

Reduction in Carotid Intima-Media Thickness after Pancreatic Islet Transplantation in  
Patients with Type I Diabetes

Short Title: Islet Transplant and CIMT

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Objective: Determine the impact of islet transplantation on carotid intima-media thickness (CIMT), a marker for atherosclerosis, in type 1 diabetes without kidney disease.

Research Design and Methods: Consecutive case-series of 15 adults (mean age, 49 [standard deviation (SD), 10] years; 87% female) with type 1 diabetes  $\geq 5$  years (mean duration, 30 [SD, 12] years; mean HbA1c, 7.2% [SD, 0.9%]), without kidney disease, presenting with severe hypoglycemic unawareness to undergo allogeneic pancreatic islet transplant(s) (1-3 each) in a phase 1/2 and 3 clinical trial. Current follow-up ranges from 1-5 years (2005-2011). CIMT of the common and internal carotid arteries was measured prior to and every 12-16 months following first transplant (2-6 CIMTs each) by one ultrasonographer and one blinded-reader. CIMT was analyzed as change from baseline to 12 and 50 month follow-up; a combined CIMT score was calculated as the sum of the standardized IMT scores (SD units) of both arteries.

Results: All patients achieved insulin independence after 1-3 transplants. CIMT decreased at 12 months (n=15) for the common carotid (-0.058 mm, p=0.006) and combined score (-1.28 SDs, p=0.004). In those with 50 month follow-up (n=7), the decrease in the combined score continued from 12 months (-1.59 SDs, p=0.04) to 50 months (-0.77 SDs, p=0.04). During follow-up, the decreasing slope of change in CIMT was associated with decreasing slopes of change in HbA1c, lipoproteins, and cardiovascular/inflammatory markers.

Conclusions: Islet transplantation may ameliorate diabetes-related atherosclerosis through improved glycemic control consequent to restoring endogenous insulin secretion, and optimal lipid management post-transplant also contributes.

Mortality from ischemic heart disease in individuals with type 1 diabetes is substantial. Risk estimates for those with type 1 diabetes <60 years of age range from 6- to 9-fold higher for men, and 13- to 15-fold higher for women, compared to the general population (1,2); and there is an exceptionally elevated risk, greater than 40-fold, for women with type 1 diabetes <40 years of age (2). Follow-up of the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort demonstrated that intensive glycemic control slows the progression of atherosclerosis as quantified by carotid intima-media thickness (CIMT) (3,4), with the largest benefit evident during the first six of 12 years following intensive treatment (4). Further, intensive glycemic control prevents cardiovascular events in those with type 1 diabetes (5).

Despite known benefits, long-term maintenance of optimal glycemic control is difficult (6). Many patients cannot tolerate intensive insulin therapy and experience debilitating hypoglycemic episodes. One treatment for type 1 diabetes is pancreas transplant, which has been shown not only to improve glycemic control, but also to decrease CIMT to levels comparable to those in individuals with type 1 diabetes without kidney disease over two years of follow-up (7). However, whole pancreas transplant represents a difficult and risky surgical procedure (8). While currently considered an experimental surgery, islet transplantation has emerged as an alternative treatment for patients with type 1 diabetes and debilitating hypoglycemia. This minimally invasive procedure is associated with less procedural-related morbidity than whole pancreas transplantation and may therefore represent a safer and simpler treatment option than whole organ transplant to stabilize glucose metabolism and achieve insulin

independence while limiting hypoglycemic episodes (9,10). However, adverse events can occur with islet transplantation including peritoneal bleeding and a decline in kidney function from immunosuppressive drugs (9,11). Fortunately, a recent report indicated that adverse event rates occurring with islet transplantation have steadily improved over the last decade and that mortality is low (12).

Due to the relatively recent development and clinical implementation of this treatment, long-term benefits remain largely unknown. Islet transplantation may represent a treatment that may not only be a safer alternative to whole pancreas transplantation in achieving insulin independence, but may also be a way to prevent the considerable morbidity and mortality associated with ischemic heart disease in type 1 diabetes (13). To our knowledge, only one study has explored the effect of islet transplantation on CIMT in type 1 diabetes. Conducted in individuals with end-stage renal disease, several of who had previous cardiovascular events, this study found that those receiving a kidney-islet transplant had a small, nonsignificant increase in CIMT compared to the kidney-only transplant group, which experienced a significant increase in CIMT over three years of follow-up (14).

