ORIGINAL ARTICLE

Criteria for prediabetes and posttransplant diabetes mellitus after kidney transplantation: A 2-year diagnostic accuracy study of participants from a randomized controlled trial

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Posttransplant diabetes mellitus (PTDM) and prediabetes (impaired glucose tolerance [IGT] and impaired fasting glucose [IFG]) are associated with cardiovascular events. We assessed the diagnostic performance of fasting plasma glucose (FPG) and HbA$_{1c}$ as alternatives to oral glucose tolerance test (OGTT)-derived 2-hour plasma glucose (2hPG) using sensitivity and specificity in 263 kidney transplant recipients (KTRs) from a clinical trial. Between visits at 6, 12, and 24 months after transplantation, 28%–31% of patients switched glycemic category (normal glucose tolerance [NGT], IGT/IFG, PTDM). Correlations of FPG and HbA$_{1c}$ against 2hPG were lower at 6 months ($r = 0.59$ [FPG against 2hPG]; $r = 0.45$ [HbA$_{1c}$ against 2hPG]) vs. 24 months ($r = 0.73$ [FPG against 2hPG]; $r = 0.74$ [HbA$_{1c}$ against 2hPG]). Up to 69% of 2hPG-defined PTDM

cases were missed by conventional HbA_{1c} and FPG thresholds. For prediabetes, concordance of FPG and HbA_{1c} with 2hPG ranged from 6%–9%. In conclusion, in our well-defined randomized trial cohort, one-third of KTRs switched glycemic category over 2 years and although the correlations of FPG and HbA_{1c} with 2hPG improved with time, their diagnostic concordance was poor for PTDM and, especially, prediabetes. Considering posttransplant metabolic instability, FPG's and HbA_{1c}'s diagnostic performance, the OGTT remains indispensable to diagnose PTDM and prediabetes after kidney transplantation.

1 | INTRODUCTION

Persistent hyperglycemia after solid-organ transplantation has been recognized as an own diabetes entity[1] and is referred to as posttransplant diabetes mellitus (PTDM). Pathophysiologically, PTDM is linked to glucocorticoids and calcineurin inhibitors, which are required immunosuppressants after transplantation but have diabetogenic properties.[2] Predisposing factors that associate with diabetes in the general population and additional transplant-specific factors add to individual PTDM risk.[3] PTDM has long been underdiagnosed due to a lack of standardized definition or diagnosis,[4] despite its clinical relevance, especially regarding increased risk for cardiovascular events and mortality.[5–7]

At an international PTDM consensus guidelines meeting held in 2003,[8] it was recommended that PTDM be diagnosed with the diabetes criteria established by the American Diabetes Association (ADA)[9] and World Health Organization (WHO).[10] The diagnostic glycemia thresholds for type 2 diabetes in the general population were justified by their association with increased risk for microvascular complication (retinopathy).[11] Glycated hemoglobin (HbA_{1c}) for diabetes diagnosis was recommended in 2008 by an international expert committee,[12] again considering retinopathy. A large study published in 2010 confirmed that HbA_{1c} is also associated with cardiovascular risk.[13]

In contrast to type 2 diabetes, the evidence linking PTDM to microvascular complications is scarce,[14] and retinopathy after transplantation is understudied,[15] as was acknowledged at a subsequent PTDM expert consensus meeting, held in 2014.[16] The pitfalls of using HbA_{1c} in diagnosing PTDM during the early posttransplant phase,[17] and studies assessing HbA_{1c}'s diagnostic accuracy in kidney transplant recipients (KTRs)[18–20] led to the recommendation that the OGTT should be considered the most important diagnostic test.[16] Indeed, not only studies of undiagnosed type 2 diabetes[21,22] and impaired glucose tolerance (IGT)[23] in the general population, but also two studies from KTRs in particular[18,19] observed relatively low sensitivity of fasting plasma glucose (FPG) compared with the OGTT in identifying PTDM. Subsequent to the 2014 PTDM consensus meeting, two additional studies used single measurements of HbA_{1c} in KTRs and found sensitivities of only 38% at 10 weeks[24] and 43% at 1 year[25] after transplant, compared with the OGTT.

However, a meta-analysis investigating type 2 diabetes[26] and the study of KTRs at 10 weeks[18] indicated that lowered thresholds for HbA_{1c} and FPG could be used in the early detection of previously undiagnosed individuals and, ultimately, could reduce the number of OGTTs needed. Indeed, the authors of all previous receiver operating characteristic (ROC) curve analyses[18–20,24,25] have eventually asked the same question: Under which circumstances could FPG and HbA_{1c} be used safely to diagnose PTDM without missing patients at risk? Alternatively, might the diagnostic thresholds have to be altered for this purpose? To arrive at a definite conclusion, we here employed well-characterized participants of a randomized controlled trial[27] to evaluate FPG and HbA_{1c} against the OGTT at 6, 12, and 24 months after transplantation. Our specific aim was to determine the ability of FPG and HbA_{1c} to identify PTDM and posttransplant prediabetes, in view of the fact that IGT and/or impaired fasting glucose (IFG)[6] are also strong predictors of cardiovascular events.

