Cystic fibrosis-related diabetes and transplant outcomes

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INTRODUCTION

Cystic fibrosis (CF) is one of the most common and deadly inherited genetic disorders with a prevalence of nearly 1 in 2500 Caucasian live births. In the US alone, there are approximately 30,000 people affected by CF and over 100,000 people worldwide. About 80% of people with CF will die due to respiratory complications with an expected median lifespan of approximately 37 years (Boyle, 2007). However, before the success of lung transplant (LTx) in the early 1980’s the expected life expectancy was far worse (Ratjen & Doring, 2003).

While the transplanting of lungs improves pulmonary function, the effects of CF continue to affect many other organ systems. One of the biggest challenges of CF is the development of cystic fibrosis related diabetes (CFRD). CFRD is unique in that CFRD shares characteristics of both type 1 diabetes mellitus (DM) with a decrease in production of insulin due to destruction of pancreatic islet cells and type 2 DM with the development of insulin resistance (Bloomgarden, 2002; Pietreopaolo & Le Roith, 2001). Studies show that the prevalence of diabetes in CF patient varies widely based on age and gender and has been estimated to be between 12-76% (Dean & Santis, 1994; Hadjiliadis et al., 2005; Lanng, Thorsteinsson, Nerup, & Koch, 1992; Mackie, Thorton, & Edenborough, 2003; Meachery et al., 2008). The development of CFRD prior to transplant has been linked to worse outcomes than patients with CF and no pre-existing diagnosis of DM (Belle-van Meerkerk et al., 2012; Mackie et al.). Interestingly, some research suggests that CF patients are at no more risk of developing diabetes post lung transplant than other populations receiving lung transplants (Belle-van Meerkerk et al.). However, the current literature remains unclear if the diagnosis of new-onset DM post-LTx is associated with worse, neutral, or improved outcomes (Belle-van Meerkerk et al.; Bradbury, Shirkhedkar, Glanville, & Campbell, 2009; Hadjiliadis et al.; Hofer et al., 2012)
The aim of this study was to analyze existing data from a regional transplant hospital within the United States. We evaluated the patients’ metabolic state prior to and post-LTx surgery and examined the rate of occurrence for developing DM post-LTx. We also compared the morbidity and mortality between those with pre-existing DM, new-onset DM, and those that remained undiagnosed with DM. The goal of this study was to better understand the effects of DM on CF patients prior to and following LTx in order to better guide patient care.
METHODS

We performed a retrospective study at the University of Michigan Health System (UMHS). Inclusion criteria for this study consisted of age 18 and older, receiving a LTx from January of 2001 through January of 2011 at the UMHS. Patient demographic data as well as, age of diagnosis of CF, age of diagnosis of diabetes (if applicable), number and causes of readmissions, cause of mortality (if applicable), survival days, and length of time on transplant list were also collected.

Definition of variables

A clinical diagnosis of DM was made by primary care physicians using the guidelines of the American Diabetic Association:

1) A1C ≥ 6.5%
2) Fasting plasma glucose ≥ 126mg/dl (7.0 mmol/L)
3) 2-hour plasma glucose ≥ 200mg/dl (11.1 mmol/L) during oral glucose tolerance test
4) Patients with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥ 200mg/dL (11.1 mmol/L).

The first three methods were repeated on a separated day in the absence of unequivocal hyperglycemia (American Diabetes Association, 2012). In addition, if a patient’s chart did not explicit state a diagnosis of diabetes from the primary care physician, we also considered use of maintenance insulin or other hypoglycemic agents as a definition for diabetes. Insulin therapy and other hypoglycemic agents are first-line treatment of diabetes in cystic fibrosis (Moran et al., 1999). Thus, any patient on insulin therapy prior to transplant was defined to be diagnosed with DM, if that insulin use was not specifically coupled with steroid medications. Post-transplant diabetes was determined using the same criteria, with an allowance of an initial nine months
post-transplant due to the intensive use of higher doses of IV and oral steroids as an immunosuppressant therapy to prevent allograft acute rejection which ultimately effect blood sugar levels (Rolon et al., 2007).

