Diabetologia
DOI 10.1007/s00125-011-2105-9

ARTICLE

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

T. G. Valderhaug · J. Hjelmesæth · A. Hartmann · J. Røislien · H. A. Bergrem · T. Leivestad · P. D. Line · T. Jenssen

Received: 18 October 2010 / Accepted: 7 February 2011

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-

T. G. Valderhaug and J. Hjelmesæth contributed equally to this study.

T. G. Valderhaug · A. Hartmann · H. A. Bergrem · T. Jenssen
Section for Nephrology, Department for Organ Transplantation, Gastroenterology and Nephrology,
Division for Specialized Medicine and Surgery,
Oslo University Hospital, Rikshospitalet,
Oslo, Norway

T. G. Valderhaug · A. Hartmann
Institute of Clinical Medicine,
Faculty Division Rikshospitalet,
University of Oslo,
Oslo, Norway

T. G. Valderhaug (✉)
Department of Thoracic and Cardiovascular Surgery,
Oslo University Hospital, Rikshospitalet,
Sognsvannsveien 20,
0027 Oslo, Norway
e-mail: t.g.valderhaug@medisin.uio.no

J. Hjelmesæth · J. Røislien
Morbid Obesity Centre,
Vestfold Hospital Trust,
Tønsberg, Norway

J. Røislien
Department of Biostatistics,
Institute of Basic Medical Science,
University of Oslo,
Oslo, Norway

T. Leivestad
Institute of Immunology,
Oslo University Hospital, Rikshospitalet,
Oslo, Norway

P. D. Line
Section for Transplantation Surgery,
Department for Organ Transplantation,
Gastroenterology and Nephrology,
Division for Specialized Medicine and Surgery,
Oslo University Hospital, Rikshospitalet,
Oslo, Norway

T. Jenssen
Institute of Clinical Medicine,
University of Tromsø,
Tromsø, Norway

Published online: 16 March 2011

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]

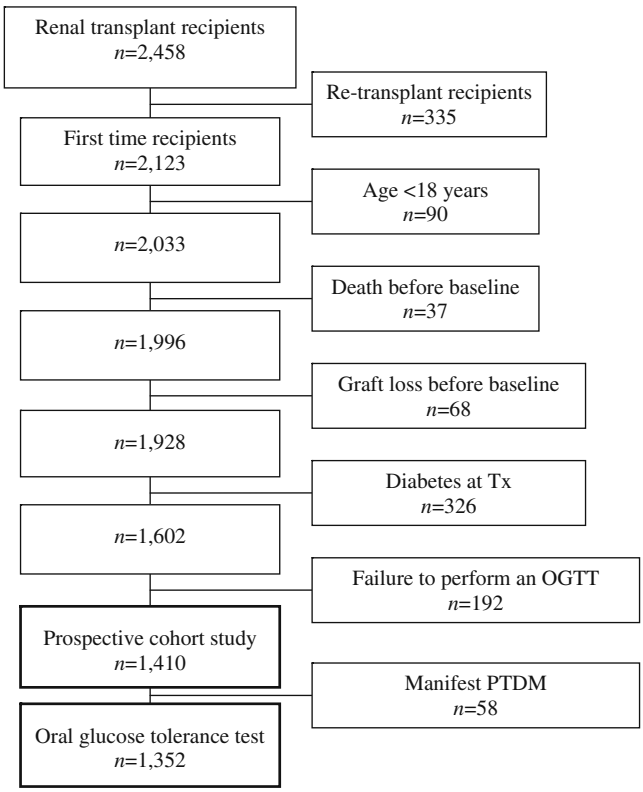

Fig. 1 The number of patients receiving their first kidney transplant without pre-existing diabetes mellitus at the time of transplantation (Tx). Re-transplant recipients were excluded. Failure to perform an OGTT denotes patients who were transferred to local hospitals before the scheduled OGTT at baseline 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 OGGT

days) after renal transplantation. The participants gave informed consent and the study was approved by the regional ethics committee and was performed in accordance with the Declaration of Helsinki [17].

