Published in final edited form as:

J Heart Lung Transplant. 2014 February ; 33(2): 215–217. doi:10.1016/j.healun.2013.10.018.

Impact of pre-diabetes on heart transplant outcomes in patients with advanced heart failure

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The prevalence of type 2 diabetes (T2D) is significant in patients with advanced heart disease, and is further increased after transplantation.¹ Increasing attention has focused on abnormal metabolic states that precede the onset of T2D. The American Diabetes Association (ADA) has advocated for specific definitions of pre-diabetes,² a condition that overlaps with the metabolic syndrome. Pre-diabetes predicts future diabetes with an estimated incidence of 5% to 10% per year, and is associated with early microvascular disease and increased cardiovascular risk.³ Despite this, data concerning the impact of pre-diabetes in patients undergoing heart transplant is scarce.

In this study, we evaluated survival and post-transplant complications among patients with pre-diabetes and no diabetes in a cohort of cardiac transplant patients. This was a retrospective observational analysis using data collected and entered prospectively in an institutional database of all adult patients who underwent a first heart transplant at Brigham and Women's Hospital between January 2000 and July 2012, who also had hemoglobin A_{1c} (HgbA_{1c}) levels measured within 1 year prior to transplant. Pre-diabetes was defined using the ADA definition of HgbA_{1c} 5.7% to 6.4% in patients without known diabetes.²

The following post-transplant outcomes were recorded during follow-up in all patients: (1) all-cause mortality; (2) acute cellular rejection episodes (International Society for Heart and Lung Transplantation [ISHLT] Grade 2R on routine surveillance endomyocardial biopsies during the first year post-transplant); (3) cardiac allograft vasculopathy (CAV, any coronary artery stenosis >50% or diffuse distal coronary artery disease on routine post-transplant angiography); and (4) new-onset diabetes (NODM, a new diagnosis of diabetes after heart transplant, excluding patients having transient hyperglycemia or anti-diabetic therapy only in the immediate peri-operative setting or <1 month post-transplant). The local institutional review board approved the protocol. Survival was analyzed at 1, 5 and 10 years post-transplant by the Kaplan–Meier method using the log-rank test for comparison between groups with statistical significance defined by $p < 0.05$.

Disclosure statement

The authors have no conflicts of interest to disclose.

A total of 160 heart transplant recipients were included in the study. Mean follow-up was 55 ± 36 months (range 1 to 143 months; median 50 months). Before transplant 46 patients (29%) had diabetes. Of those without diabetes, 60 (37% of the total population) had HgbA_{1c} in the pre-diabetes range. The remaining 54 (34%) patients had no diabetes or pre-diabetes. Baseline characteristics were similar between patients with pre-diabetes and those with no diabetes or pre-diabetes (Table 1). Absolute mortality during follow-up was not significantly different in patients with pre-diabetes (7 of 60 [12%]) compared to patients with no diabetes or pre-diabetes (9 of 54 [17%]; $p = 0.59$). Kaplan–Meier survival analysis showed non-significant differences in overall 10-year survival rate between groups (log rank, $p = 0.95$; Figure 1).

The proportion of patients with acute rejection (43% vs 46%, $p = 0.85$) and the mean number of rejection episodes per patient (0.8 ± 1.1 vs 1.0 ± 1.4 , $p = 0.36$) were similar between patients with pre-diabetes and those with no diabetes or pre-diabetes. CAV developed in 11% of patients during follow-up, and was not significantly different between the two groups ($p = 0.54$). NODM developed during follow-up in 29 of 114 patients (25%) without pre-transplant diabetes, and was similar in pre-diabetes patients compared to those with no diabetes or pre-diabetes (15 of 60 [25%] vs 14 of 54 [26%], $p = 0.91$). The majority (79%) of NODM cases developed during the first year post-transplant. Of the patients with pre-diabetes, those developing NODM post-transplant had similar rates of CAV, acute rejection and mortality during follow-up compared with pre-diabetic patients not developing NODM (7% vs 9%, $p = 0.78$; 46% vs 42%, $p = 0.77$; 7% vs 13%, $p = 0.66$, respectively).

Unlike the similar characteristics and outcomes of patients with and without pre-diabetes before transplant, patients with overt pre-transplant diabetes were older and had a higher prevalence of hypertension and ischemic heart disease and lower peak oxygen consumption (Table 1). In addition, absolute mortality rates were higher in patients with pre-transplant diabetes (13 of 46 [28%] vs 16 of 114 [14%], $p = 0.04$). Although overall 10-year survival rates were not significantly different, impaired survival was noted in patients with diabetes in the early (1 year: 89% vs 95%, $p = 0.03$) and late (5 to 10 years: 48% vs 76%, $p = 0.038$) post-transplant periods (Figure 1). Moreover, post-transplant complications of acute rejection and CAV developed during follow-up at a similar rate in the diabetes group, compared with the other two groups.

These findings show that pre-diabetes before heart transplantation does not seem to increase the risk of developing NODM or other important clinical post-transplant outcomes such as allograft rejection, CAV or mortality. In contrast, transplant recipients with pre-existing diabetes had lower survival rates compared to patients with no diabetes or pre-diabetes, specifically in the early (1-year) and later (5- to 10-year) post-transplant periods.