2 | MATERIALS AND METHODS

2.1 | Study participants

KTRs of this post-hoc analysis of a multicenter randomized clinical trial previously participated in the Insulin Therapy for the Prevention of New Onset Diabetes After Transplantation study (ITP-NODAT, ClinicalTrials.gov NCT03507829).[27] In ITP-NODAT, individuals were randomized into two groups before transplantation. Participants allocated to the intervention group had received capillary blood glucose measurements and intermediate-acting insulin isophane therapy for afternoon glucose surpassing 140 mg/dl (7.8 mmol/L). Standard-of-care participants had been allowed short-acting insulin and sulfonylureas upon discharge. The ITP-NODAT trial was performed from November 21, 2012, through May 22, 2018, at four European transplant centers (Medical University of Vienna, Austria; Medical University of Graz, Austria; Hospital del Mar Barcelona; and Charité Universitätsmedizin Berlin), with 2 years' follow-up for each patient. Of all 263 adult KTRs in ITP-NODAT (all without previously known impairment of glucose metabolism before transplantation, receiving glucocorticoids, mycophenolate acid, and tacrolimus), diagnostic test accuracy was evaluated in 217 participants. These were participants without continuous glucose-lowering treatment and

who had OGTT and HbA_{1c} data available at 6, 12, and 24 months. All ITP-NODAT trial participants provided written informed consent following approval from the institutional review board at each participating center. Approval for the present retrospective analysis of ITP-NODAT trial data was additionally obtained from the ethics committee of the Medical University of Vienna (EK 1611/2020 [protocol and ethics vote available from the authors upon request]).

2.2 │ Laboratory measurements and definitions

For the evaluation of PTDM during the ITP-NODAT trial, three OGTTs and HbA_{1c} measurements had been scheduled at months 6, 12, and 24 after transplantation for all participants. As part of the previous clinical trial, the results of the OGTT at month 6 were blinded to study participants and study investigators and were revealed only in the final analysis. OGTTs were performed using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water, as described by the WHO.[28] Plasma samples before glucose intake and after 2 h were separated promptly from whole blood and stored at −80°C for the subsequent study-related measurements at the central laboratory site (Medical University of Vienna).

Glucose was assessed by the hexokinase method, and HbA_{1c} was assessed by high-performance liquid chromatography separation of hemoglobin fractions.[29] OGTTs and HbA_{1c} measurements were obtained at the day of the study visit and were not available to the performers of the tests. Missing OGTT or HbA_{1c} data led to exclusion of the patient for the respective time point. An independent investigator assessed the conclusiveness of the test results (e.g., whether unphysiological glucose values existed), during the data extraction process of the original study.

We used ADA criteria[1] and defined OGTT-derived 2hPG ≥200 mg/dl (11.1 mmol/L) as PTDM and 140–199 mg/dl (7.8–11.0 mmol/L) as IGT in the absence of glucose-lowering treatment (reference standard). PTDM can also be defined by FPG during an OGTT, and the combined FPG and 2hPG criteria are in this paper referred to as *plasma glucose criteria* to diagnose PTDM. FPG and HbA_{1c} were evaluated as index tests, and besides $HbA_{1c} ≥ 6.5\%$ (48 mmol/mol) and FPG ≥ 126 mg/dl (7.0 mmol/L), a previously proposed, lowered screening threshold for HbA_{1c} of 6.2% (44 mmol/mol) and a combined screening criterion (FPG ≥ 126 mg/dl [7.0 mmol/L] and/or $HbA_{1c} ≥ 6.5\%$ [48 mmol/mol])[24] were assessed. Apart from PTDM, we evaluated thresholds for increased diabetes risk using ADA criteria for *prediabetes*, on the basis that IGT[5] as well as IGT and/or IFG pose specific risk factors after transplantation.[6] In the general population, IGT and IFG have also been shown to be characterized by distinct metabolic characteristics.[30] HbA_{1c} was not added as a reference criterion for prediabetes because, to our knowledge, HbA_{1c} 5.7%–6.4% (39–47 mmol/mol) has not been linked to cardiovascular events after transplantation[6] and was only evaluated as an index test, in contrast to IGT and IFG. The diagnostic accuracy of FPG 100–125 mg/dl (5.6–6.9 mmol/L) and HbA_{1c} 5.7%–6.4% (39–47 mmol/mol)[1] were

therefore assessed in the absence of PTDM and compared with the OGTT-derived diagnosis of IGT and IGT and/or IFG.

Using these cut-offs, we longitudinally evaluated HbA_{1c} and FPG as index tests intended for use in diagnosis and screening and as a potential replacement for OGTT.

2.3 │ Statistical analyses

Categorical outcomes were described using frequencies and proportions, while continuous variables were described using means ± standard deviations (SDs) or medians and interquartile ranges (IQR) when appropriate. Group differences were evaluated using 95% confidence intervals, and p-values were reported according to two-tailed analysis and considered statistically significant when <.05. Linear correlations among FPG, HbA_{1c}, and 2hPG were reported using Pearson's r. Classifier performance was assessed by the area under the curve (AUC) obtained by ROC curve analysis, and exploratory cut-off points were identified for clinical application. For the diagnosis of IGT and IGT and/or IFG, the ordinal variables were dichotomized by excluding patients with diabetes. Area-proportional Venn diagrams were drawn using eulerAPE_3.0.0.[31] Calculations were performed using Microsoft Excel 2020 for macOS (Microsoft Corporation), IBM SPSS Statistics for macOS Version 26.0 (IBM), and R 4.0.3 (R Core Team, 2020).

We used the Standards for the Reporting of Diagnostic Accuracy Studies (STARD) statement to ensure completeness of reporting[32](Appendix S1).

3 │ RESULTS

3.1 │ Characteristics of the trial participants

Detailed information on the patient flow of 263 KTRs leading to the study population is provided in Figure S1. After omitting participants with continuous glucose-lowering medication or missing OGTT and HbA_{1c} data, diagnostic accuracy was analyzed in $n = 217$ participants ($n = 188$ participants at month 6, $n = 183$ at month 12, and $n = 163$ at month 24). The clinical and transplant-specific characteristics of the trial participants at baseline are reported in Table 1. Steroid doses decreased from month 6 until month 24 (mean 5.2 mg vs. 4.0 mg prednisone per day in paired observations, $p < .001$).