It has not yet been determined whether minimally invasive islet transplantation slows or even reverses the progression of atherosclerosis, as occurs with pancreas transplant, in the absence of kidney disease and previous cardiovascular events. The current study represents the first report to assess the impact of islet transplant on atherosclerosis, as measured by changes in CIMT, in individuals with type 1 diabetes without kidney disease.

## Research Design and Methods

### Study and Participants

This consecutive case-series consists of 15 adult patients who underwent allogeneic pancreatic islet transplant(s) as part of an ongoing phase 1/2 and 3 clinical trial (NCT00679042) to achieve insulin independence. The trial has been previously described (11). Briefly, patients were eligible for transplant if they were 18-65 years of age, had type 1 diabetes for  $\geq 5$  years, and presented with hypoglycemic unawareness despite optimal insulin management efforts. Patients were excluded if one of the following conditions was present: untreated cardiac, kidney (based on creatinine clearance, serum creatinine, and urinary albumin/creatinine), or liver disease, hyperlipidemia, history of cancer or stroke, active infection, substance abuse including cigarette smoking, HbA1c  $>12\%$  or body-mass index (BMI)  $>26$ , uncontrolled psychiatric disorder, use of corticosteroids or anticoagulants, and pregnancy. The 15 patients are from the University of Illinois at Chicago (UIC) Medical Center and have received a total of 27 islet transplants (1-3 transplants each). Current follow-up ranges from 1-5 years after first transplant (2005-2011). Study approval was obtained from the Institutional Review Board at the University of Illinois at Chicago and patients provided written informed consent.

The first four patients received the “Edmonton Protocol” of immunosuppression, including daclizumab (1 mg/kg before transplantation, and 2, 4, 6, and 8 weeks after each islet transplant), sirolimus (0.2 mg/kg loading dose, thereafter 0.1 mg/kg aiming at trough levels of 10-15 mg/ml), and tacrolimus (0.5 mg starting dose, thereafter adjusted to trough levels of 3-6 mg/ml). Sirolimus was stopped and substituted with

mycophenolate mofetil (MMF) when patients presented with side-effects such as recurrent mouth sores or the development of macroalbuminuria (urine albumin/creatinine >300 mg/g). The remaining 11 patients received the UIC Protocol, which included etanercept (50 mg intravenous before, and 25 mg subcutaneous 3, 7, and 10 days after, each transplant) and exenatide (5 µg subcutaneous bid for 2 weeks, then 10 µg subcutaneous bid for 6 months) in addition to the Edmonton Protocol. The study protocol followed the American Diabetes Association guidelines for lipid and blood pressure control; addition or adjustment of the statin and antihypertensive dose were permitted due to the side-effects of the immunosuppressive therapy. Islet transplant outcomes for the first 10 of the 15 patients, at 15 months post-first transplant, have been reported recently (11). Three patients have withdrawn: one patient at 13 months post-first transplant due to side effects of the immunosuppression therapy, one patient after 19 months due to islet graft loss, and one patient after 22 months due to diagnosis of local breast cancer; one patient died 19 months after transplant due to sepsis of unknown origin. These four participants had data available from their pre-transplant and 12 month post-transplant follow-up exams. The remaining 11 are currently enrolled and continue to be actively followed.

#### Measurement of Carotid Intima-Media Thickness (Dependent Variable)

CIMT was assessed prior to and approximately every 12-16 months following the first islet transplant (totaling 2-6 CIMT assessments over 5 years). The outcomes of interest were change from baseline to 12 and 50 month follow-up after the first transplant. Measurement of CIMT and technician performance have been previously described (15). Briefly, carotid arteries were imaged by high-resolution B-mode carotid

