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Original Paper

Dynamics of Glucose Metabolism After Kidney Transplantation

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Key Words
Kidney transplantation • Posttransplantation diabetes mellitus • Prediabetes • Incidence • Dynamics • Risk factors

Abstract
Background/Aims: Posttransplantation diabetes mellitus (PTDM) impacts patient and allograft survival after kidney transplantation. Prediabetes, which is an independent risk factor for PTDM, is modifiable also in a post-transplant setting. Understanding the risks and dynamics of impaired glucose metabolism after transplantation is a key component for targeted intervention. ***Methods:*** A retrospective chart analysis of all adult non-diabetic renal allograft recipients (*n*=251, 2007-2014) was performed. Longitudinal follow-up included fasting plasma glucose and HbA1c, as well as data on allograft function and immunosuppression at consecutive time points (months 3-6 to >5 years post transplantation). ***Results:*** Throughout follow-up, median prevalence of prediabetes and PTDM was 53.3 [52.4-55.7]% and 15.4 [15.0-16.5]%, respectively. Continuously high fluxes between states of glucose metabolism, with individual patients' state deteriorating or improving over time, resulted in a high number of incident patients even long after transplantation. The greatest number of patients shifted between normal glucose tolerance and prediabetes, followed by those between prediabetes and PTDM. ***Conclusion:*** Prediabetes and PTDM are highly prevalent after kidney transplantation and incidences remain relevant throughout follow-up. Patient fluxes into and out of the prediabetic state show that glucose metabolism is highly dynamic after transplantation. This provides a continuous opportunity for intervention in an aim to reduce diabetes-associated complications.

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Introduction

Posttransplantation diabetes mellitus (PTDM) has been recognized as an increasing problem in solid organ transplantation, with a profound impact on patient morbidity and mortality. PTDM affects not only patient outcome [1] but also, via death with a functioning graft, allograft survival [2]. Incident PTDM within the first year after kidney transplantation doubles long-term mortality [3]. Diabetes-associated complications develop at a faster rate in PTDM than in non-transplant patients [4]. Comprehension of the risk factors and dynamics of PTDM is therefore crucial for developing preventive strategies in post-transplant patient care.

As in type 2 diabetes, insulin sensitivity and -secretion are key determinants of glucose homeostasis after transplantation [5–8]. However, differences in relative contribution compared to a non-transplant population have been reported [5]. As in type 2 diabetes, reduced ß-cell function will eventually result in overt PTDM [5]. This is underlined by the fact that PTDM and type 2 diabetes share several risk genes, most of which affect ß-cell function [9, 10]. In addition to the classic risk factors, other transplant-specific factors such as immunosuppression contribute to the overall risk of developing PTDM [11, 12]. Prediabetes, one of the classic risk factors for progression to overt type 2 diabetes [13–15], has also been shown to increase the risk for PTDM [16–18]. Prediabetes comprises (i) impaired fasting glucose (IFG), (ii) impaired glucose tolerance (IGT) in standardized oral glucose tolerance test (OGTT), and (iii) glycated haemoglobin A1c (HbA1c) levels between 5.7% and 6.4% [19]. In type 2 diabetes, intervention in the state of prediabetes has been shown to be highly effective in reducing diabetes incidence [20].

Published incidences of PTDM after kidney transplantation vary between 7 and 46% [21–23]. This is largely due to the lack of uniform diagnostic criteria. In light of this, a consensus meeting was held in 2013 to establish diagnostic and therapeutic approaches to patients with PTDM [12]. Definition of PTDM was clarified and diagnostic criteria were adopted from the American Diabetes Association (ADA) guidelines for type 2 diabetes [19].

To date, most publications describe single point prevalence or cumulative incidences of prediabetes [24] or PTDM [21–23] at different time points. Glucose metabolism, however, is not static. So, instead of regarding incident prediabetes or PTDM as an endpoint, we provide longitudinal data on the dynamics of glucose metabolism after kidney transplantation on the basis of the long-term follow-up of individual patients. We demonstrate that patient fluxes between different states of glucose metabolism are continuously high after kidney transplantation, and thus identify prediabetes as a key target for intervention in post-transplant care.

Materials and Methods

The aim of the present analysis was to assess incidence, prevalence and dynamics of prediabetes and PTDM in long-term follow-up after kidney transplantation.

