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Coronary Artery Calcium May Stabilize Following Islet Cell Transplantation in Patients with Type 1 Diabetes

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Abstract

Islet cell transplantation can functionally cure type 1 diabetes, and also improve carotid-intima media thickness. This study provides a preliminary description of changes in coronary artery calcium following islet transplantation, and associated factors. Coronary artery calcium was measured in 14 patients with type 1 diabetes (11 had measures both pre- and post-transplant [mean 2.3 years]) in the University of Illinois at Chicago's clinical trial. Multivariable mixed-effects linear regression of repeated measures was used to quantify calcium change, and determine if this change was longitudinally associated with risk/protective factors. Thirteen of the patients were female, with mean baseline age, diabetes duration, and BMI of 47.6 and 28.7 years and 23.1, respectively. Over half (57%) had detectable coronary artery calcium pre-transplant. Minimal change (0.39 mm³/year, p=0.02) occurred in coronary artery calcium levels pre- to post-transplant. No patient met criteria for calcium progression. Coronary artery calcium was positively associated with total and small VLDL particles (p = 0.02), statin dose (p=0.02), and urine albumin-to-creatinine ratio (p=0.04); and negatively associated with free fatty acids (p=0.03), total HDL (p=0.03), large HDL particles (p=0.005), and tacrolimus dose (p=0.02). Islet transplant may stabilize coronary artery calcium, with optimal management of lipids and kidney function remaining key therapeutic targets. [NCT00679041]

Keywords

Type 1 diabetes; islet cell transplantation; coronary artery calcium

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DISCLOSURES

None.

AUTHOR CONTRIBUTIONS

J.M.M. analyzed the data and prepared the manuscript. K.K.D. and R.S.M. wrote, reviewed and edited the manuscript. B.H., J.O., G.T.K., and K.A.V. contributed to study design and reviewed the manuscript.

INTRODUCTION

Cardiovascular disease (CVD) is the main cause of morbidity and mortality among individuals with type 1 diabetes (1, 2). Epidemiologic studies have demonstrated that after 20 years duration of type 1 diabetes, over 40% of deaths are attributable to CVD (2). Despite the beneficial effects of intensive insulin therapy on reducing the risk of CVD events in recent decades (3), compared to men and women without type 1 diabetes, having type 1 diabetes is still associated with fourfold and eightfold increased risk for CVD events in men and women, respectively (1). The increased risk of death from CVD is even higher in women who were diagnosed with type 1 diabetes before or during puberty.

Coronary artery calcium (CAC), a marker of atherosclerotic plaque, can be measured using electron-beam tomography (EBT), a highly sensitive noninvasive method (4). CAC is used to screen for CVD and can predict future fatal and non-fatal cardiovascular events across all levels of CVD risk (5), particularly in asymptomatic intermediate-risk persons (6). The Coronary Artery Calcification in Type 1 Diabetes (CACTI) study showed type 1 diabetes is associated with higher CAC prevalence in both sexes across all ages compared to people without diabetes (7). The Epidemiology of Diabetes Interventions and Complications (EDIC) study measured CAC 7–9 years after the close of the Diabetes Control and Complications Trial (DCCT) and found the intensive treatment group had lower average CAC scores and lower prevalence of CAC > 0 compared to the conventional treatment group (8). However, it is unknown how useful CAC is in predicting CVD risk in patients with type 1 diabetes. Greater progression of CAC in type 1 diabetes has been associated with poor glycemic control (9), impaired kidney function (10), inflammation (11), and insulin resistance (7).

Islet cell transplantation is an experimental therapy that provides a potential functional cure for patients with type 1 diabetes who experience hypoglycemic unawareness despite optimal insulin therapy (12). Islet cells from deceased human donors are isolated, purified, then infused through the recipient's portal vein to engraft into the liver, reestablishing endogenous insulin secretion; one to three transplants are performed to establish/maintain glycemic control (13). Multiple improvements in islet transplant outcomes have been achieved over the last decade (14), allowing patients with type 1 diabetes to achieve insulin independence and essentially eliminate hypoglycemic events (13, 15). Regarding cardiovascular health, islet cell transplantation has also been shown to improve the function of circulating angiogenic cells involved in vascular repair (16), and significantly reduce carotid intima-media thickness (CIMT), a marker of atherosclerosis, within one year following transplant (17).