Primary comparison variables included body mass index (BMI), random blood glucose level (RBGL), forced expiratory volume in 1 second (FEV1) and forced vital capacity (FVC). Pre-transplant BMI was calculated using the admission weight and height prior LTx surgery. RBGLs were the average of last two RBG levels prior to admission for LTx. Similarly, FEV1 and FVC were determined by the average of the last two measured values prior to LTx. Baseline post-transplant FEV1 were the calculated means of the two highest FEV1 values that were at least three weeks apart and less than one year post-transplant. Corresponding FVC values from the measured FEV1 values were averaged and used to determine post-transplant FVC values. Post-transplant RBGLs were the average of the first two blood sugar measures at least nine months post-transplant and again were assumed to be random measures as fasting status could not be verified. Finally, although the ADA guidelines for diagnosis of diabetes recommend using HA1c as diagnosing criteria, HA1c was not used in this study because of the lack of consistency in monitoring and the suggested inaccuracy of using HA1c in CFRD patients (Lanng et al., 1992).

The number and cause of readmission were determined based on hospital discharge summaries and only readmissions to the University of Michigan Health Systems were recorded. The reasons for readmission were classified into three categories 1) infection, 2) acute or chronic rejection, 3) other. A classification of infection included primary diagnosis of an infections agent (aspergillus, cytomegalovirus (CMV), pseudomonas, etc), pneumonia, or bacteremia. A diagnosis of rejection was made based on the institution’s definition of acute and chronic
rejection. Acute rejection was defined as six biopsies during a single bronchoscopy showing acute cellular rejection; while chronic rejection was defined as the patient having two consecutive FEV1 values that are at least three weeks apart and less than or equal to 80% of the baseline FEV1 value. All other diagnosis requiring admissions were grouped into the “other” category and were generally less life threatening than the other two afore mentioned categories.

Statistical Analysis

We used repeated-measures ANOVA with Tukey post-hoc analysis to compare the means for each variable. Our criterion for statistical significance was p<0.05.
RESULTS

A total of 37 patients’ charts were reviewed. A total of 23 males and 14 females were included in this study with a mean age at transplant of 31. A total of 15 (40.5%) patients were diagnosed with diabetes prior to transplant and 22 (59.5%) patients without diabetes. Of the 22 patients without diabetes prior to transplant, 15 (68.2%) patients from that group developed diabetes post-transplant. A total of 30 (81.1%) patients developed diabetes before the conclusion of our study.

We compared the three groups: pre-transplant diabetes, post-transplant diabetes, and those who remained undiagnosed. There was a significant difference among the groups when it came to gender with patients diagnosed with diabetes prior to LTx being female compared to patients being diagnosed with diabetes post LTx or to not develop diabetes at all (73% vs 13.3% and 14.3% respectively, p = 0.001). There were no other statistically significant baseline differences noted between the three CF groups (Table 1).

Overall mortality rates were lowest among the patients diagnosed with diabetes post-LTx at 33.3%, compared to the undiagnosed and pre-LTx diagnosed diabetes groups (42.9% and 46.7%). Also, one-year survival rates were highest among the patients diagnosed with diabetes post-LTx without a single death occurring, while one death occurred in the first year in each of the other two groups. The three year mortality rates was very high for both the non-diabetic and pre-LTx diabetic group with 100% and 57.1% of all deaths occurring during this time, respectively compared to only 20% in the post-LTx diabetic group. Long-term survival rate trends are highest among the post-LTx diabetic group being the only group to have patients’ currently living post-transplant greater than 10yrs. The ten year survival of the patients
diagnosed with diabetes post-LTx significantly differed from those undiagnosed with diabetes and those diagnosed prior to LTx 26.7% vs 0%, p = 0.046).

Overall readmission rates did not significantly differ between groups, nor did the diagnosis for the need to be readmitted. However, post-LTx diabetics had a tendency to be admitted for infections reasons compared to the other two groups (4.1 vs 2.3 and 2.7, p = 0.43).
DISCUSSION

Our study suggests that a diagnosis of diabetes has no impact on overall mortality of cystic fibrosis lung transplant. Our results are in agreement with Hadjiliadis et al. (2005) study, which reported that the development of DM post-LTx was not associated with worse outcomes. In fact, our findings imply that the development of post-LTx diabetes may provide some beneficial effect, which differs from Hofer et al. (2011) study that described patients diagnosed with DM prior to LTx may improve long-term outcomes. Additionally, our findings suggest that patients that have not developed diabetes following LTx may be at increased risk of mortality within the first three years post-transplant which is the opposite of what Bradbury et al. (2009) reported.

