An unexpectedly high prevalence of undiagnosed diabetes in patients awaiting lung transplantation

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KEYWORDS:
lung transplantation; diabetes mellitus; prevalence; oral glucose tolerance test

BACKGROUND: Diabetes mellitus (DM) is a common complication after lung transplantation but its prevalence prior to transplantation has not been determined. We sought to determine the prevalence of and risk factors for DM in adults awaiting lung transplantation and to determine whether pre-transplant DM could be diagnosed by hemoglobin A1c (HbA1c) alone.

METHODS: All patients wait-listed for lung transplantation over a 2-year period had HbA1c measured. Those not known to have DM also underwent an oral glucose tolerance test (OGTT) with insulin levels.

RESULTS: Of 190 patients listed for lung transplantation, 30 (16%) had been diagnosed previously with DM. Twelve patients received transplants and 1 came off the waiting list before having an OGTT. The remaining patients underwent OGTT: 14 were newly diagnosed with DM and 29 with pre-diabetes. One patient vomited during the test and was excluded from analyses. Thus, 41% of all screened waiting list patients had DM (known or newly diagnosed) or pre-diabetes. Neither age, BMI, prednisolone dose nor family history correlated with dysglycemia. Patients with newly diagnosed DM and pre-diabetes were more insulin-resistant than those with normoglycemia. HbA1c correlated poorly with OGTT.

CONCLUSIONS: Patients awaiting lung transplantation have unexpectedly high rates of DM and pre-diabetes despite close medical follow-up. Screening for DM with an OGTT will allow early intervention, which may improve outcomes after transplantation.

J Heart Lung Transplant 2013;32:86–91
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test. These tests are quick and simple. However, the current gold standard for DM diagnosis is the oral glucose tolerance test (OGTT). Not only does it have a higher sensitivity than HbA1c for detecting DM, it is the only way to diagnose impaired glucose tolerance, which is associated with an increased risk of diabetes and cardiovascular disease. The OGTT may be used less frequently as it takes 2 hours and requires several blood samples.

In this study we aimed to determine the prevalence of abnormal glycemic control (DM, impaired glucose tolerance or impaired fasting glucose) and the risk factors for dysglycemia in patients awaiting lung transplantation. We also assessed whether the diagnosis of DM could be simplified with the use of a single, non-fasting blood test—the HbA1c—rather than the standard OGTT.

Methods

Patients

All patients aged >18 years (n = 190), who were on the waiting list for lung transplantation at The Alfred Hospital, Melbourne, from August 1, 2010 to July 31, 2012 and who had not received a prior solid-organ transplant, were evaluated for DM. Patients were placed on the waiting list according to international guidelines for recipient suitability. Twelve patients who proceeded to transplantation, 1 who withdrew from the waiting list before OGTT and 1 who vomited during the OGTT were excluded from subsequent analyses (Figure 1). Patient demographics and underlying diagnoses were obtained from medical records. The study was reviewed and approved by the ethics committee of The Alfred Hospital.

Approach to study

To determine pre-transplant diabetes status, all patients not known to have DM underwent a standard 2-hour 75-g OGTT after an overnight fast. Insulin levels were measured on each blood sample (0, 1 hour and 2 hours). The HbA1c, standardized to the Diabetes Control and Complications Trial (DCCT) assay, was also measured. Most tests were performed at The Alfred Hospital, although some patients were tested at their local pathology service. Prednisolone dose was recorded at the time of OGTT. Patients were asked about family history of diabetes.

The homeostasis model assessments of insulin resistance (HOMA-IR) and beta-cell function (HOMA-B) were calculated from baseline fasting glucose and insulin levels on the OGTT. The simplified HOMA equations for insulin resistance and beta-cell function, where FPI is fasting plasma insulin concentration (mU/liter) and FPG is fasting plasma glucose (mmol/liter), were used:

- HOMA-IR = (FPI × FPG) / 22.5
- HOMA-B(%) = (20 × FPI) / (FPG-3.5)

Glucose was measured by the hexokinase method and insulin by the chemiluminescent microparticle-enhanced immunoassay (CMIA) on an Abbott Architect ci16 200 (Abbott Diagnostics, Abbott Park, IL). HbA1c was measured by boronate affinity high-performance liquid chromatography (CLC 330; Primus Diagnostics, Kansas City, MO).

