Patterns of Metabolic Progression to Type 1 Diabetes in the Diabetes Prevention Trial–Type 1

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OBJECTIVE — There is little information regarding the pattern of metabolic deterioration before the onset of type 1 diabetes. The goal of this study was to utilize data from the Diabetes Prevention Trial–Type 1 (DPT-1) to obtain a picture of the metabolic progression to type 1 diabetes over a period of approximately 2.5 years before its diagnosis.

RESEARCH DESIGN AND METHODS — Fifty-four DPT-1 participants (22 in the parenteral trial and 32 in the oral trial) were studied. All had oral glucose tolerance tests (OGTTs) at 6-month intervals from approximately 30 to 6 months before diagnosis. The vast majority also had OGTTs at diagnosis. Changes in OGTT glucose and C-peptide indexes from 30 to 6 months before diagnosis were examined by calculating slopes of the indexes for each individual over that time period. Changes from 6 months before diagnosis to diagnosis were examined by paired comparisons of the OGTT metabolic indexes between the time points.

RESULTS — Glucose levels increased gradually from 30 to 6 months before diagnosis in both the parenteral and oral groups ($P < 0.001$ for all indexes). Area under the curve (AUC) C-peptide ($P < 0.05$) and AUC C-peptide–to–AUC glucose ratio ($P < 0.001$) values decreased in the oral group; peak C-peptide–to–2-h glucose ratio values decreased in both groups ($P < 0.001$). In participants who also had OGTTs at diagnosis, AUC C-peptide (parenteral group, $P < 0.05$) and peak C-peptide (oral group, $P < 0.05$) values decreased from the last 6 months before diagnosis; stimulated C-peptide–to–glucose ratio values decreased in both groups ($P < 0.001$). Conversely, fasting C-peptide levels increased in both groups (oral group, $P < 0.01$). Fasting C-peptide–to–fasting glucose ratio values remained constant throughout the 30-month follow-up.

CONCLUSIONS — These data indicate that over a period of at least 2 years, glucose tolerance gradually deteriorates as stimulated C-peptide levels slowly decline in a substantial number of individuals who develop type 1 diabetes. However, fasting C-peptide levels are maintained, even at diagnosis.

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Abbreviations: AUC, area under the curve; DPT-1, Diabetes Prevention Trial–Type 1; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; OGTT, oral glucose tolerance test.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Abundant evidence indicates that type 1 diabetes occurs as a result of chronic, immunologically mediated destruction of pancreatic β-cells. Support for type 1 diabetes's pathogenetic chronicity includes the presence of islet cell autoantibodies well before the onset of type 1 diabetes (1–9). Metabolic abnormalities that include a deficient first-phase insulin response (10–13) and impaired glucose tolerance (14–17) have also been found to be present before type 1 diabetes occurs. However, the pattern of metabolic evolution to type 1 diabetes has not been characterized as yet. Little information exists regarding the nature of the progression of abnormalities of glycemia and insulin secretion. It is not known for how long metabolic deterioration typically occurs and whether the rate of this deterioration changes before the diagnosis of type 1 diabetes.

The Diabetes Prevention Trial–Type 1 (DPT-1) parenteral and oral insulin clinical trials provide a unique opportunity to characterize the metabolic progression to type 1 diabetes. These trials were designed to determine whether the administration of either low-dose parenteral or oral insulin could affect the immunologic milieu so that the occurrence of type 1 diabetes could be prevented or delayed in individuals at risk. DPT-1 includes the largest number of individuals at risk for type 1 diabetes that has been followed until diagnosis. Of those entered into the DPT-1 trials, an appreciable proportion was seen over an extended period of time before the onset of type 1 diabetes. We have utilized glucose and C-peptide measurements from the semiannual oral glucose tolerance tests (OGTTs) that were performed during DPT-1 to provide a picture of the pattern of metabolic progression to type 1 diabetes.