artery ultrasound using Siemens Acuson Sequoia 512 with a linear–array 7.5 MHz transducer (Phillips Medical Systems NA, Bothell, WA) without contrast. All measurements were performed by a single ultrasonographer at the same center using the same equipment, and assessed by a single reader who was blinded to the study question, patient, and time point of follow-up. For each patient, three measurements were taken on the right and left sides of the near and far walls of the common and internal carotid arteries; the mean of these measurements for the common and internal artery were analyzed. A combined CIMT score, developed by the DCCT/EDIC study (3), was calculated as the sum of the standardized IMT measurements (Z-scores; standard deviation units [SDs]) of both the common and internal carotid arteries (Combined Score=Common Z-score + Internal Z-score). CIMT Z-scores for the common and internal arteries were calculated as  $([\text{patient value} - \text{“population” mean}] / \text{“population” standard deviation})$ , where the age- and sex-specific CIMT “population” mean and standard deviation in those with type 1 diabetes were taken from published DCCT/EDIC data (16).

#### Clinical Measurements (Independent Variables)

Patient characteristics included age and sex. At baseline and each follow-up exam, diabetes- and cardiovascular-related factors were measured using the same standardized protocols. Body composition was assessed using BMI (weight [kg]/(height<sup>2</sup> [m])) and abdominal adipose tissue distribution (visceral, subcutaneous, and total) was measured with a 150 Electron Beam Tomography (EBT) scanner (Imatron, San Francisco, CA). Blood pressure was measured after patients were seated for five minutes. Data on insulin independence (yes/no), antihypertensive and statin medication

use (yes/no), and immunosuppressive regimen (sirolimus/tacrolimus vs. MMF/tacrolimus) were collected. An extensive lipid and cardiovascular and inflammatory marker profile was performed (Clinical Reference Lab, Lenexa, KS), including: total cholesterol, lipoproteins (high, low, and very low density), triglycerides, free fatty acids, high sensitivity C-reactive protein, apolipoprotein B, apolipoprotein A-1, fibrinogen, inter-cellular adhesion molecule-1 (ICAM-1), monocyte chemotactic protein-1 (MCP-1), matrix metalloproteinase-9 (MMP-9), plasminogen activator inhibitor-1 (PAI-1) antigen and activity, vascular cell adhesion molecule-1 (VCAM-1), and tissue plasminogen activator (tPA). HbA1c and urine albumin/creatinine ratio were measured at the UIC Pathology Laboratories (Chicago, IL) by high-performance liquid chromatography and the Beckman LX20 standard chemistry method, respectively. Urine and serum creatinine were used to calculate creatinine clearance; serum creatinine was used to estimate glomerular filtration rate (eGFR) with the Modification of Diet in Renal Diseases equation (17).

### Statistical Analysis

Analyses were performed in SAS (version 9.2; SAS Institute, Cary, NC). The Sign test was used to compare paired medians for non-normally distributed clinical characteristics. McNemar's test was used to compare paired proportions. Paired t-tests were used to compare normally distributed clinical characteristics, and baseline CIMT levels with 12 and 50 month follow-up CIMT levels for the common and internal arteries and the combined score. Correlation analyses explored cross-sectional associations of CIMT with diabetes- and cardiovascular-related factors pre-transplant,



and at 12 and 50 month follow-up. These statistical tests were considered significant at  $p < 0.05$ .

Whether the slope of the change in CIMT levels during follow-up (e.g. a decline in common artery IMT) was associated with the slope of change in levels of diabetes- and cardiovascular-related factors during the same follow-up period (e.g. a decline in HbA1c) was determined using unadjusted and multivariable mixed-effects linear regression models of repeated measures. Empirical standard errors were calculated and the autoregressive variance matrix was specified for the correlation of the repeated measures. Variables not normally distributed, including internal carotid artery CIMT, were log-transformed. The multivariable models estimating slope of change in common, internal, and combined CIMT score were built by first entering all independent variables with  $p < 0.15$  from the unadjusted regressions and then using a stepwise approach to remove the nonsignificant covariates. Therefore, only those covariates that were significantly associated with change in CIMT levels during follow-up at  $p < 0.01$  (to minimize type 1 error from the multiple factors analyzed) were left in the final models. Interactions between the significant covariates were tested in each model and interactions that were statistically significant at  $p < 0.01$  remained in the final models. The association between change in CIMT level and change in HbA1c during follow-up was also explored for confounding and mediation by other covariates (e.g. insulin independence, antihypertensive use, immunosuppressive regimen); the magnitude of the HbA1c regression coefficients did not change by  $>10\%$  when other covariates were entered. Therefore, nonsignificant covariates did not remain in the final models as none were found to be confounders or mediators of the CIMT/HbA1c association. Adjusting

for islet transplant protocol (Edmonton/UIC) did not substantially change the regression coefficients. Sensitivity analyses were conducted by excluding the two males, and the four patients who had resumed a small dose of insulin at the end of their follow-up, and the results did not appreciably change.

