Prevalence and Predictors of Diabetes After Lung Transplantation: A Prospective, Longitudinal Study

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OBJECTIVE

To determine incidence and prevalence of diabetes mellitus (DM) after lung transplantation (LTx), identify risk factors for persistent DM after LTx, and determine its effect on survival.

RESEARCH DESIGN AND METHODS

This was a prospective, longitudinal study comparing DM status before and after LTx using oral glucose tolerance tests (OGTTs). DM prevalence and changes in metabolic control over time were determined. Risk factors for persistent DM and survival differences by DM status were assessed.

RESULTS

Between August 2010 and December 2012, 156 patients underwent LTx. DM prevalence after 3, 12, and 24 months was 47%, 44%, and 40%, respectively. A further 20%, 11%, and 7% had impaired glucose tolerance and/or impaired fasting glucose. Incidence of new-onset DM after transplant (NODAT) was 32%, 30%, and 24% after 3, 12, and 24 months. Nonfasting insulin levels and second phase insulin release fell 3 months after transplant (Tx) but returned to baseline by 2 years. The only risk factors for NODAT were 1- and 2-h glucose levels on pre-Tx OGTT (OR 1.73 [95% CI 1.19–2.50], $P = 0.004$, and 1.84 [1.22–2.77], $P = 0.004$, respectively). Survival was reduced in patients with DM at study end versus those without (estimated mean 979 days [95% CI 888–1,071] vs. 1,140 days [1,070–1,210], $P = 0.023$).

CONCLUSIONS

Most patients had dysglycemia during the first year after LTx, and 32% developed NODAT. Hyperglycemia was caused both by β-cell dysfunction and by insulin resistance. Only pre-Tx OGTT glucose levels predicted persistent NODAT. As DM was common and associated with reduced survival, early detection and management of DM in LTx recipients are warranted.

Diabetes mellitus (DM) is a common complication of solid organ transplantation and is associated with increased morbidity and mortality (1). It is especially common after lung transplantation (LTx), firstly because LTx recipients (LTR) require high-dose immunosuppression with glucocorticoids in combination with calcineurin inhibitors and secondly because a significant minority of patients have cystic fibrosis (CF), which results both in lung damage necessitating LTx and in destruction of insulin-producing β-cells in the pancreas.

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The reported prevalence of DM after LTx is 25–40% depending on the duration of follow-up (2,3). Similarly, cumulative incidence of new-onset DM after transplant (NODAT) ranges from 6 to 43% at 1 year (4,5) to 21–60% at 3–5 years (3,5–8). The lower figures are from earlier studies when cyclosporin, rather than the more diabetogenic tacrolimus, was the predominant calcineurin inhibitor. Most data come from large registries (2,7), which do not have standard requirements for DM screening, or from retrospective studies, which rely on use of hypoglycemic medication to define NODAT (4–6). To date, no studies have examined the prevalence of DM after LTx or the incidence of NODAT by actively screening all patients prior to LTx using the gold standard oral glucose tolerance test (OGTT). This may result in a falsely elevated incidence of "new onset" posttransplant DM. Similarly, without guidelines for when to screen, patients with early, transient posttransplant hyperglycemia may be misclassified as having NODAT. Conversely, studies reliant on use of hypoglycemic medication to capture the DM cohort will underestimate its prevalence.

Despite these limitations, the high prevalence of DM after LTx is concerning. DM is associated with increased mortality in LTR (2), irrespective of whether it is diagnosed pre- or post-LTx (8). LTR survival is relatively poor compared with renal, liver and heart recipients: median survival after LTx is 5.6 years, and less than one-third survive 10 years (2). There are many factors contributing to the increased mortality, primarily the high rates of acute rejection and bronchiolitis obliterans syndrome. We have recently demonstrated that DM confers a fourfold increased mortality risk in LTR (8). Data from the International Society for Heart & Lung Transplantation (ISHLT) are more conservative, with DM conferring a hazard ratio of 1.14 for 5-year mortality (2), but patients in this database were not actively screened for DM pre- or post-LTx.

The aims of this prospective study were *1*) to determine the incidence and prevalence of DM at prespecified time points after LTx, *2*) to evaluate the changes in metabolic parameters at these times, *3*) to determine the risk factors for new-onset DM post-LTx, and *4*) to determine the effect of DM on survival.