Despite these benefits, the effect of islet transplant on other markers of CVD is not clear, and additional research is needed to understand the impact on cardiovascular health, particularly given the negative effects immunosuppression can have on blood pressure and lipid levels (18, 19). Serial cardiac EBT may allow monitoring of cardiovascular risk by quantifying CAC before and after islet cell transplantation, which to the best of our knowledge has not been done. We therefore describe changes in CAC over time in patients with longstanding

type 1 diabetes following islet transplant, and provide a preliminary analysis of factors associated with change in CAC in the University of Illinois at Chicago's (UIC's) phase 1/2 and 3 islet transplant clinical trials. We hypothesized that CAC would either regress or stabilize (similar to CIMT) following transplant, and that these changes in CAC would be associated with beneficial changes in factors such as inflammation, lipid levels, blood pressure, and glycemic control after islet transplantation.

MATERIALS AND METHODS

Study Participants

The current study includes the first 14 patients enrolled in UIC's phase 1/2 (n=10) and phase 3 (n=4) clinical trials (NCT00679042) of allogeneic pancreatic islet transplant, who also had data available on CAC. The trials have been previously described (13, 15). Briefly, patients were eligible if they were 18–70 years of age, had type 1 diabetes for ≥ 5 years and presented with hypoglycemic unawareness despite optimal insulin management. Patients were excluded for any of the following: history of myocardial infarction or stroke in the previous six months, untreated cardiac, kidney, or liver disease, previous organ transplant, hyperlipidemia, history of cancer, active infection, substance abuse (including active cigarette smoking), $HbA_{1c} > 12\%$ (108 mmol/mol), BMI > 26 (Phase 1/2) or BMI > 27 (Phase 3), uncontrolled psychiatric disorder, use of corticosteroids or anticoagulants, and/or pregnancy. All 14 patients had CAC measured pre-transplant (same inclusion/exclusion criteria as the clinical trial), and the 11 patients transplanted during the study period (2004–2008) had CAC measurements during follow-up post-transplant as well. The 11 transplanted patients had a total of 19 islet transplants; five patients received one transplant, four received two transplants, and two received three transplants during the study period. Follow-up in the 11 transplanted patients ranged from one to four years following first islet transplant. At the end of the study period (2008), three of the 11 transplanted patients had withdrawn due to either adverse events (n=2) or loss of islet cell function with subsequent pancreas transplant (n=1), but all their available data pre- and post-transplant were included in the current analysis. The clinical trials were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. The study was approved by the UIC Institutional Review Board (2004-0532, 2007-0330) and patients provided written informed consent.

The first four transplanted patients received immunosuppression per the Edmonton protocol. (20). The remaining seven transplanted patients received the UIC protocol (13), which added etanercept (one dose before and three doses after transplant) and exenatide (varying doses twice daily for six months) to the Edmonton protocol of immunosuppression. Sirolimus was stopped if poorly tolerated/severe side-effects, and mycophenolate mofetil was substituted. The concurrent American Diabetes Association guidelines for blood pressure and lipid management were followed throughout the study, allowing for addition or adjustment of statins or antihypertensive medications as required.

Measurement of CAC (dependent variable)

All 14 patients underwent EBT pre-transplant, with the 11 transplanted patients receiving subsequent scans approximately every 12–18 months post-transplant at the UIC Medical

Center. Measurement of CAC was performed according to the UIC scanning protocol as previously described (21). Briefly, images were obtained using a GE Imatron computed tomography scanner (GE Imatron, San Francisco, CA). CAC volume was calculated individually for the left main, left anterior descending, circumflex, and right coronary arteries using isotropic interpolation (22), then summed to produce a total CAC volume score. A published population-based estimate of the prevalence of CAC progression in people with type 1 diabetes not receiving islet transplant, but similar to our sample (CACTI), was used for comparison (23). Three islet transplant patients received one CAC scan, six patients received two scans, three patients received three scans, and two patients received four scans across one to four years following their first islet transplant.