## Results

All 15 patients achieved insulin independence following 1-3 transplants. At the end of their respective follow-up in the current analysis, 11 patients remained insulin free; three of the patients on insulin therapy at the end of their follow-up had large declines in their average dose compared to pre-transplant (37.5 to 10 units/day; 33 to 6 units/day; and 25.5 to 1.5 units/day), and one patient was on 20 units/day when withdrawn from the trial due to islet graft loss as previously discussed. During follow-up, there were no severe hypoglycemic events.

Mean age and diabetes duration were 49 (SD, 10) and 30 (SD, 12) years, respectively; 13 patients were female (Table 1). HbA1c decreased from 7.2% before transplant to 5.9% 12 months post-transplant ( $p<0.001$ ). Based on clinical trial exclusion criteria, no patient was classified as having kidney disease at baseline, and no patient presented with urine albumin/creatinine  $>300$  mg/g at 12 and 50 month follow-up. However, two patients had an eGFR  $<60$  (44 and 53) ml/min/1.73 m<sup>2</sup> at baseline. There was an increase in urine albumin/creatinine ratio (7 vs. 26 mg/g;  $p=0.04$ ; to convert to mg/mmol, multiply by 0.113) between baseline and 12 months; eGFR did not significantly change during follow-up.

Patients experienced a small decline in BMI (22.6 vs. 21.6;  $p=0.01$ ) between baseline and 12 months. Blood pressure and lipids were well controlled with

nonsignificant changes in both parameters during follow-up; 12 patients were on either antihypertensive or statin medication at baseline (of which 10 were treated with both, one with only statins, and one with only antihypertensives). The 11 patients on statin therapy at baseline were using atorvastatin, pravastatin, rosuvastatin or simvastatin, with an average dose of 20 (range: 10-40) mg/day. At their last follow-up visit, 11 patients were using similar brand statins or ezetimibe with an average dose of 26 (range: 10-80) mg/day.

There was a significant decrease in CIMT at 12 months ( $n=15$ ) for the common carotid ( $-0.058$  mm,  $p=0.006$ ) and combined score ( $-1.28$  SDs,  $p=0.004$ ) (Table 2 and Figure 1). The power to detect the significant changes in CIMT (two-sided paired t-test with  $\alpha=0.05$ ) was  $>85\%$ . There was a trend towards a decrease at 12 months for internal CIMT ( $-0.047$  mm,  $p=0.10$ ). For those with 50 month follow-up ( $n=7$ ), there was a slightly larger reduction in CIMT at 12 months for the three CIMT measures, which was statistically significant for the combined score ( $-1.59$  SDs,  $p=0.04$ ). At 50 months post-transplant, there was a continued reduction in CIMT, but of smaller magnitude, which was significant for the combined score ( $-0.77$  SDs,  $p=0.04$ ; Figure 1) and marginally significant for the internal artery ( $-0.037$  mm,  $p=0.06$ ). The power to detect the significant changes in the combined score was  $>55\%$ . Power for the nonsignificant changes ranged from 11-50%. Taken together, those with 50 month follow-up demonstrated a significant reduction in CIMT 12 months post-transplant, with subsequent progression of CIMT. Common carotid IMT progressed from 12 months ( $0.739$  mm; Table 2) to 50 months ( $0.775$  mm) at an average rate of  $0.011$  mm/year ( $((0.775 \text{ mm} - 0.739 \text{ mm})/38 \text{ months} \times 12)$ ).

