

Supplemental Information

Supplemental Table 1: Baseline Demographics of the Progressors ≥ 5 and Aab- Relatives at Study Entry

Characteristic	Progressors ≥ 5 (n=75)	Progressors < 5 (n=474)	Aab- Controls (n=144)	p- value
Age at study entry Median (IQR) Mean (SD)	10.5(6.1-17.0) 15.0 (12.6)	9.8(6.6-13.8) 12.0 (9.1)	13.4(9.4-17.5) 16.3(10.4)	<0.001 <0.001
Age at T1D diagnosis Median (IQR) Mean (SD)	17.0(12.8-23.8) 21.6(12.8)	11.6(8.3-16.0) 13.9(9.3)	NA	<0.001 <0.001
Length of follow-up in years Median (IQR) Mean (SD)	6.2(5.6-7.4) 6.6 (1.3)	1.7(0.9-2.8) 1.9 (1.3)	1.5(0.4-7.1) 3.3(3.2)	<0.001 <0.001
Gender, n (%) Male Female Unknown/not reported	32(42.7) 43(57.3) 0(0.0)	232(49.0) 236(49.8) 6(1.2)	69(47.9) 73(5.7) 2(1.4)	NS
Race, n (%) White Other Unknown/ not reported	70(93.3) 3(4.0) 2(2.7)	414(87.3) 51(10.8) 9(1.9)	133(92.4) 6(4.1) 5(3.5)	NS
Ethnicity, n (%) Hispanic or Latino Not Hispanic or Latino Unknown/ not reported	7(9.3) 64(85.4) 4(5.3)	43(9.1) 403(85.0) 28(5.9)	10(6.9) 128(88.9) 6(4.2)	NS
Relationship to Proband Sibling Offspring Parent Other Unknown	44(58.7) 16(21.3) 10(13.4) 4(5.3) 1(1.3)	297(62.7) 102(21.5) 34(7.2) 27(5.7) 14(3.0)	84(58.3) 27(18.8) 20(13.9) 12(8.3) 1(0.7)	NS
Aab# at study entry, n (%) 1 ≥ 2	9 (12.0) 66 (88.0)	53(11.2) 421(88.8)	NA NA	NS
BMI z score Median (IQR) Mean (SD)	0.41 (-0.31,1.14) 0.36 (1.07)	0.69 (0.04,1.46) 0.69 (1.16)	0.83 (-0.09,1.60) 0.76 (1.24)	0.032 0.054

Pearson Chi-square tests were used to compare categorical variables. For comparisons of continuous variables, ANOVA tests were used to compare three means, while Kruskal Wallis tests were used to compare three medians. SD: Standard Deviation; IQR: Interquartile Range

Supplemental Table 2: Comparison of Metabolic Parameters for Progressors \geq 5 and Progressors $<$ 5 at Study Entry

	T1D \geq 5 years (n = 75) Mean (SD)	T1D $<$ 5 years (n = 474) Mean (SD)	p-value*	p- value#
Fasting C-peptide (ng/ml)	1.3 (0.7)	1.4 (0.8)	0.2	0.048
Early C-peptide Response (ng/ml)	3.0 (1.7)	2.8 (1.8)	0.53	0.16
C-peptide AUC (mg/dL/120 min)	4.9 (2.2)	4.8 (2.2)	0.84	0.83
Fasting Glucose (mg/dL)	87.3 (9.2)	89.8 (11.6)	0.04	0.005
2 hr Glucose (mg/dL)	118.8 (28.6)	140.2 (31.0)	$<.001$	$<.001$
Glucose AUC	136.20 (22.02)	153.45 (25.06)	$<.001$	0.002
^Index 60	0.52 (0.87)	0.97 (0.96)	$<.001$	0.002

* Student's t-test; #Multivariate linear regression with age and BMI z score as covariates.

^ Index 60 values were log-transformed for comparisons.

AUC: Area under the curve. SD: standard deviation.