Clinical Measurements (independent variables)

Patient characteristics included age and duration of type 1 diabetes at first transplant, sex, history of smoking, and timing of CAC measurements relative to first transplant. Transplant characteristics included clinical trial phase, immunosuppression protocol, number of islet transplants received, and the cumulative number of transplanted islet cell equivalents per kilogram (IEQs/kilogram) body weight. All serial clinical measurements were performed at baseline pre-transplant and at scheduled follow-up visits post-transplant, then matched by date to the closest CAC measurement. Blood pressure was measured after being seated for five minutes then repeated five minutes later; the second reading was used for analysis. Numerous cardiovascular, lipid and inflammatory biomarkers were measured in fasting morning blood samples pre-transplant, then after each islet transplant at 1 week, 20 weeks, 52 weeks, then yearly including: a standard lipid panel (total cholesterol, HDL, LDL, and triglycerides); a detailed lipid panel including: small, medium, large and total VLDL particles; very small, small, medium-small, large, and total LDL particles; intermediate density lipoprotein (IDL) particles; small, medium, large, and total HDL particles; HDL, LDL, and VLDL size; VLDL triglycerides; apolipoprotein B and apolipoprotein A-1, and free fatty acids (FFA); inflammatory and/or vascular markers including: high-sensitivity C-reactive protein, monocyte chemoattractant protein-1, matrix metalloproteinase-9, intercellular adhesion molecule-1, VCAM-1, and plasminogen activator inhibitor-1 antigen and activity; and coagulation factors including fibrinogen and tissue plasminogen activator (Clinical Reference Laboratory, Lenexa, KS). As part of an ancillary study in 2013, leptin and adiponectin levels were measured in archived serum samples collected pre-transplant, 1 week, and 20 weeks after first islet transplant using high-sensitivity enzyme immunoassay (R&D Systems, Minneapolis, MN). Body composition was assessed using BMI (weight [kilogram]/height [meter]²) at each study visit, and abdominal fat distribution (total adipose tissue [TAT], visceral [VAT], and subcutaneous [SAT]) measured from the CAC EBT scans. Data on insulin independence (yes/no), daily insulin dose (units/kilogram), antihypertensive medication use (yes/no), and use (yes/no) and dose (milligrams/day) of statins, tacrolimus, sirolimus, and mycophenolate mofetil were collected at each study visit. Fasting C-peptide was measured by quantitative chemiluminescent immunoassay by ARUP Laboratories (Salt Lake City, UT) at each study visit. At each visit, a comprehensive metabolic profile was performed which included a fasting glucose and serum creatinine (Jaffe reaction). HbA_{1c} was measured using high performance liquid chromatography pre-transplant, then approximately every 4–12 weeks post-transplant, while urine albumin-to-creatinine ratio

was measured using the Beckman LX20 standard chemistry method pre-transplant, then approximately every six months post-transplant (all UIC Pathology Laboratory, Chicago, IL). Creatinine was used to estimate GFR (eGFR) using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (24) at each study visit.

Statistical Analysis

Data from 32 serial EBT scans were available. The data were analyzed using SAS version 9.4 (SAS Institute, Cary, NC). Statistical significance was set at $p < 0.05$. The distribution of variables was assessed and transformed if skewed. Means and standard deviations (SDs) were calculated for continuous variables, and frequencies and percentages for categorical variables, both at baseline and over follow-up. Scatter plots were used to examine associations between the dependent and independent variables and to identify outliers. One abdominal fat observation was an extremely influential outlier, so was replaced with the value from the prior EBT scan.