Factors associated with the slope of change in CIMT during follow-up are presented in Table 3. For the common and internal artery, and combined CIMT score, the decreasing slope in CIMT was associated with a decreasing slope of change in HbA1c, but this was limited to individuals with smaller very low density lipoprotein (VLDL) particle size. For those individuals with larger VLDL particle size, the slope in CIMT was not related to the slope in glycemic control. The decreasing slope of change in CIMT during follow-up was also associated with decreasing slopes in apolipoprotein B, VCAM-1, and MCP-1, and increasing slopes in the proportion of the number of small VLDL particles relative to the total number of VLDL particles and PAI-1 activity. Statin use post-transplant was associated with a decreasing slope of change in common carotid IMT. CIMT was not associated with age, BMI, blood pressure, kidney function (creatinine clearance, albumin/creatinine ratio, eGFR), insulin independence, antihypertensive use, or immunosuppressive regimen in repeated measures modeling or cross-sectional analyses; nor did these factors confound or mediate the association between the slope of change in CIMT and HbA1c.

### Conclusions

The current prospective study demonstrated a significant decrease in CIMT following islet transplantation in individuals with type 1 diabetes. In the first year following transplant, common carotid artery IMT decreased approximately 0.060 mm. A slightly smaller decrease in CIMT was found in the first prospective study to look at the effect of pancreas transplant; 1.8 years following transplant, common artery IMT had significantly decreased by 0.045 mm (7). Minimally invasive islet transplantation therefore appears to reverse the progression of atherosclerosis within the first few years

following transplant, similar to pancreas transplant. Between 12 and 50 months following islet transplant, our results showed a progression of common artery IMT, on average 0.011 mm/year. However, at 50 months post-transplant, the combined CIMT score continued to be significantly reduced compared to pre-transplant levels.

Previous intervention studies aimed at achieving superior glycemic control have slowed the progression of CIMT in individuals with diabetes, but actual regression of CIMT is rare (18). For example, the CHICAGO Trial demonstrated that anti-diabetic medications stabilize (pioglitazone: -0.001 mm over 72 weeks) or slow the progression (glimepiride: 0.012 mm over 72 weeks) of common carotid IMT in type 2 diabetes (15). For type 1 diabetes, the DCCT/EDIC demonstrated six years after the end of the trial that common carotid IMT progressed at a significantly slower rate of 0.006 mm/year in the intensive treatment group, versus 0.008 mm/year in the conventional treatment group (3). In the one previous study to look at the effect of islet transplantation on CIMT, conducted in individuals with end-stage renal disease, there was a nonsignificant increase in CIMT (0.020 mm/year) in those receiving a kidney-islet transplant compared to a significant increase in CIMT (0.033 mm/year) in the kidney-only transplant group over three years of follow-up (14). For comparison, the mean progression of CIMT in healthy individuals without diabetes is 0.005 mm/year of age (19). The average rate of common carotid IMT progression seen in the current study during follow-up (0.011 mm/year), after the initial large decrease one year post-transplant, was larger than the progression in individuals with type 1 diabetes without transplant over six years following conventional therapy (0.008 mm/year) (3), and twice that seen in healthy individuals (0.005 mm/year) (19). However, it was half that seen in patients with end-

stage renal disease with a kidney-islet transplant (0.020 mm/year) (14). Therefore, although there is a significant decrease in CIMT initially after islet transplant, the substantial progression in CIMT after transplantation may increase CIMT back to pre-transplant levels such that it may no longer remain significantly reduced beyond 50 months post-transplant.

Greater CIMT is associated with an increased risk of coronary heart disease (20,21). In terms of clinical significance, for individuals without diabetes, a 0.100 mm increase in common carotid IMT is associated with an 11% increase in the risk of acute myocardial infarction (20). The Multi-Ethnic Study of Atherosclerosis demonstrated a 20% increase in coronary heart disease for a one standard deviation increase (0.190 mm) in common carotid artery IMT (21). In the DCCT/EDIC, a 0.002 mm/year slower progression in common artery CIMT in the intensive versus conventional treatment group (3) paralleled a 57% reduction in nonfatal myocardial infarction, stroke, or death from cardiovascular disease in the intensive versus conventional group (5). Therefore, the initial reduction in common carotid IMT of 0.060 mm in the first year after islet transplant, with continued reduction of approximately 0.030 mm after 50 months, may have a clinical impact on the risk of ischemic heart disease in those with type 1 diabetes in the first years following transplant. However, the progression in CIMT of 0.011 mm/year after transplant may limit the clinical impact on long-term cardiovascular outcomes. During follow-up after islet transplant in the current study, no patient experienced a myocardial infarction or stroke; two patients required cardiac procedures (the first patient, with the second highest combined CIMT score during follow-up, required two stents placed in the left anterior descending artery one year after the first

