included additional adjustments for transplant-related risk factors: donor status; pre-emptive transplantation; CMV infection; early rejection; and usage of ciclosporin A [2, 3, 11]. The assumption of linearity was assessed by fitting multifrational models, which allows for several types of non-linearity, and testing for the best fit [26].

Model discrimination between predicted and estimated risk was assessed using Harrell’s concordance index (c-statistic) [27, 28]. A result was considered to be statistically significant when p<0.05. Statistical analyses were conducted with the use of Stata 11.0 (StataCorp, College Station, TX, USA) and PASW 18.0 (Chicago, IL, USA).

Results

Out of 1,410 recipients included in the prospective study, a total of 638 (45%) had NGT, 217 (16%) had IFG, 313 (22%) had IGT and 242 (17%) had PTDM.

Demographic and clinical characteristics of the patients who underwent an OGTT (n=1,352) according to the presence or absence of post-challenge hyperglycaemia are presented in Table 1. The recipients with a 2hPG ≥7.8 mmol/l were significantly older, had less favourable kidney function and were more likely to have a history of smoking, pre-transplant CVD, CMV infection and rejection than those with 2hPG <7.8 mmol/l. Unadjusted all-cause and CV mortality HRs of prevalent risk factors inherent to the transplant population are presented in Table 2.

A total of 282 (20%) of the 1,410 recipients died during the study period: 79 (12%) of the patients with NGT, 31 (14%) of the patients with isolated IFG, 90 (29%) of the patients with IGT, and 82 (34%) of the patients with PTDM (p<0.001). A total of 120 (42%) patients died from CVD, 65 (23%) from malignancy, 67 (24%) from infectious diseases, 17 (6%) from other causes and 13 (5%) from unknown causes. Septicaemia and bacterial pneumonia accounted for 57% and 31% of the infectious deaths, respectively.

Mortality according to glucose as a continuous variable Both fPG and 2hPG were associated with increased all-cause and CV mortality risk in the unadjusted Cox regression analyses (Tables 3 and 4). After adjustments for confounders, the impact of fPG became statistically non-significant, while 2hPG remained a significant predictor of overall mortality risk (Table 3). In the multivariable cause-specific Cox regression analyses, both fPG and 2hPG remained associated with increased risk of CV death (Table 4). The fPG and 2hPG were correlated (r=0.59, p<0.001), but there was no statistically significant interaction between fPG and 2hPG (p=0.527). When both 2hPG and fPG were included in the multivariable model 3, only 2hPG was found to be a predictor of all-cause mortality (2hPG, HR 1.05 [95% CI 1.00, 1.11] p=0.038; fPG, HR 0.97 [95% CI 0.84, 1.14] p=0.740). For all the regressions analyses, a linear model was the best fit for the continuous glucose measurements (data not shown).

Mortality and glucose as categorical variables Cumulative mortality according to glucose category is shown in Fig. 2. The logrank test indicated a significant difference in mortality between the subgroups (p<0.001). Recipients with PTDM, IGT or post-challenge hyperglycaemia at baseline had an approximately twofold unadjusted increased death risk compared with those with NGT or post-challenge normoglycaemia (Table 3). The overall mortality risk was attenuated after multiple adjustments in Cox models 1–3, but remained statistically significant in all the multivariable analyses. Conversely, IFG failed to show any association with mortality (Tables 3 and 4).

Table 4 shows that post-challenge hyperglycaemia was associated with an approximately twofold increased risk of death from CV disease, malignancy and infectious disease. PTDM was associated with a nearly threefold increased risk from CVD, while IGT was associated with a twofold increased risk of infectious death. After multivariable adjustments, PTDM remained associated with a twofold increased risk of CV death, whilst post-challenge hyperglycaemia, but not IGT, remained associated with a nearly
twofold higher mortality risk from infectious disease (Table 4). Including the various glucose variables into model 3 had minimal effect on overall and CV mortality with an increase in c-statistic of less than 0.01 (data not shown).

Of the 184 recipients with new-onset PTDM diagnosed from an OGTT, 92 (50%) were diagnosed from an fPG ≥ 7.0 mmol/l and an equal number of patients were diagnosed from an isolated 2hPG ≥ 11.1 mmol/l (n = 92), whereas 63 (34%) patients fulfilled both the criteria. Mean fPG for recipients with an isolated 2hPG ≥ 11.1 mmol/l was 5.9 (0.69) mmol/l. Compared with recipients without PTDM, the multi-adjusted HRs of recipients diagnosed from fPG ≥ 7.0 mmol/l and 2hPG ≥ 11.1 mmol/l were 1.49 (95% CI 1.00, 2.23) and 1.22 (0.80, 1.86).