CAC volume score, the primary dependent variable, was highly variable and positively skewed. CAC volume score was square-root transformed to normalize the distribution of the residuals and stabilize interscan variation across repeated measurements (25). CAC progression or regression was defined as a ± 2.5 unit change (25) (increase or decrease, respectively) in the square-root transformed CAC volume score from baseline to last follow-up assessment. The proportion for progression was compared to a reference type 1 diabetes sample (CACTI) using Fisher's exact test.

Multivariable mixed-effects linear (or generalized linear) regression modeling of repeated measures was used, with random effects allowing correlation between the repeated measurements per patient to be incorporated into the estimates. This allows the estimation of the slope of change in each variable (e.g., CAC) within each individual patient. The autoregressive variance matrix was specified to account for the larger within person correlation of observations that are closer together in time. Regression modeling utilized restricted maximum likelihood estimation to determine whether CAC volume (or potential risk/protective factors) changed since enrollment ($n=11$ patients with their 29 serial measurements). In addition, this procedure was used to determine if CAC volume was associated with risk/protective factors ($n=14$ patients; due to missing values for some risk/protective factors, these models utilized 29 of their 32 serial measurements). All regression models (adjusted for baseline transformed CAC volume score) were built, first with the factor alone (crude), then with potential confounders individually, which were retained if they produced a 10% change in the estimate. The final model for change in CAC volume over time since enrollment was adjusted for IEQs/kilogram, and the final individual risk/protective factor models were adjusted for IEQs/kilogram and the adiposity ratio VAT/SAT. Sensitivity analyses excluding the one male from all models were performed.

RESULTS

Tables 1A and 1B summarize the characteristics of the 14 patients with a baseline CAC scan (individual patient data are available in Supplementary Table 1). There were 13 females, all Non-Hispanic white, with a mean age (SD) and type 1 diabetes duration (SD) of 47.6 (9.5)

years and 28.7 (11.3) years, respectively. Due to clinical trial exclusion criteria, all patients had normal BMIs, fairly good glycemic control, well-controlled cholesterol and blood pressure, and had a mean (SD) eGFR of 78.9 (20.3) and albumin-to-creatinine ratio of 10.5 (15.0). Six patients had a history of smoking, but quit prior to study enrollment. Of the 14, three patients were not transplanted during the study period and did not receive a follow-up CAC scan.

The 11 transplanted patients with serial EBT achieved insulin independence after one to three transplants over a mean (SD) follow-up of 2.3 (1.0) years (Table 1B). Baseline and mean change across follow-up for clinical measures and labs within these 11 patients are shown in Table 2. Patients experienced decreases in HbA_{1c} and in all measures of adiposity, including SAT and TAT, following islet transplant. Increases were seen in blood pressure but also HDL, with an increase in kidney damage (increase in urine albumin-to-creatinine ratio), though kidney function (i.e., eGFR) did not change.

CAC Outcomes

More than half (57%) of the 14 patients had detectable CAC at baseline; the mean (SD) baseline CAC volume score (square-root transformed) was 8.7 (11.1) mm³, ranging from 0 to 32.6 mm³ (Table 1). Baseline mean (SD) CAC volume score in the 11 patients with repeated CAC measures (Figure 1) was 8.7 (10.7) mm³, with the same range. Over follow-up, mean (SD) CAC volume score was 10.5 (12.2) mm³, ranging from 0 to 34.6 mm³. Overall, most patients (n=10, 91%) experienced a slight increase in CAC volume score during follow-up, whereas one patient experienced a decrease (Figure 1). The unadjusted yearly change in CAC volume score ranged from -1.4 to 2.1 mm³, with an average of 0.81 mm³. After adjustment for baseline total CAC volume score and confounding by transplanted IEQs/kilogram, the yearly change in CAC volume in islet transplant recipients was small but statistically significant (0.39 mm³, p=0.02); this did not substantially change (0.31 mm³, p=0.03) in the sensitivity analysis restricted to women. Based on a 2.5 unit change in the transformed CAC volume score defining progression or regression of CAC, none of the patients met the criteria for either (Figure 1 inset). Compared to a reference population of mostly non-Hispanic white women enrolled in another study in 2000–2005 with a similar mean (SD) age and duration of type 1 diabetes of 37 (9) years and 24 (9) years, but slightly higher BMI (~26) and HbA_{1c} (~8%) (23), islet transplant recipients trended toward less progression, though it did not reach statistical significance (19% vs. 0%, p=0.22).

