Acceleration of the Loss of the First-Phase Insulin Response During the Progression to Type 1 Diabetes in Diabetes Prevention Trial–Type 1 Participants

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We studied the change in the first-phase insulin response (FPIR) during the progression to type 1 diabetes (T1D). Seventy-four oral insulin trial progressors to T1D from the Diabetes Prevention Trial–Type 1 with at least one FPIR measurement after baseline and before diagnosis were studied. The FPIR was examined longitudinally in 26 progressors who had FPIR measurements during each of the 3 years before diagnosis. The association between the change from the baseline FPIR to the last FPIR and time to diagnosis was studied in the remainder (n = 48). The 74 progressors had lower baseline FPIR values than nonprogressors (n = 270), with adjustments made for age and BMI. In the longitudinal analysis of the 26 progressors, there was a greater decline in the FPIR from 1.5 to 0.5 years before diagnosis than from 2.5 to 1.5 years before diagnosis. This accelerated decline was also evident in a regression analysis of the 48 remaining progressors in whom the rate of decline became more marked with the approaching diagnosis. The patterns of decline were similar between the longitudinal and regression analyses. There is an acceleration of decline in the FPIR during the progression to T1D, which becomes especially marked between 1.5 and 0.5 years before diagnosis. ***Diabetes*** **62:4179–4183, 2013**

A low first-phase insulin response (FPIR) to intravenous glucose is considered to be an indicator of faltering β-cell function and is a predictor of type 1 diabetes (T1D) (1–4), yet there have been no descriptions of changes in the FPIR during the progression to T1D. Such information could be of value for optimizing the timing of interventions to prevent the loss of β-cells. We have used, therefore, FPIR measurements from the serial intravenous glucose tolerance tests (IVGTTs) obtained in the oral insulin trial of the Diabetes Prevention Trial–Type 1 (DPT-1) (5) to describe the decline of the FPIR during the progression to T1D.

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*For a complete list of the Type 1 Diabetes TrialNet and Diabetes Prevention Trial–Type 1 Study Groups, see Supplementary Data online.

See accompanying commentary, p. 3990.

RESEARCH DESIGN AND METHODS

Individuals included in the analysis participated in the DPT-1 oral insulin trial (5). All oral insulin trial participants were relatives of T1D patients who were positive for islet cell autoantibodies and insulin autoantibodies. The participants initially had normal oral glucose tolerance (fasting glucose value <110 mg/dL; 30-, 60-, and 90-min values <200 mg/dL; 2-h value <140 mg/dL) and were above defined FPIR thresholds (≥100 μU/mL for ≥8.0 years [with the exception of ≥60 μU/mL for parents of T1D patients], ≥60 μU/mL for <8.0 years). IVGTTs were performed at baseline and at yearly intervals. DPT-1 parenteral trial participants (6) were not included in the analyses because they only had IVGTTs at 2-year intervals, and many in that trial were selected on the basis of having low FPIR values. T1D was diagnosed either through oral glucose tolerance test (OGTT) surveillance according to standard American Diabetes Association criteria or through clinical presentation. Two nonprogressors with baseline FPIR values of 675 μU/mL and 953 μU/mL (474 μU/mL being the next highest value) were excluded from the analysis because they were outliers. In addition, three others were excluded because of missing values.

The IVGTTs were performed after a minimum 10-h fast. A standard infusion of 0.5 g/kg to a maximum of 35 g at a 25% glucose concentration was administered over a 3-min period. Samples were obtained in the fasting state and at 1, 3, 5, 7, and 10 min. The FPIR was defined as the sum of the insulin measurements at 1 and 3 min. Insulin was measured by radioimmunoassay (coefficient of variation <8.5%) (7). There was high cross-reactivity with proinsulin. Autoantibody procedures for DPT-1 have been previously described (8).

Data analysis. For progressors to be included in the analysis, in addition to the baseline FPIR measurement, at least one additional FPIR measurement before diagnosis was required. There were 74 progressors who fulfilled this criterion of whom 44 (59%) were diagnosed through OGTT surveillance. (Supplementary Table 1 shows that there were no significant differences in baseline characteristics between the progressors included in and the progressors excluded from the analysis.) There were no significant differences between the 35 (47%) receiving oral insulin and the 39 (53%) receiving placebo in the baseline FPIR values or in the changes from the baseline FPIR to the last FPIR. Two analyses were used to examine changes in the FPIR during the progression to T1D in these individuals. A longitudinal analysis (analysis 1) examined serial FPIR values in the 26 progressors who had three IVGTTS after the baseline IVGTT: 2–3 years before diagnosis, 1–2 years before diagnosis, and within 1 year of diagnosis (see flowchart in the Supplementary Data). The mean times from diagnosis of the FPIR measurements within each of the yearlong intervals are shown in the RESULTS for simplicity.