### Discussion

The main finding of this large single-centre study of renal transplant recipients was that as a predictor of long-term mortality, post-challenge 2hPG measured early after renal transplantation was superior to, and independent of, fPG, even after adjustments for confounding risk factors. Each 1 mmol/l increment in 2hPG was associated with a 5% (95% CI 1%, 9%) increased risk of death from any cause and 6% (95% CI 1%, 12%) increased risk of death from CV

| Characteristic | Total | Post-challenge normoglycaemia (<7.8 mmol/l) | Post-challenge hyperglycaemia (≥7.8 mmol/l) | p value |
|----------------|-------|------------------------------------------|------------------------------------------|---------|
| n (%)          | 1,352 | 863 (64)                                 | 489 (36)                                 | –       |
| Age (years)    | 51 (15)| 49 (15)                                  | 55 (14)                                  | <0.001  |
| Male, n (%)    | 892 (66)| 564 (65)                                 | 328 (67)                                 | 0.550   |
| BMI (kg/m²)    | 24.3 (3.6)| 24.2 (3.5)                              | 24.6 (3.7)                               | 0.062   |
| Obese (BMI ≥30 kg/m²), n (%) | 87 (7) | 51 (6)                                  | 36 (8)                                   | 0.300   |
| Creatinine (μmol/l) | 132 (41) | 129 (36)                              | 137 (47)                                 | 0.002   |
| GFR (ml min⁻¹ 1.73 m⁻²) | 53.7 (14.7)| 54.5 (14.1)                            | 52.0 (15.8)                              | 0.006   |
| Pre-transplant CVD, n (%) | 216 (16) | 116 (13)                                 | 100 (20)                                 | 0.001   |
| Total cholesterol (mmol/l) | 6.53 (1.50)| 6.51 (1.45)                            | 6.57 (1.59)                              | 0.519   |
| HDL-cholesterol (mmol/l) | 1.55 (0.49)| 1.59 (0.49)                            | 1.46 (0.46)                              | <0.001  |
| Triglyceride (mmol/l) | 2.14 (2.17) | 2.03 (2.45)                          | 2.38 (1.43)                              | 0.008   |
| LDL-cholesterol (mmol/l) | 4.02 (1.53)| 4.01 (1.61)                            | 4.05 (1.36)                              | 0.657   |
| Hypertension, n (%) | 745 (83) | 487 (84)                                 | 258 (83)                                 | 0.925   |
| Active or former smoker, n (%) | 603 (61) | 393 (57)                                 | 210 (69)                                 | 0.001   |
| Deceased donor, n (%) | 745 (55) | 427 (50)                                 | 318 (65)                                 | <0.001  |
| Months on dialysis | 15 (13) | 14 (14)                                  | 15 (11)                                  | 0.578   |
| Pre-emptive transplantation, n (%) | 328 (24) | 214 (25)                                 | 114 (23)                                 | 0.553   |
| CMV infection, n (%) | 740 (55) | 445 (52)                                 | 295 (61)                                 | 0.002   |
| Early rejection, n (%) | 490 (36) | 277 (32)                                 | 213 (44)                                 | <0.001  |
| Prednisone level (mg/day) | 13.1 (5.2) | 12.5 (4.6)                              | 14.3 (6.0)                               | <0.001  |
| Use of ciclosporin A, n (%) | 1,137 (90) | 732 (90)                                 | 405 (90)                                 | 0.768   |
| Cyclosporin A trough level (μg/l) | 219 (76) | 212 (73)                                 | 233 (81)                                 | <0.001  |
| Use of tacrolimus, n (%) | 124 (10) | 78 (10)                                  | 46 (10)                                  | 0.767   |
| Tacrolimus trough level (μg/l) | 9.7 (3.3) | 9.4 (3.3)                                 | 10.2 (3.2)                               | 0.194   |

Data are given as mean (SD) or frequency (%). p values denote differences between groups.

LDL-cholesterol was calculated using Friedewald’s equation.

Pre-emptive transplantation denotes patients who received a kidney transplant before starting dialysis.