Associations with CAC

Individual models of factors associated with the slope of change in CAC volume score, adjusted for confounding by baseline CAC volume score, adiposity, and transplanted IEQs/kilogram, are presented in Table 3. Increasing CAC levels were associated with increases in total VLDL particles, particularly small VLDL particles, following transplant. Increasing CAC was also associated with both a higher statin daily dose and a higher urine albumin-to-creatinine ratio after transplant. Decreases in CAC were associated with higher HDL levels, particularly the large HDL particles, and FFAs following transplant. A higher tacrolimus dose was also associated with a decrease in CAC over time. Further adjustment by other

covariates (e.g., adjusting HDL levels for statin use) did not change these results, nor did excluding the one male recipient. Changes in CAC were not associated with any measure of adiposity (weight, BMI, VAT, SAT, or TAT), despite decreasing trends in all measures of adiposity across follow-up. Additionally, changes in CAC were not associated with age, duration of type 1 diabetes, glycemic control, blood pressure, inflammatory or vascular biomarkers, leptin, adiponectin, clinical trial phase, other study medications, or measures of islet graft function including exogenous insulin use after transplant and fasting C-peptide and glucose levels.

DISCUSSION

To the best of our knowledge, this study was the first to describe changes in CAC following islet transplant, and to provide a preliminary analysis of factors associated with changes in CAC following transplant. This study demonstrated that islet transplant may have beneficial cardiovascular effects by stabilizing CAC in patients with longstanding type 1 diabetes. In our patients, the average change in CAC volume was 0.39 mm³ per year. In comparison, there was a trend towards greater change in CAC in a type 1 diabetes cohort of similar sex and age as our transplant patients (23) that showed an average increase in CAC volume of 7.5 mm³ per year. This same study (23) found progression of CAC in 19% of patients with type 1 diabetes, in comparison to 0% of UIC's islet transplant patients, both over approximately 2.5 years. Other studies of CAC have shown an average increase of 5.1 mm³ per year in older adults without metabolic syndrome or heart disease (26) and 16.1 mm³ per year in adults with type 2 diabetes without known heart disease (27). However, future research is needed to confirm our findings and to determine clinical significance.

Increasing CAC after transplant was associated with several factors, mainly related to atherogenic lipoproteins, increasing kidney damage, and a lower tacrolimus dose. Hyperlipidemia is a well-established contributor to atherosclerosis, particularly in type 1 diabetes (28), that may be exacerbated in islet transplant recipients by certain immunosuppressive drugs (18, 19). The positive association between a higher statin dose following transplant and greater CAC in our patients likely reflects the higher lipid levels associated with CAC following transplant that require more aggressive treatment. The significant positive association between VLDL particle level and CAC observed in our study is consistent with a previous study of men and women with type 1 diabetes taken from type 1 diabetes registers in London (29), however, that study did not find an association with small VLDL particles and CAC, whereas the current study did. Cardiovascular and renal complications in type 1 diabetes are closely related, and a higher albumin excretion ratio is a known risk factor for CVD in those with type 1 diabetes (28). The demonstrated relationship between increasing kidney damage and increasing CAC following transplant is similar to findings by the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study that observed albumin excretion rate to be a predictor of CAC progression in patients with type 1 diabetes (30). Kidney function and damage may be negatively impacted by both tacrolimus (31) and sirolimus (32), respectively, which were taken by all patients in our study. However adjusting for immunosuppressive medication class did not change the significant association between CAC and kidney damage after transplant.