Patients

All consecutive renal transplant recipients between 01/2007 and 05/2014 at the Tübingen University Hospital Collaborative Transplant Center were retrospectively analyzed by chart review. Inclusion criterion was kidney transplantation at our transplant center, exclusion criteria were known diabetes prior to transplantation, combined transplantation (liver/kidney or pancreas/kidney) and children (below 18 years of age). As a retrospective chart analysis, the need for approval was waived by the institutional review board.

Definition of prediabetes and PTDM

Definition of prediabetes and PTDM was in accordance with ADA criteria [19] and the consensus paper on PTDM [12]: Prediabetes was defined as fasting plasma glucose (FPG) of 5.6-6.9 mmol/l or an HbA1c level of 5.7-6.4%, PTDM was defined as FPG of ≥ 7 mmol/l or an HbA1c of ≥ 6.5%. To rule out transient post-transplant hyperglycemia, data collection did not begin until 3 months after transplantation.

Parameters and time intervals

At each follow-up, FPG, HbA1c and anthropometrics, as well as data on allograft function and immunosuppression were collected. Estimated glomerular filtration rate (eGFR) was calculated according to the abbreviated modification of diet in renal disease (MDRD) equation in all patients [25, 26]. Corticosteroid use was documented as dose of prednisolone (in mg); for calcineurin inhibitor (CNI) and mammalian target of rapamycin (mTOR) inhibitor use, respective trough levels were recorded. Antimetabolite use was recorded qualitatively. At every follow-up, the necessity of increased corticosteroid dose (due to rejection or other causes) since the last observation point was assessed.

As in a retrospective analysis appointments for post-transplant care were not uniform, time intervals were defined in which a single individual follow-up was recorded. Time intervals were defined as follows: month 3-6, month 6-9, month 9-12, year 1-2, year 2-3, year 3-5 and > 5 years post transplantation.

Dynamics of glucose metabolism

At each individual follow-up, patients were classed according to their glucose metabolism into normal glucose tolerance (NGT), prediabetes or PTDM. Both FPG and HbA1c were taken into account at each time point. Prevalent and incident changes in glucose metabolism were described as follows: Prevalence was calculated as the number of patients with a present condition in proportion to the total number of patients at the respective time point. Incidence was calculated as the number of patients with a newly present condition compared to the preceding time point in proportion to the total number of patients at the respective time point. Since no baseline data was available from the date of transplantation, prevalences are described from the initial time interval on, whereas incidences are not reported until months 3-6. Throughout follow-up, shifts among states of glucose metabolism were assessed for each individual patient. Patient fluxes between states could thus be calculated for each time interval. Upon initiation of antidiabetic drug therapy, patients were excluded from further analysis. Patients who were treated by dietary means only continued follow-up.

Statistical analysis

Unless otherwise stated, data are given as median [interquartile range] or mean ± standard error of the mean. The association of factors with glycemic variables in every observation period was examined with linear mixed models. By default, we used random intercept models, taking the patient ID as random variable and also adjusting for time after transplantation. If appropriate, we also accounted for random slopes associated with time after transplantation. Calculations were carried out with R version 3.2.2 (R foundation for statistical computing, Vienna, Austria) using the lme4 package. Results with values of $p \leq 0.05$ were considered statistically significant.

Results

During the period of time investigated, 365 kidney transplantations were performed at the Tübingen University Hospital Collaborative Transplant Center. Of those, 23 children, 13 patients with combined transplantation and 74 patients with known diabetes prior to transplantation were excluded from analysis. Four patients were lost to follow-up.

Of the 251 patients included in the analysis, 214 underwent their first transplantation, while 37 patients had a second or higher transplantation. Median follow-up was 2.3 [1.6 - 4.6] yrs. During follow-up, graft failure occurred in 5 patients and a further 4 patients died with a functioning allograft.

Patient characteristics

Patient characteristics are displayed in Table 1. Median body mass index (BMI) throughout follow-up was in the upper normal range. Median eGFR ranged between 46 and 50 ml/min/1.73m^2 during the period of observation. The majority of the patients started on standard immunosuppression regimen comprising tacrolimus, mycophenolate and corticosteroids. Since late corticosteroid withdrawal (> 1 yr. after transplantation) was center practice in standard immunological risk patients during the period of observation, most patients later progressed to corticosteroid-free maintenance immunosuppression.

