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Original Article: Retrospective cohort analysis

Dynamics of glucose metabolism after liver transplantation: Prediabetes as a window of opportunity for patient survival and long-term kidney function

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Abbreviations:

BMI: body mass index; CKD: chronic kidney disease; CNI: calcineurin inhibitor; eGFR: estimated glomerular filtration rate; FPG: fasting plasma glucose; INR: international normalized ratio; IQR: interquartile range; LTx: liver transplantation; mTOR: mammalian target of rapamycin; NASH: non-alcoholic steatohepatitis; NGT: normal glucose tolerance; PTDM: posttransplantation diabetes mellitus

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Abstract

Posttransplantation diabetes mellitus (PTDM) is a relevant complication following liver transplantation with profound impact on morbidity and mortality. To date, little is known about the evolution and dynamics of glucose metabolism and the impact of prediabetes in long-term follow-up.

To address this issue, all consecutive adult liver transplant recipients (n=429) from a European university hospital transplant center between 2007 and 2017 were analyzed retrospectively. In patients without pre-existing diabetes (n=327), we conducted a longitudinal characterization of glucose metabolism.

Median follow-up was 37 [9–64, IQR] months. Median prevalence of prediabetes was 39 [37-39]% and of PTDM 21 [17-22]%. Throughout follow-up, intra-individual glucose regulation of patients was highly variable, continuously fluctuating between different states of glucose metabolism (normal glucose tolerance, prediabetes, PTDM). Whereas overall survival and long-term kidney function of patients with PTDM were significantly lower than that of patients with normal glucose metabolism, prediabetes was not associated with adverse outcome.

This study provides new insight into the dynamics and impact of glucose metabolism after liver transplantation. Unlike PTDM, prediabetes is not associated with adverse outcome, providing a window of opportunity for targeted intervention. The results underline the need for constant screening and intervention in post-transplant care of liver allograft recipients.

1. Introduction

The burden of diabetes mellitus is growing rapidly worldwide [1] and contributes considerably to population morbidity and mortality. The risk for diabetes mellitus is even higher in patients after solid organ transplantation, where posttransplantation diabetes mellitus (PTDM) is a frequent complication [2].

The prognostic relevance of PTDM after liver transplantation (LTx) has been increasingly recognized over the last few years: Its presence is associated with an increased risk for chronic kidney disease (CKD) as well as for cardiovascular and infectious complications [3–7]. Moreover, PTDM was associated with lower overall survival in most studies [7–9]. Data on prediabetes, a state in which glucose metabolism is disturbed, yet not fulfilling the criteria for manifest diabetes, are scarce. Whereas prediabetes has been shown to affect patient outcome in the general population [10,11], its impact after liver transplantation is not clear.

Predisposing factors for disturbed glucose metabolism after LTx are, on the one hand, risk factors patients share with the general population. These include, for example, central obesity or genetic predisposition [2,12,13]. On the other hand, there are transplant-specific risk factors, such as choice of immunosuppressive regimen, with calcineurin inhibitors (CNI) and corticosteroids in particular showing high diabetogenic potential [2,4,14]. Finally, the underlying liver disease may hold an increased risk for PTDM, in particular non-alcoholic steatohepatitis (NASH) [3,15,16].

The incidence of PTDM in patients after LTx varies considerably in the literature, and percentages reported range between 7% and 56% [3,5,15,17–19], data on prediabetes are scarce and range from 8% to 54% [20,21]. Among reasons are variable diagnostic criteria, differing time points of assessment, as well as differences in patient populations. Furthermore, studies usually report single time point or cumulative incidences, respectively. This precludes an assessment of the course of glucose metabolism over time in individual patients. However, recent data on patients after kidney transplantation point to the fact that glucose metabolism in these patients is highly dynamic over time [22]. We therefore assume that only longitudinal and individual analysis can adequately portray glucose metabolism after solid organ transplantation. In our opinion, this is crucial to the identification of risk factors as well as to a targeted intervention for the prevention of adverse outcomes.

Therefore, for the first time, we analyzed data of patients after LTx with long-term follow-up in a longitudinal approach, while focusing on the course of glucose

metabolism in the individual patients. We provide novel insight into the nature of glucose metabolism after liver transplantation and the significance of prediabetes, as a pre-stage of PTDM, in patient survival and long-term kidney function.

2. Patients and Methods

2.1 Patients

Data of all consecutive adult patients who received liver transplantation at our university hospital between 01/2007 and 12/2017 were included. In case of a repeat transplantation, we analyzed the current organ only.

For analysis of mortality, data of all patients transplanted during the above period of time were used. For longitudinal analysis of glucose metabolism, only data of patients without a medical history of diabetes mellitus prior to transplantation were included.

The study was conducted in accordance with the 2000 Declaration of Helsinki and the Declaration of Istanbul 2008. The institutional review board gave its approval for this retrospective chart analysis (project number 348/2018BO2) and waived the need for patient informed consent.

2.2 Collected data and time intervals

Collected data comprised fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) as well as additional laboratory results including liver enzymes, bilirubin, INR (international normalized ratio), albumin and plasma creatinine concentrations for the estimation of eGFR using the CKD-EPI equation [23]. Around 2014, for a time period of approximately one year, HbA1c values were not routinely available due to a temporary change in standard operating procedures in the outpatient clinic. In these cases, determination of glucose metabolism was assessed by FPG only. If no parameter for glucose metabolism was available, the respective visit was omitted.

HbA1c was measured by high performance liquid chromatography (Tosoh 11c 2.2 HLC-723, Tokyo, Japan).

