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**Clinical Research Article**

# Metabolic Phenotype of Stage 1 and Stage 2 Type 1 Diabetes Using Modeling of β Cell Function

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## Abstract

**Background:** Staging preclinical type 1 diabetes (T1D) and monitoring the response to disease-modifying treatments rely on the oral glucose tolerance test (OGTT). However, it is unknown whether OGTT-derived measures of beta cell function can detect subtle changes in metabolic phenotype, thus limiting their usability as endpoints in prevention trials.

**Objective :** To describe the metabolic phenotype of people with Stage 1 and Stage 2 T1D using metabolic modelling of β cell function.

**Methods:** We characterized the metabolic phenotype of individuals with islet autoimmunity in the absence (Stage 1) or presence (Stage 2) of dysglycemia. Participants were screened at a TrialNet site and underwent a 5-point, 2-hour OGTT. Standard measures of insulin secretion (area under the curve, C-peptide, Homeostatic Model Assessment [HOMA] 2-B) and sensitivity (HOMA Insulin Resistance, HOMA2-S, Matsuda Index) and oral minimal model–derived insulin secretion (φ total), sensitivity (sensitivity index), and clearance were adopted to characterize the cohort.

**Results:** Thirty participants with Stage 1 and 27 with Stage 2T1D were selected. Standard metrics of insulin secretion and sensitivity did not differ between Stage 1 and Stage 2 T1D, while the oral minimal model revealed lower insulin secretion ($P < .001$) and sensitivity ($P = .034$) in those with Stage 2 T1D, as well as increased insulin clearance ($P = .006$). A higher baseline φ total was associated with reduced odds of disease progression, independent of stage (OR 0.92 [0.86, 0.98], $P = .016$).

**Conclusion:** The oral minimal model describes the differential metabolic phenotype of Stage 1 and Stage 2 T1D and identifies the φ total as a progression predictor. This supports its use as a sensitive tool and endpoint for T1D prevention trials.

**Key Words:** preclinical T1D, insulin secretion, insulin sensitivity, islet autoimmunity, oral minimal model

**Abbreviations:** AAb, autoantibody; AUC, area under the curve; BMI, body mass index; GADA, Glutamic Acid Decarboxylase antibodies; HOMA-IR, Homeostatic Model Assessment Insulin Resistance; ZnT8A, Zinc transporter 8 antibodies; φ total, phi total; OGTT, oral glucose tolerance test; OMM, oral minimal model; T1D, type 1 diabetes.

Preclinical type 1 diabetes (T1D) is featured by the presence of 2 or more islet autoantibodies (AAbs) without (Stage 1) or with (Stage 2) dysglycemia as measured during an oral glucose tolerance test (OGTT) (1,). The onset of dysglycemia is driven by the progressive loss of insulin secretion, though growing evidence suggests that a reduction of insulin sensitivity and a relative increase of its clearance may have in disease progression (2-4). Quantifying the individual components of the metabolic phenotype of preclinical T1D, including insulin secretion, sensitivity, and clearance, hold the potential to provide novel risk measures and metabolic endpoints to inform prevention trials (5). Nonetheless, tools to accurately describe the metabolic phenotype are limited (6). Area under the curve (AUC) C-peptide during dynamic tests such as the OGTT or the mixed-meal tolerance test (MMTT) has been accepted as a surrogate endpoint to quantify residual beta cell function in Stage 3—clinical—diabetes (7), but it has shown low predictive values for disease progression in preclinical T1D when compared with measures that include both glucose and C-peptide (8).

Additionally, other individual covariates such as body mass index (BMI), age, and sex may need to be accounted for to improve the accuracy of metabolic metrics (9) as disease prevention trials include heterogeneous groups of participants with physiologic fluctuation of insulin sensitivity (10) that need to be considered when metabolic outcomes are examined.

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To this end, mathematical models of insulin secretion and sensitivity, such as the oral minimal model (OMM), may represent a valuable option. The OMM is a simplified representation of β cell physiology and insulin action using data from a dynamic test, for instance the OGTT. The OMM adopts quasi-linear differential equations to estimate insulin secretion and sensitivity as a result of metabolic fluxes among different body compartments with adjustments for BMI, sex, and age. As it uses glucose and C-peptide to estimate insulin secretion and glucose and insulin to estimate insulin sensitivity, the model provides an unbiased estimate of glucose metabolic phenotype using an OGTT (6, 11-14). The OMM has been able to describe early metabolic response to disease-modifying treatments such as anti-CD3 teplizumab 3 months after a cycle of treatment and may represent a promising tool to develop metabolic endpoints in preclinical T1D (2).

We hypothesized that the OMM-derived metrics may describe the complexity of the metabolic phenotype in Stage 1 and Stage 2 T1D identifying differences in insulin secretion, sensitivity, and clearance.

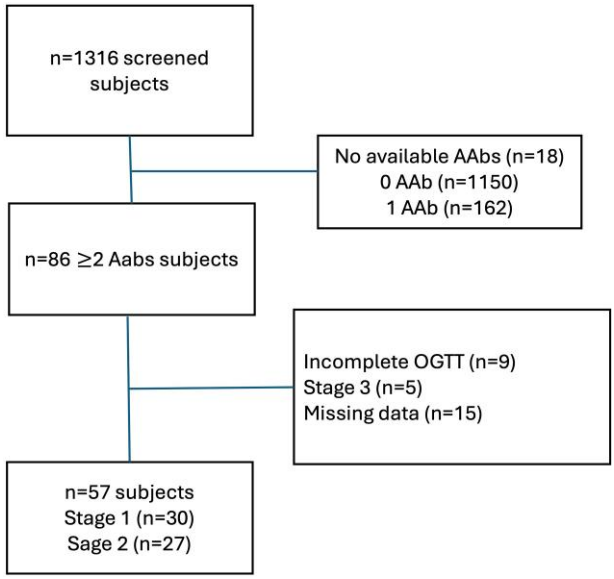


**Figure 1.** CONSORT diagram.

## Materials and Methods

### Selection of the Study Cohort

We conducted a longitudinal study aimed at comparing the metabolic phenotype in preclinical stages of T1D in a contemporary cohort of youth and adult relatives of patients with T1D participating in the TrialNet Pathway to Prevention Study (TNPTP) at the TrialNet Clinical Center of Ospedale San Raffaele (Milan, Italy). Institutional Review Board approval of the study was obtained (IRB# NHPROT32803-TN01), as well as written informed consent and assent, as applicable. First- and second-degree relatives of individuals with T1D were screened for islet AAbs to Glutamic Acid Decarboxylase (GADA), insulin (microinsulin antibody assay), and islet antigen 2 (IA-2A). If any of these were positive in screening, Zinc transporter 8 (ZnT8A) and islet cell antibodies (ICA) were also tested. Participants identified as AAb positive were monitored with AAb testing, HbA1c, and scheduled for OGTT at 12-month intervals as per TNPTP protocol (15).