and only transplant; the second patient, with the lowest combined CIMT score during follow-up, required balloon angioplasty of the posterior descending artery between the second and third transplant). Long term follow-up is underway to document any additional cardiovascular events.

The decreasing trend in CIMT during follow-up was associated with improvements in HbA1c, particularly in those individuals with small VLDL particle size, a factor strongly affected by enhanced insulin sensitivity (22). It is well documented that euglycemia can contribute to stabilization of endothelial function and proliferation (23), and indeed, lower mean HbA1c largely explained the slower progression of CIMT in the intensive glycemic control group in the DCCT/EDIC (4). Our results expand upon the DCCT/EDIC data by demonstrating that the superior level of glycemic control that can be achieved with islet transplant compared to intensive insulin management may have not only contributed to a slower progression of CIMT but significant improvements in CIMT, specifically for the insulin sensitive patients. Therefore, the reduction in CIMT during the first year after transplant may be explained by the significant reduction in HbA1c consequent to restoring endogenous insulin secretion through transplant (11), and subsequent progression of CIMT may be explained by declining islet graft function and glycemic control after the first year (9). The twofold rate of progression in CIMT compared to healthy individuals (19) may also be associated with chronically higher HbA1c levels compared to those without diabetes.

The decreasing trend in common CIMT was also associated with statin use and improvements in lipids, specifically declining apolipoprotein B and increasing concentrations of the small (vs. large) VLDL particles. This is consistent with previous

research demonstrating that statin therapy can promote regression of atherosclerotic plaques (24) and CIMT (25). Improvements in internal CIMT were also associated with decreasing trends in VCAM-1 and MCP-1, and an increasing trend in PAI-1 activity, consistent with decreased inflammation and atherogenesis. CIMT was not associated with kidney function, periods of insulin independence, or medications such as antihypertensives and immunosuppressive regimen post-transplant.

A strength of the current study is that it is prospective with up to 50 months of follow-up, in which each individual was his/her own control, measured before and after the intervention. The lack of a concurrent control group of similar patients without transplant to study 12 month change in CIMT may be considered a weakness, but such a concurrent control group was not feasible in this study; the average time on the islet transplant waiting list at the UIC Medical Center was only 4.4 months, and only one patient was on the list for over one year. Additionally, the FDA has stated that historical control data such as the DCCT/EDIC are sufficient, as concurrent control groups in islet transplantation trials are not practical, due to: the unwillingness of patients to be controls; the potentially high control drop-out rate that may occur, even if controls are able to be recruited, due to the open-label nature of the trial; the limitations of the comparative information which would result from the inability to blind patients and investigators; and the inability to power a trial to detect treatment-related effects given the limited availability of islets and the high costs of each patient (26,27). An additional strength of the study is that it did not enroll individuals with kidney disease or previous cardiovascular events, as defined by the clinical trial exclusion criteria, two potentially confounding factors. However, there were decreases in kidney function for some



patients after islet transplant, a concerning and not uncommon side-effect of immunosuppressive medications in islet transplantation (9).

The current study was limited to a case-series of 15 individuals with half of the cohort followed for the full five years; to increase statistical power, analyses evaluating predictors of CIMT utilized repeated measures. These results are suggestive of potentially important changes for those with type 1 diabetes and will need validation in a larger cohort of patients. It would also be informative to determine whether regression of CIMT and/or the slowing of other cardiovascular outcomes occur in a xenotransplant setting in light of the recent successes in xenotransplantation (28). As periods of insulin independence have been found to increase with potent induction immunotherapy (29), longer-term follow-up will also be needed in other cohorts to see if improvements in CIMT could potentially be sustained for longer than 50 months as insulin independence becomes more durable; though insulin independence was not significantly associated with CIMT in the current study.