Definitions

The 2006 World Health Organization criteria were used to diagnose DM, venous fasting plasma glucose ≥7.0 mmol/liter or 2-hour glucose ≥11.1 mmol/liter; impaired glucose tolerance (IGT) 2-hour glucose 7.8 to 11.0 mmol/liter; and impaired fasting glucose (IFG) 6.1 to 6.9 mmol/liter. Patients known to have DM at the time of transplant listing were termed “known DM.” Patients newly diagnosed with DM by OGTT were termed “new DM,” and those with IGT and/or IFG were termed “pre-diabetes.”

Statistics

Differences between groups were assessed using the independent-samples Kruskal–Wallis test for ordinal data and chi-square analyses for categorical data. p < 0.05 was considered statistically significant. PASW version 18 (IBM, Armonk, NY) was used for all analyses.

Results

Study subjects and incidence of DM

Thirty patients were known to have DM. Of the 146 patients who completed the OGTT, 14 had new DM, 29 had pre-diabetes (1 of whom had isolated IFG), and 103 had normal results (Figure 1). Thus, of the 176 patients assessed for DM prior to transplantation (25.0%) had DM and a further 29 (16.5%) had pre-diabetes. Of the 14 patients with new DM, all had 2-hour glucose ≥11.1 mmol/liter, whereas only 2 had fasting plasma glucose ≥7.0 mmol/liter. Demographic data of these patients are presented in Table 1.

OGTT and insulin levels in patients not known to have DM

As expected, there were significant differences in the area under the curve (AUC) for glucose during OGTT (p < 0.001) and HbA1c (p < 0.001) across the 3 groups (DM, pre-diabetes, normal; Table 2). In addition, there was a significant difference between insulin levels at 2 hours
(p < 0.001), but not at baseline or 1 hour. Interestingly, insulin levels remained elevated throughout the OGTT in patients with abnormal glucose tolerance (DM or pre-diabetes), but fell from 1 to 2 hours in patients with normal glucose tolerance (Figure 2).

There were no differences in age, gender, body mass index (BMI), prednisolone dose or family history between the 14 patients who did not complete the OGTT and those whose DM status was assessed, and there were no obvious differences in underlying lung disease.

**Insulin resistance and beta-cell function**

The pathophysiology of abnormal glycemic control was assessed using HOMA. Insulin resistance was higher in those with new DM and pre-diabetes (normal 1.23 [interquartile range 0.76 to 1.73] vs pre-diabetes 1.67 [0.94 to 2.54] vs new DM 1.86 [1.37 to 2.11]; p = 0.029). There was no difference between groups in beta-cell function as assessed by HOMA-B (p = 0.37).

Baseline insulin and HOMA-IR were higher in men. Although these were statistically significant (p = 0.031 and p = 0.036, respectively), the differences were small and unlikely to be clinically relevant (e.g., median baseline insulin 6.7 mU/liter in men vs 5.5 mU/liter in women). Consistent with the higher fasting insulin levels, there was a trend toward increased beta-cell function in men compared with women (median HOMA-B: 95.0 vs 73.3, respectively; p = 0.056).

**Risk factors for pre-transplant dysglycemia**

Twelve of 14 patients newly diagnosed with DM were women, but a gender difference was not observed in patients with known DM or pre-diabetes and there was no overall gender difference between groups (p = 0.088). There were no significant differences in age, BMI, family history of DM, prednisolone use or prednisolone dose between groups.

Fifty-six of 146 patients were taking prednisolone at the time of OGTT. When these patients were excluded to avoid possible bias due to this medication, none of the previously noted risk factors for dysglycemia became significant.

We assessed whether prednisolone use in the 59 patients with BMI > 25 kg/m² in our cohort was

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Table 1: Patients’ Demographics