A limited number of studies (33) in kidney transplant recipients have compared the impact of calcineurin inhibitors on traditional cardiovascular risk factors and suggest that compared to cyclosporine, tacrolimus may confer less cardiovascular risk in transplant patients. A negative association was observed between total daily tacrolimus dose and CAC in our study, which may lend support to tacrolimus use after islet transplant. We observed a negative association between serum FFAs and CAC. In a prior study of men and women with type 1 diabetes, fasting FFAs were not associated with CAC (34), however, research in adults without diabetes has found positive associations between FFAs and risk of hypertension and CVD (35). The discrepant findings could potentially be a function of alterations in metabolism and FFA dynamics due to the use of immunosuppression which significantly increases FFA levels (36), the substantial changes in VAT and SAT following islet transplant, and/or by factors such as changes in diet or physical activity following transplant.

The relationship between glycemic control and cardiovascular disease in patients with type 1 diabetes is not well established (28). Previous reports by both the CACTI (9) and DCCT/EDIC (8) research groups have found worse glycemic control to be a strong predictor of CAC progression. However, similar to the Pittsburgh EDC Study (37) and a study from the United Kingdom (38), we did not observe this association. The demonstrated significant association may be a function of the higher HbA_{1c} levels in patients with type 1 diabetes in those cohorts (8, 9) which ranged from 7.2 to 9.2% (55–77 mmol/mol), as well as from differences in study design and characteristics of the sampled patients. In comparison, the islet transplant patients exhibited lower HbA_{1c} and less variation (mean: 6.0 [42 mmol/mol]; range: 5.4–7.0 [36–53 mmol/mol]) following islet transplant, perhaps resulting in the null association. Prior studies of CAC in patients with type 1 diabetes have also found associations with adiponectin (39), inflammation (11), and adiposity (7, 9, 40), however our study found no association between either adiponectin or inflammatory markers and CAC. Also, despite overall decreases in weight and all measures of abdominal adiposity across follow-up, we did not observe any association between adiposity and CAC.

Therefore, while some predictors of CAC progression were similar between patients living with type 1 diabetes and those functionally cured after islet transplant, significant predictors also differed. Given these differences, it is important to note that the clinical trial exclusion criteria resulted in relatively healthy patients with normal BMIs, fairly good glycemic control, well-controlled cholesterol and blood pressure, and without active cardiovascular disease at study enrollment. One patient however did have a prior history of cardiac stenting (outside of the six month window prior to study enrollment), but remained asymptomatic during the study. In addition, almost half our cohort (43%) had a history of smoking, with the two patients with the highest baseline calcification (Figure 1) each having smoked for more than 20 years. Despite this, the islet transplant patients overall appeared to be a more select group than people living with type 1 diabetes participating in population-based studies. Review of the UIC islet transplant patients enrolled in five and ten year follow-up shows that no patients have experienced any major cardiovascular events (e.g., stroke, myocardial infarction) since their last EBT scan, with just one, a former smoker, requiring coronary stents to date.

A strength of this study was the prospective design consisting of pre-transplant and longitudinal measures of both the dependent and independent variables. This allowed the assessment of changes in CAC following intervention, in this case islet transplantation. Additionally, CAC was measured more than once after transplant in the majority of patients, allowing the assessment of change in CAC over time. The nature of the inclusion/exclusion criteria for the study provided a study sample that was free from active cardiovascular disease at baseline. A limitation of the current study is the small number of patients in whom CAC was measured. Of the 14 participants with baseline EBT scans, 11 received additional CAC imaging following transplant, resulting in 32 observations for analysis. Islet transplant clinical trials are not powered for robust analysis of diabetes complications, but instead for safety and efficacy (41). Also, given the current experimental nature of islet cell transplant as a treatment for a select subgroup with type 1 diabetes, larger numbers of participants are not yet available. Therefore, this study provides an exploratory analysis of CAC in this patient population, where associations with statistical significance $p < 0.05$ may be considered associations of interest for future research. As has been previously described by the Food and Drug Administration, there are no control groups in islet cell transplant clinical trials because of the inability to blind patients/investigators, as well as the unwillingness of patients to be assigned to a control group (41). However this might be seen as a limitation, so a control group from the literature was used. It is also considered unethical to randomize these patients to either islet transplant or an alternative treatment for hypoglycemic unawareness purely for research reasons, because in order to be eligible for islet transplantation, they would have already tried and failed such existing treatments (42). Additional limitations include the participant sample was comprised of mostly female patients, limiting the generalizability of findings, and information such as patients' dietary and physical activity behaviors were not available.