Furthermore, data on patient history and on immunosuppression were obtained. For prednisolone, dosage was recorded in milligrams (mg). For calcineurin inhibitors (CNI), trough level concentrations were collected.

In order to enable longitudinal analysis, time intervals were defined to categorize the individual time points of patients' posttransplant visits. Time intervals, with reference to the date of transplantation, were defined as follows: months 3-6, months 6-9, months 9-12, months 12-18, months 18-24, year 2-3, year 3-4, year 4-5, years 5-7, years 7-10. As a rule, the first visit in the respective time interval was chosen for data

collection. In exceptional cases, a later visit was recorded if no data on glucose metabolism was available from the patients' first visit.

2.3 Definition of prediabetes and PTDM

Prediabetes and PTDM were defined in accordance with ADA criteria [24] and the consensus paper on PTDM [25]: Prediabetes was defined as 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 HbA1c ≥ 6.5%. To rule out transient posttransplant hyperglycemia, data collection did not commence until 3 months after LTx.

2.4 Analysis of glucose metabolism

For each time interval, the patients' state of glucose metabolism was classified either as normal glucose tolerance (NGT), prediabetes, or PTDM.

Prevalence and incidence of the different states of glucose metabolism were calculated for each interval. Prevalence was defined as number of patients with a certain state of glucose metabolism at an interval in relation to all patients of whom data were available for the respective time interval. Incidence was defined as the number of patients in whom a certain state of glucose metabolism had newly developed since the preceding interval, again in relation to the total number of patients available per time interval.

For each individual patient, changes in glucose metabolism were noted per interval, enabling the display of the natural course of patient fluctuations into and out of the different states of glucose metabolism over time. Upon initiation of antidiabetic treatment other than dietary measures, patients were excluded from this analysis of glucose metabolism, in order not to falsify data on natural evolution. In exceptional cases, fluctuations were caused by the absence of either HbA1c or FPG at a certain interval. In these cases, the single fluxes affected were not included in the analysis.

2.5 Statistical analysis

Unless otherwise stated, data are given as median [interquartile range (IQR)] or mean ± standard deviation (SD).

Statistical analyses were performed using R version 3.6.0 (R foundation for statistical computing, Vienna, Austria) [26]. Survival analyses were performed using the "survival" package [27]. Linear mixed models were calculated with lme4 package

[28]. Linear variables were scaled prior to analysis, and certain outcomes needed to be logarithmized to achieve homoscedasticity. In the first step, we assessed age and time after transplantation for interaction with the fixed effect to be investigated. If no interaction was found, the model was simplified by removing the interaction. Time after transplantation and age were entered into different models. Visual inspection of residual plots did not reveal any obvious deviations from homoscedasticity or normality.

For outcome analysis, glucose metabolism at time point one year after transplantation was stratified into NGT, prediabetes or PTDM. To do so, the least favorable classification at intervals 6-9 months, 9-12 months and 12-18 months was used for each individual patient. Kaplan-Meier curves were generated for mortality as well as for patients with a decline in eGFR by >25% by calculating the probability for the event for each time point, taking censored patients into consideration. For estimation of eGFR, the respective time-point was excluded from analysis of kidney function if a patient received hemodialysis.

P values are reported two-sided, $p \leq 0.05$ was considered statistically significant.

3. Results

3.1 Patient characteristics

Within the observed period of time, 429 patients received a liver transplantation at our transplant center. Of these patients, 102 had a history of diabetes mellitus prior to transplantation.

Longitudinal analysis was carried out in the remaining 327 patients. Of these, 199 patients (61%) were male, and 128 (39%) were female. Median age at time of transplantation was 54 [45 – 61] years. Common primary diseases leading to LTx were alcoholic liver disease (26%), chronic viral hepatitis C (20%) or B (8%), cholestatic liver diseases (12%), acute liver failure (8%), and cryptogenic liver disease (5%). Six patients (1.8%) received liver transplantation on account of non-alcoholic steatohepatitis (NASH) or non-alcoholic fatty liver disease (NAFLD), respectively. Hepatocellular carcinoma was diagnosed in 109 patients (33%). Twenty-nine patients had undergone liver transplantation twice, two patients had been transplanted three times. Median follow-up time since transplantation was 37 [9 – 64] months. *Table 1* provides an overview of patient characteristics, immunosuppression, and laboratory results for the respective time intervals. Median BMI increased during the years after transplantation from 22.0 [19.3 - 25.0] to 27.2 [24.2 - 29.5] kg/m².

3.2 Immunosuppression and liver allograft function

Immunosuppressive regimens over time as well as the corresponding trough levels are displayed in *Table 1*. The percentage of patients receiving tacrolimus as part of their immunosuppressive regimen remained at or above 65% throughout follow-up. Use of corticosteroids decreased over time, as we aim for corticosteroid withdrawal at three months, unless in patients where corticosteroids are indicated for other reasons. Those remaining on corticosteroids received mean dosages of 5 mg or below per day.

Forty-seven patients (14%) suffered one, seven patients (2%) two or more biopsy-proven acute allograft rejections. The number of rejections per time interval is given in *Table 1*. Allograft rejections were treated with corticosteroid pulse therapy and, in a number of cases, adaptation of maintenance immunosuppression.

Median values of liver enzymes and bilirubin were within normal ranges throughout the period of observation (*Table 1*). This also applied to parameters of liver synthesis,

INR and albumin (data not shown). 60 patients (18%) had allograft steatosis, diagnosed via ultrasound, at the end of follow-up, and 5 patients (1.5%) had known cirrhosis of the liver allograft.