3.2 │ Evolution of posttransplant diabetes mellitus

The evolution of PTDM defined by the glucose-lowering medication or OGTT (*plasma glucose criteria*) of the clinical trial population is provided in Figure 1A, and detailed classification is provided in Figure S2. PTDM was present in $n = 43$ (19.5%), $n = 34$ (16.1%), and $n = 33$ (18.1%) participants, and IGT and/or IFG was present in $n = 71$ (32.3%), $n = 65$ (30.8%), and $n = 58$ (31.9%) participants at months

TABLE 1 Participant characteristics at baseline

Characteristics	All (n = 263)	Study population (n = 217)
Demographic and metabolic characteristics		
Female, n (%)	100 (39.8)	85 (39.5)
Age, years	53.0 (40.0–61.0)	51.0 (39.3–60.0)
≥60 years, n (%)	76 (30.0)	55 (25.5)
BMI, kg/m^2	25.2 (22.1–29.1)	25.2 (22.1–28.4)
≥30 kg/m^2, n (%)	48 (20.6)	37 (18.7)
Plasma glucose, mg/dl	94 (84–110)	93 (84–106)
Plasma glucose, mmol/L	5.2 (4.7–6.1)	5.2 (4.7–5.9)
≥100 mg/dl (5.6 mmol/mol), n (%)	90 (37.0)	70 (33.5)
NGSP HbA$_{1c}$, %	5.2 (4.9–5.5)	5.1 (4.8–5.4)
IFCC HbA$_{1c}$, mmol/mol	33.3 (30–36.6)	32.2 (29–35.5)
≥5.7% (39 mmol/mol), n (%)	36 (15.7)	27 (13.8)
Pre-transplant history		
Primary kidney disease		
Glomerular disease, n (%)	91 (39.4)	79 (40.5)
Vascular disease, n (%)	29 (12.6)	25 (12.8)
Tubulointerstitial disease, n (%)	16 (6.9)	16 (8.2)
Polycystic disease, n (%)	39 (16.9)	28 (14.4)
Unknown, n (%)	53 (22.9)	44 (22.6)
Other primary disease, n (%)	3 (1.3)	3 (1.5)
Family history of diabetes, n (%)	38 (18.7)	32 (18.5)
Chronic hepatitis C, n (%)	3 (1.2)	3 (1.4)
CMV antibody positive, n (%)	171 (69.0)	147 (69.3)
Transplantation information		
Living donor, n (%)	53 (21.2)	49 (22.8)
Graft number		
First, n (%)	218 (82.9)	187 (86.2)
Second, n (%)	32 (12.2)	26 (12.0)
More than two, n (%)	3 (1.2)	3 (1.4)
CMV high risk, n (%)	42 (17.0)	33 (15.6)
PRA highest ≥ 10%, n (%)	26 (11.8)	22 (11.7)
Immunosuppression early after transplantation		
Tacrolimus, n (%)	254 (100.0)	217 (100.0)
Mycophenolate mofetil, n (%)	120 (50.2)	102 (50.2)
Mycophenolic sodium, n (%)	119 (49.8)	101 (49.8)
Glucocorticosteroid, n (%)	253 (100.0)	216 (100.0)

Note: Values are presented as median (interquartile range) or number (percent). Missing entries early after transplantation were excluded, therefore percentages of immunosuppression are slightly deviating from the original publication, where percentages refer to 263 participants.

Abbreviations: BMI, body mass index; CMV, cytomegalovirus; IFCC, International Federation of Clinical Chemistry and Laboratory Medicine; KTR, kidney transplant recipients; NGSP, National Glycohemoglobin Standardization Program; PRA, panel reactive antibody.

6, 12, and 24, respectively. Between visits at 6, 12, and 24 months after transplantation, 28%–31% of patients switched glycemic category (normal glucose tolerance [NGT], IGT/IFG, PTDM). Specifically, n = 11 (28.2%) and n = 5 (17.2%) participants with PTDM improved their glucose metabolism while, conversely, n = 4 (2.5%) and n = 9 (6.0%) participants without diabetes developed PTDM after months 6 and 12. Among trial participants without PTDM at month 6 who were classified as having PTDM at months 12 and 24, the majority had both IGT and IFG at the previous month-6 visit (n = 3 [75.0%] and n = 7 [77.8%] individuals at months 12 and 24, respectively).

Among trial participants without PTDM at month 12 who developed PTDM at month 24, $n = 5$ (55.6%) had both IGT and IFG at month 12. Two participants (2.2%) developed PTDM after having normal glucose tolerance at month 12. When we compared male and female KTRs at 6–24 months, women more often than men had PTDM defined by 2hPG and PTDM in the absence of glucose-lowering medication. Specifically, at month 12, 4 (57.1%) men versus 9 (100.0%) women had diabetic 2hPG ($p = .06$) and 18 (51.4%) men versus 21 (70%) women had IGT in the group of individuals with prediabetes ($p = .13$). There were 7 (35.0%) men versus 9 (64.3%) women who had PTDM in the absence of glucose-lowering medication at month 12 ($p = .09$) (Figure S3).

3.3 | Diagnostic criteria for posttransplant diabetes mellitus and prediabetes

Diagnostic criteria were not perfectly concordant (Figure 1 panels B), showing that over the course of 24 months up to 69% of transplanted patients with PTDM (defined by 2hPG) remained below the diagnostic thresholds of FPG or HbA$_{1c}$. The sensitivity of HbA$_{1c}$ and FPG criteria identifying PTDM defined by 2hPG (Table 2) or by *plasma glucose criteria* (Table S4) increased through 24 months. Still, at month 24, 20% of ITP-NODAT trial participants with PTDM (defined by 2hPG) would have been missed without an OGTT.

IGT, IFG, and HbA$_{1c}$ 5.7%–6.4% (39 mmol/mol) were more inhomogeneous than diabetes criteria. Over the course of 24 months, concordance between FPG, HbA$_{1c}$, and 2hPG ranged from 6% to 9% (Figure 1) and up to 33% of IGT would have been missed in the absence of an OGTT (Table 2). At month 24, HbA$_{1c}$ ≥5.7% (39 mmol/mol) identified 55% of individuals with IGT, with a positive predictive value (PPV) of 0.42.