Glucose measurements The OGTT was performed after an overnight fast with patients instructed not to eat or drink, to refrain from smoking and not to take any medication less than 8 h before the test. Each patient drank 75 g of anhydrous glucose dissolved in 250 ml of water. Blood samples were drawn at 0 and 120 min. From May 1995 to August 1996, glucose was measured in serum using a glucose dehydrogenase method (Cobas Mira, Roche, Basel, Switzerland). From September 1996 until December 2006 venous whole blood glucose was measured using the Hemocue AB B-glucose Analyzer, Angelholm, Sweden. The glucose measurements are presented as plasma (serum) glucose [18]. Plasma glucose was calculated by multiplying whole blood glucose with the constant factor of 1.11 [19].

Assessment of diabetes and glycaemia The current ADA criteria were used to classify patients into the following glucose categories: PTDM, fPG ≥7.0 mmol/l or 2hPG ≥11.1 mmol/l; IFG, fPG 5.6–6.9 mmol/l and 2hPG <7.8 mmol/l; IGT, fPG <7.0 mmol/l and 2hPG 7.8–11.0 mmol/l; and normal glucose tolerance (NGT), fPG <5.6 mmol/l and 2hPG <7.8 mmol/l [20]. Patients were also categorised as either post-challenge hyperglycaemia defined as a 2hPG ≥7.8 mmol/l or normoglycaemia defined as a 2hPG <7.8 mmol/l [20].

Immunosuppressive therapy Our immunosuppressive protocol has been described previously [13]. In summary, the standard protocol from February 1995 to January 2000 consisted of prednisolone, ciclosporin A, azathioprine, and thereafter the protocol included prednisolone, ciclosporin A 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 data were collected 10 weeks after renal transplantation: recipient age, sex, BMI, fPG, 2hPG, HbA_{1c}, serum creatinine, Cr-EDTA-measured glomerular filtration rate, serum lipids and immunosuppressive medication. Friedewald's equation was used to calculate LDL-cholesterol. We searched the Norwegian Renal Registry [21] and the DataCor database [22] to identify patients with pre-transplant CVD. Patients were classified as having pre-transplant CVD if they had: suffered a CV event (myocardial infarction, angina pectoris, stroke/transient ischaemic attack or claudication); or had undergone a revascularisation procedure (percutaneous coronary intervention or coronary artery bypass graft surgery) or surgery on pre-cerebral arteries or for peripheral vascular disease. Data on smoking habits, pre-transplant renal status and hypertension were collected from the Norwegian Renal Registry [21]. According to National Kidney Foundation Disease Outcome Quality guidelines, hypertension was defined if patients were using anti-hypertensive therapy within the first post-transplant year or had a systolic blood pressure ≥140 mmHg or a diastolic blood pressure ≥90 mmHg. Patients who did not receive pre-transplant dialysis were encoded as pre-emptive transplantation. Early cytomegalovirus (CMV) infection was diagnosed in patients with at least one positive test for either CMV-pp65 antigen in leucocytes or CMV-PCR in plasma before baseline [23].

The study outcomes were all-cause and cause-specific mortality after renal transplantation as defined by the European Renal Association–European Dialysis and Transplant Association causes of death codes: CV 11–18 and 21–29; infection 31–43; malignancy 66–67; other diagnoses (43–46, 51–53, 61–64, 69–73, 81–82); and unknown (0) [24]. Nephrologists at 24 centres annually report data on all Norwegian patients undergoing renal replacement therapy to the Norwegian Renal Registry [21], from which numbers and causes of deaths were retrieved. The numbers of death were cross-checked with the official Norwegian National Registry and the causes of death were encoded by experienced local nephrologists.