3.3 Incidence and prevalence of prediabetes and PTDM

Incidence and prevalence of prediabetes and PTDM within the individual time intervals are shown in *Figure 1*. Median overall prevalence of prediabetes was 39 [37-39]% and 21 [17-22]% for PDTM. Median overall incidence was 16 [15-18]% for prediabetes and 6 [5-7]% for PTDM. Of note, incidences of prediabetes and PTDM persisted at a high level throughout follow-up. Cumulative incidence of prediabetes was 139/327 patients (43%), and 120/327 patients (37%) presented with PTDM at least once during follow-up. Only 68 patients (21%) displayed NGT throughout the complete period of observation.

Patients with PTDM were treated either with dietary measures, oral antidiabetic medication or insulin.

3.4 Dynamics of glucose metabolism

The natural evolution of intra-individual patient fluctuations between the different states of glucose metabolism are displayed in *Figure 2*. In the course of the observation period, 43 patients required antidiabetic medication and were therefore excluded from further longitudinal analysis of the natural evolution of glucose metabolism. During all time intervals and throughout the whole observation period, patients constantly fluctuated between the different states of glucose metabolism in comparison to the respective preceding interval. Particularly between the states of NGT and prediabetes, continuously high patient fluctuations were recorded. In the state of prediabetes, the median percentage of patients improving their glucose metabolism to NGT in the subsequent time interval was 11.7 [11.1-12.0] %, whereas median percentage of patients worsening to PTDM was 5.0 [3.7-5.5] %.

3.5 Factors affecting glucose metabolism

The factors analyzed with regard to their effect on HbA1c levels are presented in *Table 2*. In linear mixed model analysis, age, prednisolone use and -dosage, CNI use, days since transplantation, and BMI were all associated with a significant

increase in HbA1c. With regard to FPG, BMI and the presence of steatosis showed a significant positive correlation.

3.6 Association of glucose metabolism with liver allograft function

Factors with an effect on alanine transaminase (ALT) and gamma-glutamyltransferase (GGT) are depicted in *Table 3*. Both HbA1c and FPG showed a significant association with liver enzymes, which increased as glucose metabolism deteriorated. Further factors that had a significant effect on liver enzymes were time since transplantation, allograft steatosis, prednisolone use, and patient age.

3.7 Patient survival

The one- and five-year survival rates following LTx for all patients (n=429) were 89.7% and 77.3%, respectively. In Kaplan-Meier estimate, patients' survival was significantly lower in patients with known diabetes prior to transplantation in comparison to patients without pre-existing diabetes mellitus (p=0.029, *Figure 3A*).

Of all deaths, 12.3% occurred perioperatively within the first 21 days after liver transplantation. Thereafter, underlying causes of death with a functioning allograft were infections (25.5%), malignancies including tumor recurrence (18.9%), bleeding (8.5%) and cardiovascular complications (4.7%). In 14.2% of cases, death was attributed to liver allograft failure. In 16.0% of cases, the cause of death was other or unknown (if patients died outside our hospital and cause of death could not be retrieved). The numbers in each entity were too small to test for any statistically significant association with pre-existing diabetes.

Looking in detail at the group of patients without pre-existing diabetes mellitus, the overall survival rates differed significantly (p=0.004), depending on the patients' state of glucose metabolism one year after LTx (*Figure 3B*): PTDM was associated with a lower survival rate, compared to NGT. The survival rate of patients with prediabetes was close to the patients with NGT. Cardiovascular events were recorded in 26 patients (6%). However, no significant correlation between state of glucose metabolism and cardiovascular events could be ascertained.

3.8 Association of glucose metabolism with kidney function

Patients with pre-existing diabetes had significantly lower eGFR shortly after transplantation than patients without diabetes (67 [52-93] ml/min/1.73 m² vs. 83 [61-100] ml/min/1.73 m², p=0.005).

In patients without diabetes mellitus prior to liver transplantation, eGFR trajectories were significantly linked to their state of glucose metabolism one year after LTx: Patients with PTDM displayed the highest annualized loss of eGFR during follow-up (descriptive eGFR trajectories in *Figure 4A*). Kaplan-Meier estimate of patients with a decline in eGFR of >25% confirmed this finding (p=0.034, *Figure 4B*), showing markedly reduced kidney function in patients with PTDM, whereas in patients with prediabetes, the number of patients with a decline in eGFR >25% was comparable to those with NGT.

In linear mixed model analysis, factors independently associating with eGFR were HbA1c and FPG, as well as patient age, use of tacrolimus, and time since liver transplantation (*Table 4*). During follow-up, 15 patients reached end-stage-renal-disease after a median time of 18.4 [3.2-60.7] months.

4. Discussion

Our study shows three main findings. First, disturbances in glucose metabolism are highly prevalent after liver transplantation. Second, we are the first to show the substantial dynamics of glucose metabolism in liver transplant recipients during long-term follow-up. Third, our analyses reveal prediabetes, as a pre-stage of PTDM, not to be associated with detrimental effects on patient survival and long-term kidney function. A number of relevant clinical implications can be derived from these main findings:

There is an unmet need to comprehend the magnitude and pathophysiology of disturbed glucose metabolism after LTx. In our cohort, only one sixth of the patients (68 out of 429, 16%) displayed normal glucose tolerance throughout the whole period of observation. All others either had pre-existing diabetes mellitus (24%), or developed prediabetes or PTDM during follow-up (60%). By comparison, in the European general population, the prevalence of impaired glucose tolerance and diabetes mellitus is currently estimated to be around 5% and 8%, respectively [29]. Thus, both liver disease and liver transplantation involve a considerably higher risk for disturbances in glucose metabolism. The major role of the liver in glucose metabolism has been well established. Glucose homeostasis is maintained via glycogenolysis and gluconeogenesis, and the liver is the primary site for endogenous insulin degradation. In liver disease, loss of skeletal muscle mass leads to impaired glucose uptake and to insulin resistance [30]. Certain entities, such as chronic viral hepatitis C or NASH, are particularly associated with a higher risk for diabetes mellitus [31–34], potentially via increased inflammation as shown in kidney transplantation [12], albeit our data could not detect such a connection, in part due to the small number of patients with these underlying diseases.