Of the 184 recipients with new-onset PTDM diagnosed from an OGTT, 92 (50%) were diagnosed from an fPG ≥ 7.0 mmol/l and an equal number of patients were diagnosed from an isolated 2hPG ≥ 11.1 mmol/l (n = 92), whereas 63 (34%) patients fulfilled both the criteria. Mean fPG for recipients with an isolated 2hPG ≥ 11.1 mmol/l was 5.9 (0.69) mmol/l. Compared with recipients without PTDM, the multi-adjusted HRs of recipients diagnosed from fPG ≥ 7.0 mmol/l and 2hPG ≥ 11.1 mmol/l were 1.49 (95% CI 1.00, 2.23) and 1.22 (0.80, 1.86).
Table 3  HRs estimated by Cox regression analyses for all-cause mortality according to plasma glucose (as categorical or continuous variables)

| Variable                          | Unadjusted HR (95% CI) | Multivariable HR (95% CI) |
|----------------------------------|------------------------|---------------------------|
|                                  |                        | Model 1 | Model 2 | Model 3 |
| Normal glucose tolerance         | 1.00                   | 1.00     | 1.00    | 1.00    |
| Impaired fasting glucose         | 0.74 (0.49, 1.13)      | 0.77 (0.50, 1.17)         | 0.77 (0.51, 1.18) | 0.79 (0.52, 1.23) |
| Impaired glucose tolerance       | 1.78 (1.32, 2.42)*     | 1.43 (1.05, 1.94)*        | 1.42 (1.05, 1.94)* | 1.39 (1.01, 1.91)* |
| Post-transplant diabetes mellitus| 2.03 (1.49, 2.77)*     | 1.51 (1.10, 2.07)*        | 1.54 (1.12, 2.13)* | 1.54 (1.09, 2.17)* |
| p values for trend               | <0.001                 | 0.001    | 0.002   | 0.006   |
| Harrell’s concordance index      | 0.597                  | 0.738    | 0.759   | 0.757   |

Level of 2hPG

| Post-challenge normoglycaemia    | 1.00                   | 1.00     | 1.00    | 1.00    |
| Post-challenge hyperglycaemia    | 1.98 (1.55, 2.54)*     | 1.53 (1.19, 1.97)*        | 1.55 (1.21, 2.00)* | 1.49 (1.15, 1.95)* |
| Harrell’s concordance index      | 0.583                  | 0.737    | 0.755   | 0.759   |

fPG

| fPG (mmol/l)                     | 1.13 (1.03, 1.24)*     | 1.10 (1.00, 1.21)         | 1.12 (1.01, 1.24)* | 1.11 (0.99, 1.24)  |
| Harrell’s concordance index      | 0.538                  | 0.734    | 0.750   | 0.755   |

2hPG

| 2hPG (mmol/l)                    | 1.08 (1.05, 1.12)*     | 1.04 (1.01, 1.08)*        | 1.05 (1.01, 1.09)* | 1.05 (1.01, 1.09)* |
| Harrell’s concordance index      | 0.594                  | 0.742    | 0.754   | 0.757   |

Model 1 is adjusted for age and sex. Model 2 is additionally adjusted for traditional risk factors: BMI; creatinine; pre-transplant CVD; total cholesterol; hypertension; and smoking status. Model 3 is additionally adjusted for transplant-related risk factors: donor status; pre-emptive transplantation; CMV infection; early rejection; and use of ciclosporin A

*p<0.05

Table 4 HR estimated by Cox regression analyses for CV death, death from malignancy and from infectious disease according to plasma glucose (as categorical or continuous variables)

| Variable                          | Unadjusted HR (95% CI) | Multivariable HR (95% CI) (model 3) |
|----------------------------------|------------------------|-------------------------------------|
|                                  |                        | CVD | Malignancy | Infection | CVD | Malignancy | Infection |
| Normal glucose tolerance         | 1.00                   | 1.00 | 1.00       | 1.00             | 1.00 | 1.00             | 1.00             |
| Impaired fasting glucose         | 0.73 (0.37, 1.41)      | 0.94 (0.42, 2.08) | 0.44 (0.16, 1.17) | 0.76 (0.39, 1.49) | 0.97 (0.42, 2.00) | 0.50 (0.18, 1.37) |
| Impaired glucose tolerance       | 1.52 (0.93, 2.50)      | 1.73 (0.92, 3.25) | 1.89 (1.05, 3.41)* | 1.04 (0.62, 1.74) | 1.37 (0.71, 2.64) | 1.75 (0.92, 3.34) |
| Post-transplant diabetes mellitus| 2.72 (1.73, 4.29)*     | 1.80 (0.93, 3.48) | 1.45 (0.75, 2.82) | 1.80 (1.10, 2.96)* | 1.36 (0.65, 2.83) | 1.37 (0.66, 2.86) |
| p values for trend               | <0.001                 | 0.138 | 0.011     | 0.023             | 0.687 | 0.055             |
| Harrell’s concordance index      | 0.627                  | 0.572 | 0.595     | 0.782             | 0.736 | 0.816             |