Table 1. Patient characteristics

	month 3-6	month 6-9	month 9-12	1-2 yrs.	2-3 yrs.	3-5 yrs.	> 5 yrs.
n	222	195	182	179	140	98	60
days	128 ± 30	228 ± 40	320 ± 30	517 ± 96	873 ± 121	1372 ± 215	1998 ± 193
gender (f/m)	93/129	82/113	75/107	77/102	61/79	34/64	23/37
age (yrs.)	50.3 [42.6-61.3]	50.7 [42.4-61.3]	50.7 [42.2-62.4]	50.8 [43.2-62.5]	51.1 [40.7-64.7]	55.7 [47.0-68.5]	59.1 [47.5-69.7]
BMI[a] (kg/m^2)	24.0 [21.7-26.7]	24.3 [21.5-26.6]	25.1 [22.0-27.6]	23.9 [21.2-26.7]	24.6 [22.5-28.0]	25.3 [23.2-28.6]	25.3 [22.5-27.4]
eGFR[b] (ml/min/1.73 m^2)	47 ± 19	47 ± 20	48 ± 21	47 ± 20	46 ± 20	49 ± 24	50 ± 22
immunosuppression							
Tac[c] (%)	95.9	88.2	85.1	82.1	81.4	77.6	78.3
(ng/ml)	8.1 ± 3.0	6.9 ± 2.4	6.9 ± 2.0	6.7 ± 2.4	5.8 ± 2.1	5.7 ± 1.9	5.6 ± 1.7
CsA[d] (%)	2.7	5.6	7.7	8.4	9.3	8.2	10.0
(ng/ml)	119 ± 32	130 ± 28	120 ± 40	105 ± 31	98 ± 27	98 ± 19	97 ± 19
MPA[e] (%)	92.3	90.8	90.7	91.6	89.3	91.8	83.3
mTOR[f] (%)	2.7	5.6	7.1	11.7	10.7	15.3	13.3
CS[g] (mg/d)	5.2 ± 3.0	4.5 ± 2.3	4.4 ± 3.8	4.0 ± 1.6	4.5 ± 3.2	4.0 ± 1.8	4.5 ± 2.5
CS free (%)	6.3	17.9	28.6	45.8	65.7	68.4	65.0
CS pulse (*n*)	9 (4.1%)	0	5 (2.7%)	6 (3.4%)	4 (2.9%)	2 (2.0%)	0
rejections *(n)*	6	0	0	3	2	0	0

Data are given as median [interquartile range] or mean ± SEM. a: body mass index, b: estimated glomerular filtration rate, c: tacrolimus, d: ciclosporin A, e: mycophenolic acid, f: mammalian target of rapamycin inhibitor, g: corticosteroids

Incidence and prevalence of prediabetes and PTDM

Incidence and prevalence of prediabetes and PTDM are shown in Figure 1 A, B. Median incidence of prediabetes and PTDM throughout follow-up was 21.0 [19.6-22.3]% and 7.2 [5.4-7.8]%, respectively. A transient decline in the incidence of prediabetes was observed in the year 2-3 interval.