3.4 | Relationship of fasting plasma glucose and HbA$_{1c}$ versus 2hPG

Scatter plots showing individual values for 2hPG, FPG, and HbA$_{1c}$ and their corresponding Pearson correlation coefficients are provided in Figure 2. The correlation between HbA$_{1c}$ and 2hPG improved considerably from month 6 to month 24 after transplant ($r = 0.45$ [95% confidence interval 0.31, 0.56] vs. $r = 0.74$ [0.60, 0.82]). We also observed that in patients with PTDM, median 2hPG, HbA$_{1c}$, and FPG results increased over time (Table S5). Reflecting the correlation coefficients, the discriminatory power (area under the curve [AUC, 95% CI]) of FPG and HbA$_{1c}$ were also lowest in month 6 for both HbA$_{1c}$ (0.85 [0.77, 0.93]) and FPG (0.89 [0.82, 0.96]), and both tests improved until month 24, but their 95% CIs indicated no statistically significant difference (Table S6).

The predictive strength for IGT and IGT/IFG were similarly low at each time point and FPG was generally better than HbA$_{1c}$. However, the AUC of HbA$_{1c}$ identifying IGT increased at month 24.

Lowered HbA$_{1c}$ and FPG diabetes thresholds for screening purposes derived by ROC curve analysis are provided in Table S7. HbA$_{1c}$ ≤5.5% (37 mmol/mol) and FPG ≤95 mg/dl (5.3 mmol/L) always ruled out PTDM (defined by 2hPG). The sensitivity and specificity of HbA$_{1c}$ ≥6.2% (44 mmol/mol) are provided in Table S8.

4 | DISCUSSION

We observed metabolic instability in the extended posttransplant period and persistently decreased diagnostic performance of single FPG and HbA$_{1c}$ measurements. These findings imply that the OGTT remains the most important diagnostic test after kidney transplantation. Our results may be applied to populations of White individuals without a history of diabetes before transplantation.

The proportion of individuals with 2hPG-defined PTDM not reaching the diagnostic thresholds of FPG or HbA$_{1c}$ ranged from 20% to 69%. In line, Ussif et al. identified 26% of patients with PTDM by 2hPG only, and not by FPG, at 1 year after transplant in a large study cohort.[25] The proportion of PTDM (10% vs. 8%) and the sensitivity of HbA$_{1c}$ ≥6.5% in identifying PTDM (43% vs. 50%) were similar to our findings.[25] Other studies investigating month 12 had considerably lower sample sizes and HbA$_{1c}$ showed sensitivities ≤50%.[20,33] These findings indicate that FPG and HbA$_{1c}$ are not optimal replacements for the OGTT to diagnose PTDM. However, it should be noted that the proportion of patients with PTDM, identified by FPG alone, is also not small, and that those individuals with isolated 2hPG ≥200 mg/dl (≥11.1 mmol/L) are more likely to revert to prediabetes.[34]

Recent studies showed that IGT and prediabetes are not only intermediate stages in the transition to PTDM, but specific risk factor for adverse outcomes such as cardiovascular disease[6] and death.[5] These studies go against previous efforts that sought a replacement for the OGTT. In fact, Valderhaug et al.[5] found evidence that 2hPG is superior for the prediction of death, compared to FPG. For the general population the DECODE[35] and DECODA[36] trials, as well as a previous meta-analysis of 20 studies[37] also showed that IGT is a stronger predictor for death and cardiovascular disease than IFG. Individuals with HbA$_{1c}$ measurements just below the diabetes threshold might even represent a population with exceptionally high cardiovascular risk compared to those above this threshold.[38] No similar finding correlating HbA$_{1c}$ with adverse outcomes has been shown in transplanted patients. Finally, a recent epidemiological study of type 2 diabetes showed that 2hPG will improve prediction of adverse outcomes in models that include FPG and HbA$_{1c}$.[39]

Another principal finding of the present analysis is that prediabetes and especially IGT may only be identified by an OGTT. Specifically, the concordance of FPG, HbA$_{1c}$, and 2hPG criteria for prediabetes ranged from only 6% to 9% with all three criteria and as many as 45% to 56% of individuals with IGT had an HbA$_{1c}$ value <5.7% (39 mmol/mol). Poor correlation might be why Porrini et al.[6] found no association of HbA$_{1c}$ at 12 months with cardiovascular events in individuals without PTDM, while prediabetes (IGT and/or IFG) was significantly