Missing data Some variables in the data set had missing data: hypertension (32%), smoking status (27%), total cholesterol (10%), height (3%), weight (3%), creatinine (3%) and CMV infection (1%). To compensate for missing data, multiple imputation was used to generate ten iterations for the variables with missing data, each containing 1,410 complete cases [25]. Both complete and incomplete 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, HbA_{1c}, 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 multifractional 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

Table 1 Baseline characteristics of the study population according to post-challenge glycaemia

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/m^2)	24.3 (3.6)	24.2 (3.5)	24.6 (3.7)	0.062
Obese (BMI ≥30 kg/m^2), *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
Triacylglycerol (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
Prednisolone dose (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
Ciclosporin 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

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).

Table 2 Unadjusted HR risk estimates by Cox proportional regression analyses for all-cause and CV mortality

Variable	Overall mortality HR (95% CI)	CV mortality HR (95% CI)
Age (years)	1.06 (1.05, 1.07)	1.07 (1.06, 1.09)
Male	1.31 (1.01, 1.69)	1.66 (1.09, 2.52)
BMI (kg/m^2)	0.97 (0.94, 1.01)	1.01 (0.96, 1.06)
Creatinine (μmol/l)	1.00 (1.00, 1.01)	1.01 (1.00, 1.01)
Pre-transplant CVD	2.07 (1.59, 2.71)	2.56 (1.73, 3.79)
Total cholesterol (mmol/l)	1.01 (0.92, 1.10)	0.96 (0.84, 1.09)
Hypertension	0.66 (0.48, 0.92)	0.88 (0.46, 1.67)
Active or former smoker	1.17 (0.79, 1.74)	1.28 (0.71, 2.32)
Deceased donor	2.39 (1.83, 3.12)	2.77 (1.82, 4.23)
Pre-emptive transplantation	0.62 (0.46, 0.84)	0.58 (0.36, 0.93)
CMV infection	1.62 (1.26, 2.07)	1.91 (1.29, 2.84)
Early rejection	1.02 (0.81, 1.30)	1.31 (0.92, 1.88)
Use of ciclosporin A	1.83 (1.02, 3.27)	1.57 (0.69, 3.58)

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

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
Glucose category				
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
Glucose category						
Normal glucose tolerance	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	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

*$p<0.05$

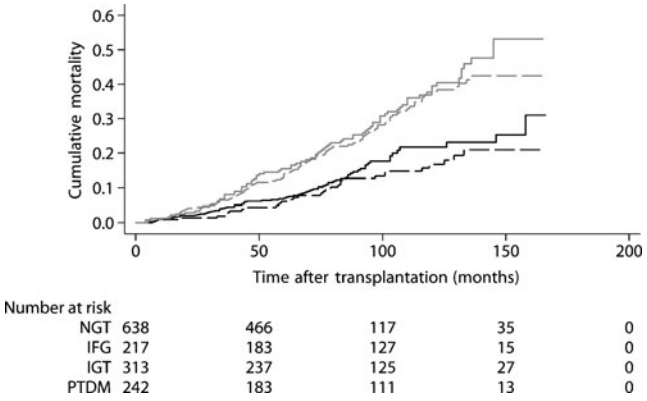

Fig. 2 Cumulative mortality for recipients with NGT (solid black line), IFG (dashed black line), IGT (dashed grey line) and PTDM (solid grey line)

disease. 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 demonstrating 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 as a continuous variable and both overall and CV 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 septicaemia. However, our finding of 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 HbA_{1c} ≥6.5% [20]. The diagnostic value of HbA_{1c} 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 at 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 HbA_{1c} levels early after kidney transplantation [38].The usage of HbA_{1c} 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.

Acknowledgements For their contribution to data we acknowledge the efforts of K. Midtvedt, H. Holdaas and A. Varberg Reisæter at Oslo University Hospital, Rikshospitalet, Section of Nephrology. Thanks are also due to K. Lund, J. Narverud, E. Breistein and J. Stenstrøm at the Laboratory of Renal Physiology for their laboratory assistance and to M. McGee (Morbid Obesity Centre, Vestfold Hospital Trust) for proofreading the manuscript. This study was funded by Oslo University Hospital, Rikshospitalet, Section of Nephrology.