RESEARCH DESIGN AND METHODS

Patients

All 156 patients aged ≥16 years who received single, bilateral, or heart-lung transplants at the Alfred Hospital between 1 August 2010 and 1 December 2012 were included. Patients not already receiving treatment for DM were screened with a standard 75-g OGTT with insulin levels, and HbA_{1c} was measured in all patients before and 3, 12, and 24 months after LTx. DM, impaired glucose tolerance (IGT), and impaired fasting glycemia (IFG) were diagnosed according to the 2006 World Health Organization criteria (9). Patient demographics, BMI, and prednisolone dose at the time of testing were determined from medical records.

The study was approved by the Alfred Hospital Ethics Committee and the Monash University Human Research Ethics Committee.

Classification of DM Status

Patients were grouped into six clinically relevant categories of DM status at each time point. Those taking hypoglycemic medications for DM were considered to have the condition without undergoing further tests, and classification of the remainder was based on OGTT: *1*) no DM; *2*) DM pre- and posttransplant (DM Pre&Post); *3*) NODAT; *4*) IFG and/or IGT; *5*) resolution of DM, as evidenced by a normal OGTT after a previous diagnosis of DM (DM resolved); and *6*) unknown.

Those with a previous diagnosis of DM who subsequently had IFG/IGT on OGTT were considered to have ongoing DM. Patients in the intensive care unit when OGTT was due were classed in the unknown category unless previously diagnosed with DM and on hypoglycemic agents. Those who did not complete the OGTT but had HbA_{1c} <5.3% were considered not to have DM, as we have previously found that no patient with HbA_{1c} below this level had dysglycemia (results not shown).

LTx Donor Assessment, Recipient Selection, Transplantation, and Management

The Alfred Hospital approach to lung donor referral, assessment, and transplantation has previously been described (10,11). Recipient selection is based on international guidelines (12). Donor-recipient matching was generally undertaken according to our standard protocol as previously described (11,13). Prospective donor-recipient T- and B-cell lymphocytotoxic cross-matching was performed in all patients. Transplantation (Tx) followed standard practice (14). All patients at risk for cytomegalovirus (CMV) reactivation (either donor- or recipient-positive CMV serostatus) received prophylaxis with 2 weeks of intravenous ganciclovir and then oral valganciclovir for at least 5 months. All LTR received standard triple immunosuppression with initial tacrolimus, azathioprine, and corticosteroids. Initial once-daily dose of corticosteroid was 1 mg/kg prednisolone, with weaning to 15 mg by 3 months and 5–7.5 mg by 1–2 years. Therapy was clinically modified in the presence of significant rejection, renal impairment, or systemic sepsis.

Assessments of β-Cell Function and Insulin Sensitivity

Insulin sensitivity was assessed using the homeostasis model assessment of β-cell function (HOMA β), insulin resistance (HOMA IR), and insulin sensitivity (HOMA S) (the reciprocal of HOMA IR) (15). The quantitative insulin sensitivity check index (QUICKI) was also calculated, as this has been validated in patients with and without DM across a range of BMIs (16,17). QUICKI = 1/[(log(Ins0h) + log(G0h))], where Ins0h is fasting plasma insulin (milliunits per liter), and G0h is fasting blood glucose (milligrams per deciliter).

Estimates of first- and second-phase insulin release were calculated from models using BMI and 0-, 60-, and 120-min OGTT levels that were validated by hyperglycemic clamps (18).

Statistics

Statistical analysis was performed using PASW 18 (IBM, Armonk, NY). Results are shown as mean (SD). χ^2 tests were used to analyze categorical variables. The prevalence of NODAT was calculated from the proportion of surviving patients with NODAT at each time point.

Change in Metabolic Parameters

Changes in continuous metabolic parameters over time were assessed using one-way repeated-measures ANOVA and mixed between-within subjects ANOVA.

When sample size was <30, the nonparametric Friedman test was used. Paired *t* tests were used to analyze change in metabolic control between two time points. Unpaired *t* tests and Mann-Whitney tests were used to analyze between-group differences.

Risk Factors for NODAT

Univariate logistic regression analyses were used to determine risk factors for NODAT 1 and 2 years after LTx. Patients with DM pre-LTx and those whose post-LTx DM status was unknown or who had died prior to follow-up were excluded from analyses. Results are reported using odds ratios (95% CI).