A total of 86 relatives with 2 or more islet AAbs, enrolled from 2010 to 2019 at the Ospedale San Raffaele clinical site, were initially considered. Exclusion criteria included the absence of height, weight, and all islet AAbs, as well as complete data for all points of the OGTT for glucose, insulin, and C-peptide. Furthermore, subjects with glucose levels in the diabetic range (fasting glucose ≥7.0 mmol/L or 2-hour glucose ≥11.1 mmol/L) were excluded (Fig. 1). The final selection included n = 30 Stage 1 and n = 27 Stage 2 individuals. Participants who did not complete the extended 5-point OGTT as per TNPTP protocol were also excluded from the current analysis. Follow-up data were based on the last available monitoring OGTT.

### Preclinical Stages of T1D

In this study, we included 2 stages of preclinical T1D (ie, Stage 1 and Stage 2) based on the following definition: Stage 1 was defined as the presence of AAb ≥2 with normoglycemia; Stage 2 by the presence of AAb ≥2 associated with dysglycemia (1). Dysglycemia was defined by impaired fasting blood glucose (5.6-6.9 mmol/L), and/or impaired glucose tolerance (7.8-11 mmol/L at 2 hours), and/or glucose levels ≥11.1 mmol/L at 30, 60, or 90 minutes during an OGTT (16).

The definition of progression to Stage 2 was based on at least 1 OGTT following the baseline test meeting the criteria for dysglycemia. Progression to Stage 3 was defined by the presence of at least 1 OGTT meeting the ADA criteria for diabetes or HbA1c ≥6.5% (48 mmol/mol). The presence of "symptomatic diabetes" record also identified progression to Stage 3 disease.

### Procedures and Calculations

#### Oral glucose tolerance test

Subjects were admitted to the Ospedale San Raffaele TrialNet Clinical Center after a 10-hour overnight fast. A baseline sample was obtained for measurements of plasma glucose, insulin, and C-peptide. Thereafter, flavored glucose in a dose of 1.75 g per kilogram of body weight (up to a maximum of 75 g) was given orally, and blood samples were obtained at 30, 60, 90, and 120 minutes for the measurement of plasma glucose, insulin, and C-peptide (17). The 5-point OGTT was conducted as part of the TNPTP monitoring program.

#### Biochemical analysis

Plasma insulin was measured by a radioimmunoassay (Linco, St. Charles, MO) that has <1% cross-reactivity with C-peptide and proinsulin. Plasma C-peptide levels were determined with an assay from Diagnostic Product (Los Angeles, CA).

#### T1D risk scores: Diabetes Prevention Trial Risk Score and Index60

Diabetes Prevention Trial Risk Score (DPTRS) and Index60 are validated predictors of Stage 3 T1D. The DPTRS calculation is based on a proportional hazards model that includes the glucose sum of 30-, 60-, 90-, and 120-minute values divided by 100, the C-peptide sum of 30-, 60-, 90-, and 120-minute values divided by 10, log fasting C-peptide, log BMI, and age (18).

A DPTRS threshold of 7.0 has been previously validated in the TrialNet natural history study as a risk marker for progression to clinical T1D among those with normoglycemia (19, 20).

Index60 was calculated based on the following formula: 0.36953 (log fasting C-peptide [ng/mL]) + 0.0165 × glucose60 (mg/dL) −0.3644 × C-peptide60 (ng/mL), where glucose60 and C-peptide60 are the blood glucose and C-peptide values at 60 minutes during the OGTT, respectively (21). A Index60 threshold of 1.0 has been described to outperform 2-hour glucose in the TrialNet pathway to preventions study as predictor of clinical T1D among those with normoglycemia (22).

### Minimal model estimates of beta cell function: insulin secretion and insulin sensitivity

Beta cell function was quantified through the OMM as the results of insulin secretion and sensitivity. Briefly, the model relies on 2-hour serial measures of glucose and insulin for insulin sensitivity (SI term) estimates and glucose and C-peptide for insulin secretion ($\phi_{total}$ term). The OMM expresses beta cell function (disposition index) as the product of $\phi_{total}$ term and SI (23, 24). The use of glucose and insulin for insulin sensitivity estimates and glucose and C-peptide for insulin secretion allows an unbiased identification of both the components of beta cell function (23, 25, 26). The model also allows the estimates of subcomponents of insulin secretion, namely φ dynamic and φ static. However, we previously demonstrated that the accuracy of the early insulin secretion (φ dynamic) is reduced in the absence of early measure of glucose and C-peptide at 10 and 20 minutes of the OGTT (4, 13), thus we excluded these from our analysis as their interpretation is limited. Minimal model parameters were estimated by implementing the model of C-peptide secretion in SAAM-II 2.3 software (Nanomath LLC, Spokane, WA).

### Standard indices of beta cell function

The AUC for C-peptide over 2 hours was computed using the trapezoidal rule including all C-peptide measures during the OGTT. Insulin sensitivity was also computed using standard indices based on fasting insulin and glucose (Homeostatic Model Assessment Insulin Resistance [HOMA-IR]) and glucose and insulin during the OGTT (Matsuda Index). HOMA-IR was calculated as [fasting plasma insulin (μU/mL) × fasting plasma glucose (mg/dL)/405]; the Matsuda Index [10 000/$\sqrt{}$[fasting glucose (mg/dL) × fasting insulin (μU/mL) × [mean glucose$_{0\text{-}120}$ (mg/dL) × mean insulin$_{0\text{-}120}$ (μU/mL)] with mean glucose and insulin estimated during the 2-hour OGTT (27). As a static measure of insulin secretion HOMA2-B (beta cell function) was computed using the Oxford University Calculator (www.dtu.ox.ac.uk/homacalculator) and based on fasting glucose and insulin.