<table>
<thead>
<tr>
<th></th>
<th>Known DM (n = 30)</th>
<th>New DM (n = 14)</th>
<th>Pre-diabetes (n = 29)</th>
<th>Normal (n = 103)</th>
<th>p-value across groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>53 (34–62)</td>
<td>59 (50–63)</td>
<td>55 (46–61)</td>
<td>54 (43–61)</td>
<td>0.46</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>24.0 (21.1–27.8)</td>
<td>27.0 (19.5–28.6)</td>
<td>22.2 (19.2–27.2)</td>
<td>22.7 (20.1–26.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Pred (mg)</td>
<td>5.0 (0–11.3)</td>
<td>0.0 (0–10)</td>
<td>0.0 (0–5.0)</td>
<td>0.0 (0–5.0)</td>
<td>0.24</td>
</tr>
<tr>
<td>Taking pred [n (%)]</td>
<td>8 (57%)</td>
<td>10 (34%)</td>
<td>38 (38%)</td>
<td>38 (38%)</td>
<td>0.32</td>
</tr>
<tr>
<td>Gender (M/F) (n)</td>
<td>15/15</td>
<td>2/12</td>
<td>15/14</td>
<td>41/62</td>
<td>0.09</td>
</tr>
<tr>
<td>Obstructive (n)</td>
<td>7</td>
<td>7</td>
<td>13</td>
<td>54</td>
<td></td>
</tr>
<tr>
<td>Restrictive (n)</td>
<td>10</td>
<td>4</td>
<td>4</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>CF/bronch (n)</td>
<td>12</td>
<td>2</td>
<td>10</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>PHT (n)</td>
<td>1</td>
<td>1</td>
<td>2</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>FHx DM</td>
<td>46%</td>
<td>29%</td>
<td>20%</td>
<td>38%</td>
<td>0.21</td>
</tr>
</tbody>
</table>

Results are shown as median and interquartile range (IQR). CF, cystic fibrosis; bronch, bronchiectasis; DM, diabetes mellitus; PHT, pulmonary hypertension; pred, prednisolone.

*The p-value is given for independent-samples Kruskal Wallis test for age, BMI and prednisolone dose, and for chi-square test for number taking prednisolone, gender and first-degree relative (FHx) with DM.

Table 2: Biochemistry of Patients Who Had OGTT

<table>
<thead>
<tr>
<th></th>
<th>New DM (n = 14)</th>
<th>Pre-diabetes (n = 29)</th>
<th>Normal (n = 103)</th>
<th>p-value across groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose 0 h</td>
<td>5.7 (5.2–6.2)</td>
<td>5.0 (4.7–5.6)</td>
<td>4.8 (4.6–5.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose 1 h</td>
<td>12.2 (11.2–15.6)</td>
<td>11.0 (9.3–12.3)</td>
<td>7.7 (6.1–9.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose 2 h</td>
<td>12.0 (11.1–16.8)</td>
<td>8.9 (8.3–9.8)</td>
<td>5.7 (4.7–6.6)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Glucose AUC</td>
<td>22.0 (19.3–25.6)</td>
<td>17.9 (16.1–19.4)</td>
<td>12.8 (11.0–14.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin 0 h</td>
<td>7.2 (5.4–8.0)</td>
<td>6.8 (4.5–11.2)</td>
<td>5.6 (3.7–8.0)</td>
<td>0.192</td>
</tr>
<tr>
<td>Insulin 1 h</td>
<td>37.4 (31.3–51.0)</td>
<td>54.8 (35.8–99.5)</td>
<td>55.3 (37.9–82.3)</td>
<td>0.280</td>
</tr>
<tr>
<td>Insulin 2 h</td>
<td>66.0 (35.0–123.0)</td>
<td>73.5 (45.0–134.5)</td>
<td>33.2 (20.3–56.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Insulin AUC</td>
<td>78.9 (62.8–123.4)</td>
<td>109.9 (61.4–153.1)</td>
<td>74.0 (54.1–115.4)</td>
<td>0.373</td>
</tr>
<tr>
<td>HbA1c</td>
<td>6.0 (5.6–6.4)</td>
<td>6.0 (5.8–6.3)</td>
<td>5.7 (5.5–5.9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>HOMA-IR</td>
<td>1.90 (1.37–2.11)</td>
<td>1.67 (0.94–2.54)</td>
<td>1.23 (0.76–1.73)</td>
<td>0.029</td>
</tr>
<tr>
<td>HOMA-B</td>
<td>63.3 (43.7–105.5)</td>
<td>88.4 (58.6–152.3)</td>
<td>83.8 (55.6–133.3)</td>
<td>0.374</td>
</tr>
</tbody>
</table>

Results are presented as median (IQR). Glucose measured in millimoles per liter (mmol/liter); insulin measured in milli-units per liter (mU/liter). AUC, area under the curve; HOMA, homeostasis model assessment of insulin resistance (IR) or beta-cell function (B).
associated with increased risk of dysglycemia, as the effects of prednisolone use and high BMI may be additive. However, there was no difference in prednisolone use across the groups with dysglycemia and normoglycemia in these patients ($p = 0.35$).