Survival

Kaplan-Meier survival analyses were performed with DM status as the categorical variable. Results are reported as mean (95% CI).

RESULTS

Over the course of the study, 156 patients (75 male and 81 female) underwent LTx, of whom 145 survived ≥1 year and 81 of a possible 99 survived ≥2 years. More than 95% of patients were Caucasian.

Prevalence of DM

Prior to LTx, 39 of 156 patients (25%) had DM and a further 23 (15%) had IGT/IFG. Three months after LTx, almost half of the cohort (72 of 152 [47%]) had DM (37 NODAT and 35 DM Pre&Post), and another 30 of 152 (20%) had IGT/IFG. At 1 and 2 years, respectively, 64 of 145 (44%) and 32 of 81 (40%) had DM, and a further 16 of 145 (11%) and 6 of 81 (7%) had IGT/IFG (Fig. 1).

Incidence of NODAT

The incidence of NODAT was 37 of 115 (32%) at 3 months, 34 of 113 (30%) at 1 year, and 15 of 63 (24%) at 2 years. The majority of patients with NODAT were diagnosed within the first 3 months. Between 3 months and 1 year, an additional 5 of 79 (6%) were diagnosed with NODAT on OGTT. Three of the 55 patients (5%) who had an OGTT at 2 years were newly diagnosed with DM: two of these had IGT since LTx, and the other, a patient with CF, had elevated 1-h glucose levels (>13.3 mmol/L) at all previous time points, although fasting and 2-h glucose levels were normal. There was no difference in prevalence or incidence of DM by sex. However, at study end, men were more likely than women to have IGT/IFG (9 of 73 [12%] vs. 1 of 74 [1%], $P = 0.03$) and at 2 years were less likely to have DM resolved (3 of 50 [6%] vs. 8 of 48 [17%], $P = 0.04$).

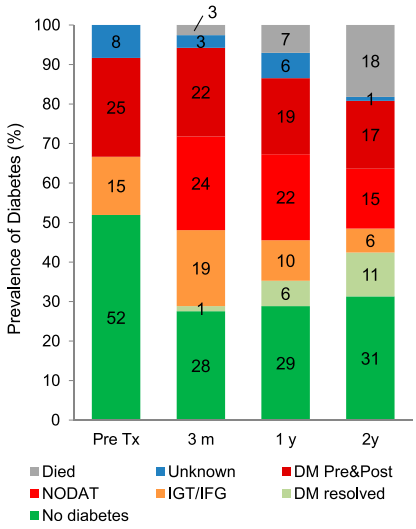

Figure 1—Prevalence (%) of DM pre- and post-LTx. A total of 156 patients were followed for 1 year and 99 for 2 years.

Resolution of DM

DM resolved in 11 of 81 (14%) patients who survived ≥2 years. Nine had NODAT, but two, both with pulmonary fibrosis, were diagnosed with DM on pre-Tx OGTT. DM resolved by 3 months in one and by 1 year in the other.

Underlying Lung Disease and DM Prevalence

Owing to small numbers, patients transplanted for pulmonary hypertension or lymphangiomyomatosis ($n = 8$) and those whose DM status was unknown at study end ($n = 9$) were excluded from analyses. There was a significant difference in DM status at study end or death between the main groups of underlying lung disease ($P = 0.032$). DM was present in 27 of 40 (68%) patients with CF or bronchiectasis (Bro) vs. 27 of 63 (43%) and 16 of 37 (43%) patients with obstructive (OLD) and restrictive (RLD) lung disease, respectively. Most patients with CF/Bro and DM had DM Pre&Post (17/27, 63%). NODAT incidence was similar in those with OLD, RLD, and CF/Bro (27, 24, and 25%).

Changes in Metabolic Parameters Over Time

Changes in glucose, insulin, and HOMA parameters were analyzed over time in subjects followed for at least 2 years (Table 1). Extreme outliers (results more than three times the interquartile range) were excluded ($n \leq 6$ for each variable). Only patients not known to have DM underwent OGTT, which greatly reduced the sample size. No individual changes in glucose or insulin levels reached statistical significance. However, insulin sensitivity, as determined by HOMA S and QUICKI, decreased over the first year after Tx but improved by 2 years ($P = 0.04$).