Level of 2hPG

| Post-challenge normoglycaemia    | 1.00                   | 1.00 | 1.00       | 1.00             |
| Post-challenge hyperglycaemia    | 2.00 (1.36, 2.93)*     | 1.79 (1.07, 2.97)* | 2.07 (1.24, 3.46)* | 1.34 (0.89, 2.00) | 1.34 (0.78, 2.30) | 1.91 (1.09, 3.33)* |
| Harrell’s concordance index      | 0.593                  | 0.572 | 0.568     | 0.779             | 0.738 | 0.817             |

fPG

| fPG (mmol/l)                     | 1.21 (1.06, 1.37)*     | 1.17 (0.98, 1.40) | 0.95 (0.75, 1.20) | 1.19 (1.01, 1.39)* | 1.16 (0.94, 1.44) | 0.95 (0.73, 1.24) |
| Harrell’s concordance index      | 0.562                  | 0.557 | 0.512     | 0.777             | 0.732 | 0.810             |

2hPG

| 2hPG (mmol/l)                    | 1.11 (1.06, 1.16)*     | 1.05 (0.98, 1.13) | 1.06 (1.00, 1.14) | 1.06 (1.01, 1.12)* | 1.01 (0.93, 1.09) | 1.05 (0.97, 1.14) |
| Harrell’s concordance index      | 0.626                  | 0.573 | 0.556     | 0.780             | 0.734 | 0.813             |

Model 3 is adjusted for age, sex, BMI, creatinine, pre-transplant CVD, total cholesterol, hypertension, smoking status, donor status, pre-emptive transplantation, CMV infection, early rejection and use of ciclosporin A

*p<0.05
In addition, our findings are the first to indicate that renal transplant recipients with IGT have lower long-term chance of survival than those with NGT.

**Glucose measurements as continuous variables** This study demonstrates an independent continuous relationship between 2hPG and long-term mortality in a renal transplant population without known diabetes. These findings are in accordance with two previous community-based cohort studies of non-diabetic persons of comparable age [6, 29]. Our results also partly support the findings from a population-based prospective cohort of more than 10,000 adult men and women in a continuous positive relationship between non-diabetic hyperglycaemia and mortality [30]. In our study the association between fPG and mortality became statistically non-significant after adjustments for transplant-related risk factors. Some studies have reported a J-shaped relationship between fPG and mortality, whereas a linear relationship best described the association between 2hPG and overall and CV mortality [30, 31]. We cannot completely rule out the possibility that a non-linear relationship between fPG and mortality might have influenced the Cox proportional hazard risk. However, by fitting our models using multifractional models, no non-linear model outperformed a standard linear model in our sets of data.

**Post-challenge hyperglycaemia and glucose categories** Recipients with post-challenge hyperglycaemia, PTDM and IGT had an increased overall mortality risk. Our findings confirm the results of two large cohort studies that demonstrated that PTDM, diagnosed by Medicare claims or required treatment for hyperglycaemia, is associated with reduced patient survival [8, 10]. We now extend this conclusion to PTDM diagnosed by fasting glucose as well as to PTDM and IGT diagnosed by an OGTT.

Our findings also concur with those from two large meta-analyses addressing the impact of IFG and IGT on mortality in non-transplant European populations that found that IGT is superior to IFG in predicting all-cause and CV mortality and from five Asian populations that found that IGT but not IFG was associated with all-cause and CV mortality [7, 32]. In contrast to the latter analysis, we diagnosed patients with isolated IFG (fPG of 5.6–6.9 mmol/l) (excluding concomitant IGT), which might have reduced the mortality risk in this group. Nevertheless, IFG was not associated with death after the inclusion of all recipients with an fPG of 5.6–6.9 mmol/l in the present study (data not shown).