In addition to liver disease, transplantation itself markedly increases the risk for disturbances in glucose metabolism. Factors contributing to this risk include immunosuppression with CNI, corticosteroids, and – as in the general population – an increase in body weight [2,4,14]. All these associations were confirmed in our study. Moreover, longitudinal patient-by-patient analysis revealed considerable fluctuations between the different states of glucose metabolism at all time points throughout observation. To our knowledge, this has not yet been shown in liver transplant patients, since most studies on glucose metabolism after LTx provide time-

point or cumulative incidences only [3,5,9,18]. Furthermore, the fluctuations shown in our study differ from what is known about the course of glucose metabolism in the general population. Numbers in the literature for progression from prediabetes to diabetes mellitus for observation periods of 2 – 6 years vary greatly between 6% and 29% [35–37]. Improvement of glucose metabolism with regression from prediabetes to NGT is reported for 22% – 69%, whereas the majority of patients in the general population remain at the stage of prediabetes during observation periods [35–37]. This is at variance with the very vivid and partly short-lived fluctuations depicted in our data; a finding that had already been observed in kidney transplantations [22]. These findings underline the presence of transplant-specific factors, which show greater variation over time and point towards the extrinsic nature of these risk factors. Of note, fluctuations between NGT and prediabetes were higher than between prediabetes and PTDM, indicating that spontaneous improvement of glucose metabolism occurred more often than progression to PTDM. Nevertheless, patients who developed PTDM almost always did so from the state of prediabetes, which, as a pre-stage, serves as an alert sign.

When looking at the impact of post-transplant glucose metabolism on outcome, our analyses demonstrate an independent association of glucose metabolism and markers of liver allograft function. Elevation of liver enzymes is an unspecific response to hepatic stress, requiring further diagnostic clarification [38,39]. We now propose that glucose metabolism is included in differential diagnosis, since there might be glucose-mediated damage to the liver at earlier stages, prior to the development of NASH. However, as inflammation is known to worsen glucose metabolism [12], the association may also be bidirectional with chronic hepatitis leading to prediabetes and PTDM.

Besides allograft function, our data confirm the notion that glucose metabolism has a significant impact on patient survival following LTx. This holds true for both pre-existing diabetes mellitus and PTDM. Data on the impact of pre-existing diabetes on long-term survival after LTx in the literature are limited and have not yet been able to conclusively prove a significant association [5,8]. Studies on the impact of PTDM have demonstrated its detrimental impact on outcome [5,7–9,17]. In line with these findings, our study confirms the significant impact of both pre-existing diabetes mellitus and PTDM on long-term patient survival after LTx. Of note, prediabetes, as a

key risk factor for the progression to diabetes, was not associated with a markedly poorer outcome. This finding provides novel insight into glucose metabolism after LTx, with the state of prediabetes providing a window of opportunity for timely intervention. Unlike with patient survival, a significant association between glucose metabolism and cardiovascular events could not be detected in our study. This might be due on the one hand to the small number of patients affected. On the other hand, this number might not have been adequately captured in a retrospective analysis, since patients are often admitted to the nearest hospital in case of an emergency and records are not always forwarded to the respective transplant center.

In addition to overall and cardiovascular mortality, diabetes is a well-known cause of chronic kidney disease (CKD) in the general population. CKD is also a frequent complication after LTx, thus resulting in lower patient survival [40–42]. Following solid organ transplantation, the impact of disturbed glucose metabolism on kidney function is unclear, even in patients after kidney transplantation, due to the notion that other factors such as CNI are thought to prevail over glucose-induced damage to the kidney. Published reports addressing the interaction between glucose metabolism and renal function after LTx have only used crude criteria for either description of renal endpoints (eGFR <60 ml/min/1.73 m^2, end stage renal disease) [5,7] or for glucose metabolism (presence or absence of known diabetes) [42–44]. Our study provides a comprehensive analysis of post-transplant glucose metabolism as well as of kidney function, thus enabling a considerably more precise description of its association. Again, prediabetes was not associated with a higher rate of renal functional deterioration.

Drawing a close on our findings, screening for disturbances in glucose metabolism and early intervention warrants high priority in follow-up care after liver transplantation. While PTDM is more and more acknowledged in kidney allograft recipients, physicians involved in the post-transplant care of liver allograft recipients should also increase awareness and implement screening in their routine follow-up. HbA1c and fasting plasma glucose can be readily determined in routine laboratory, even in outpatient care. As demonstrated for both overall survival and kidney function, the state of prediabetes is not associated with a significantly less favorable outcome. Prediabetes is therefore an ideal window of opportunity for targeted intervention. Possible tools include lifestyle intervention, consisting of reduced caloric

intake, and an increase in physical activity, which has been shown to be highly effective in PTDM after kidney transplantation [45]. A second option is a switch in maintenance immunosuppression. While not recommended in kidney transplant recipients due to the high risk of immunological complications, it might be an option after liver transplantation in patients with low immunological risk, especially in later follow-up, where reduction in immunosuppression can be performed safely in most patients. Reversal of PTDM has been shown after switch from tacrolimus to ciclosporin [46]. Another option would be the withdrawal of corticosteroids, since these increase insulin resistance [47]. Finally, timely treatment of manifest PTDM is recommended, with novel antidiabetic substances such as SGLT2 inhibitors bearing the potential to target both glucose metabolism and cardiovascular and renal outcomes, albeit no data for post-LTx are available so far. Whether all these measures will result in improved patient and allograft survival after LTx, however, has yet to be determined [48].