In conclusion, the current study describes potential stabilization of CAC in patients with type 1 diabetes that were functionally cured after receiving islet cell transplantation. Relative stabilization of CAC was associated with better lipid profiles, less kidney damage and higher doses of tacrolimus. Our central goal is to better understand how islet transplant impacts the progression of cardiovascular complications that are common among people with type 1 diabetes. This study provides preliminary data and insights into potentially important factors to cardiovascular health in these patients, and indicate that optimal management of lipids and kidney function after transplant remain key therapeutic targets. Future research is needed to confirm our preliminary findings and to determine if the slower progression of subclinical atherosclerosis in islet transplant recipients demonstrated in this study translates into fewer clinical cardiovascular events relative to individuals with type 1 diabetes receiving current standard of care treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure 1. Individual patients' coronary artery calcium (CAC) volume scores (square root transformed) before and after transplant (n=11). Squares represent initial and subsequent islet cell transplants received during the follow-up period. Color coded per individual patient. (Inset) Change in individual patients' CAC volume scores (square root transformed) before and after transplant (n=11).

Table 1**A. Patient Demographics and Clinical Characteristics Pre-transplant (n=14)**

Variable	Mean (SD) or n (%)	
Age (years)	47.6	(9.5)
Female	13	(93%)
Non-Hispanic white	14	(100%)
Diabetes duration (years)	28.7	(11.3)
History of smoking	6	(43%)
BMI (kg/m ²)	23.1	(2.1)
Weight (kg)	62.7	(5.5)
HbA _{1c} (mmol/mol) *	56.9	(10.3)
HbA _{1c} (%) †	7.4	(0.9)
Baseline CAC > 0	8	(57%)
Baseline CAC volume score (mm ³) ‡	8.7	(11.1)
Systolic blood pressure (mmHg)	115	(12.0)
Diastolic blood pressure (mmHg)	65	(7.4)
Antihypertensive medication use	9	(64%)
Total cholesterol (mmol/L) §	4.4	(0.7)
Total cholesterol (mg/dL)	170	(26.1)
LDL cholesterol (mmol/L) §	2.3	(0.6)
LDL cholesterol (mg/dL)	88	(21.3)
HDL cholesterol (mmol/L) §	1.7	(0.6)
HDL cholesterol (mg/dL)	65	(21.6)
Statin use	7	(50%)
Estimated glomerular filtration rate (mL/min/1.73 m ²)	78.9	(20.3)
Urine albumin-to-creatinine ratio (mg/g)	10.5	(15.0)

B. Patient Clinical Characteristics Post-transplant (n=14)

Variable	Mean (SD) or n (%)	
EBT scans:	1	3 (21%)
	2–4	11 (79%)
Transplants: *	1	5 (46%)
	2	4 (36%)
	3	2 (18%)
IEQs/kg cumulative across transplants *	18,730	(12,610)
Actual islet number cumulative across transplants *	668,973	(463,657)
Follow-up post first transplant (years) *	2.3	(1.0)