Although our findings imply that cystic fibrosis patients that develop diabetes following lung transplant have decreased morbidity and better ten year survival outcomes, I would caution the reader before drawing a cause and effect relationship. In fact, there are many studies that suggest the effects of insulin provide an anabolic effect which may prove to be beneficial post-LTx (Rolon et al. 2007). Furthermore, healthcare providers may be more aware of the increased incidents of DM post-solid organ transplant and may encourage a stricter adherence to controlling blood sugars and diabetic patient education. There are many more aspects that should be considered as well including long-term effects of diabetes on other organ systems that may affect those diagnosed with diabetes prior to LTx, and possible nutritional deficits in those that remain undiagnosed with diabetes.

Healthcare providers working with CF patients need to recognize that calorie limiting diets are not recommended in CF patients and their patients are likely to develop diabetes as they age, and most certainly after LTx. Similar to other studies, our study found that nearly 41% of
CF patients developed diabetes prior to transplant. And of those without a prior diagnosis of diabetes, 68.2% of CF patients developed diabetes post transplant. Overall our study suggests that 81.1% of CF patients will develop diabetes within their lifetime following lung-transplant. Even though high energy diets are encouraged, patients still need to be aware that glycemic control is still highly encouraged, and the energy demands of breathing following LTx can be significant.

The biggest limitation to this study is related to population size. Although this study encompassed a ten year lung transplant enrollment at one of the United States’ largest lung transplant hospital. Ideally, combing similar researching methods and drawing data from other transplant hospitals in the country could improve sample size and allow for stronger statistical trends and analysis. Consequently, our sample size for this study was less than 40, making statistical significance difficult to achieve when comparing three groups. Similar to other studies, another weakness is the retrospective study design. We were unable to verify all data drawn from the charts and were forced to make some reasonable assumptions. Further studies could be better served by developing guidelines for a longitudinal study that collected the necessary data over a longer period of time and with greater consistency and reliability.
CONCLUSIONS

Overall, a diagnosis of CFRD does not affect lung transplant outcomes or mortality. Our study suggests that a diagnosis of post-LTx diabetes in CF patients may provide some beneficial effect, although the exact mechanism remains unclear. Our study further adds depth to the prior research discussing the overall prevalence of CFRD and the increase in incidence that can be expected following LTx.
REFERENCES


<table>
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<tr>
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<th>No Diabetes (n=7)</th>
<th>Post-LTx Diabetes (n=15)</th>
<th>Pre-LTx Diabetes (n=15)</th>
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<tr>
<td>Gender</td>
<td>6 males:1 female</td>
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<tr>
<td>Age of CF Diagnosis</td>
<td>7.91</td>
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<td>Age at Transplant</td>
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<td>42.8% (3/7)</td>
<td>33.3% (5/15)</td>
<td>46.7% (7/15)</td>
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Table 1. CF patients’ group demographics based on diabetic diagnosis preceding and following lung transplant.
ABSTRACT

Objective: Cystic fibrosis related diabetes (CFRD) is a prevalent diagnosis among cystic fibrosis (CF) patients. We aim to better understand the effects of CFRD on CF patients prior to and following lung transplant to better guide patient care.

Methods: A retrospective study examining 37 CF patients that underwent lung transplant (LTx) at the University of Michigan Health System from January 2001 through January 2011.

Results: Overall mortality rates were lowest among post-LTx diabetics (33.3%) compared to the undiagnosed and pre-LTx diabetic groups (42.9% and 46.7%). Ten year survival of the patients diagnosed with diabetes post-LTx significantly differed from undiagnosed CF patients and those diagnosed with CFRD pre-LTx 26.7% vs 0%, p = 0.046).

Conclusions: Overall, a diagnosis of CFRD does not affect LTx outcomes or mortality. Our study suggests that a diagnosis of post-LTx diabetes in CF patients may provide some beneficial effect, although the exact mechanism remains unclear.