(A) Classification by OGTT in n = 263 kidney transplant recipients
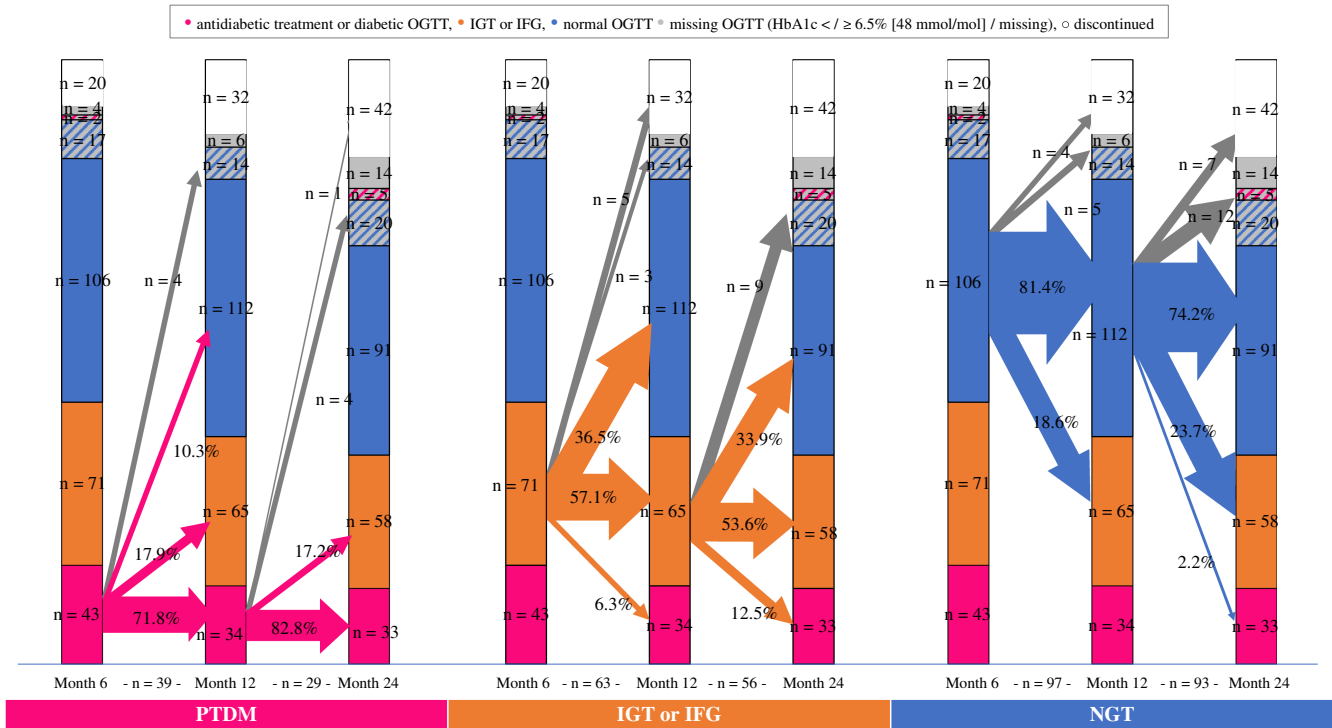
(B) Venn diagrams illustrating the overlap between FPG, 2hPG and HbA1c
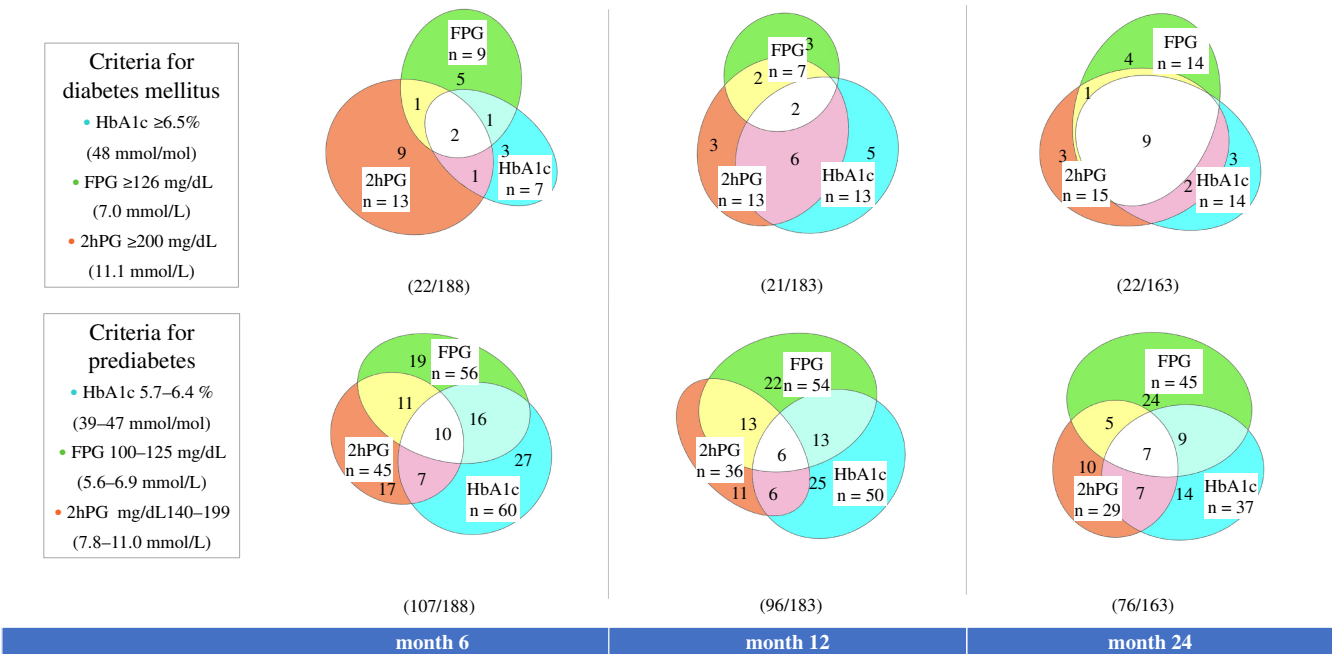
associated. The second, important message regarding prediabetes is, that we observed high metabolic instability and that one in three KTRs switched glycemic category between 6, 12, and 24 months. Similarly, high fluctuations between 3 and 36 months after transplant have been shown by Porrini et al.,[34] which indicates that the OGTT is even more important in the identification of prediabetes in a metabolically unstable period. The practical implication of these findings is, that the OGTT should be repeated, for example, annually, in patients with high risk for PTDM.