Patient numbers were too small to compare DM status between the 5 categories of underlying lung disease. However, because DM is a known complication of CF, this group was compared against those with non-CF lung disease. As expected, patients with CF were significantly younger ($p < 0.001$), leaner ($p < 0.001$) and on lower prednisolone doses ($p = 0.011$). Patients with CF had a higher prevalence of known DM (36% vs 13%, CF vs others), which probably reflects increased routine screening in these patients. There was no significant difference in newly diagnosed dysglycemia (new DM or pre-diabetes) between patients with CF and non-CF lung disease (24% vs 25%). However, when known DM was taken into account, patients with CF had a higher prevalence of abnormal glycaemia (known DM, new DM or IGT) than patients with other diagnoses (61% vs 37%, $p = 0.023$).

**Comparison of HbA1c and OGTT for diagnosis of dysglycemia**

Using the HbA1c cut-point of $\geq 6.5\%$ suggested for DM diagnosis by the 2009 International Expert Committee report$^{12}$ and adopted by the American Diabetes Association (ADA),$^{13}$ the sensitivity for detection of new DM was only 21% with a specificity of 98%. An HbA1c of $\geq 6.0\%$, the level suggested by the International Expert Committee to diagnose patients at high risk of developing DM,$^{12}$ had a sensitivity for detecting pre-diabetes or new DM of 60% and a specificity of 80%. The ADA-suggested level of $\geq 5.7\%$ for the diagnosis of “pre-diabetes” (IGT or IFG) detected 81% of patients with either pre-diabetes or new DM but with a specificity of only 37%.

**Discussion**

This is the first prospective study to examine the prevalence of DM and dysglycemia in patients awaiting lung transplantation and the results are surprising. Using the OGTT in this study to allow definitive diagnosis of DM and detection of pre-diabetes, one quarter of all patients listed for lung transplantation had DM and just under half had either DM or pre-diabetes. Over half of those with abnormal glucose tolerance were newly diagnosed by OGTT. Moreover, no specific risk factors for those with dysglycemia were identified.

This high rate of newly diagnosed dysglycemia is significant in a population already closely monitored in tertiary institutions. It is noteworthy that the “standard” tests of fasting glucose and HbA1c were inadequate to diagnose DM and pre-diabetes with sufficient sensitivity. We therefore advocate use of OGTT to screen all waiting list patients, as diagnosis and management prior to transplantation may improve outcomes.

Lung recipients have the highest rates of DM after solid-organ transplantation with a 26% prevalence at 5 years and 38% at 10 years.$^{5,7,14,15}$ Lung recipients also have increased mortality compared with other solid-organ transplant recipients.$^{5,16,17}$ Hyperglycemia is associated with worse outcomes, including increased mortality and morbidity, in hospitalized patients.$^{18}$ Although there is no evidence that the high rates of DM in lung transplant recipients are a direct cause, DM is an independent risk factor for 5-year mortality.$^{7}$ The link may not be mediated by DM-induced vascular damage, as donor history of DM is also a significant risk factor for mortality.$^{19}$ This raises the possibility that DM may also be associated with non-vascular, small-airway complications in lung transplant recipients.