Our study does have limitations: Oral glucose tolerance test was not performed on a regular basis at outpatient visits in our center. Therefore, the percentage of patients with disturbed glucose metabolism that could be identified via oral glucose tolerance test only [25] was not captured and their number after LTx might still be underestimated in our study. It is also important to mention that the prognostic relevance of FPG and HbA1c remains controversially discussed [49]. However, it has been demonstrated that the combination of both was good diagnostic criteria after kidney transplantation [50]. Furthermore, HbA1c starting at three months after liver transplantation has been shown to be associated with mortality [51]. Therefore, we consider the findings of our study in the present form to be of relevance. Last, , our analysis is of a retrospective nature. However, to date, it is one of the largest single-center analyses to provide comprehensive and unique insight into glucose metabolism after LTx and its clinical implications. Our data places renewed emphasis on the importance of continuous screening and timely intervention with regard to prediabetes as an alert sign in long-term follow-up care following liver transplantation.

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Data Accessibility Statement

Upon acceptance, a data file will be archived in the Dryad Digital Repository. The data file will be restricted regarding patient demographic and anthropometric variables to strictly ensure anonymity. All measured values relevant to the analysis will be included. Background to this is the fact that our cohort is a selected cohort from a single university hospital, hence an otherwise very closely described patient group.

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Figure Legends

Figure 1: Incidence (A) and prevalence (B) of prediabetes and posttransplantation diabetes mellitus (PTDM) for the respective time intervals (m = months, y = year/years). NGT = normal glucose tolerance, LTx = liver transplantation, IQR = interquartile range.

Figure 2: Natural evolution of glucose metabolism over time. For each time interval (m = months, y = year/years), prevalence of normal glucose tolerance (NGT), prediabetes, and posttransplantation diabetes mellitus (PTDM) is depicted as stacked bars (%). Arrows indicate patient fluxes between the different stages of glucose metabolism for each time interval in comparison to the respective preceding interval. Arrow width corresponds to the number of patients affected (%). Red arrows pointing upwards represent deterioration; green arrows pointing downwards indicate improvement of state of glucose metabolism.

Figure 3: A) Kaplan-Meier curve of overall survival probability after LTx (all patients, n = 429) with respect to pre-existing diabetes mellitus prior to transplantation.
B) Kaplan-Meier curve of overall survival probability after LTx (patients without preexisting diabetes mellitus prior to LTx and available glucose metabolism for stratification, n = 228) depending on their state of glucose metabolism one year after LTx.

Figure 4: A) Trajectories of median eGFR [IQR] dependent on glucose metabolism one year after LTx.
B) Kaplan-Meier curve of patients with a decline in eGFR of >25% compared to baseline, depending on the patients' state of glucose metabolism one year after LTx. The analysis was discontinued three years after LTx due to the small number of patients at risk in the respective subgroups.

Tables

Table 1: Patient characteristics, immunosuppression and laboratory results

	3-6 m[a]	6-9 m	9-12 m	12-18 m	18-24 m	2-3 y[b]	3-4 y	4-5 y	5-7 y	7-10 y
n	253	224	186	199	172	173	155	126	100	53
days	120 ± 24	216 ± 26	313 ± 26	428 ± 49	623 ± 57	839 ± 88	1221 ± 98	1592 ± 94	2051 ± 182	2804 ± 224
gender (f / m)	96 / 157	95 / 129	76 / 110	79 / 120	68 / 104	66 / 107	62 / 93	51 / 75	40 / 60	19 / 34
age (yrs)	55.3 [47.8 - 61.2]	55.6 [47.8 - 61.6]	56.3 [47.6 - 61.7]	56.2 [47.7 - 61.7]	57.0 [48.5 - 63.6]	57.7 [50.1 - 63.7]	58.2 [50.1 - 64.5]	59.3 [49.9 - 66.1]	60.9 [51.9 - 68.3]	60.4 [53.5 - 71.8]
BMI[c] (kg/m²)	22.0 [19.3 - 25.0]	22.9 [20.1 - 26.3]	23.5 [20.0 - 26.9]	24.5 [21.7 - 27.0]	24.7 [21.8 - 27.7]	24.5 [21.1 - 27.6]	25.4 [22.7 - 29.5]	26.4 [23.1 - 29.7]	25.5 [23.4 - 27.8]	27.2 [24.2 - 29.5]
Rejections (n)	11	4	2	1	3	4	0	2	1	0
Immunosuppression										
Tac[d] (%)	75.1	76.8	78.5	75.4	71.5	67.1	67.1	65.1	75.0	71.7
Tac (ng/mL)	8.8 [6.8 - 10.9]	7.8 [6.2 - 9.3]	7.2 [5.5 - 8.9]	6.7 [5.2 - 8.3]	6.1 [5.1 - 7.7]	6.2 [4.8 - 7.7]	6.0 [4.6 - 7.7]	5.6 [4.6 - 6.9]	6.0 [4.9 - 6.9]	6.5 [4.9 - 8.0]
CsA[e] (%)	19.4	16.1	18.8	16.6	16.3	21.4	17.4	15.1	10.0	5.7
CsA (ng/mL)	119 [93 - 152]	120 [100 - 143]	110 [103 - 125]	101 [83 - 116]	98 [91 - 115]	101 [91 - 133]	90 [79 - 122]	92 [85 - 106]	86 [80 - 105]	93 [81 - 96]