In the other analysis (analysis 2), the change in the FPIR value per year from the baseline FPIR to the last FPIR before diagnosis was calculated for each individual (n = 74). The change in the FPIR per year was then used as the dependent variable for simple linear regression and multiple regression models. The independent variable of interest was the time to diagnosis from the midpoint of the time interval between the baseline FPIR and the last FPIR (Fig. 1). The other variables included in the multiple regression analysis were the FPIR measurement at baseline and the time between the baseline and the last FPIR measurements. Coefficients from the multivariate model were used to develop a curve describing the change in the FPIR during the progression to T1D (Supplementary Data) in the 48 progressors who were not included in analysis 1. The pattern of change in FPIR during progression in those individuals was then compared with the pattern of change in the 26 progressors studied in analysis 1.

Wilcoxon rank sum and t tests were used for comparisons. Analyses of covariance were used to adjust for comparisons between groups. SAS version 9.1.3 software was used for the analyses. The P values are two-sided. Although

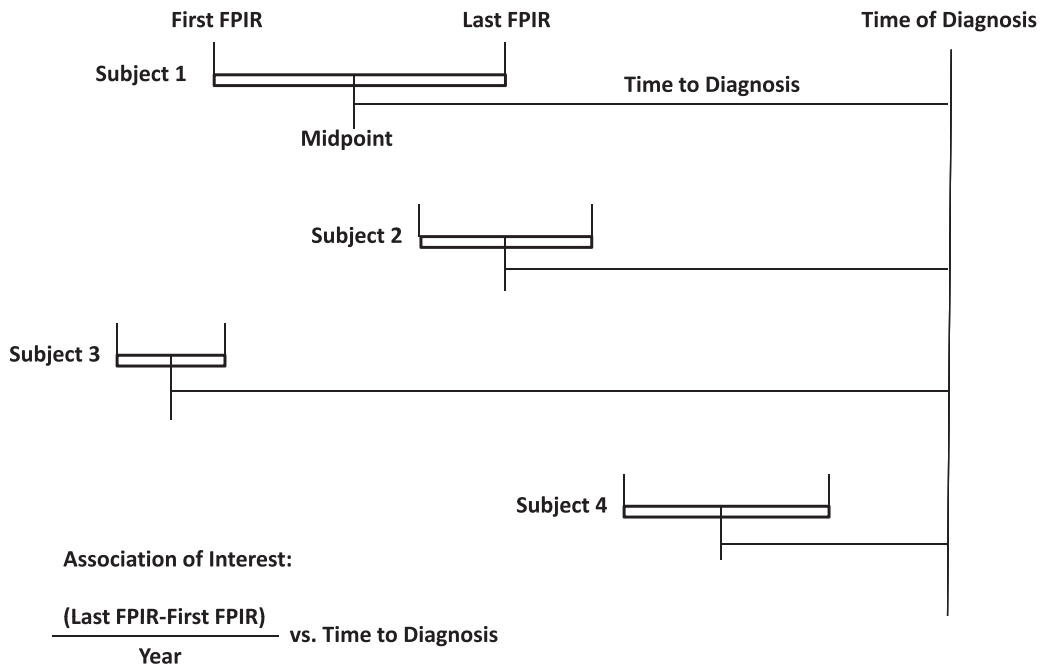

FIG. 1. Diagrammatic representations of the variables of interest included in analysis 2. The time to diagnosis and the times between the first and last FPIR are shown in four hypothetical individuals.

$P < 0.05$ was considered to be statistically significant, Bonferroni corrections are also shown.

RESULTS

Table 1 shows comparisons of baseline characteristics between the 74 progressors (76% of all progressors in the oral insulin trial) who had at least one FPIR measurement after the baseline measurement (those included in the analyses below) and 270 nonprogressors (those not diagnosed during follow-up). Aside from the younger age of the progressors ($P = 0.003$), there were initially no significant differences in FPIR, log BMI, and sex. However, because the FPIR was associated with both age ($r = 0.17$, $P = 0.001$) and log BMI ($r = 0.38$, $P < 0.001$), we compared the FPIR between the progressors and the nonprogressors after adjusting for those variables. The baseline FPIR was significantly lower in the progressors ($P < 0.020$) with the adjustments. Additionally, with adjustments for age and sex, the BMI was significantly higher in the progressors ($P = 0.035$). The median duration of follow-up for the oral insulin trial participants was 4.3 years.