The prevalence of pre-diabetes is progressively increasing, which exposes populations to a higher risk of developing diabetes, microvascular disease and cardiovascular events.³ It is estimated that 5% to 10% of individuals with pre-diabetes develop diabetes annually in the general population.⁴ However, the conversion rate varies with population characteristics and the specific definitions of pre-diabetes; some subjects with pre-diabetes do not progress to diabetes, further complicating our understanding of the impact of pre-diabetes on

cardiovascular outcomes. Given national trends, a significant percentage of patients may have pre-diabetes even prior to insults that will culminate in the need for transplant. Separately, the post-operative state, accompanied by use of immunosuppressive therapy, may foster the development of NODM.

Pathophysiologic mechanisms operative in pre-diabetes include insulin resistance, increased insulin-secretory demand, glucotoxicity and lipotoxicity, all of which may contribute to beta-cell dysfunction and failure, and progression to diabetes.⁴ Given these issues, one might assume that pre-diabetes before transplant would result in a higher rate of progression to NODM post-transplant. However, we observed no differences in baseline characteristics or development of post-transplant NODM in patients with pre-diabetes compared with no diabetes. Furthermore, pre-diabetes was associated with similar post-transplant survival, acute rejection rate and CAV, as in the non-diabetes group.

Our study results support the overall importance of diabetes with regard to cardiovascular issues, but do not demonstrate worse outcomes associated with pre-transplant pre-diabetes on post-transplantation outcomes. However, similar to recommendations for the general population, it would be prudent to consider lifestyle interventions targeting modifiable cardiometabolic risk factors to delay development of diabetes in the longer term. Conceivably, the duration of post-transplant follow-up in our study may not have been sufficient for increased progression to NODM or adverse outcomes associated with pre-diabetes to become manifest. However, published data and our results suggest that NODM develops early after transplantation.⁵ In addition, by combining HgbA_{1c} with fasting plasma glucose or oral glucose tolerance tests, the nature of pre-diabetes and the risk for developing NODM may be better defined. Although our survival curves suggest impaired early and late outcomes in patients with diabetes, the certainty of these findings is limited by small patient numbers. A need exists for greater insight into the relationship between pre-diabetes and heart transplant outcomes and further studies are warranted.

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Figure 1.

Survival analysis by 10-year post-transplant period, according to the presence of pre-transplant diabetes (DM), pre-diabetes (Pre-DM) or no DM (no DM vs DM: $p = 0.21$; no DM vs pre-DM: $p = 0.95$).

Table 1
Baseline Characteristics of Study Population According to Presence or Absence of Pre-transplant Diabetes or Pre-diabetes

Variable	No DM, N = 54 (34%)	Pre-diabetes, N = 60 (37%)	DM, N = 46 (29%)	p-value (pre-diabetes vs no DM)	p-value (DM vs no DM)
Female	13 (24%)	20 (33%)	12 (26%)	0.31	0.82
Age (years)	49 ± 12	48 ± 13	57 ± 7	0.82	<0.001
White race	44 (81%)	51 (85%)	33 (72%)	0.43	0.71
BMI	26.5 ± 5.1	24.9 ± 4.9	28.3 ± 4.5	0.12	0.06
LVEF (%)	22 ± 11	23 ± 14	21 ± 8	0.65	0.56
Ischemic etiology	16 (30%)	14 (23%)	25 (54%)	0.52	0.02
VAD before transplant	25 (46%)	24 (40%)	18 (39%)	0.57	0.54
Smoking	25 (46%)	29 (48%)	23 (50%)	0.85	0.84
Hypertension	16 (30%)	21 (35%)	23 (50%)	0.55	0.04
Total cholesterol (mg/dl)	142 ± 43	142 ± 42	149 ± 46	0.96	0.49
Triglycerides (mg/dl)	137 ± 181	117 ± 92	141 ± 121	0.52	0.89
Sleep apnea	5 (9%)	7 (12%)	8 (17%)	0.76	0.25
Atrial fibrillation	18 (33%)	24 (41%)	14 (30%)	0.44	0.83
ICD/CRT	35 (65%)	47 (78%)	32 (70%)	0.14	0.67
Creatinine 1.5 mg/dl	15 (28%)	18 (30%)	19 (41%)	0.83	0.20
Hematocrit (%)	36.7 ± 6.7	36.9 ± 6.4	37.2 ± 6.6	0.82	0.67
Bilirubin (mg/dl)	1.2 ± 0.7	1.2 ± 0.7	1.2 ± 0.7	0.79	0.98
Peak VO ₂ (ml/kg/min; n = 96)	13.0 ± 4.5	12.6 ± 4.6	10.5 ± 3.1	0.68	0.02
PCWP (mm Hg; n = 132)	23 ± 10	20 ± 8	26 ± 8	0.12	0.06
PASP (mm Hg; n = 133)	42 ± 18	36 ± 15	42 ± 12	0.08	0.89
Warfarin therapy	10 (19%)	19 (31%)	7 (15%)	0.13	0.51
HgbA _{1c} (%)	5.1 ± 0.5	6.1 ± 0.4	6.9 ± 1.3	<0.001	<0.001
Rejection in first year	25 (46%)	26 (43%)	20 (44%)	0.85	0.84
CAV	7 (13%)	5 (8%)	6 (13%)	0.54	0.99

BMI, body mass index; CAV, cardiac allograft vasculopathy; DM, diabetes mellitus; ICD/CRT, implantable cardioverter-defibrillator/cardiac resynchronization therapy; LVEF, left ventricular ejection fraction; PASP, pulmonary artery systolic pressure; PCWP, pulmonary capillary wedge pressure; VAD, ventricular assist device; VO₂, oxygen consumption.