Analyzing even more closely those individuals who progressed to PTDM, we could observe that patients with PTDM often had combined IGT + IFG at the previous visit and, although our number of observations was small, these results reflect studies showing that subjects with IGT + IFG have a higher risk of

FIGURE 1 Posttransplant diabetes mellitus evolution and concordance of diabetes criteria. (A) Diabetic status and the metabolic instability after transplantation using oral glucose tolerance testing (OGTT). The size of the crossing arrows is proportional to the number of patients changing category. Proportions of patients within the deriving category changing to another category are displayed on the arrows (excluding missing OGTT or discontinuations, gray arrows). Number of patients from which proportions are derived are below the baseline. Categories arranged from bottom up and divided into subgroups: posttransplant diabetes mellitus (pink, defined by glucose-lowering medication or diabetic OGTT—diabetic 2hPG and/or FPG), prediabetes (IGT and/or IFG, orange), NGT = normal glucose tolerance (blue, normal 2hPG and FPG values). HbA$_{1c}$ measurements in participants with missing OGTT (gray) and with diabetic HbA$_{1c}$ (pink stripes) or normal HbA$_{1c}$ (blue stripes). Discontinuations (white) refer to the clinical trial dropouts (Schwaiger et al.) and not to the study flow in Figure S1. (B) Overlap of HbA$_{1c}$, fasting plasma glucose (FPG), and 2-h plasma glucose (2hPG) diagnostic criteria in participants who had both OGTT and HbA$_{1c}$ data available. Numbers within the categories refer to patient numbers. Diabetes and prediabetes criteria were overlapping in most patients. Therefore, the sum of patients in the upper (diabetes) and lower (prediabetes) diagrams within a group are not equivalent to the total number of patients with diabetes or prediabetes.

**TABLE 2** Diagnostic accuracy of HbA$_{1c}$ and FPG criteria for PTDM and IGT

	TPR (95% CI)	TNR (95% CI)	LR+	PPV	TP	FN	TN	FP
PTDM (2hPG reference)								
FPG ≥ 126 mg/dl (7.0 mmol/L)								
Month 6	0.23 (0.05, 0.54)	0.97 (0.93, 0.99)	6.8	0.34	3	10	169	6
Month 12	0.31 (0.09, 0.61)	0.98 (0.95, 1.00)	17.1	0.57	4	9	167	3
Month 24	0.67 (0.38, 0.88)	0.97 (0.93, 0.99)	24.7	0.71	10	5	144	4
HbA$_{1c}$ ≥ 6.5% (48 mmol/mol)								
Month 6	0.23 (0.05, 0.54)	0.98 (0.94, 0.99)	10.0	0.43	3	10	171	4
Month 12	0.62 (0.32, 0.86)	0.97 (0.93, 0.99)	21.2	0.62	8	5	165	5
Month 24	0.73 (0.45, 0.92)	0.98 (0.94, 1.00)	36.7	0.79	11	4	145	3
FPG ≥ 126 mg/dl (7.0 mmol/L) or HbA$_{1c}$ ≥ 6.5% (48 mmol/mol)								
Month 6	0.31 (0.09, 0.61)	0.95 (0.90, 0.98)	6.0	0.31	4	9	166	9
Month 12	0.77 (0.46, 0.95)	0.95 (0.91, 0.98)	16.4	0.56	10	3	162	8
Month 24	0.80 (0.52, 0.96)	0.95 (0.90, 0.98)	17.0	0.63	12	3	141	7
Impaired glucose tolerance								
≥100 mg/dl (5.6 mmol/L)								
Month 6	0.58 (0.42, 0.72)	0.79 (0.71, 0.86)	2.8	0.49	26	19	103	27
Month 12	0.58 (0.41, 0.74)	0.80 (0.72, 0.86)	2.9	0.44	21	15	107	27
Month 24	0.52 (0.33, 0.71)	0.75 (0.66, 0.82)	2.1	0.33	15	14	89	30
HbA$_{1c}$ ≥ 5.7% (39 mmol/mol)								
Month 6	0.44 (0.30, 0.60)	0.72 (0.64, 0.80)	1.6	0.36	20	25	94	36
Month 12	0.44 (0.28, 0.62)	0.75 (0.66, 0.82)	1.8	0.32	16	20	100	34
Month 24	0.55 (0.36, 0.74)	0.82 (0.73, 0.88)	3.0	0.42	16	13	97	22
FPG ≥ 100 mg/dl (5.6 mmol/L) or HbA$_{1c}$ ≥ 5.7% (39 mmol/mol)								
Month 6	0.67 (0.51, 0.80)	0.60 (0.51, 0.68)	1.7	0.37	30	15	78	52
Month 12	0.78 (0.61, 0.90)	0.63 (0.55, 0.72)	2.1	0.36	28	8	85	49
Month 24	0.69 (0.49, 0.85)	0.63 (0.54, 0.72)	1.9	0.31	20	9	75	44

Note: Reference standard: 2hPG (2-h plasma glucose) derived by an oral glucose tolerance test (OGTT). Exact confidence intervals (95% CI) were based on binomial probabilities. Impaired glucose tolerance (IGT): ordinal variables were dichotomized by excluding individuals with diabetes mellitus defined by 2hPG.

Abbreviations: FN, false negative; FP, false positive; FPG, fasting plasma glucose; HbA$_{1c}$, hemoglobin A$_{1c}$; LR+, positive likelihood ratio (shift from pretest to post-test probability); PPV, positive predictive value (precision); TN, true negative; TNR, true negative rate (without exclusions = specificity); TP, true positive; TPR, true positive rate (without exclusions = sensitivity).