Analysis 1. Twenty-six of the 74 progressors analyzed had FPIR measurements at baseline (mean ± SD 4.4 ± 3.4 years before diagnosis), <3.0 to ≥2.0 years before diagnosis (2.5 ± 0.3 years), <2.0 to ≥ 1.0 year before diagnosis (1.5 ± 0.3 years), and <1.0 year before diagnosis (0.5 ± 0.2 years). Table 2 shows FPIR values of the 26 progressors according to the time before diagnosis along with the percent change in the FPIR (per year) from the preceding FPIR. (Data are presented in the table and below according to the mean time from diagnosis of the FPIR measurements within each yearlong interval.) There was a small decline in the FPIR from baseline until 1.5 years before diagnosis, with no evidence of acceleration. The decline then accelerated from 1.5 years before diagnosis to 0.5 years before diagnosis. The median (25th, 75th percentile) percent change in FPIR from 2.5 to 1.5 years before diagnosis was −4.1% (−29.8%, 30.2%, not significant), whereas the median percent change from 1.5 to 0.5 years before diagnosis was −29.3% (−56.4%, –3.5%, $P = 0.001$). Of the 26 progressors, the FPIR declined in 21 from 1.5 to 0.5 years before diagnosis and in 14 from 2.5 to 1.5 years before diagnosis. Compared with the change from 2.5 to 1.5 years before diagnosis, there was a decline (vs. a prior increase) or a more marked decline from 1.5 to 0.5 years before diagnosis in 16. The median overall percent change from the baseline FPIR to the last FPIR was −47.7% (−58.2%, –27.7%, $P < 0.001$).

Another measure of the insulin response, the mean of the values from 1, 3, 5, 7, and 10 min, was also examined longitudinally in 25 progressors (1 fewer because of

TABLE 1
Baseline characteristics of progressors to T1D with at least one FPIR measurement after baseline and nonprogressors

	Progressors (n = 74)	Nonprogressors (n = 270)	P value
FPIR (μU/mL)	144 ± 84	158 ± 74	0.020*
Age (years)	9.9 ± 6.4	12.7 ± 8.9	0.003
Log BMI (kg/m^2)	2.97 ± 0.20 (n = 71)	2.97 ± 0.23 (n = 259)	0.035**
Male sex (%)	59	61	0.752

Data are mean ± SD. *Adjusted for age and BMI. **Adjusted for age and sex. With the Bonferroni corrections, the P values were not significant [threshold <0.013] for the differences in the FPIR and the log BMI.

TABLE 2
FPIR values and the percent change from the previous values according to the time before diagnosis in 26 progressors

	Time before diagnosis*			
	4.4 years (baseline)	2.5 years	1.5 years	0.5 years
FPIR (μU/mL)	127 ± 52	116 ± 76 [0.042]	112 ± 71 [0.815]	75 ± 50 [<0.001]
Percent change	—	–11.2 (−25.1, 0.0) [0.039]	–4.1 (−29.8, 30.2) [0.912]	–29.3 (−56.4, –3.5) [0.001]

Data are mean ± SD or median (25th, 75th percentile). *The mean times before diagnosis are indicated for baseline and the 2- to 3-year, 1- to 2-year, and <1-year intervals. *P* values for change per year from previous FPIR measurement are in brackets. With the Bonferroni corrections, *P* values were not significant (threshold <0.017) for the change in the FPIR per year from 4.4 to 2.5 years and for the percent change per year from 4.4 to 2.5 years.

a missing value). The pattern was similar to the FPIR, with 53 ± 22 μU/mL at baseline, 50 ± 32 μU/mL at 2.5 years, 47 ± 26 μU/mL at 1.5 years, and 33 ± 2 μU/mL at 0.5 years. The differences were significant from baseline to 2.5 years and from 1.5 to 0.5 years ($P = 0.025$ and $P < 0.001$, respectively).

The longitudinal pattern of FPIR values was also examined in the 111 nonprogressors who had FPIR measurements ~2 years (2.5–1.5 years) and 1 year (1.5–0.5 years) from the last FPIR measurement. There was a small, nonsignificant increase over time (2 years: 158 ± 81 μU/mL; 1 year: 162 ± 74 μU/mL; last: 168 ± 93 μU/mL).