MPA[f] (%)	71.5	72.3	69.9	66.3	65.1	67.1	66.5	66.7	68.0	54.7
mTOR[g] (%)	13.0	16.5	15.1	18.6	22.7	22.0	25.2	23.8	22.0	28.3
AZA[h] (%)	1.2	0.4	1.1	1.0	2.3	1.2	1.9	0.8	1.0	1.9
CS[i] (%)	72.7	50.9	43.5	36.2	30.2	28.9	17.4	15.9	16.0	18.9
CS (mg/d)	5.0 [5.0 - 5.0]	5.0 [2.5 - 5.0]	5.0 [2.5 - 5.0]	5.0 [2.5 - 5.0]	5.0 [2.5 - 5.0]	5.0 [2.5 - 5.0]	5.0 [2.5 - 5.0]	5.0 [2.5 - 5.0]	2.5 [2.5 - 5.0]	2.5 [2.1 - 2.5]
Laboratory results										
AST[j] (U/L)	24 [18 - 34]	26 [18 - 37]	25 [18 - 35]	26 [19 - 35]	24 [18 - 32]	24 [19 - 32]	21 [18 - 32]	22 [18 - 28]	21 [16 - 26]	20 [17 - 24]
ALT[k] (U/L)	25 [16 - 45]	27 [18 - 48]	24 [18 - 39]	26 [18 - 39]	23 [17 - 32]	24 [17 - 33]	22 [16 - 34]	20 [16 - 29]	21 [15 - 28]	18 [14 - 25]
GGT[l] (U/L)	39 [19 - 115]	40 [17 - 104]	32 [16 - 93]	28 [17 - 69]	27 [16 - 69]	27 [16 - 60]	29 [16 - 70]	24 [14 - 51]	28 [16 - 64]	31 [19 - 39]
Bilirubin (µmol/L)	10.3 [6.8 - 13.7]	10.3 [6.8 - 13.7]	10.3 [8.6 - 13.7]	10.3 [6.8 - 17.1]	10.3 [6.8 - 15.4]	10.3 [6.8 - 15.4]	10.3 [6.8 - 13.7]	10.3 [8.6 - 13.7]	10.3 [8.6 - 13.7]	10.3 [6.8 - 13.7]
Creatinine (µmol/L)	89 [71 - 106]	89 [71 - 115]	89 [71 - 124]	97 [71 - 115]	93 [71 - 122]	89 [71 - 115]	93 [71 - 115]	93 [71 - 115]	93 [71 - 115]	106 [89 - 124]
eGFR (mL/min/1.73 m²)	78 [59 - 96]	74 [55 - 93]	73 [52 - 95]	73 [52 - 93]	74 [52 - 92]	76 [53 - 94]	76 [52 - 93]	72 [50 - 89]	73 [50 - 89]	59 [43 - 84]

Data are given as median [interquartile range] or mean ± standard deviation.

a: months, b: years, c: body mass index, d: tacrolimus, e: ciclosporin A, f: mycophenolic acid, g: mammalian target of rapamycin inhibitor, h: azathioprine i: corticosteroids, j: aspartate transaminase, k: alanine transaminase, l: gamma glutamyl transpeptidase

Table 2: Factors affecting HbA1c and fasting plasma glucose

	HbA1c*,[a]			FPG[#,b]		
	nObs[c]	Estimate	p-value	nObs[c]	Estimate	p-value
Age*	1455	0.84	**< .001**	1887	0.08	0.66
Prednisolone use	1455	0.24	**0.001**	1886	0.11	**0.03**
Prednisolone dosage*	1455	-0.07	**0.008**	1886	0.01	0.59
CNI[d] use (yes)	1455	0.42	**< .001**	1887	-0.04	0.73
Tacrolimus use (yes)	1455	-0.18	0.08	1887	-0.14	0.14
Days since transplantation*	1455	0.12	**< .001**	1886	-0.04	0.49
BMI*,[e]	642	0.22	**< .001**	817	0.13	**0.002**
Hepatitis C (no)	1455	0.06	0.71	1887	-0.04	0.81
Hepatitis C, active (no)	1455	-0.18	0.51	1887	-0.10	0.71
Steatosis	1455	-0.05	0.71	1887	-0.38	**0.006**

*data scaled for analysis. a: glycated hemoglobin A1c, b: fasting plasma glucose, c: number of observations, d: calcineurin inhibitor, e: body mass index.

Table 3: Factors affecting liver enzymes

	ALT[#,a]			GGT[#,b]		
	nObs[c]	Estimate	p-value	nObs[c]	Estimate	p-value
HbA1c*[,d]	1453	0.06	**0.004**	1451	-0.09	**0.002**
FPG*[,e]	1880	0.12	**< .001**	1884	0.23	**< .001**
Age*	1880	-0.09	**0.003**	1884	-0.12	0.07
Prednisolone use	1880	0.02	**< .001**	1884	0.05	**< .001**
Days since transplantation*	1880	-0.08	**< .001**	1884	-0.09	**< .001**
Steatosis (yes)	1880	0.14	0.12	1884	0.20	0.23