To investigate time-dependent changes in more detail, we separately assessed the change in OGTT from pre-Tx to 3 months and from 3 months to 2 years (Table 2). From pre-Tx to 3 months, there were significant increases in fasting (G0h) and 2-h glucose (G2h) levels and HbA_{1c}, whereas 1-h and 2-h insulin levels, second-phase insulin release, and insulin sensitivity (HOMA S and QUICKI) decreased. There were no significant sex differences. Only 11 patients had a 3-month OGTT consistent with NODAT, which limited comparison of changes between patients with and without DM, but glucose levels increased and nonfasting insulin levels fell from 0 to 3 months in both groups (results not shown). The metabolic parameters returned toward baseline between 3 months and 2 years with decreases in G2h and increases in 1- and 2-h insulin levels. β-Cell function improved (increased HOMA β and first- and second-phase insulin release), but insulin sensitivity remained unchanged.

As all patients had HbA_{1c} measured at each time point, we determined whether the change in HbA_{1c} over time was different between patients with and without DM at 2 years. There was a significant interaction between DM status and time ($P = 0.001$), such that HbA_{1c} increased in the first year before plateauing in patients with DM, whereas there was a slight rise at 3 months before returning to baseline in those without DM (Supplementary Fig. 1).

Risk Factors for Posttransplant DM

The main risk factor for persistent DM after LTx was the presence of pretransplant DM. Of the 35 patients with pre-Tx

Table 1—Metabolic parameters on OGTT pre- and post-LTx

	Pre-Tx	3 months	1 year	2 years	*P* for change
G0h (*n* = 39)	4.8 (0.5)	5.0 (0.7)	5.0 (0.7)	4.8 (0.7)	0.15
G1h (*n* = 35)	8.2 (2.4)	8.9 (2.4)	8.3 (2.4)	8.5 (3.3)	0.45
G2h (*n* = 37)	6.0 (1.8)	7.4 (2.4)	6.6 (2.0)	6.3 (2.0)	0.07
Ins 0h (*n* = 19)	7.3 (4.9)	8.2 (3.8)	8.2 (3.7)	9.4 (5.5)	0.07
Ins 1h (*n* = 16)	89.1 (60.3)	49.0 (37.8)	74.6 (73.3)	66.9 (37.1)	0.10
Ins 2h (*n* = 16)	57.7 (37.6)	38.6 (28.8)	43.4 (32.8)	57.5 (43.2)	0.90
HOMA β (*n* = 18)	108.1 (75.4)	125.7 (85.9)	126.7 (77.2)	152.0 (92.7)	0.15
HOMA IR (*n* = 20)	1.6 (1.1)	1.9 (1.1)	2.7 (3.9)	2.0 (1.3)	0.02
HOMA S (*n* = 18)	0.72 (0.48)	0.59 (0.35)	0.45 (0.21)	0.54 (0.29)	0.04
1st phase (*n* = 14)	206 (95)	149 (55)	197 (96)	204 (115)	0.23
2nd phase (*n* = 15)	55 (24)	39 (16)	51 (23)	53 (27)	0.38
QUICKI ($\times 10^2$) (*n* = 21)	16.0 (2.2)	15.2 (1.1)	15.0 (1.4)	15.4 (1.8)	0.04

Data are means (SD). Estimated first- and second-phase insulin release, mIU/L; glucose, mmol/L; insulin, mIU/L.

DM who were alive at 1 year, 30 (86%) still had DM. Similarly, 17 of 19 (89%) patients with pre-Tx DM who were alive at 2 years had persistent DM.

We determined the risk factors for NODAT at 2 years using univariate logistic regression. Patients who died earlier and those with pre-Tx DM were excluded, leaving 46 patients without DM and 15 patients with NODAT at 2 years. The only significant pre-Tx risk factors were 1- and 2-h glucose levels during OGTT (OR 1.73 [95% CI 1.19–2.50], *P* = 0.004, and 1.84 [1.22–2.77], *P* = 0.004, respectively). Post-Tx, 3-month glucose levels on OGTT and HbA_{1c} were also predictive of DM at 2 years. Sex, underlying lung disease, family history of DM, BMI change, and insulin levels on OGTT were not predictive of NODAT (Supplementary Table 1). The risk factors for NODAT at 1 year were similar: the only pre-Tx risk factors were 1- and 2-h glucose levels on OGTT (1.24 [1.01–1.52], *P* = 0.041, and 1.31 [1.03–1.68], *P* = 0.031, respectively).