Analysis 2. Because the findings in analysis 1 suggested that the rate of decline accelerates with progression, we performed another analysis to further assess this possibility in all 74 progressors who had at least one FPIR measurement after the baseline measurement. For this analysis (Fig. 1), the difference between the baseline FPIR and last FPIR before diagnosis was calculated for each of those progressors. The interval between the last FPIR measurement and diagnosis was 0.76 ± 0.66 years. In univariate linear regression (Table 3), there was a significant association between the decline per year from the baseline FPIR to the last FPIR and the proximity to diagnosis ($P < 0.05$). The association was more pronounced ($P < 0.001$) with adjustments for the baseline FPIR and the length of the interval between the FPIR measurements.

The same regression analyses were also performed in the 48 progressors who did not meet the multiple FPIR measurement criteria and, thus, were not included in analysis 1; the association was again apparent (Table 3). To further examine the association between the decline of the FPIR and the time from diagnosis, the 48 progressors were divided according to the median time from diagnosis, which was 1.66 years. In a univariate analysis, those <1.66 years from diagnosis had a greater rate of decline (72.0 ± 29.0 μU/mL per year from diagnosis, $P = 0.021$) than those >1.66 years from diagnosis (11.2 ± 13.6 μU/mL, not significant). This difference was also evident in the multivariate analysis (<1.66 years from diagnosis: 76.6 ± 23.9 μU/mL [$P = 0.004$], >1.66 years from diagnosis: 35.4 ± 12.7 μU/mL [$P = 0.011$]).

Comparison of findings between analysis 1 and analysis 2. To further examine the consistency of the findings between analysis 1 and analysis 2, we used the regression coefficients from the 48 progressors excluded from analysis 1 to develop a curve to describe the change in FPIR with the approaching diagnosis. This curve is shown in Fig. 2 along with the curve of those followed longitudinally in analysis 1. (Baseline characteristics of the two groups are shown in Supplementary Tables 2 and 3. There were no significant differences.) Starting from the same value (116.4 μU/mL) as the mean of the FPIR 2.5 years before diagnosis of those followed longitudinally, the pattern of decline was almost the same: a gradual decline from 2.5 to 1.5 years before diagnosis followed by a steep decline from 1.5 to 0.5 years before diagnosis. Thus, using separate samples and different analyses, the pattern of decline predicted by the regression procedure (analysis 2) was consistent with the actual decline (analysis 1).

DISCUSSION

The findings show that the decline in the FPIR during the progression to T1D accelerates as the diagnosis approaches. This was evident in the two separate samples of the progressors studied. In the longitudinal analysis of serial FPIRs (analysis 1), there was a gradual loss that was followed by a more substantial loss. In the regression analysis (analysis 2), there was an association between the rate of loss of the FPIR and the proximity to diagnosis of T1D both for all the progressors and with the exclusion of those in analysis 1.

The high degree of consistency of the findings, derived from different samples of progressors and different analyses, provides additional supporting evidence for the acceleration of the decline in the FPIR. Although the curves appear to show an abrupt increase in the acceleration of

TABLE 3
Multiple regression analysis for the association of change in FPIR* [(last–baseline)/year] with years to diagnosis** in progressors to T1D

	Univariate		Multivariate***	
	Coefficient ± SE	*P* value	Coefficient ± SE	*P* value
All ($n = 74$)	13.8 ± 5.7	0.019	28.3 ± 5.8	<0.001
Analysis 1 excluded ($n = 48$)	15.9 ± 7.9	0.049	31.0 ± 7.4	<0.001

The coefficients represent the rate of change in the FPIR per year from the baseline FPIR to the last FPIR vs. the number of years from diagnosis. Thus, the positive coefficients indicate that the rate of loss becomes greater as the time from diagnosis decreases. *μU/mL. **Defined as time of diagnosis to middle of interval between baseline and last FPIR. ***Covariates in the model were baseline FPIR and time between baseline and last FPIR (see Supplementary Data for regression equations).