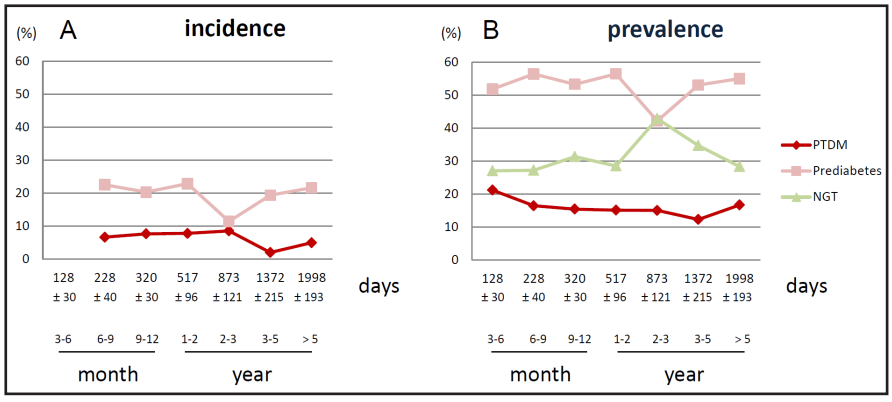
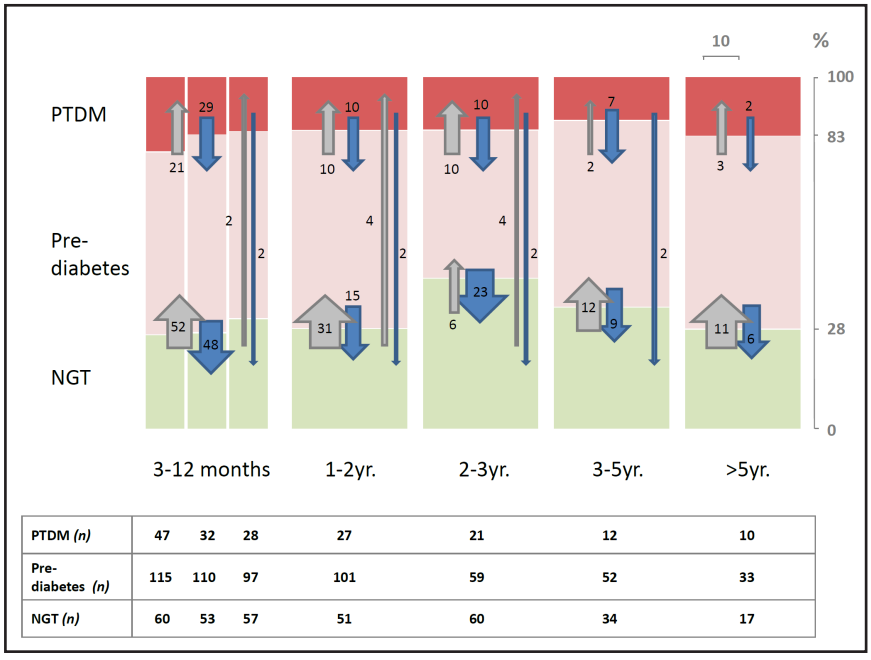


Fig. 1. Incidence (A) and prevalence (B) of prediabetes and posttransplantation diabetes mellitus (PTDM) in the respective time intervals.

Median prevalence of prediabetes and PTDM was 53.3 [52.4-55.7]% and 15.4 [15.0-16.5]%, respectively. Accordingly, a transient decrease in the prevalence of prediabetes was observed in the 2-3 year interval, with an increase in normal glucose tolerance (NGT) in return. Throughout follow-up, prevalence of allograft recipients with normal glucose regulation was approximately one third of the patients.

Dynamics of glucose metabolism after transplantation

Figure 2 summarizes the dynamics of glucose metabolism after kidney transplantation over time. For each follow-up, both the proportion of patients in respective states of glucose metabolism (NGT, prediabetes and PTDM; colored bars) and patient fluxes compared to the preceding time interval (arrows) are provided. In between time intervals, the glucose metabolism of a substantial proportion of patients deteriorated (gray arrows) or improved (blue arrows) without any antidiabetic treatment other than dietary measures. Absolute numbers of patients in respective states of glucose metabolism and absolute patient fluxes are indicated in the figure. Width of arrows indicates the percentage of patients shifting between



PTDM *(n)*	47	32	28	27	21	12	10
Pre-diabetes *(n)*	115	110	97	101	59	52	33
NGT *(n)*	60	53	57	51	60	34	17

Fig. 2. Patient fluxes among different states of glucose metabolism over time. Height of colored bars displays percentage of patients in the respective state of glucose metabolism (vertical axis), absolute numbers are provided in the table below. Arrows indicate patients shifting from one state of glucose metabolism to another, compared to the preceding time interval. Shifts within the first year are given as cumulated data, in comparison to months 3-6 (baseline). Gray arrows indicate worsening; blue arrows improvement of glucose metabolism. Absolute numbers are given in the Fig.. Width of arrows indicates the percentage of patients shifting between time intervals (axis on top of Fig.). NGT: normal glucose tolerance; PTDM: Posttransplantation diabetes mellitus.

time intervals. Highest fluxes were observed between NGT and prediabetes, followed by prediabetes and PTDM. Only a small number of patients surpassed the state of prediabetes and moved from NGT to PTDM or vice versa. Even after the first year, substantial fluxes among states of glucose metabolism were continuously detected throughout the period of observation.

Factors influencing glucose metabolism after transplantation

Factors associated with glucose metabolism throughout the observation intervals were analyzed with mixed models. Recipient age had a significant influence on both FPG and HbA1c. Within our cohort, changes in BMI were minor, and BMI was not associated with glucose metabolism. Furthermore, allograft function, expressed as eGFR, was not significantly associated with glucose metabolism.