### Insulin clearance

Insulin clearance was measured as the ratio of AUC of the insulin secretion rate over AUC insulin during the OGTT, with lower values mirroring a reduced insulin clearance and a higher circulating insulin (28). The insulin secretion rate is computed assuming 2-compartment kinetics for insulin secretion based on glucose and C-peptide measurements as previously described (28). This methodology to quantify insulin clearance is more accurate than measures based on the AUC of C-peptide over the AUC of insulin (28) and account for the differential elimination of C-peptide (2-3 minutes) and insulin (~30 minutes) from the plasma, thus reducing the bias of the simplified AUC C-peptide (28).

### Statistical Analysis

For the primary analysis, we compared metrics of beta cell function and insulin clearance between Stage 1 with Stage 2 disease.

The Kruskal–Wallis test, followed by the post hoc pair-wise Mann–Whitney test, was used to compare continuous variables, and categorical variables were compared using the chi-square test.

Data were summarized using median (25th percentile, 75th percentile) for continuous variables and count (%) for categorical variables. Participants were grouped by age group into children (<12.0 years), adolescents (12.0-18.0 years), and adults (>18 years) for a secondary analysis of baseline characteristics.

Linear regression analysis was conducted to explore the association between sensitivity index (SI) and BMI, as well as insulin clearance and insulin secretion (φ total) and sensitivity (SI) after normally log transformation of the variables.

Adjusted analyses of the effect of baseline OMM-derived parameters (φ total and SI), AUC C-peptide, BMI, sex, age, and Stage on the binary outcome "progression" were performed using multivariable logistic regression modeling. Prior to including the covariates into the model, we examined them for multicollinearity using the Spearman correlation coefficient (<0.90) and variance inflation factor (<2.0). The association between the outcome and each variable was summarized as odds ratio (OR) and 95% CI.

We estimated the power of OMM derived φ total, the AUC C-peptide or Index60 and DPTRS to identify a minimum difference over time equal to 25% of the one observed between Stage 1 and Stage 2 disease in this population. Both φ total and AUC C-peptide were naturally log transformed and a paired t test with an intrasubject correlation of 0.5 and alpha = 0.05 were adopted for the power analysis. The analysis had a solely exploratory purpose.

Analyses were performed using STATA.13 software (StataCorp, College Station, TX) and Prism 8.0 (GraphPad Software, San Diego, CA).

## Results

### Participants' Characteristics

A total of 57 AAb-positive relatives of people with T1D from a single TrialNet Clinical Center were selected according to inclusion and exclusion criteria, with 30 classified as having Stage 1 and 27 as having Stage 2 T1D. The characteristics of the cohort are reported in Table 1. The 2 groups did not differ with respect to age, sex distribution, and anthropometric characteristics at inclusion. Twenty participants with Stage 1 (67%) and 17 with Stage 2 disease (63%) had 3 or more AAbs, with no significant difference in the number of AAbs between Stage 1 and Stage 2 ($P = .932$).

### T1D Risk Scores

Both DPTRS and Index60 were higher in those with Stage 2T1D ($P < .001$). Fourteen out of 16 individuals with DPTRS >7.00 were in Stage 2T1D and 2 in Stage 1, while 15/27 (55%) participants in Stage 2 had an Index60 ≥ 1.0 and only 1/30 (3%) in the Stage 1 group.

### Age Groups and Baseline Characteristics

As described in Table 2, we analyzed the distribution of the AAb number and type according to the age group in Stage 1 and Stage 2 disease. Adults (>18 years) with Stage 2 disease

**Table 1. Participants' characteristics by T1D stage**

| | Stage 1 (n = 30) | Stage 2 (n = 27) | S1 vs S2 |
|---|---|---|---|
| Age (y) | 13.8 (8.6, 25) | 13.8 (9.9, 21.6) | 0.417 |
| Sex (AFAM), n (%) | 12 (40) | 13 (48) | 0.536 |
| BMI (kg/m$^2$) | 20.4 (17.6, 23.2) | 19.1 (15.6, 21.8) | 0.113 |
| Autoantibodies, n (%) | | | |
| 2 | 10 (33) | 10 (37) | |
| 3-5 | 20 (67) | 17 (63) | 0.932 |
| T1D risk scores | | | |
| DPTRS | 5.89 (5.01, 6.35) | 7.25 (6.10, 7.78) | <0.001 |
| Index60 | 0.13 (−0.58, 0.56) | 1.3 (0.09, 2.08) | <0.001 |
| Standard metrics of beta cell function | | | |
| Fasting glucose (mg/dL) | 89 (85, 92) | 97 (84, 103) | 0.093 |
| 1-h glucose (mg/dL) | 121 (104, 157) | 185 (161, 222) | <0.001 |
| 2-h glucose (mg/dL) | 98 (84, 120) | 145 (135, 154) | <0.001 |
| Time to glucose peak <60 minutes, n (%) | 22 (73) | 5 (18) | <0.001 |
| Fasting insulin (μU/mL) | 6.5 (5, 7.8) | 6.1 (5.1, 8.6) | 0.420 |
| Fasting C-peptide (pmol/L) | 465.0 (407.1, 519.7) | 466.7 (374.0, 662.0) | 0.314 |
| AUC C-peptide (pmol/L*min) | 33242.2 (22699.7, 47608.0) | 28783.5 (18814.0, 51108.2) | 0.362 |
| HOMA-2B (%) | 4.78 (4.41, 6.24) | 4.65 (2.58, 7.33) | 0.429 |
| HOMA-2S (mmol$^{-1}$ × L$^{-1}$) | 97.23 (89.73, 113.67) | 94.13 (82.41, 112.78) | 0.264 |
| HOMA-IR | 1.45 (1.06, 1.70) | 1.55 (1.08, 2.02) | 0.264 |
| WBISI (Matsuda Index) (min$^{-1}$ × μU$^{-1}$ × mL$^{-1}$ × mg$^{-1}$) | 6.75 (5.44, 9.03) | 5.77 (3.86, 7.87) | 0.130 |
| Oral Minimal Model–derived metrics of beta cell function | | | |
| φ total ($10^{-9}$ minutes$^{-1}$) | 66.9 (51.5, 99.2) | 35.0 (22.4, 58.5) | <0.001 |
| SI ($10^{-9}$ dL/kg/min per μU//mL) | 2.6 (1.2, 6.5) | 1.4 (0.67, 2.5) | 0.034 |
| $DI_{MM}$ ($10^{-12}$) | 202.1 (76.2, 421.6) | 62.1 (26.7, 107.9) | <0.001 |
| Insulin clearance (AUC $ISR_{C-peptide}/AUC_{insulin}$) | 0.43 (0.38, 0.38) | 0.49 (0.39, 0.65) | 0.006 |