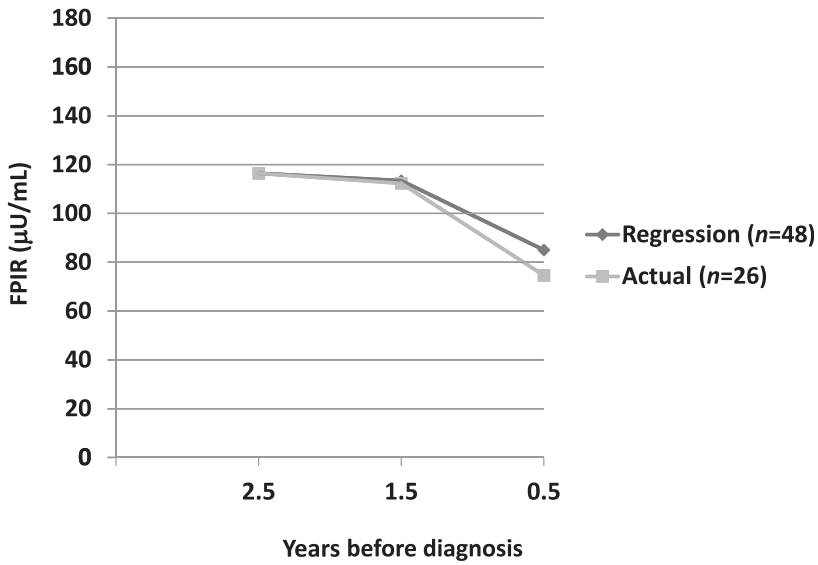

FIG. 2. Curves of FPIR values during the progression to T1D from the actual serial values of the progressors in analysis 1 and the values derived from the regression model for the other progressors from analysis 2. The curve for analysis 1 is plotted according to the mean times from diagnosis of the FPIR measurements within each yearlong interval. For the purpose of comparison, the curve from analysis 2 was assigned the same starting value of 2.5 years and plotted according to the same time points. The patterns are similar, with a gradual decline from 2.5 to 1.5 years and a marked decline from 1.5 to 0.5 years before diagnosis.

decline, this is not necessarily the case; the acceleration could occur in a more gradual manner. Still, the data show that the decline in the FPIR becomes more rapid as the diagnosis of T1D approaches. The acceleration appears to become especially marked between 1.5 and 0.5 years before diagnosis. Of note, this time period appears to coincide with the time that the loss of β-cell sensitivity to glucose becomes appreciable (9).

The overall loss of the FPIR from the baseline measurement to the last measurement was marked in the 26 progressors followed longitudinally, with a decline of 47.7% by 0.5 years before diagnosis. However, the extent of insulin loss before diagnosis is almost certainly greater for several reasons. It is likely that there already had been some loss of the FPIR before the baseline measurement because the baseline FPIR values were lower in the progressors than in the nonprogressors with adjustments for age and BMI. In addition, the shape of the curves in Fig. 2 and data from an analysis of serial OGTTs (10) suggest that the rate of decline could be even greater during the last 6 months before diagnosis. Finally, DPT-1 participants were mostly diagnosed through OGTT surveillance rather than through clinical presentation (11).

The longitudinal analysis for the nonprogressors showed little change in the FPIR over time. The interpretation of FPIR trends in the nonprogressors is complicated by the likelihood that a number of them would have been diagnosed with further follow-up.

To our knowledge, no prior studies have described the pattern of decline of the FPIR during the progression to T1D. The oral insulin trial was unique in that such a large number of autoantibody positive individuals were followed with serial IVGTTs at yearly intervals. We have previously shown that the 30- to 0-min C-peptide difference from OGTTs (which correlates with the FPIR) also declines appreciably during progression (12).

It is possible that the findings pertaining to the loss of the FPIR are not fully representative. Those studied were all relatives of T1D patients. Additionally, the criteria for inclusion in the longitudinal analyses could have excluded faster progressors. However, data from prior studies suggest that T1D characteristics are similar between T1D patients who have relatives with T1D and T1D patients who have no relatives with the disease (sporadic cases) (13–15). Moreover, 76% of the progressors in the oral insulin trial were included in the analyses.

The basis for the accelerating decline in the FPIR is unclear. Although several explanatory hypotheses can be formulated, it would be important to discern whether the accelerated decline of the FPIR is the result of the primary pathogenetic process or whether it relates more to secondary factors, such as the possible impact of increasing glucose levels on β-cells during progression. It is possible that an impaired β-cell could be particularly susceptible to small changes in glucose concentration; however, there are no data available to support this.

In conclusion, the findings show that the loss of β-cell function accelerates well before the diagnosis of T1D. Thus, as treatments that preserve insulin secretion become available, it will be essential to identify individuals as early as possible during progression. With this in mind, there is a need to refine our ability to identify very-high-risk individuals years before diagnosis and to test potential interventions at that time.

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J.M.S. analyzed the data and wrote the manuscript. J.S.S., J.P.K., C.J.G., L.E.R., and D.M. conducted the study and reviewed the manuscript. C.A.B. contributed statistical support. J.M. and K.C.H. reviewed the manuscript. J.P.P. conducted the study, reviewed the manuscript, and assisted in writing the manuscript. J.M.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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