proceeding to type 2 diabetes.[40] Moreover, women were more often identified by isolated 2hPG ≥200 mg/dl (11.1 mmol/L) and isolated IGT than men, but again this finding was limited by the number of observations. In the general population, IGT is also more prevalent in women and at older ages, while IFG is considerably more common in men.[40] It has also been shown that
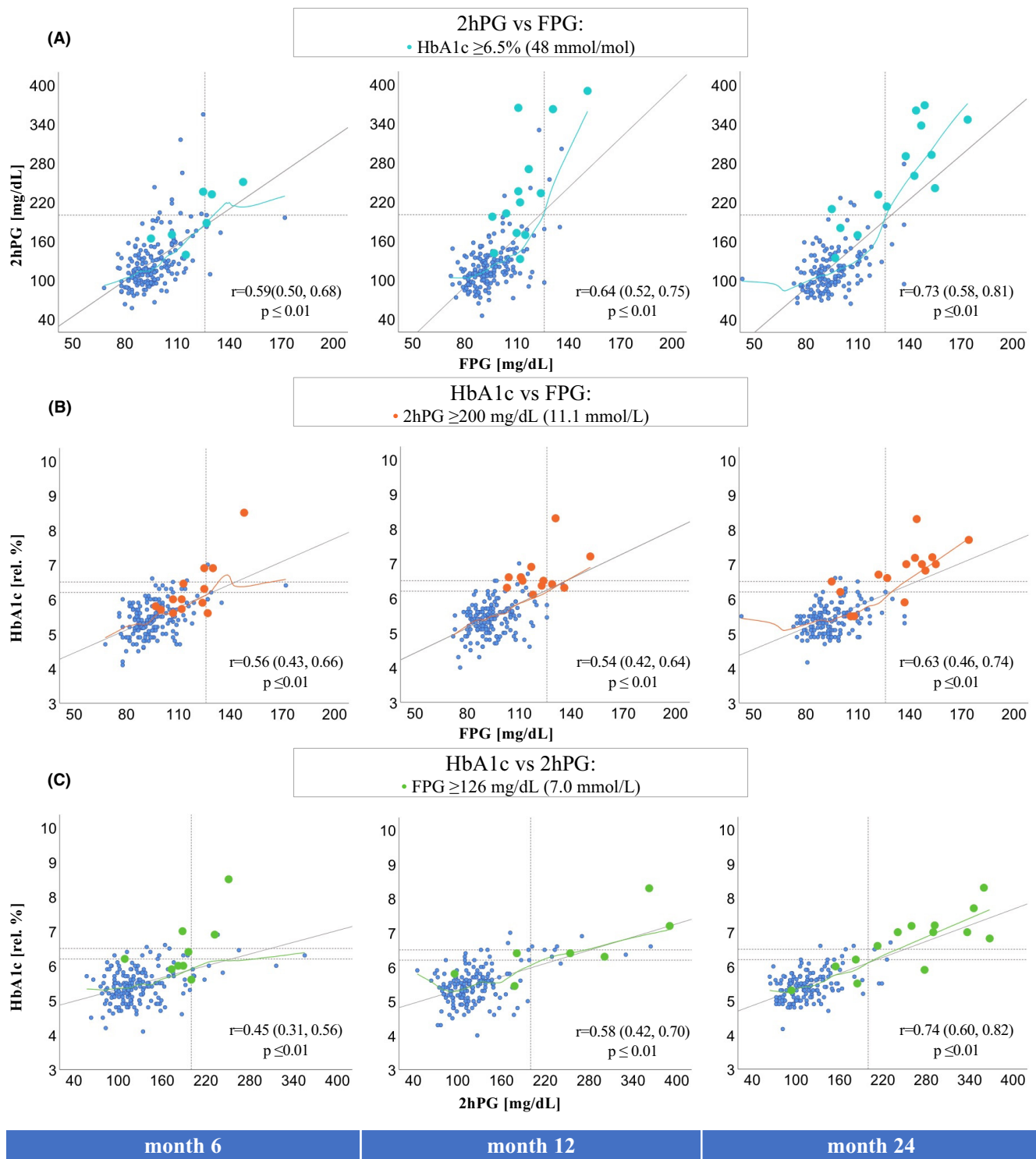
FIGURE 2 Linear correlations of FPG, 2hPG, and HbA$_{1c}$. r = Pearson correlation coefficient and 95% confidence interval (95% CI) obtained by bootstrapping. (A) Correlation of 2hPG versus FPG, blue dots (= HbA$_{1c}$ ≥ 6.5% [48 mmol/mol]). (B) Correlation of HbA$_{1c}$ versus FPG, orange dots (= 2hPG ≥ 200 mg/dl [11.1 mmol/L]). (C) Correlation of HbA$_{1c}$ versus 2hPG, green dots (= FPG ≥ 126 mg/dl [7.0 mmol/L]). Non-linearity was described by loess curves (colored lines, locally estimated scatterplot smoothing). Gray line = linear regression line, dotted lines = diabetes mellitus (DM) thresholds (FPG ≥ 126 mg/dl [7.0 mmol/L], 2hPG ≥ 200 mg/dl [11.1 mmol/L], HbA$_{1c}$ ≥ 6.2% [44 mmol/mol], ≥6.5% [48 mmol/mol]). 2hPG, 2-h plasma glucose; FPG, fasting plasma glucose.

diabetes, especially, in elderly women is rather identified by isolated 2hPG than by FPG[41] in comparison with younger individuals and elderly men. These findings might be partially explained by the standardized glucose load and studies that showed slower intestinal glucose absorption in females, explained by height and fat-free mass.[42]

Apart from statistical associations, it is important that clinicians are aware of influences that may affect the individual patient. Except for possible pathophysiological influences on FPG, there may be analytical difficulties. These include intraindividual variability of 5.7%–8.3%[43] and reproducibility of diabetic results of only 70% that have been reported in the general population.[44] Also, interindividual variation of glucose measurements of up to 12.5%[43] and decay of glucose in test tubes in the range of 5% to 7% per hour have been reported in previous studies.[43] Factors influencing the pre-analytical variation include medications, food ingestion, prolonged fasting or exercise, and stress hyperglycemia due to illness.[45]