In conclusion, minimally invasive islet transplantation leads to insulin independence and may also slow the progression of atherosclerosis caused by type 1 diabetes. The underlying mechanism is likely related to improved glycemic control consequent to restoring endogenous insulin secretion through the islet transplant, and optimal lipid management post-transplant also contributes.

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KKD contributed to the discussion and wrote the manuscript. BH researched data, contributed to the discussion, and reviewed/edited the manuscript. KK researched data, contributed to the discussion, and reviewed/edited the manuscript. BK contributed to the discussion and reviewed/edited the manuscript. JM researched data and reviewed/edited the manuscript. MQ contributed to the discussion and reviewed/edited the manuscript. AM researched data and reviewed/edited the manuscript. EB contributed to the discussion and reviewed/edited the manuscript. JO researched data, contributed to the discussion, and reviewed/edited the manuscript.

KKD and JO had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

The authors have no relevant conflicts of interest to disclose.

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Table 1. Demographic and clinical characteristics of islet transplant recipients

	All Participants (n=15)			Participants with 50 month CIMT (n=7)		
	Pre-	12 months	p-value	Pre-	50 months	p-value
	transplant <sup>a</sup>	post-transplant		transplant	post-transplant	
Age (years)	49.4 (9.5)			47.3 (9.4)		
Female, No. (%)	13 (86.7)			6 (85.7)		
Diabetes duration (years)	30.1 (12.2)			28.7 (10.3)		
BMI (kg/m <sup>2</sup> )	22.6 (1.7)	21.6 (1.9)	0.01	22.5 (1.7)	21.5 (1.5)	0.23
HbA1c (%)	7.2 (0.9)	5.9 (0.4)	<0.001	7.5 (1.1)	6.0 (0.4)	0.01
Urine albumin/creatinine (mg/g)	7 (23)	26 (130)	0.04	14 (23)	20 (137)	0.45
eGFR (ml/min/1.73m <sup>2</sup> )	83.7 (24.0)	83.6 (22.8)	0.98	84.2 (28.6)	79.3 (20.5)	0.56
Antihypertensive use, No. (%)	11 (73.3)	13 (86.7)	0.32	4 (57.1)	7 (100)	0.08
Systolic blood pressure (mm Hg)	120 (13)	127 (16)	0.28	116 (16)	125 (18)	0.25
Diastolic blood pressure (mm Hg)	67 (6)	71 (11)	0.28	66 (8)	71 (10)	0.25
Statin use, No. (%)	11 (73.3)	13 (86.7)	0.16	5 (71.4)	6 (85.7)	0.32
Total cholesterol (mg/dL)	165 (33)	185 (49)	0.18	162 (34)	169 (67)	0.74
LDL (mg/dL)	85 (25)	104 (42)	0.11	80 (26)	76 (31)	0.71
HDL (mg/dL)	63 (22)	62 (23)	0.75	63 (19)	71 (38)	0.38
Triglycerides (mg/dL)	61 (30)	90 (122)	0.12	61 (23)	73 (24)	0.69

Abbreviations: CIMT=carotid intima-media thickness; BMI=body-mass index; eGFR=estimated glomerular filtration rate; LDL=low-density lipoprotein; HDL=high-density lipoprotein

SI conversion factor: To convert albumin/creatinine to mg/mmol, multiply by 0.113; to convert total cholesterol, LDL, and HDL to mmol/L, multiply by 0.0259; to convert triglycerides to mmol/L, multiply by 0.0112

<sup>a</sup> Data presented as mean (standard deviation) or No. (%); urine albumin/creatinine and triglycerides are median (interquartile range)

Table 2. Absolute values and change in CIMT pre-transplant to 12 and 50 months post-transplant