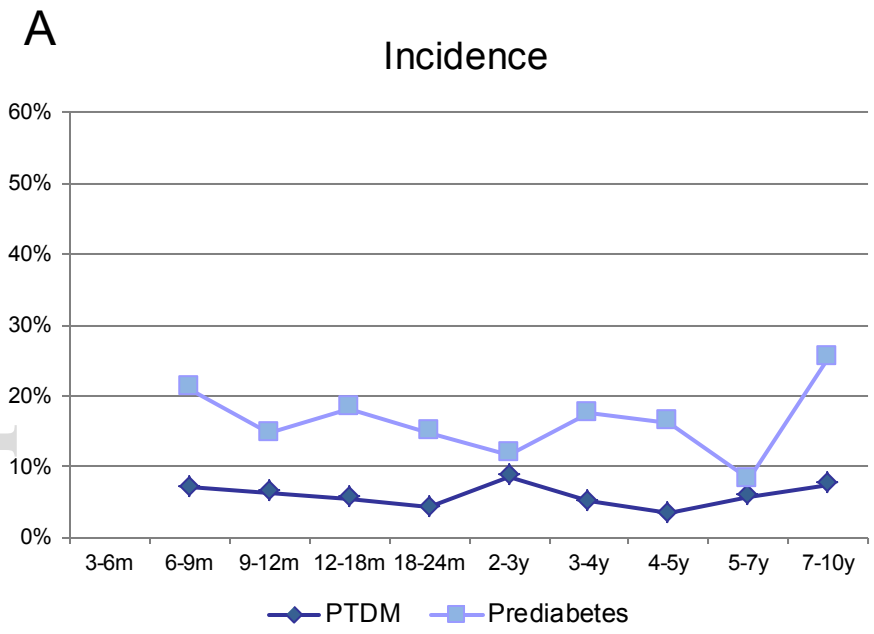
[#]data logarithmized for analysis, *data scaled for analysis. a: alanine transaminase, b: gamma-glutamyltransferase, c: number of observations, d: glycated hemoglobin A1c, e: fasting plasma glucose.

Table 4: Factors affecting kidney function

	eGFR*[a]		
	nObs[b]	Estimate	p-value
HbA1c*[d]	1355	-0.05	**0.003**
FPG*[e]	1778	-0.05	**0.02**
Age*	1778	-0.48	**< .001**
CNI[c] use (yes)	1778	0.05	0.62
Tacrolimus use (yes)	1778	0.18	**0.02**
Days since transplantation*	1778	-0.08	**< .001**

*data scaled for analysis. a: estimated glomerular filtration rate, b: number of observations, c: calcineurin inhibitor, d: glycated hemoglobin A1c, e: fasting plasma glucose.

Figure 1



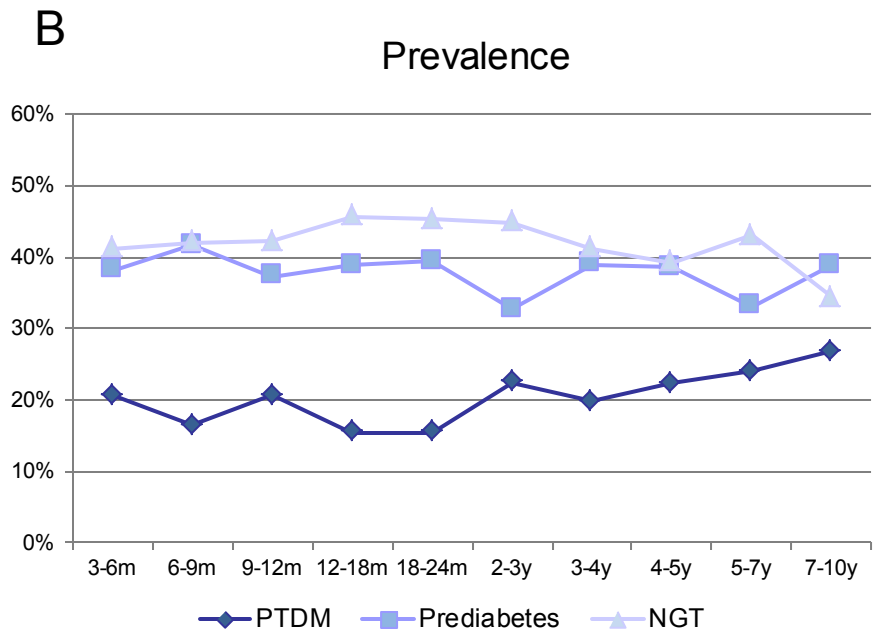
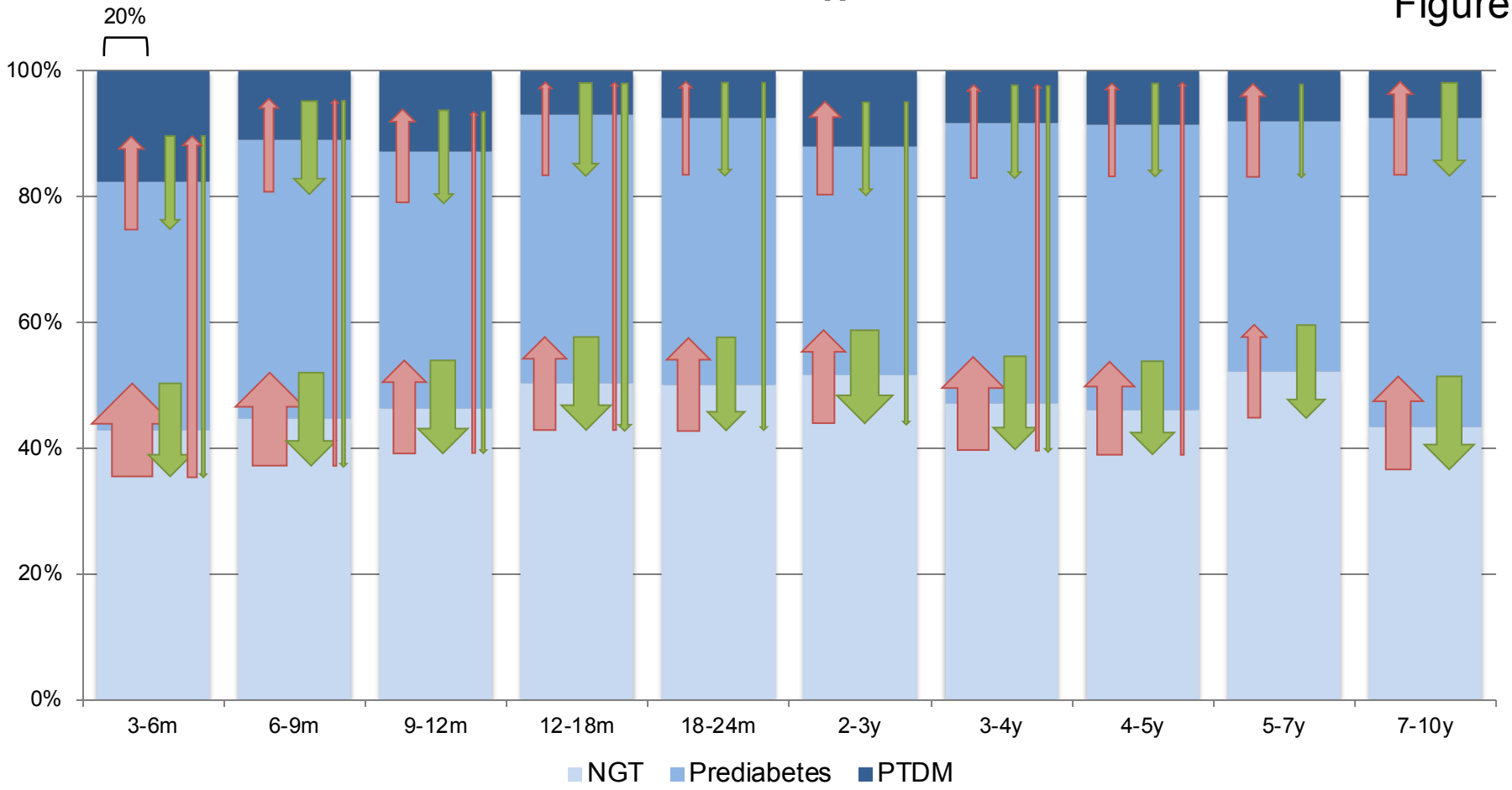