Throughout follow-up, corticosteroid withdrawal was routinely performed in standard immunologic risk in about two thirds of the patients investigated. However, some patients required higher doses of corticosteroids (above maintenance therapy) due to allograft rejection or for other reasons (*Table 1*). Corticosteroid use had a significant association with HbA1c, which was dose dependent, whereas no association of corticosteroids with FPG was observed (*Table 2*).

Discussion

The present investigations reveal two main findings. Firstly, incidence and prevalence of prediabetes and PTDM are consistently high after kidney transplantation, with only about one third of patients showing normal glucose regulation. Secondly, the persistent patient fluxes into and out of the prediabetic state reflect the fact that glucose metabolism is highly dynamic, even several years after transplantation.

Table 2. Factors influencing glucose metabolism after transplantation

	FPG[a]		HbA1c[b]	
variable	*p*	effect size	*p*	effect size
recipient age	0.005	Δ 0.012 (mmol/l)/yr.	<0.001	Δ 0.01 %/yr.
BMI[c]	0.67		0.28	
eGFR[d]	0.84		0.86	
CS[e] use (yes vs. no)	0.06		0.003	Δ 0.10 %
CS dose	0.58		<0.001	Δ 0.02 %/mg

a: fasting plasma glucose, b: glycated hemoglobin A1c, c: body mass index, d: estimated glomerular filtration rate e: corticosteroids.

The observed prevalences of prediabetes and PTDM are exceedingly high, with only some 30% of patients after kidney transplantation displaying normal glucose metabolism. By comparison, the combined prevalence of prediabetes and diabetes in the general population is currently around 15% [27]. The higher prevalence may be explained by the fact that transplantation entails a number of risk factors for disturbed glucose metabolism, such as infection, hypomagnaesemia, allograft rejection and immunosuppression [11]. In our cohort, the state of prediabetes invariably comprised the largest proportion of patients throughout follow-up. Data on the prevalence of prediabetes after kidney transplantation is scarce. In a cross-sectional analysis of a post-transplant cohort of 187 patients, Tilmann and co-workers report a single point prevalence of 30% at a mean of 60 months after kidney transplantation [24]. Given the magnitude of the problem, continuous screening and the development of preventive strategies are highly warranted.

To date, prediabetes and PTDM have mostly been reported as single point prevalence or as cumulative incidences at different time points after transplantation [21–24]. The present investigations now clearly demonstrate the dynamic nature of glucose metabolism after transplantation, questioning in particular the concept of reporting cumulative incidences in long-term follow-up after transplantation. Porrini and colleagues were the first to demonstrate the reversibility of prediabetes and PTDM in follow-up after kidney transplantation [18]. Our results are in line with and extend these findings, illustrating not only the overall evolution between months 3 and 36 but also the highly dynamic nature of glucose metabolism at sequential time points after kidney transplantation. The natural history of prediabetes in the general population is such that, after 3-5 years, about 25% of patients progress to manifest diabetes, whereas 50% remain in the state of prediabetes and a further 25% reverse to normal glucose metabolism [28]. In kidney transplant recipients, within a similar period of observation, both Porrini *et al.* and our data demonstrate substantial shifts from the prediabetic state towards both manifest diabetes and NGT. In comparison to the general population, the proportion of patients normalizing glucose metabolism (43%) is higher after transplantation [18].

Our current understanding of the pathophysiology of type 2 diabetes in a non-transplant population comprises a genetic predisposition [29–31] as well as environmental factors [32]. A genetic predisposition largely contributes to defects in insulin secretion [15, 33], whereas environmental factors such as BMI predominantly determine insulin sensitivity [34]. PTDM differs from type 2 diabetes in the general population as far as the relative contribution of insulin secretion and -sensitivity is concerned [5]. Genetics, as an inherent predisposition, has been shown to play a role in PTDM [9]. Our finding of substantial patient fluxes, however, may point towards a contribution of external, fluctuating factors in a post-transplant setting.