	All Participants (n=15)				Participants with 50 month CIMT (n=7)			
	Pre <sup>a</sup>	Post	Change (Post – Pre)	p-value	Pre	Post	Change (Post – Pre)	p-value
Common carotid artery (mm)								
12 month	0.789 (0.147)	0.731 (0.111)	-0.058 (0.069)	0.006	0.801 (0.188)	0.739 (0.130)	-0.062 (0.090)	0.12
50 month					0.801 (0.188)	0.775 (0.151)	-0.026 (0.080)	0.42
Internal carotid artery (mm)								
12 month	0.767 (0.148)	0.720 (0.088)	-0.047 (0.104)	0.10	0.771 (0.165)	0.708 (0.082)	-0.063 (0.120)	0.21
50 month					0.771 (0.165)	0.734 (0.157)	-0.037 (0.042)	0.06
Common + Internal Z-score (SDs)								
12 month	2.06 (2.51)	0.78 (1.96)	-1.28 (1.45)	0.004	2.36 (2.77)	0.77 (1.92)	-1.59 (1.69)	0.04
50 month					2.36 (2.77)	1.59 (2.53)	-0.77 (0.80)	0.04

Abbreviations: CIMT=carotid intima-media thickness; SDs=standard deviation units

<sup>a</sup> Data are presented as mean (standard deviation)

Table 3. Factors significantly associated with the slope of change in CIMT pre-transplant through 50 months post-transplant

	Common carotid artery (mm)		Internal carotid artery (log; mm)		Common + Internal Z-score (SDs)	
n=15 with 53 repeated measures	$\beta^a$ (SE) <sup>b</sup>	p-value	$\beta$ (SE)	p-value	$\beta$ (SE)	p-value
HbA1c (%): <sup>c</sup>						
when VLDL size $\leq 47$ nm <sup>d</sup>	0.035 (0.011)	0.004	0.101 (0.028)	0.001	1.11 (0.23)	<0.001
when VLDL size >47 nm	-0.011 (0.012)	0.35	-0.014 (0.026)	0.59	0.13 (0.22)	0.55
VLDL size >47 nm (v. $\leq 47$ nm) at HbA1c=6% <sup>d</sup>	0.025 (0.017)	0.14	0.070 (0.038)	0.08	0.24 (0.32)	0.45
Statin use (v. no use)	-0.070 (0.024)	0.006	-		-	
Apolipoprotein B (10 mg/dL)	0.012 (0.003)	<0.001	-		-	
Small VLDL particles / Total VLDL particles (%)	-0.009 (0.002)	<0.001	-		-0.14 (0.04)	0.002
VCAM-1 (log; ng/mL)	-		0.107 (0.037)	0.007	-	
MCP-1 (10 pg/mL)	-		0.009 (0.002)	<0.001	-	
PAI-1 activity (log; U/mL)	-		-0.054 (0.014)	<0.001	-	

Abbreviations: CIMT=carotid intima-media thickness; SDs=standard deviation units; VLDL=very low-density lipoprotein; VCAM-1=vascular cell adhesion molecule-1; MCP-1=monocyte chemotactic protein-1; PAI-1=plasminogen activator inhibitor type 1

SI conversion factor: To convert apolipoprotein B to g/L, multiply by 0.01

<sup>a</sup> Coefficients from mixed-effects linear regression modeling of repeated measures; additional variables that were tested in all models but were not significantly associated with change in CIMT, nor did they confound or mediate the association between change in HbA1c and CIMT, included: age, body composition, blood pressure, kidney function, antihypertensive use, immunosuppressive regimen, and all other lipids and cardiovascular/inflammatory markers not presented in the table above

<sup>b</sup> Empirical standard errors

<sup>c</sup> p-values for interactions between HbA1c and VLDL size on CIMT: common,  $p=0.006$ ; internal,  $p=0.01$ ; and Z-score,  $p=0.001$ ; standard errors and p-values for HbA1c when VLDL size  $\leq 47$  and  $>47$  were estimated separately using identical models but with reverse coding (0,1) for VLDL size; HbA1c was centered at the sample mean post-transplant (6%)

<sup>d</sup> Mean VLDL size and HbA1c post-transplant

Figure 1. Combined Score (standard deviation units) prior to, and 12 and 50 months after, islet transplant. The dotted line represents the mean change in the score between baseline and 12 month follow-up (n=15). The dashed line represents the mean change in the score between baseline, 12, and 50 month follow-up (n=7).