Figure 2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100%
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4-5y
5-7y
7-10y
NGT
Prediabetes
PTDM

Figure 3

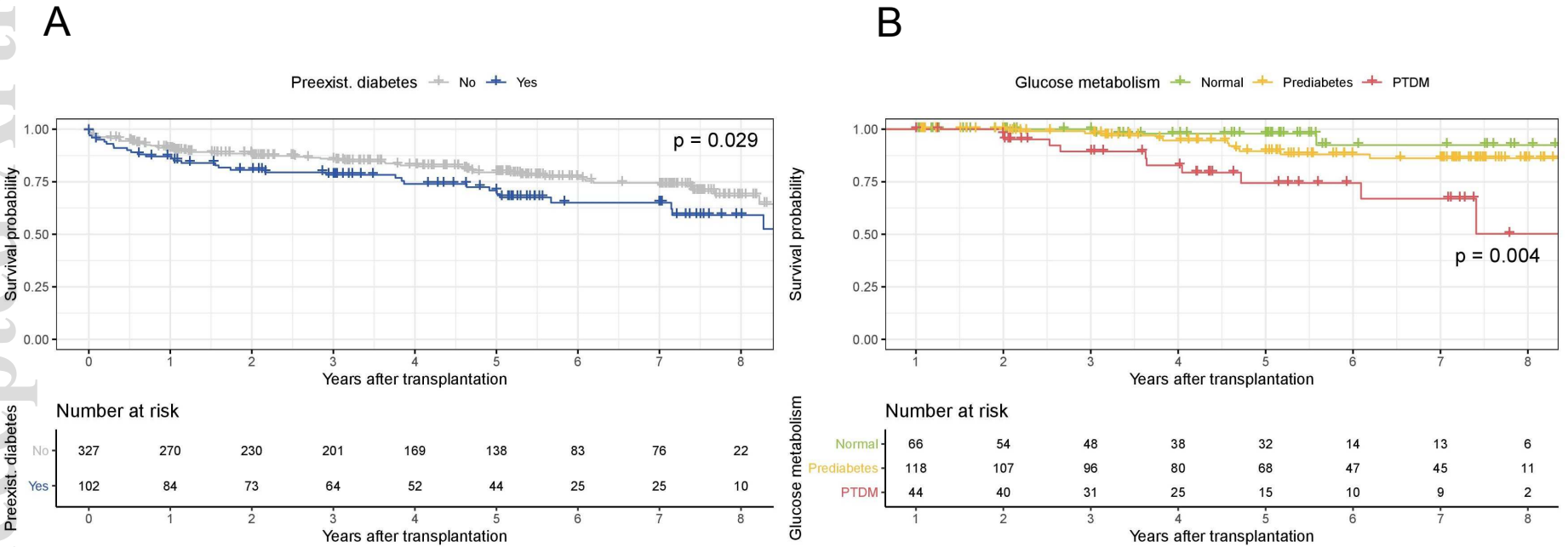

Figure 4