Supplemental Table 3: Patterns of Metabolic Decline in Progressors \geq 5 and Progressors $<$ 5

	3 Years to 1 Year Before Diagnosis					1 Year Before to Diagnosis				
	Progressors \geq 5 (n=29)		Progressors $<$ 5 (n=72)		*p value	Progressors \geq 5 (n=29)		Progressors $<$ 5 (n=72)		*p value
	Abs Change Median (IQR)	% Change Median (IQR)	Abs Change Median (IQR)	% Change Median (IQR)		Abs Change Median (IQR)	% Change Median (IQR)	Abs Change Median (IQR)	% Change Median (IQR)	
Fasting C-Peptide	0.2 (-0.02, 0.43)	15 (-1, 25)	0.26 (-0.08, 0.55)	25 (-5, 49)	0.6	0.13 (-0.23, 0.81)	5 (-9, 30)	0.12 (-0.12, 0.43)	9 (-10, 35)	0.86
Early C-peptide Response	-0.2 (-1.01, 0.49)	-9 (-36, 24)	-0.33 (-1.26, 0.29)	-11 (-37, 12)	0.48	-0.44 (-2.05, -0.02)	-35 (-47, -2)	-0.75 (-1.76, -0.17)	-36 (-59, -12)	0.62
C-Peptide AUC	0.03 (-0.37, 0.77)	0 (-9, 23)	0.19 (-0.54, 0.85)	4 (-13, 21)	0.68	-0.58 (-1.58, 0.09)	-12 (-22, 2)	-0.82 (-1.54, -0.16)	-20 (-33, -3)	0.49
Fasting Glucose	4 (1, 13)	4 (1, 15)	3.5 (-1.5, 10)	4 (-2, 12)	0.37	6 (0, 26)	7 (0, 25)	10.5 (1, 19)	12 (1, 23)	0.85
2 hr Glucose	28 (-4, 48)	21 (-4, 49)	17.5 (-9.5, 52.5)	15 (-7, 43)	0.52	85 (60, 118)	62 (30, 95)	74 (40, 137)	51 (25, 98)	0.66
Glucose AUC	21.42 (-0.17, 32.92)	13 (0, 29)	16.92 (4.21, 34.38)	12 (3, 25)	0.71	39.67 (20.17, 64.92)	27 (12, 44)	42.96 (16.67, 75.08)	27 (10, 48)	1.00
Index 60	0.23 (-0.12, 0.95)	28 (-29, 59)	0.56 (-0.12, 1)	31 (-53, 96)	0.45	1.09 (0.68, 1.68)	70 (-9, 224)	1.11 (0.51, 1.78)	68 (14, 154)	1.00

Analysis limited to Progressors \geq 5 and Progressors $<$ 5 who had paired OGTTs at the two time intervals.

*Wilcoxon rank sum tests were used to compare absolute changes between groups. IQR: Interquartile Range. AUC: Area Under the Curve. Abs: Absolute Change

Supplemental Table 4: Comparison of Metabolic Parameters for Progressors \geq 5 and Progressors $<$ 5 at T1D Diagnosis

	Progressors \geq 5 (n=31) Mean (SD)	Progressors $<$ 5 (n=303) Mean (SD)	*p-value	#adjusted p-value
Fasting C-peptide	2.36 (1.21)	1.66 (0.92)	<0.001	0.09
Early C-peptide Response	1.79 (1.24)	1.66 (1.3)	0.57	0.59
C-Peptide AUC	5.38 (2.70)	3.95 (2.04)	<0.001	0.07
Fasting Glucose	108.03 (16.61)	102.84 (23.68)	0.23	0.33
2 hr Glucose	245.13 (67.34)	235.43 (76.33)	0.49	0.34
Glucose AUC	212.53 (39.46)	206.68 (47.34)	0.51	0.61
$^{\wedge}$ Index 60	2.13 (1.22)	2.38 (1.14)	0.37	0.86

Analysis limited to those subjects in Progressor groups who had an OGTT at the time of T1D diagnosis. *Student's t-test; #Multivariate linear regression with age and BMI z-score as covariates. $^{\wedge}$ Index60 values were log transformed for comparisons. SD: Standard Deviation.

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