Data are expressed as median (25th, 75th centile) or n (%);
Abbreviations: AFAM, assigned female at birth; AUC, area under the curve; BMI, body mass index; DI, disposition index; DPTRS, Diabetes Prevention Trial Risk Score; IGI, insulinogenic index; ISR, insulin secretion rate; IR, insulin resistance; SI, insulin sensitivity; T1D, type 1 diabetes; WBISI, Whole Body Insulin Sensitivity Index (or Matsuda index).

were more likely to have 2 AAbs, while >80% of children and adolescents had 3 or more islet AAbs. Anti-GAD were the most frequent AAbs in all age groups (100% of participants in both the stages had GAD). Younger individuals with Stage 2, but not Stage 1 T1D, demonstrated higher insulin sensitivity and overall better beta cell function, as reflected by the disposition index, without alterations in insulin secretion. Adults with Stage 2 were more likely to be screened because of a daughter or a son with diabetes, while the affected relative in children or adolescents with Stage 2 was either a parent or a sibling. The BMI was lower in children than adolescents and adults in both stages, with an inverse relationship between BMI and SI ($r = -0.64$, $P < .001$) as described in Fig. S1 (29).

## Insulin Secretion and Sensitivity in Stage 1 and Stage 2T1D

Insulin secretion and its action were explored by the use of standard metrics for insulin secretion (AUC C-peptide, HOMA2-B), sensitivity (HOMA-IR, Matsuda Index, and HOMA2-S) and minimal model–derived metrics (φ total for insulin secretion and SI for insulin sensitivity). The disposition index resulting from both insulin secretion and sensitivity was also computed.

Fasting glucose and C-peptide were similar between those with Stage 1 and 2 T1D. As described in Table 1, the AUC C-peptide and the HOMA2-B did not differ between Stage 1 and Stage 2 T1D ($P = .362$ and $P = .429$). None of the standard measures of insulin sensitivity (Matsuda Index, HOMA-IR, and HOMA-2S) differed between the 2 groups ($P = .130$, $P = .264$, and $P = .264$).

The OMM-derived metrics identified differences in terms of insulin secretion and sensitivity between Stage 1 and Stage 2 T1D. Insulin secretion (φ total) was ∼2 times higher in Stage 1 ($P < .001$), with a decrease of insulin sensitivity in Stage 2 ($P = .034$). As a result, those with Stage 1 T1D had ∼2.5 higher disposition index than their peers with Stage 2 ($P < .001$).

The differences measured through the OMM were mirrored by a differential profile of glucose, insulin, and C-peptide during the OGTT. The time to glucose peak was delayed in those with Stage 2 disease, with more than 80% (22/27) people with Stage 2 disease having a glucose peak at or after 60 minutes vs only 27% (8/30) in the Stage 1 group ($P < .001$) (Fig. 2). This trend was paralleled by delayed insulin and C-peptide peaks in the absence of a return to baseline after 2 hours (Fig. 2).

## Insulin Clearance in Stage 1 and Stage 2 Disease

A modest but significant increase of insulin clearance was observed in Stage 2 T1D ($P = .006$). Therefore, we explored the relationship between insulin clearance and beta cell function

**Table 2. Participants' characteristics by age group and stage**

| | Stage 1 (N = 30) | | | | Stage 2 (N = 27) | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | Children (<12.0 y) N = 11 | Adolescents (12-18 y) N = 9 | Adults (>18.0) N = 10 | *P* | Children (<12.0 y) N = 10 | Adolescents (12-18 y) N = 8 | Adults (>18.0) N = 9 | *P* | *P* S1 vs S2 |
| Gender (AFAM) | 3 (27) | 4 (44) | 5 (50) | .483 | 3 (30) | 5 (62) | 5 (55) | .391 | .632 |
| N AAbs | | | | .265 | | | | .022 | .385 |
| 2 | 1 (9) | 2 (22) | 4 (40) | | 2 (20) | 1 (13) | 7 (78) | | |
| 3-5 | 10 (91) | 7 (78) | 6 (60) | | 8 (80) | 7 (87) | 2 (22) | | |
| GAD65 | 11 (100) | 9 (100) | 10 (100) | .412 | 10 (100) | 8 (100) | 9 (100) | .791 | <.001 |
| ICA512 | 2 (18) | 6 (67) | 1 (1) | | 4 (4) | 6 (75) | 2 (22) | | |
| mIAA | 10 (91) | 3 (33) | 3 (3) | | 7 (7) | 3 (37) | 1 (11) | | |
| ICA | 7 (64) | 8 (89) | 6 (6) | | 6 (6) | 6 (75) | 4 (44) | | |
| ZnT8 | 6 (54) | 7 (78) | 4 (4) | | 6 (6) | 6 (75) | 4 (44) | | |
| BMI ($kg/m^2$) | 17.6 (15.9, 19.7) | 20.1 (17.5, 20.8) | 23.7 (21.4, 27.0) | .002 | 15.7 (15.1, 17.1) | 19.1 (15.6, 21.8) | 20.7 (20.1, 26.1) | .003 | .113 |
| φ total ($10^{-9}$ $minutes^{-1}$) | 64.5 (48.2, 78.7) | 67.9 (46.6, 159.6) | 80.3 (130.8, 54.6) | .531 | 32.2 (20.4, 58.5) | 37.9 (23.9, 56.3) | 35.0 (24.5, 52.5) | .852 | <.001 |
| SI ($10^{-9}$ dL/kg/min per μU//mL) | 5.7 (2.5, 12.3) | 2.1 (1.2, 4.3) | 1.8 (0.8, 2.9) | .076 | 3.3 (1.6, 9.7) | 1.3 (0.5, 2.0) | 1.1 (0.6, 1.4) | .044 | .034 |
| $DI_{MM}$ ($10^{-12}$) | 416.1 (110.3, 585.2) | 169.5 (51.2, 388.4) | 109.3 (53.4, 266.1) | .144 | 100.6 (63.3, 213.3) | 44.5 (25.5 (71.0) | 35.5 (21.9, 62.1) | .025 | <.001 |
| Insulin clearance (AUC $ISR_{C-peptide}/AUC_{insulin}$) | 0.42 (0.32, 0.50) | 0.39 (0.38, 0.43) | 0.48 (0.40, 0.49) | .173 | 0.39 (0.37, 0.53) | 0.46 (0.45, 0.55) | 0.58 (0.49, 0.65) | .246 | .006 |
| Affected family members[a] | | | | | | | | | |
| Mother | 3 (27) | 1 (11) | 1 (10) | .168 | 1 (10) | 4 (50) | 1 (11) | .024 | .006 |
| Father | 1 (9) | 2 (22) | 1 (10) | | 4 (40) | 3 (37) | 2 (22) | | |
| Sibling | 6 (54) | 7 (77) | 5 (50) | | 6 (60) | 0 (0) | 3 (33) | | |
| Daughter/Son | 0 (0) | 0 (0) | 3 (30) | | 0 (0) | 0 (0) | 4 (44) | | |
| Second-degree relative | 3 (27) | 0 (0) | 0 (0) | | 1 (10) | 2 (25) | 3 (33) | | |