In further contrast with our study, the previous studies implemented the criteria of the WHO for IFG (fPG 6.1–6.9 mmol/l) [33]. However, our results were largely unchanged when we reclassified the glucose categories according to the WHO criteria (data not shown). Partly in contrast with our findings, one large Australian prospective study showed that both isolated IFG (WHO criteria) and IGT were independent predictors of all-cause and CV mortality [34]. Our findings indicate persons with increased risk of death, but do not necessarily imply that lowering of glucose excursions would reduce this risk. In a recently published study of non-transplanted persons with IGT and either established CVD or known risk factors for CVD, a 5-year period of treatment with nateglinide did not influence the incidence of CVD. In this study, however, the participants had a lower mortality risk as compared with a transplant population.

Whether glucose-lowering therapy in renal transplant recipients with either IGT or PTDM is associated with lower long-term morbidity or mortality remains to be shown.

In the cause-specific analysis, PTDM was associated with increased mortality from CVD whilst post-challenge hyperglycaemia predicted increased mortality from infectious disease. The reduction in deaths from infectious disease is considered one of the major improvements in short-term mortality outcome after renal transplantation during the recent decades, and the predominant cause of infection beyond 6 months post-transplant is bacterial rather than viral [1]. In the present study, 90% of the infectious deaths were caused by either bacterial pneumonia or sepsis. However, our study has shown a possible relationship between post-challenge hyperglycaemia and long-term mortality from infectious diseases needs verification and should be interpreted with care.

**Strengths and limitations** The inclusion of a large number of consecutively included non-diabetic renal transplant recipients at the single transplant centre in Norway reduced the possibility of sample selection bias and increased the internal validity of the study. Only 10% of the eligible patients were unable to participate. The study population...
consisted predominantly of white individuals, and thus the results cannot be extended to populations of other ethnicities. However, comparable results for PTDM have been reported in two other studies that included individuals of multiple races and ethnicities [8, 10].

The OGTT has poor reproducibility and a repeated test diagnostic of diabetes is recommended by the current guidelines [20]. However, according to the WHO an epidemiological diagnosis of diabetes can be based on a single OGTT or fPG [35]. Furthermore, although the OGTT is more time consuming and has a higher intraindividual coefficient of variance compared with fasting plasma glucose, it is a more sensitive test for diagnosing PTDM and IGT after renal transplantation [13, 36].

To account for missing data on hypertension (32%), smoking status (27%) and total cholesterol (10%), we performed ten iterations of multiple imputations. Also, the prognostic effect of 2hPG on overall mortality was attenuated after adjustment for age and sex, but was largely unchanged after further adjustments for both traditional and transplant-related risk factors. Thus, the imputed covariates contributed little to the prognostic effect of early post-transplant glucose levels on long-term mortality.

The estimated outcomes coincided with the observed mortality in this study (multi-adjusted c-statistics: all-cause >75% and CV mortality >77%). The additional effect of including the various glucose variables in the multi-adjusted models was, however, minimal. Nevertheless, early post-transplant glycaemia remained an independent predictor of both all-cause and CV mortality.

We used fPG and 2hPG as diagnostic criteria for diabetes without including the recently introduced ADA criteria of HbA1c ≥6.5% [20]. The diagnostic value of HbA1c in patients with end-stage renal disease awaiting renal transplantation is poor, possibly because of uraemia, usage of erythropoietin and dialysis [37]. In the early post-transplant period haemoglobin levels stabilise and normalised levels of erythropoietin and haematocrit have been reported as early as 2 months post-transplant [38]. However, blood loss related to surgical procedures and subsequent inflammation, immunosuppressant agents causing bone marrow suppression and abrupt cessation of erythropoietin are among the factors that may affect HbA1c levels early after kidney transplantation [38]. The usage of HbA1c as a diagnostic criterion might therefore not apply in the early post-transplant period.

Conclusions

This study indicates that 2hPG, when measured early after renal transplantation, is superior to fPG in predicting long-term all-cause and CV mortality. It also demonstrates that PTDM predicts both all-cause and CV mortality, whereas IGT predicts all-cause, but not CV mortality and finally that post-challenge hyperglycaemia predicts all-cause mortality and death from infectious disease. Post-challenge hyperglycaemia may be a predictor of long-term outcome in renal transplant patients, and an OGTT might provide a method to identify renal transplant recipients with increased risk of premature death.

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