We then determined whether baseline characteristics differed in 108 patients with and without NODAT at study end or death after patients with pre-Tx DM and those whose DM status was unknown at study end were excluded. Patients with NODAT had higher 0-, 1-, and 2-h glucose levels on baseline OGTT ($P \leq 0.017$) and higher HbA_{1c} (*P* = 0.015). Again, there were no differences in age, sex, BMI, underlying lung disease, smoking history, family history of DM, prednisolone dose pre-Tx, insulin levels, or donor/recipient CMV status (Supplementary Table 2).

Survival

Thirty-five patients died, and four underwent repeat LTx. Of the four who died <90 days post-LTx, two had DM Pre&Post. Of the 31 who died >90 days post-LTx, 16 (52%) had DM (9 DM Pre&Post and 7 new-onset DM), and 2 (6%) had IGT/IFG. Only 6 (19%) were normoglycemic at death. DM status was unknown in seven patients who were too unwell to complete the OGTT at the specified time. Two patients (50%) having redo LTx had NODAT, and one had IGT. For survival analyses, redo LTx was considered equivalent to a terminal event, as these patients would otherwise have died.

Patients whose DM status was unknown at study end (*n* = 9) were excluded from survival analyses. Estimated mean survival in patients with DM at study end or death was 979 days (95% CI 888–1,071) vs. 1,140 days (1,070–1,210) in those without DM (*P* = 0.023) (Fig. 2). There was no survival difference between patients with NODAT versus DM Pre&Post (estimated mean 995 days [95% CI 872–1,117] vs. 944 [804–1,084], *P* = 0.685). There were no survival differences

Table 2—Change in metabolic parameters from baseline to 3 months and 3 months to 2 years post-LTx

	Pre-Tx to 3 months					3 months to 2 years				
	n	Pre-Tx	3 months	Difference	*P**	*n*	3 months	2 years	Difference	*P**
G0h	77	4.9 (0.6)	5.2 (0.9)	0.3 (0.9)	0.01	48	5.1 (0.7)	4.9 (0.8)	−0.2 (0.8)	0.11
G1h	68	8.3 (2.3)	8.9 (2.6)	0.6 (3.2)	0.14	45	9.0 (2.5)	8.8 (3.6)	−0.2 (3.7)	0.71
G2h	72	6.3 (1.9)	7.6 (2.6)	1.2 (3.3)	0.003	45	7.6 (2.4)	6.3 (2.1)	−1.3 (3.0)	0.006
HbA_{1c}	137				<0.001					
%		6.0 (0.6)	6.2 (0.8)	0.2 (0.7)		78	6.2 (0.7)	6.1 (1.1)	−0.1 (0.9)	0.33
mmol/mol		42 (6.6)	44 (8.7)	2.2 (7.7)			44 (7.7)	43 (12.0)	−1 (9.8)	
Ins 0h	58	7.6 (6.4)	10.8 (14.7)	3.2 (16.0)	0.14	39	11.2 (17.8)	10.1 (6.7)	1.0 (19.3)	0.74
Ins 1h	53	82.9 (69.7)	54.5 (44.3)	−28.4 (71.1)	0.005	34	52.1 (31.4)	80.6 (56.5)	28.5 (60.5)	0.01
Ins 2h	53	59.5 (48.4)	35.2 (22.6)	−24.3 (48.2)	0.001	32	36.1 (24.0)	53.4 (38.6)	17.3 (38.7)	0.02
HOMA β	56	109.9 (85.6)	125.5 (85.6)	15.6 (103.8)	0.27	38	131.6 (80.8)	169.0 (105.1)	37.4 (113.1)	0.049
HOMA IR	58	1.7 (1.6)	2.5 (3.0)	0.7 (3.4)	0.11	39	2.5 (3.6)	2.4 (2.2)	0.1 (4.2)	0.88
HOMA S	58	0.90 (0.62)	0.61 (0.41)	−0.29 (0.68)	0.002	40	0.75 (0.57)	0.67 (0.52)	−0.08 (0.69)	0.48
1st phase	45	176 (91)	150 (72)	−25 (102)	0.11	27	145 (62)	192 (83)	48 (101)	0.022
2nd phase	48	47 (23)	39 (19)	−8 (25)	0.041	31	38 (17)	51 (20)	13 (24)	0.008
QUICKI ($\times 10^2$)	58	16.0 (1.7)	15.1 (1.4)	0.9 (2.0)	0.001	40	15.5 (1.7)	15.3 (1.6)	0.2 (2.0)	0.49
Prednisolone	151	4.3 (7.5)	15.4 (2.4)	11.1 (7.8)	<0.001	81	15.8 (2.3)	7.7 (2.9)	−8.2 (3.8)	<0.001

Data are means (SD). Estimated first- and second-phase insulin release, mIU/L; glucose, mmol/L; insulin, mIU/L. **P* for difference.