Data are presented as median (25th, 75th centile) or number (percentage).
Abbreviations: AAb, autoantibody; AFAM, assigned female at birth; BMI, body mass index; DI, disposition index; mIAA, microinsulin antibody assay; SI, insulin sensitivity.
[a]Participants may have more than 1 family member living with type 1 diabetes.

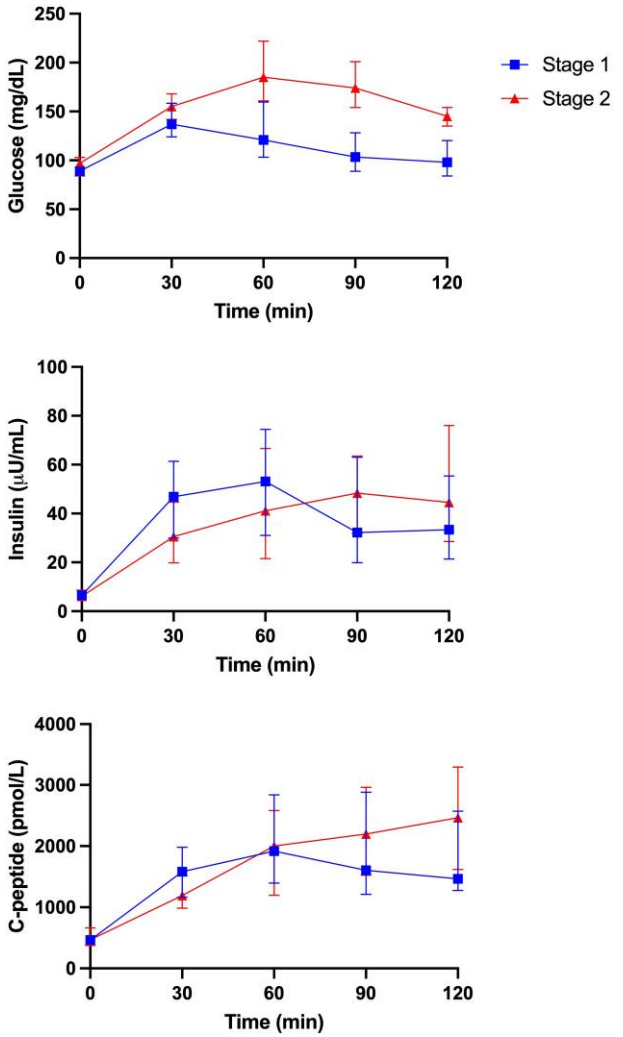


**Figure 2.** Glucose, insulin, and C-peptide during the OGTT in participants with Stage 1 (squares) and Stage 2 (triangles) T1D. Data are presented as median (25th, 75th centile).

components as derived from the OMM—insulin secretion and sensitivity. Insulin clearance was inversely associated with secretion ($-0.12 \pm 0.04$, $P = .001$) with greater insulin clearance featuring those with lower secretion, thus being prevalent in those with Stage 2 disease (Fig. 3A). Conversely, a linear relationship was identified between insulin clearance and sensitivity, with higher insulin sensitivity associated with higher clearance ($0.060 \pm 0.027$, $P = .029$) (Fig. 3B).

### Risk Determinants of Disease Progression

Five out of 30 (17%) participants with Stage 1 progressed to Stage 2 or 3 and 11/27 (41%) of Stage 2 progressed to Stage 3 over a median follow-up time of $19 \pm 15$ months. Baseline characteristics differed significantly between progressors (n = 16) and nonprogressors (n = 41). As outlined in Table S1 (29), progressors exhibited lower insulin secretion metrics, including φ total and AUC C-peptide, despite no significant differences in insulin sensitivity. Insulin clearance was higher among nonprogressors. Additionally, DPTRS and Index60 were elevated in the progressor group. The 2 cohorts showed no differences in baseline characteristics such as age, BMI, sex, or stage distribution at inclusion.

Using a multivariate logistic regression model, we evaluated baseline metabolic variables and their association with the odds of disease progression to either Stage 2 or Stage 3. Among the variables analyzed, φ total was the only one significantly associated with the risk of progression. Specifically, each 10-unit increase in φ total was linked to an 8-fold reduction in the odds of disease progression (OR 0.92 [0.86, 0.98], $P = .016$) (see Table 3; Fig. S2 (29)). Other variables, including age, BMI, sex, AUC C-peptide, OMM-derived insulin sensitivity, and stage, did not show significant associations with progression risk.

