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ISLET AUTOTRANSPLANT RECIPIENTS HAVE ELEVATED PROINSULIN:C-PEPTIDE RATIOS SUPPORTING METABOLIC STRESS AS A CAUSE OF ISLET ATTRITION

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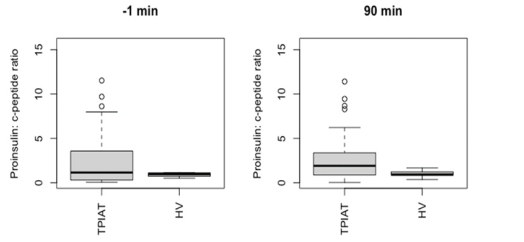
Introduction: Attrition of insulin independence and islet function is observed over time following total pancreatectomy with islet autotransplantation (TPIAT). Metabolic stress on a suboptimal islet mass is a suspected contributor but has not been tested. We measured proinsulin to C-peptide ratios (PI:CP) as an indicator of beta cell endoplasmic reticulum stress in patients >5 years post-TPIAT.
Methods: Patients ≥16 years of age and 5-20 years s/p TPIAT were invited to undergo 4-hour mixed meal tolerance testing (MMTT) and assessment of free-living glycemia by continuous glucose monitoring. Insulin use and hemoglobin A1c were obtained. PI:CP was measured from fasting and +90 minute MMTT samples. PI:CP ratios were compared to healthy controls (n=6) and were associated with MMTT and CGM measures.
Results: We included 102 participants, age 48 (IQR 34, 55) years, 75% female, 9.5 (6.9, 12.2) years post-TPIAT. Median islet mass transplanted was 3,755 (2,849, 5,402) IEQ/kg and 30% were off insulin at time of testing. PI:CP had a more variable distribution with higher values in TPIAT compared to healthy controls; (Figure 1)

Figure 1: Fasting (-1 min) and 90 minute MMTT PI:CP ratios for TPIAT recipients vs healthy controls.



p<.0001 for a difference in mean PI:CP at both timepoints). Within the TPIAT recipients, higher PI:CP ratios were associated with lower IEQ/kg transplanted, partial or failed islet function, higher HbA1c, higher BMI, reduced time in range on CGM, and more time in hyperglycemia by MMTT. (table 1)

Table 1: Univariable association of participant characteristics with fasting and 90 minute PI:CP ratios. N= 203 samples in 102 participants; CGM data was unavailable for 7 participants and MMTT AUC for 1 participant.

Characteristic	N	Beta	95% CI[1]	p-value
IEQ/kg (per 1000)	203	-0.28	-0.50, -0.05	0.015
IEQ/kg group	203			0.082
Low		—	—	
Moderate		-1.2	-2.4, 0.06	
High		-1.5	-2.9, -0.17	
Graft function group	203			0.032
Full Function (no insulin)		—	—	
On insulin with islet graft function		1.3	0.31, 2.2	
On insulin with islet graft failure		1.2	-0.60, 3.1	
HbA1c	203	0.26	-0.01, 0.52	0.058
HbA1c <= 6.5%	203	-1.3	-2.2, -0.47	0.002
BMI (kg/m2)	203	0.11	0.03, 0.20	0.009
CGM Time in range (%)	189	-0.03	-0.05, -0.02	<0.001
CGM Time in tight range (%)	189	-0.04	-0.05, -0.02	<0.001
AUC glucose (mg/dL x 240 min), per 1,000	201	0.04	0.01, 0.06	0.006

Conclusions: PI:CP ratios were elevated at a median of 10 years after TPIAT. Those who had fewer islets transplanted, more hyperglycemia, and/ or obesity were more likely to have high PI:CP. These findings support the concept that metabolic stress is a cause of islet attrition in TPIAT and that having fewer islets, poor glycemic control, or unhealthy body weight may contribute to this metabolic stress.

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CONTINUOUS GLUCOSE MONITORING AND ASSESSMENT OF LONG-TERM ISLET FUNCTION IN AUTOLOGOUS ISLET TRANSPLANTATION AFTER TOTAL PANCREATECTOMY FOR PANCREATIC NEOPLASIA: PRELIMINARY DATA FROM THE VERONA COHORT

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Introduction: Total pancreatectomy with autologous islet transplantation (TPAIT) has been proposed as an alternative to high-risk pancreatic anastomosis after pacreaticoduodenectomy for prevention of surgical complications, while maintaining low risks to develop brittle pancreatogenic diabetes. However, few studies have investigated the relationship between continuous glucose monitoring (CGM) profiles and TPAIT outcomes.
Methods: Between September 2023 and February 2025, 10 subjects with pancreatic neoplasia underwent TPAIT (males/females 5/5, age 60 [IQR 55-68] years, islet infusion 1912 [IQR 1724 – 3074] IEQ/kg) at the University Hospital of Verona. All of them underwent a glucometabolic monitoring program with visits at 1 (n=10), 3 (n=9), 6 (n=7) and 12 months (n=6) after TPAIT, including hematological exams and CGM-derived 3-month glucose profiles. Islet metabolic function at 12 months was assessed through the most recent modified Minnesota criteria, and optimal outcomes were compared to not-optimal ones.
Results: Six subjects reached 12 months of follow-up: according to modified Minnesota criteria, their islet function was classified as optimal (n=3), good (n=2) and failure (n=1). All subjects with not-optimal islet function developed diabetes. Patients with optimal versus not-optimal outcomes displayed lower coefficients of variation at 3, 6 and 12 months (17.7% vs 27.9%, 20.4% vs 30.3%, 24.6% vs 29.4% respectively, all p<0.05), higher time in range (TIR) and tight range (TITR) and lower glycemia risk index (GRI) at 3 and 12 months (TIR: 99% vs 86%, 96% vs 84% respectively; TITR: 95% vs 60%, 85% vs 56% respectively; GRI: 2.4 vs 15.2, 4.8 vs 15.2, respectively; all p<0.05), and lower time above range at 12 months (3 vs 15%, p<0.05).
Conclusions: According to our preliminary data, optimal islet function at 12 months after TPAIT was associated with lower glycemic variability and longer time spent in euglycemia, thereby suggesting that CGM metrics may be a good clinical indicator of long-term islet glucose competence.