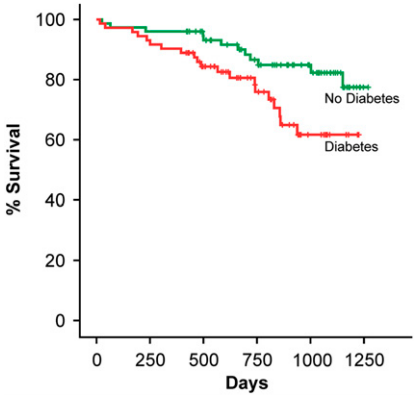

Figure 2—Kaplan-Meier survival analysis of patients with and without DM at study end or death.

between patients with and without DM pre-Tx (P = 0.712). However, many patients without pre-Tx DM developed NODAT, potentially confounding this analysis.

Causes of Death

The main causes of death were nonspecific graft failure (NSGF) (n = 12), sepsis (n = 9), and rejection (bronchiolitis obliterans syndrome, n = 6; antibody mediated, n = 3). DM was present in 6 of 9 patients with sepsis, 6 of 9 with rejection, and 5 of 12 with NSGF. DM status was unknown in 3 of 12 with NSGF. Small sample size prevented statistical analyses.

CONCLUSIONS

This study is the first to prospectively determine the incidence and prevalence of DM before and after LTx. The results were striking: 47%, 44%, and 40% of patients had DM at 3 months and 1 and 2 years, respectively. The incidence of NODAT was maximal at 3 months, occurring in one-third of patients at risk. Incidence at 1 and 2 years was 30% and 24%, respectively. The changes in DM incidence and prevalence over time were not statistically significant.

Previous studies have assessed cumulative rather than point prevalence of post-Tx DM. The ISHLT registry reports a 1-year prevalence of 25%, although the cumulative prevalence is 41% among survivors by 5 years (2). These data are compiled from 132 centers worldwide with no specific criteria for DM assessment, so many cases are likely to have been missed, especially in the early post-Tx period.

The high incidence of NODAT in this study, occurring in 32% of at-risk patients, is consistent with previous findings. Two smaller, retrospective studies found 1-year incidences of 19 and 23% (3,6). However, these were probably underestimates, as DM was defined by use of hypoglycemic agents rather than OGTT. Another study of 77 LTR assessed NODAT incidence using laboratory glucose values. One-year incidence was 56% and 44% in patients with and without CF (5). However, patients were not screened for pre-Tx DM with OGTT, and we have previously demonstrated that history alone underestimates pre-Tx DM prevalence (19).

To our knowledge, this is the first prospective, longitudinal study to assess changes in glucose and insulin levels before and after nonpancreatic solid organ Tx over a prolonged period. OGTTs were only performed in patients not taking hypoglycemic medications (irrespective of previous DM status), so observed metabolic changes relate predominantly to patients without DM.

Higher glucose levels at 3 months followed by return to pre-Tx levels may have been expected, since immunosuppression was near maximal at this time. Patients were taking prednisolone, which causes insulin resistance, upregulates hepatic gluconeogenesis, and impairs insulin secretion (20), as well as tacrolimus, which impairs β-cell function and reduces insulin secretion (21). Perhaps not expected was the 40% fall in nonfasting insulin levels and the fall in second-phase insulin release. Insulin sensitivity (HOMA S and QUICKI) also decreased, though not as dramatically. These changes may explain the high rate of DM in the early post-LTx period and support the hypothesis that transplant-associated hyperglycemia is caused by a combination of insulin deficiency and resistance (22,23). The increase in nonfasting insulin levels and first- and second-phase insulin release from 3 months to 2 years suggests β-cell recovery, which may explain both the low incidence of late-onset NODAT and the resolution of NODAT seen in some patients. Patients with persistent NODAT may not have had recovery of β-cell function, but OGTTs were not performed in this group.