### Projected Impact of OMM-Based Metrics for a Hypothetical Clinical Trial Design

We analyzed the distribution of OMM-derived φ total and AUC C-peptide, standard metrics of insulin secretion, in individuals with Stage 1 and Stage 2 T1D. Using the measured distribution of these surrogate metrics of insulin secretion (φ total and AUC C-peptide) and clinical diabetes risk indices (DPTRS and Index60) (Table S2 (29)), we estimated the statistical power to detect a difference equivalent to 25% of the 1 observed between Stage 1 and Stage 2 disease. Figure 4 illustrates the relationship between the total number of participants and the power to detect such a difference for each metric tested. The OMM-derived insulin secretion metric (φ total) would provide a power of 0.90 to detect a 25% difference with just 10 participants enrolled in a longitudinal trial with 2 subsequent evaluations. In contrast, the same number of participants would yield only 0.32 power to detect a 25% difference in AUC C-peptide compared to the measure in Stage 1 disease. Notably, applying the same approach to DPTRS, 10 participants would provide a power of 0.68 to detect a 25% change from the baseline, and 0.61 with Index60.

## Discussion

We have described, for the first time in a contemporary pediatric and adult cohort, the metabolic phenotype of Stage 1 and Stage 2 T1D, with respect to insulin secretion, sensitivity, and clearance using the OMM.

Dysglycemia in Stage 2 T1D appears to be determined by both reduced insulin secretion and sensitivity, along with a greater insulin clearance with respect to Stage 1 disease.

Although individuals with Stage 1 T1D exhibit early impairment of insulin sensitivity relative to unrelated healthy matched peers (4), it has been recently observed that the most significant decrease in insulin sensitivity occurs during the transition from Stage 1 to Stage 2 (3). The decline in insulin sensitivity has been described as an independent risk factor for progression to clinical diabetes in people with islet autoimmunity using standard metrics such as HOMA-IR (30, 31), with an accelerated drop of insulin sensitivity paralleling the rise of glucose (32) during the year preceding progression to Stage 3 disease.

The lower insulin sensitivity observed in Stage 1 disease is likely driven by the inflammatory environment accompanying the autoimmune process, including cytokines like tumor necrosis factor-α and interleukin (IL)-6 implied in both islet autoimmunity and insulin resistance (30, 33, 34). Hyperglycemia observed in Stage 2 disease may contribute to accelerating the declining of insulin sensitivity in Stage 2 disease (32). In our cohort, a younger age in those with Stage 2 T1D seemed to be associated

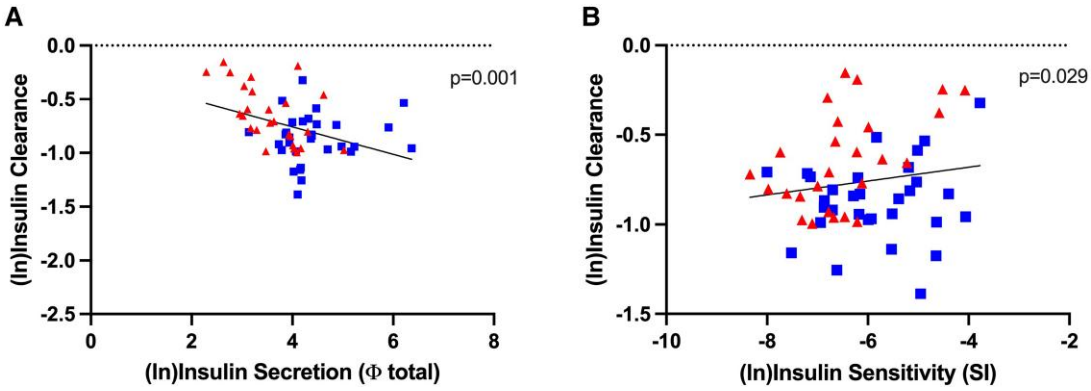


**Figure 3.** Relationship between insulin clearance and insulin secretion (A) and sensitivity (B) in relatives with Stage 1 (squares) and Stage 2 (triangles) T1D. Data are naturally log transformed.

**Table 3. Logistic regression model for the risk of disease progression (n = 57)**

| | OR | *P*-value |
|---|---|---|
| φ total | 0.922 (0.863, 0.985) | .016 |
| SI | 0.976 (0.747, 1.275) | .857 |
| AUC C-peptide | 0.999 (0.999, 1.000) | .330 |
| Stage (1 vs 2) | 0.421 (0.054, 3.289) | .409 |
| Age (y) | 0.975 (0.876, 1.087) | .656 |
| BMI (kg/m$^2$) | 1.011 (0.789, 1.295) | .931 |
| Sex (M) | 0.174 (0.024, 1.252) | .083 |

Abbreviations: AUC, area under the curve; BMI, body mass index; SI, sensitivity index.

with a higher insulin sensitivity and overall greater beta cell function (disposition index), while we did not observe significant differences of insulin sensitivity across different age groups in Stage 1 disease. Age did not impact insulin secretion itself in this cohort.

Insulin resistance is well documented in clinical T1D (35-38) and has been described as an independent risk factor for disease progression in the longitudinal cohort of people with islet autoimmunity of the TrialNet Diabetes Prevention Trial (DPT-1) (31). However, clinical features commonly associated with insulin resistance were not associated with indices of insulin resistance such as HOMA-IR in the TNPTP longitudinal cohort, and BMI itself did not appear to play a role in the transition from 1 to multiple AAbs (39).