Duality of interest The authors declare there to be no duality of interest associated with this manuscript.

References

1. Briggs JD (2001) Causes of death after renal transplantation. Nephrol Dial Transplant 16:1545–1549
2. Miller LW (2002) Cardiovascular toxicities of immunosuppressive agents. Am J Transplant 2:807–818
3. Kasiske BL, Chakkera HA, Roel J (2000) Explained and unexplained ischemic heart disease risk after renal transplantation. J Am Soc Nephrol 11:1735–1743
4. Levitan EB, Song Y, Ford ES, Liu S (2004) Is nondiabetic hyperglycemia a risk factor for cardiovascular disease? A meta-analysis of prospective studies. Arch Intern Med 164:2147–2155
5. Stattin P, Bjor O, Ferrari P et al (2007) Prospective study of hyperglycemia and cancer risk. Diab Care 30:561–567
6. deVegt F, Dekker JM, Ruhe HG et al (1999) Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. Diabetologia 42:926–931
7. DECODE study group (1999) Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. Lancet 354:617–621
8. Kasiske BL, Snyder JJ, Gilbertson D, Matas AJ (2003) Diabetes mellitus after kidney transplantation in the United States. Am J Transplant 3:178–185
9. Revanur VK, Jardine AG, Kingsmore DB, Jaques BC, Hamilton DH, Jindal RM (2001) Influence of diabetes mellitus on patient and graft survival in recipients of kidney transplantation. Clin Transplant 15:89–94
10. Cosio FG, Pesavento TE, Kim S, Osei K, Henry M, Ferguson RM (2002) Patient survival after renal transplantation: IV. Impact of post-transplant diabetes. Kidney Int 62:1440–1446