CAC=coronary artery calcium; SD=standard deviation

* n=13

† To convert from % to mmol/mol, subtract 2.152 and divide by 0.09148

[‡]Square-root transformed

^{\$}To convert from mmol/L to mg/dL, multiply by 38.67

// Presented as median (interquartile range) to account for skewed distribution

EBT=electron-beam tomography; IEQ=islet cell equivalents; SD=standard deviation

*
n=11

Table 2

Change in Clinical Characteristics Pre-Transplant Across Post-Transplant Follow-Up (n=11 patients; n=29 longitudinal observations)

Characteristic	Pre-Transplant		Follow-Up		p-value
	Mean/n	SD/%	Mean/n	SD/%	
BMI (kg/m ²)	23.0	(1.5)	21.8	(1.3)	0.03
Weight (kg)	62.6	(5.5)	60.5	(5.7)	0.06
VAT (cm ³)	27.5	(15.3)	23.8	(10.6)	0.07
SAT (cm ³)	90.7	(44.6)	66.2	(33.5)	0.003
TAT (cm ³)	118.2	(53.0)	90.0	(40.4)	0.002
HbA _{1c} (mmol/mol) *	56.9	(11.6)	42.5	(5.5)	0.002
HbA _{1c} (%) [‡]	7.4	(1.1)	6.0	(0.5)	
Fasting C-peptide (ng/mL)	0.1	(0.0)	1.4	(0.6)	<0.002
Systolic blood pressure (mmHg)	116	(12.6)	128	(18.8)	0.03
Diastolic blood pressure (mmHg)	67	(6.7)	73	(9.4)	0.05
Antihypertensive medication use	7	(64)	9	(82)	0.25
Total cholesterol (mmol/L) [‡]	4.3	(0.7)	4.9	(1.4)	0.35
Total cholesterol (mg/dL)	167	(27.9)	188	(52.6)	
LDL cholesterol (mmol/L) [‡]	2.3	(0.6)	2.6	(1.0)	0.89
LDL cholesterol (mg/dL)	89	(23.8)	101	(39.1)	
HDL cholesterol (mmol/L) [‡]	1.5	(0.4)	1.8	(0.8)	0.04
HDL cholesterol (mg/dL)	59	(16.6)	68	(31.5)	
Statin use	6	(55)	9	(82)	0.08
Estimated glomerular filtration rate (mL/min/1.73 m ²) [§]	80.1	(22.4)	82.0	(25.2)	0.70
Urine albumin-to-creatinine ratio (mg/g) [§] , //	14.0	(23.0)	46.0	(126.0)	0.01

SAT=subcutaneous adipose tissue; SD=standard deviation; TAT=total adipose tissue; VAT=visceral adipose tissue

* n=10 observations pre-transplant

[‡]To convert from % to mmol/mol, subtract 2.152 and divide by 0.09148

Presented as median (interquartile range) to account for skewed distribution

//

n=17 observations across follow-up

\$

To convert from mmol/L to mg/dL, multiply by 38.67

†

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Table 3

Factors Significantly Associated with Slope of Change in Coronary Artery Calcium (CAC) Pre-Transplant Across Post-Transplant Follow-Up (n=14 patients; n=29 longitudinal observations)

Individual Models*	β	SE	p-value
Total VLDL particles	0.42	0.16	0.02
Small VLDL particles	0.37	0.12	0.01
HDL level	-0.02	0.01	0.03
Large HDL particles	-0.11	0.03	0.005
Free fatty acids	-0.53	0.22	0.03
Statin daily dose	0.03	0.01	0.02
Tacrolimus daily dose	-0.17	0.07	0.02
Urine albumin-to-creatinine ratio	0.25	0.11	0.04

SE=standard error

* Each independent variable was adjusted in individual multivariable models for the following covariates: baseline coronary artery calcium (CAC), adiposity measured by electron-beam tomography (specifically the ratio VAT/SAT), and cumulative number of transplanted islet equivalents/kilogram body weight (IEQs/kilogram); e.g., $CAC = \text{total VLDL particles} + \text{baseline CAC} + \text{VAT/SAT} + \text{IEQs/kg}$