A higher insulin clearance has been observed for the first time in Stage 2 T1D in this cohort. This finding is suggestive for a role for insulin clearance as an additional mechanism to disease progression. Even though we are unable to discriminate the role of hepatic vs extrahepatic clearance, more than 80% of secreted insulin—but not C-peptide—is physiologically cleared during the first hepatic pass (28). Hepatic insulin clearance is a physiologic gatekeeper that controls the exposure of peripheral tissues to insulin; changes in insulin sensitivity or secretion are expected to affect hepatic insulin clearance, even though this mechanism remains largely unexplored (40-42). An increase in insulin clearance, such as the one observed in Stage 2 T1D, is expected to reduce the circulating insulin, thereby exacerbating peripheral insulin deficiency (40, 42, 43). Under physiologic conditions, a reduction in insulin secretion would typically trigger a compensatory reduction in its clearance to maintain adequate circulating insulin levels; however, this mechanism appears to fail in Stage 2 T1D. Instead, we observed increased clearance in conjunction with decreased secretion. Using the insulin secretion rate—derived from C-peptide measurements rather than insulin AUC to estimate insulin clearance—provides an unbiased method (28) to quantify this phenomenon.

The trajectory of insulin clearance across the preclinical stages of T1D appears to begin with a reduction in Stage 1, as lower insulin clearance has been observed in youths with islet autoimmunity compared with their healthy peers (4). This decrease parallels the reduced insulin secretion seen in early Stage 1, even in the absence of dysglycemia (4). This may serve as an initial compensatory response to lower insulin secretion, preserving normoglycemia by allowing a greater proportion of secreted insulin to bypass hepatic clearance and reach peripheral target organs. As hyperglycemia emerges in Stage 2, along with a further decline in insulin secretion, insulin clearance also continues to decrease—a trend that persists into Stage 3 of the disease (44). A relative increase in insulin clearance has been described in those with Stage 2 T1D who rapidly progress (<2 years) to clinical diabetes (2), supporting the role of clearance as an accelerator of disease progress. However, a greater hepatic clearance might be secondary to a more active inflammatory process involving the regulatory protein CEACAM1. CEACAM1 is expressed on both CD4+ T cells and hepatocytes, and upregulated by the inflammatory cytokines IL-7, IL-15, and by IL-2. CEACAM1 upregulation may contribute to T cell CD4+ autoimmune response, through a costimulatory role on the TCR receptor, and to increase hepatic insulin uptake.

One can speculate that reduced secretion along with higher insulin resistance and an increased hepatic clearance may result in a dramatic shortage of insulin disposal, thus accelerating the onset of dysglycemia and contribute to disease progression. However longitudinal observations are necessary to identify the temporal sequence of changes in secretion and clearance in people with preclinical T1D.

In our cohort we found that all the indices of insulin secretion were lower in progressors vs nonprogressors, as expected. Notably, when metabolic measures were tested against the risk for progression in the entire cohort, OMM-derived φ total outperformed other metabolic metrics as the AUC C-peptide

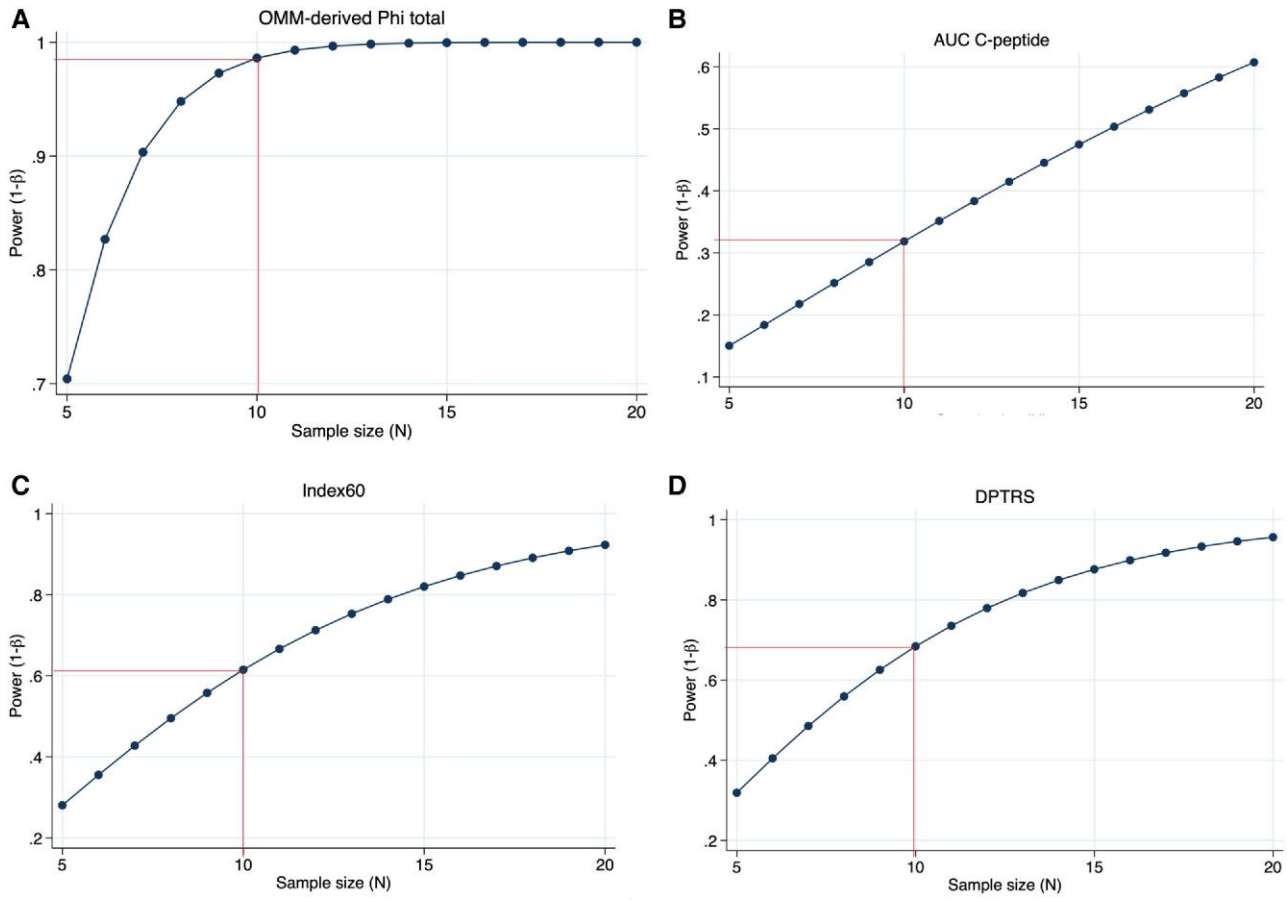


**Figure 4.** Projected study power with variable numerosity using naturally log transformed φ total (A) or naturally log transformed AUC C-peptide (B), Index60 (C), and DPTRS (D) assuming a minimum difference for the primary endpoint equal to 25% of the one observed between Stage 1 and Stage 2 disease with $\alpha = 0.05$. The red lines highlights the expected power enrolling 10 participants with 2 longitudinal measures and an intrasubject correlation fixed at 0.5.

and insulin sensitivity and the baseline stage itself. This is likely due to the heterogeneity within each stage (2). Furthermore, the follow-up of this cohort was relatively short (~19 months), so we likely included only those with a more advanced disease progression, thus limiting the generalizability of our findings. However, this observation provides a quantitative estimate of the clinical relevance of φ total changes with respect to the odds for progression, with 10 unitary increase of φ total associated with 8 times lower odds for progression.