11. Hjelmesaeth J, Hartmann A, Leivestad T et al (2006) The impact of early-diagnosed new-onset post-transplantation diabetes mellitus on survival and major cardiac events. Kidney Int 69:588–595
12. Miles AM, Sumrani N, Horowitz R et al (1998) Diabetes mellitus after renal transplantation: as deleterious as non-transplant-associated diabetes? Transplantation 65:380–384
13. Valderhaug TG, Jenssen T, Hartmann A et al (2009) Fasting plasma glucose and glycosylated hemoglobin in the screening for diabetes mellitus after renal transplantation. Transplantation 88:429–434
14. DECODE study group (1999) Is fasting glucose sufficient to define diabetes? Epidemiological data from 20 European studies. The DECODE-study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe. Diabetologia 42:647–654
15. Hofso D, Jenssen T, Hager H, Roislien J, Hjelmesaeth J (2010) Fasting plasma glucose in the screening for type 2 diabetes in morbidly obese subjects. Obes Surg 20:302–307
16. Valderhaug TG, Hjelmesaeth J, Rollag H et al (2007) Reduced incidence of new-onset posttransplantation diabetes mellitus during the last decade. Transplantation 84:1125–1130
17. World Medical Association (2000) World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects. JAMA 284:3043–3045
18. Rustad P, Felding P, Franzson L et al (2004) The Nordic Reference Interval Project 2000: recommended reference intervals for 25 common biochemical properties. Scand J Clin Lab Invest 64:271–284
19. D'Orazio P, Burnett RW, Fogh-Andersen N et al (2006) Approved IFCC recommendation on reporting results for blood glucose: International Federation of Clinical Chemistry and Laboratory Medicine Scientific Division, Working Group on Selective Electrodes and Point-of-Care Testing (IFCC-SD-WG-SEPOCT). Clin Chem Lab Med 44:1486–1490
20. American Diabetes Association (2010) Standards of Medical Care in Diabetes 2010. Diab Care 33:S11–S61
21. The Norwegian Renal Registry (2009) The Norwegian Renal Registry. Annual report 2008. Available from: www.nephro.no/nnr/AARSM2008.pdf, accessed 17 Dec 2009
22. Svennevig JL, Bech J, Karlsen H, Amlie E, Olsen A (1995) From a registry to a clinical information system. Development of the Datacor system at the surgery department A, Rikshospitalet. Tidsskr Nor Laegeforen 115:1057–1059, article in Norwegian
23. Rollag H, Sagedal S, Kristiansen KI et al (2002) Cytomegalovirus DNA concentration in plasma predicts development of cytomegalovirus disease in kidney transplant recipients. Clin Microbiol Infect 8:431–434
24. van Dijk PCW, Jager KJ, de Charro F et al (2001) Renal replacement therapy in Europe: the results of a collaborative effort by the ERA-EDTA registry and six national or regional registries. Nephrol Dial Transplant 16:1120–1129
25. Newgard CD, Haukoos JS (2007) Advanced statistics: missing data in clinical research—part 2: multiple imputation. Acad Emerg Med 14:669–678
26. Royston P, Ambler G, Sauerbrei W (1999) The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 28:964–974
27. Harrell FE Jr, Lee KL, Mark DB (1996) Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 15:361–387
28. Pencina MJ, D'Agostino RB (2004) Overall C as a measure of discrimination in survival analysis: model specific population value and confidence interval estimation. Stat Med 23:2109–2123
29. Metter EJ, Windham BG, Maggio M et al (2008) Glucose and insulin measurements from the oral glucose tolerance test and mortality prediction. Diab Care 31:1026–1030
30. Barr EL, Boyko EJ, Zimmet PZ, Wolfe R, Tonkin AM, Shaw JE (2009) Continuous relationships between non-diabetic hyperglycaemia and both cardiovascular disease and all-cause mortality: the Australian Diabetes, Obesity, and Lifestyle (AusDiab) study. Diabetologia 52:415–424
31. Sarwar N, Gao P, Seshasai SR et al (2010) Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet 375:2215–2222
32. Nakagami T (2004) Hyperglycaemia and mortality from all causes and from cardiovascular disease in five populations of Asian origin. Diabetologia 47:385–394
33. Department of Noncommunicable Disease Surveillance WHO (1999) Definition, diagnosis and classification of diabetes mellitus and its complications. Report of a WHO consultation. Part 1. Diagnosis and classification of diabetes mellitus. Geneva, World Health Organization. Available from: http://whqlibdoc.who.int/hq/1999/WHO_NCD_NCS_99.2.pdf. Accessed 13 March 2006
34. Barr EL, Zimmet PZ, Welborn TA et al (2007) Risk of cardiovascular and all-cause mortality in individuals with diabetes mellitus, impaired fasting glucose, and impaired glucose tolerance: the Australian Diabetes, Obesity, and Lifestyle Study (AusDiab). Circulation 116:151–157
35. Department of Noncommunicable Disease Management WHO (2003) Screening for type 2 diabetes. Report of a World Health Organization and International Diabetes Federation meeting. Geneva, World Health Organization. Available from: http://whqlibdoc.who.int/hq/2003/WHO_NMH_MNC_03.1.pdf. Accessed 23 June 2010
36. Armstrong KA, Prins JB, Beller EM et al (2006) Should an oral glucose tolerance test be performed routinely in all renal transplant recipients? Clin J Am Soc Nephrol 1:100–108
37. Bergrem HA, Valderhaug TG, Hartmann A et al (2010) Undiagnosed diabetes in kidney transplant candidates: a case-finding strategy. Clin J Am Soc Nephrol 5:616–622
38. Winkelmayer WC, Chandraker A (2008) Pottransplantation anemia: management and rationale. Clin J Am Soc Nephrol 3 (Suppl 2):S49–S55