OGTT was previously performed in 63 patients 10 weeks and 6 years post–renal Tx (24). Prednisolone tapering was associated with increased insulin sensitivity, and the authors postulated that this explained decreased insulin secretion in nondiabetic patients. Patients with NODAT at study end were then compared with those who had normalized their glucose tolerance. Those with NODAT had reduced insulin secretion and no change in insulin sensitivity, whereas those with normal glucose tolerance had no change in insulin secretion but increased insulin sensitivity.

We suggest that the very high incidence of NODAT, particularly early after LTx, is due to a combination of insulin resistance and β-cell dysfunction, caused by *1*) immunosuppression with prednisolone and tacrolimus, which are used in particularly high doses in LTRs, as there is a large mass of transplanted alloreactive tissue, and *2*) severe acute illness, seen almost universally perioperatively, resulting in a proinflammatory state mediated by counterregulatory hormones and neuroendocrine and cytokine pathways (25,26), Further, the transplanted organ is exposed to the external environment. Chest sepsis requiring intravenous treatment develops in 90% of LTRs in the first 12 months post-Tx (27). In addition, many LTRs have specific predisposing risk factors for DM such as CF. Our findings suggest that β-cell dysfunction is the primary driver of NODAT, but definitive clamp studies, including patients with and without NODAT, are required.

The main predictor of persistent DM at 1 and 2 years after LTx was the presence of DM prior to transplant. Among patients who did not have pre-Tx DM, higher 1- and 2-h glucose levels on pre-Tx OGTT were predictive of NODAT, but pre-Tx fasting glucose, HbA_{1c}, insulin levels, and homeostasis model assessment scores were not. We have previously demonstrated that HbA_{1c} has low sensitivity in the diagnosis of DM in an LTx population (19). Contrary to a large retrospective study (7), we did not find an increased risk of NODAT in men, older recipients (>50 years), or patients with CF. Family history of DM in a first-degree relative was also not predictive. These negative findings may have been influenced by sample size or because we assessed patients for pre-Tx DM,

which may be more common in these groups. As there was no specific risk group for NODAT, we suggest that all patients are at risk and should be actively screened.

The increased mortality in patients with DM in our study is consistent with several retrospective studies (5,8,28) and with data from the ISHLT (2). However, a mechanism has not yet been demonstrated. Suggested mechanisms for DM-related mortality after solid organ Tx are increased infection, rejection, and cardiovascular disease (1). Chronic renal failure is another risk factor for post-Tx mortality, and pre-Tx DM increased chronic renal failure risk by 53% in LTRs (29). We have previously shown that bronchiolitis obliterans syndrome is the main cause of death after LTx, irrespective of DM status (8). DM may directly impair lung function in LTRs, as it does in the general population (30,31), and in patients with CF (32,33). Supporting a lung-related mechanism of mortality are the ISHLT reports of donor DM conferring a significantly increased risk of 1-year mortality (2,34), since lungs from donors with DM may already have changes predisposing to graft dysfunction or fibrosis.

There are several limitations to this study. Firstly, data were collected from a single, albeit large, center. Secondly, only patients without DM underwent OGTT, which prevented comparison of changes in metabolic parameters between patients with and without DM. Thirdly, as this was an observational study, we did not assess whether changes in metabolic control influenced rates of persistent DM or mortality. However, patients diagnosed with DM were referred for specialist management, which may have affected outcomes. Future studies are required to determine whether earlier weaning of immunosuppressants or different dosing regimens ameliorate early hyperglycemia and reduced insulin secretion. Early insulin treatment to achieve tight glycemic control has been suggested as a means of reducing persistent NODAT in renal Tx recipients (22,35).

In summary, this prospective, longitudinal study of 156 LTR found DM or IGT/IFG in the majority of patients over the first year after LTx. The incidence of NODAT was highest at 3 months, occurring in 32% of patients. As well as increased glucose levels 3 months post-Tx, there was a 40% fall in nonfasting insulin levels, suggesting that insulin deficiency is important in the pathogenesis of NODAT. The only risk factors for NODAT were nonfasting glucose levels on pre-Tx OGTT. We suggest that all patients are at significant risk of NODAT, which is concerning, as patients with DM had reduced survival. Further studies are urgently required to determine effective strategies to prevent persistent NODAT. In the meantime, early detection and management of DM in LTR are warranted.

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