Finally, we conducted an exploratory analysis to assess the implications of using the OMM-derived insulin secretion φ total as an endpoint in clinical trials. Currently we lack surrogate endpoints for prevention trials in Stage 1 or 2, as the only accepted outcome is the time to disease progression. Establishing validated metabolic or immunologic endpoints able to identify those at higher risk for disease progression and to quantify early treatment response would enable a more efficient design of clinical trials. Therefore, we compared the OMM-derived insulin secretion with other commonly used risk indices for disease progression—as DPTRS or Index60—and with the AUC C-peptide, a measures of residual insulin secretion that is largely accepted as a surrogate endpoint of residual beta cell function in Stage 3 disease (7).

We hypothesized that a 25% change in insulin secretion might have been clinically relevant. This was based on observations in Stage 2 disease, where a 3-month loss of more than 25% of baseline insulin secretion is highly specific for progression to clinical disease (2). In Stage 3 T1D, a 25% reduction of baseline insulin secretion correlates with a clinically relevant improvement in HbA1c (33). Additionally, a ~25% difference in the OMM-derived φ total has been observed between healthy controls and individuals with Stage 1 disease (4). We estimated that 10 participants would be provide 0.90 power to measure such a difference in a longitudinal trial, while neither the AUC C-peptide nor Index60 or DPTRS would provide a power >0.80 to observe a difference equal to 25% of the 1 observed between Stage 1 and Stage 2 T1D. This threshold is certainly arbitrary and retrospective analyses of longitudinal trials will be necessary to confirm the superiority of OMM-derived metrics with respect to other existing measures.

From a practical standpoint, smaller changes in beta cell function might be clinically relevant for trial designs aimed at preventing disease progression. These changes appear to be measurable with φ total, potentially requiring fewer participants compared with using AUC C-peptide, DPTRS, or Index60 as primary endpoints. Although DPTRS and Index60 have primarily been studied as metabolic endpoints in AAb-positive relatives (20, 22), their components—including C-peptide and glucose indexes from oral glucose tolerance testing, along with age and BMI for the DPTRS—indicate they could also serve as indicators of insulin secretion. This

observation yields a major clinical relevance since AUC C-peptide has been adopted in the past as a surrogate endpoint in clinical trials (45) and failed to adequately predict disease progression in large monitoring cohort (8) with respect to metrics that combine C-peptide and glucose. The major advantages of the OMM insulin secretion are the ability to account for both glucose and C-peptide dynamics during the OGTT and to include an age-adjusted estimate of C-peptide kinetics (23, 25, 46, 47).

Our results suggest the need for testing model-based measures in existing clinical trials involving people with Stage 1 or Stage 2 disease and relate them to clinically relevant outcomes, including the time to diagnosis or the HbA1c, thus providing a novel endpoint that might speed up the development of disease modifying treatments.

A strength of this study is the selection of a cohort of matched relatives with Stage 1 and Stage 2 T1D, enrolled in an international clinical trial, with complete 5-point OGTT measures from which various beta cell function metrics were calculated. A limitation is the absence of control group of age, sex, and BMI-matched healthy individuals. Furthermore, the absence of early glucose and C-peptide measures, specifically at 10 and 20 minutes (4), is a limitation of the study protocol. This limitation prevented us from describing changes in the earliest phases of insulin secretion in response to glucose. Previous research using intravenous glucose tolerance tests in relatives of patients with T1D with islet autoimmunity has extensively demonstrated the existence of early changes in insulin secretion in Stage 1 disease (48, 49).

Our findings underscore the need for including early measures of glucose and C-peptide, as recently endorsed by the TrialNet consortium. Additionally, the relatively low number of individuals selected for this study does not allow for distinguishing the metabolic characteristics of adults vs children. Larger longitudinal cohorts of relatives of patients with T1D, both with and without islet autoimmunity, should be analyzed using OMM-derived measures to determine the metabolic transitions through the preclinical stages of the disease.

### Conclusion

In this study, we revealed that the OMM-derived measure of insulin secretion, φ total, effectively differentiates between Stage 1 and Stage 2 T1D, a distinction not achievable with the traditionally used AUC C-peptide. This is clinically significant, as the OMM approach provides a more accurate assessment by considering both glucose and C-peptide dynamics and including an age-adjusted estimate of C-peptide kinetics. Furthermore, our study suggests that using the φ total as an endpoint in clinical trials could reduce the required number of participants, enhancing the efficiency of developing disease-modifying treatments. This highlights the potential of model-based measures to expedite clinical trials and improve outcomes.

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## Author Contributions

A.G. and A.P. conceptualized and designed the study, as well as drafted the manuscript. J.B. and A.G. conducted the analysis. P.F., E.B., and A.P. contributed to the patient selection and the clinical follow up of the cohort. A.G., H.I., A.M., P.F., and E.B. contributed to the data interpretation, and critically revised the manuscript. A.P. is the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the manuscript in its final version.

## Disclosures

The authors have no financial or nonfinancial interests to disclose. No potential conflicts of interest relevant to this article were reported.

## Data Availability

Some or all datasets generated during and/or analyzed during the current study are not publicly available but are available from the corresponding author on reasonable request. Supplementary material cited in the manuscript can be accessed at the following link https://doi.org/10.6084/m9.figshare.28259654.v1.

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