The prevalence of DM in adult Australians is 7.5% with half being unaware of their disease, and a further 16% have pre-diabetes.$^{20}$ The prevalence of DM is higher in patients with lung disease than in the normal population. Insulin-dependent DM is present in 21% of adult Australian patients with CF.$^{21}$ Few studies have assessed the prevalence of DM in obstructive or restrictive lung disease. However, a study of patients aged $\geq 40$ years with COPD found a 17% prevalence of DM as reported by primary care physicians,$^{22}$ and COPD has been associated with an increased risk of DM, perhaps via upregulation of inflammatory cytokines.$^{23}$ There are no data on DM prevalence in patients with restrictive lung disease (RLD), but one study found that these patients had a 1.45-fold increased incidence of DM.$^{24}$ The 25% prevalence of DM in waiting list patients in the present study was even higher than that in the aforementioned studies, and the prevalence of dysglycemia was almost twice that of the normal population.
It is difficult to determine whether the prevalence of pre-transplant DM is higher in lung transplant recipients than in patients awaiting other solid-organ transplants, because there have been few studies in the latter. Many studies have assessed the prevalence of new DM after transplantation (termed post-transplant diabetes [PTDM]). However, almost all studies of PTDM are retrospective and assessed pre-transplant DM by documented use of diabetic medications or clinical notes. This would underestimate the true prevalence of pre-transplant DM and therefore overestimate the rate of PTDM. In the only study of heart transplant patients using the OGTT prior to transplantation, no new cases of diabetes were detected, but IGT was present in 55 of 141 (39%).25 Newly diagnosed DM is also less common in renal transplant patients. Using OGTT, newly diagnosed pre-transplant DM and pre-diabetes were found, respectively, in 15 and 115 of 378 renal transplant patients without known DM.26 Another study that excluded patients with known DM found no new DM but pre-diabetes in 12 of 78 patients who had an OGTT prior to transplantation.27 The last study demonstrated an increased incidence of PTDM in patients with pre-diabetes prior to transplantation, and there was a similar trend in the study of heart transplant patients.

No specific risk factors for new DM or pre-diabetes were identified in our study. In contrast to previous studies, age, BMI, prednisolone dose and family history did not appear to influence the risk of dysglycemia. Patients with CF were more likely to have a known diagnosis of DM at the time of listing. This may reflect increased screening for DM, a known complication of CF, in these patients.

The lack of obvious risk factors for DM suggests that all patients not known to have DM should be specifically screened prior to transplantation. Only 2 patients had fasting glucose levels in the diabetic range and only 2 had IFG (1 of whom also had IGT), indicating that the OGTT rather than fasting glucose is necessary to make the diagnosis in this population.

Patients with diabetes and pre-diabetes had higher HOMA-IR indices as well as higher 2-hour insulin levels, indicating insulin resistance. Although these findings could be consistent with sickness and/or corticosteroid treatment, they are also characteristic of the development of Type 2 DM. Patients in this study were tested either as outpatients or during an elective admission for pre-transplant work-up, so they were not acutely unwell at the time of OGTT. The increased insulin resistance in these patients is therefore most likely to reflect the natural history of the development of DM.

The American Diabetes Association (ADA) recently endorsed HbA1c as a diagnostic test for DM, in part because of its ease of accessibility in the general community. A diagnostic level of \( \geq 6.5\% \) has been determined as the prevalence of moderate retinopathy begins to rise at this level in the general population.12 However, its 21% sensitivity in progression to diabetes in the general population, this may not be the case for post-transplant DM in patients awaiting transplantation.

The most effective time to educate patients about DM may be prior to transplantation, because, after this procedure, they are often unwell, have multiple medical and allied health teams involved in their care, and may be overwhelmed by the amount of new information they must absorb. In this setting, their ability to learn about and self-manage DM is more limited and it may be more difficult for diabetes nurse educators to access the patient.

One limitation of this study is that patients were not all assessed immediately on transplantation listing. Some patients had been on the waiting list for some time and it is possible that their condition had deteriorated over time, perhaps increasing the risk of dysglycemia. Therefore, we suggest that screening should be repeated regularly after the initial pre-transplant assessment. Also, there were relatively few patients in each category of underlying lung disease, which limited our capacity to determine the relationship between specific diseases and dysglycemia.

The high prevalence of DM and IGT in patients awaiting lung transplantation in this study suggests that all patients should be routinely screened for these conditions. An OGTT should be used because HbA1c and fasting glucose lack the required sensitivity and specificity in this population. In patients with pre-diabetes, further studies are required to determine the rate of progression to diabetes and whether it increases morbidity pre-transplant and the development of post-transplant DM. Detection of DM prior to transplantation would allow for early patient education and management and potentially a better outcome while still on the waiting list. It would also minimize the risk of acute hyperglycemia and, given the association of DM with increased post-transplant morbidity and mortality, early detection and management may improve these outcomes. Further studies of the clinical consequences of pre-transplant dysglycemia are therefore required.

Disclosure statement

K.L.H. received a Monash Faculty Postgraduate Scholarship and an Alfred Research Trusts Postgraduate Scholarship. The other authors have no conflicts of interest to disclose.

We thank Melissa Vereker (The Alfred Hospital, Melbourne) for help with the creation and modification of a patient database.

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