The diagnostic accuracy of HbA$_{1c}$ was also considerably lower at month 6 compared with month 24. HbA$_{1c}$ potentially under- or over-diagnoses diabetes due to ethnicity, sex, age, or BMI,[46] of which the relevance of ethnicity is controversial as these differences have not been linked to cardiovascular outcomes.[47–49] Other reported influential factors are erythropoiesis, altered hemoglobin, glycation, erythrocyte destruction, and assay interference.[50] Assays are now greatly unaffected by carbamylation, labile intermediates, and common hemoglobin variants.[51] However, alteration in erythrocyte lifespan, ethnicity, age, and method-specific alterations due to homozygous variants[43] could influence results. HbA$_{1c}$ shows less intra-individual variability and interference during infections or illness than glucose measurements, and samples are more stable at room temperature.[43,44,52] However, the within-variation of HbA$_{1c}$ has been shown to be increased in KTRs compared with the general population[53] and might be additionally influenced by late posttransplant anemia, which is reported in 20% to 57% of patients at 1 year after transplant.[17] After transplantation, loss of kidney function and endogenous erythropoietin production, blood loss and iron deficiency, medications, bone marrow suppression, chronic inflammation, and viral infections could be involved.[54]

The clinical implications of our findings thus are the following: that PTDM and especially prediabetes are best identified by an OGTT and that the OGTT should be repeated due to metabolic instability. This is particularly true for patients with prediabetes or high cardiovascular risk. Although the OGTT has been recommended for some time,[16] not all transplant centers implemented regular screening, which may partially be due to structural difficulties, depending on the center or country. In the general population, the OGTT is actually an inexpensive screening method,[55] but there are no cost-effectiveness studies available after transplantation. Stratifying for OGTT referral using FPG and HbA$_{1c}$ could be helpful,[18] whereas this method would ignore the presence of IGT. Patients with NGT are unlikely to develop PTDM later on. Those without NGT may be in need for closer follow-up. Using an early OGTT (e.g., at 3 months) has the benefit of being able to intervene early, which may be important because PTDM is more reversible when diagnosed early.[34] Patient perspectives in prenatal screening indicate that the OGTT is not well tolerated by some patients and may be experienced as burdensome.[56,57] Therefore, successful screening may also involve active patient education and uncomplicated access.

4.1 | Study strengths and limitations

Strengths of the present study include its cohort of well-defined kidney-transplanted individuals receiving three diagnostic OGTTs over a period of 2 years. No other study has longitudinally compared the diagnostic test accuracy of FPG and HbA$_{1c}$ versus OGTT at 6, 12, and 24 months after transplantation. Only a few studies have explicitly evaluated prediabetes in the posttransplant setting and this focus was chosen in context of a recent publication that showed increased risk for cardiovascular events.[6]

This study is primarily limited by its retrospective design and relatively low sample size. Any proportion based on PTDM cases alone, such as sensitivity, could only be estimated with low precision. Further, the OGTT is strongly influenced by intraindividual fluctuation,[44,52] thereby limiting the use of a single glucose measurement as a reference test. Of note, the trial intervention led to lower odds for PTDM and might have led to less severe stages of disease and fewer undetected PTDM cases due to the extensive screening. Additionally, most treatment group participants (about 50% of total) received insulin, but it should be recognized that most of these participants were weaned off insulin before month 6 and therefore the influence on the test results should be limited. In comparison, the number of patients with PTDM identified at the 1-year OGTT was only slightly lower, as in the study by Ussif et al. (8.3% vs. 10.3%, respectively).[25]

The fact that ethnicity was not collected, was a drawback of our study, but it is likely that most patients were European White individuals and our results might not be reproducible in cohorts of different ethnicity. Studies in the general population showed a relevant effect of ethnicity on HbA$_{1c}$ results.[47] Posttransplant, ethnic disparities are discussed in graft adverse outcomes[58,59] and future studies are needed to investigate diagnosis and its relation to PTDM adverse outcomes in other ethnic groups. As long as these data are lacking for transplanted patients and because of influences on HbA$_{1c}$ after transplant, accuracy of diagnostic criteria in non-White populations is uncertain.

We acknowledge the fact that use of the term *prediabetes* has been controversial and might be misleading, as most individuals with prediabetes will in fact never develop diabetes mellitus. A previous study showed that the risk for cardiovascular events in individuals with prediabetes after transplantation is increased to a degree similar to that in individuals with PTDM,[6] and for consistency we followed its use of the term prediabetes.

5 | CONCLUSION

In our well-defined randomized trial cohort, one in three KTRs switched glycemic category over 2 years. Analysis of three consecutive OGTTs revealed that up to 69% of patients with PTDM and 33% of IGT would have been missed had no OGTT been performed. Although the correlations between FPG, HbA$_{1c}$, and 2hPG improved with time, their diagnostic concordance was poor for PTDM and, especially, prediabetes. Metabolic instability in the extended posttransplant period and the persistently decreased diagnostic performance of single FPG and HbA$_{1c}$ measurements imply that the OGTT remains the most important diagnostic test after kidney transplantation.

AUTHOR CONTRIBUTIONS

Amelie Kurnikowski, Espen Nordheim, Trond Geir Jenssen, and Manfred Hecking designed the study and wrote and submitted the study protocol. Kathrin Eller, Klemens Budde, Julio Pascual, Manfred Hecking, and Johannes Werzowa enrolled participants into the trial and actively treated the previous trial participants. Elisabeth Schwaiger, Simon Krenn, Jürgen Harreiter, Alexandra Kautzky-Willer, Michael Leutner, Johannes Werzowa, Andrea Tura, Klemens Budde, Kathrin Eller, and Julio Pascual retrieved the data. Amelie Kurnikowski, Espen Nordheim, Trond Geir Jenssen, and Manfred Hecking analyzed the data. Amelie Kurnikowski, Espen Nordheim, Trond Geir Jenssen, and Manfred Hecking wrote the manuscript. E. Schwaiger, Simon Krenn, Jürgen Harreiter, Alexandra Kautzky-Willer, Michael Leutner, Johannes Werzowa, Andrea Tura, Klemens Budde, Kathrin Eller, Julio Pascual, and Michael Krebs corrected the manuscript. All authors approved the final version of the manuscript prior to submission.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon request.

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