Prediabetes has been shown to be an independent risk factor for progression to PTDM [16–18], albeit a modifiable one. Our data clearly show that the risk zone of prediabetes prevails for many years after transplantation, thus providing a continuous opportunity for targeted intervention. The concept of a risk zone is supported by the recent work of Eide and co-workers [35], demonstrating that long-term allograft survival is not compromised in patients with early prediabetes, such as in PTDM. Prediabetes can be modified by structured

lifestyle intervention. This has proved effective in type 2 diabetes in the general population [20] as well as in a post-transplant setting [36]. Pilot studies address the concept of antidiabetic drug intervention in prediabetes after kidney transplantation [37], which may be a promising concept for the future.

The impact of maintenance immunosuppression, as a modifiable risk factor, on glucose metabolism has often been discussed. Corticosteroids are known to affect glucose metabolism via various pathways, the most predominant of which is the increase in insulin resistance [38]. In our cohort, late corticosteroid withdrawal was routinely performed in patients with standard immunologic risk, thereby enabling us to assess the impact of corticosteroid use. Parallel to corticosteroid withdrawal, with around 50 and 65% of patients on corticosteroid-free maintenance immunosuppression in the 1-2 year and 2-3 year interval, respectively, a transient drop in incident prediabetes was observed. Since the remaining immunosuppression was left unaltered, changes are likely to represent the effect of corticosteroid withdrawal. In mixed model analysis adjusted for time effects, corticosteroid use was significantly associated with higher HbA1c in our cohort. Of note, corticosteroids had no effect on FPG. This is in accordance with pathophysiological considerations that a morning dose of corticosteroids has little influence on fasting plasma glucose but causes an increase in plasma glucose concentrations at midday and in the afternoon. Determination of afternoon plasma glucose concentrations has therefore been proposed for diagnosis of PTDM [39]. In our cohort, corticosteroid withdrawal showed a beneficial effect on glucose metabolism without compromising allograft outcome. This is in line with the recently published HARMONY trial [40]. However, studies investigating the benefit of corticosteroid withdrawal or avoidance for PTDM risk yielded conflicting results [41]. Calcineurin inhibitors lead to impaired β-cell growth and function [42], in which tacrolimus is more diabetogenic than ciclosporin [43]. Reversal of manifest PTDM after conversion from tacrolimus to ciclosporin has been shown [44], however, newer studies point towards a dosing effect of the diabetogenic potential [45]. Current guidelines recommend not to choose or alter immunosuppression according to the risk of PTDM [12] since the risk of allograft injury outweighs the potential benefit of an improvement in glucose metabolism with regard to patient prognosis.

An optimum strategy to reduce PTDM and associated complications comprises all phases of transplantation and starts on the waiting list, where about one third of patients have prediabetes [46]. Already on the waiting list, lifestyle intervention can be effective in reducing the risk of later PTDM. At the time point of transplantation, early basal insulin administration has been shown to be effective in lowering the risk of PTDM by reducing glucotoxicity to ß-cells and preserving insulin secretion, as demonstrated in a pilot study by Säemann and colleagues [47]. This is particularly valuable in elderly patients, the majority of whom have impaired insulin secretion [46]. Age, also in the present analysis, was the single influencing factor of FPG after transplantation. Since age cannot be modified, it underlines the importance of specific management in these patients. As discussed above, a significant proportion of allograft recipients is continuously in a risk zone after transplantation, thus underlining the ongoing need for screening and intervention to prevent PTDM. However, it remains a matter of debate as to whether improved glycemic control will actually lead to a better patient outcome after kidney transplantation, and respective studies are therefore highly warranted.

The present investigations do have limitations. As a retrospective analysis, FPG and HbA1c were available, while OGTT was not. Given that a certain proportion of patients is diagnosed solely via OGTT [48, 49], the incidence of PTDM and prediabetes might be even higher in our population. Diagnostic accuracy of HbA1c in chronic kidney disease [50] and after transplantation [51] is hampered by higher erythrocyte turnover, again underestimating the prevalence of disturbed glucose metabolism. Nonetheless, this is the first study to report long-term follow-up of glucose metabolism in individual patients after kidney transplantation in a large European cohort.

Conclusion

We demonstrate that the prevalence of prediabetes and PTDM is continuously high, with substantial patient fluxes among different states of glucose metabolism. Prediabetes offers a continuous opportunity for active intervention to improve glucose metabolism. Prospective trials are required to determine whether this improves diabetes-associated complications and patient outcome after kidney transplantation.

Disclosure Statement

The authors of this manuscript state that they do not have any conflict of interests and nothing to disclose.

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