RESEARCH DESIGN AND METHODS

— Individuals included in the analyses were derived from the parenteral and oral insulin trials of DPT-1; neither of these trials demonstrated a treatment effect to delay the onset of type 1 diabetes. Participants in the trials were relatives of patients with type 1 diabetes

who were positive for islet cell autoantibodies and who met certain 5-year risk criteria for type 1 diabetes. The algorithm for determining risk has been described previously (18). Briefly, risk was determined on the basis of the presence of abnormalities of first-phase insulin responses to intravenous glucose tolerance tests, abnormalities on OGTTs, and the presence of insulin autoantibodies. Participants were considered to be at >50% 5-year risk and thus eligible for entry into the parenteral insulin trial if either the first-phase insulin response was less than the 1st or 10th percentile (depending on age and relation to the proband) of a distribution of age-matched control subjects on two occasions and/or there were abnormalities (other than diabetes) on OGTTs. If none of the above metabolic abnormalities were present, but insulin autoantibodies were positive, the 5-year risk was considered to be 25–50% and participants were eligible for the oral insulin trial.

The analytic inclusion criteria for this report were selected to optimize the study of within-individual variation over time. Also, the analysis was designed to provide a description of progression over an extended period of time. Thus, only those who had OGTTs performed at every routine visit (6-month intervals) over a period of approximately 24 weeks until the visit preceding the diagnosis of type 1 diabetes were included. A total of 54 individuals met these analytic inclusion criteria: 22 of the 160 parenteral insulin trial participants who progressed to type 1 diabetes and 32 of the 95 oral insulin trial participants who progressed to type 1 diabetes. The vast majority of the individuals who were included (21 of the 22 parenteral trial and 26 of the 32 oral trial participants) were subsequently diagnosed at a routine visit by OGTTs approximately 6 months later; the others were diagnosed clinically. The mean ± SD interval of observation until diagnosis was 917 ± 37 days for the parenteral group and 922 ± 42 days for the oral group. For the purpose of presentation, the visits are designated according to the approximate months before diagnosis.

The procedures for the parenteral and oral trials have been presented in detail elsewhere (18). They were both randomized controlled clinical trials. In the parenteral trial, those in the intervention group received recombinant human ultralente insulin (Humulin U, Eli Lilly) in the morning when they awoke and in the evening at bedtime. At baseline and every 12 months (±6 weeks) thereafter, participants in the intervention group were hospitalized and received continuous intravenous infusions of recombinant human regular insulin (Humulin R; Eli Lilly) for 4 days. The oral trial intervention group received recombinant human insulin crystals.

Participants attended visits at 6-month intervals (±3 months), during which OGTTs were performed. At each visit, height and weight measurements were obtained, from which BMI values were calculated. The dose of oral glucose was 1.75 g/kg (maximum, 75 g of carbohydrate). Blood samples were obtained for plasma glucose and C-peptide measurements in the fasting state and then 30, 60, 90, and 120 min later. Diabetes was diagnosed at a routine visit if the fasting glucose was ≥126 mg/dl or if the 2-h glucose was ≥200 mg/dl with confirmation by either an elevated fasting or 2-h glucose level at a follow-up visit. If diabetes was not confirmed at that visit, participants continued to be followed at 6-month intervals. The OGTT results were not made available to the researchers or the participants unless diabetes was diagnosed.

Laboratory measures

The presence of islet cell autoantibodies was determined by indirect immunofluorescence, and titers of 10 JDF units or higher were considered positive (19,20). Insulin autoantibodies were measured by competitive liquid-phase radioassay, and 39 nU/ml (3 SDs above normal) was considered the upper limit of normal (21, 22). The interassay coefficient of variation among assays with low positive values was 10.3%. In the Immunology of Diabetes–sponsored combined autoantibody workshop, the islet cell autoantibody assay had 100% specificity and 74% sensitivity, and the insulin autoantibody titer had 91% specificity and 49% sensitivity (23).

C-peptide levels were determined by radioimmunoassay (18). The interassay coefficient of variation for the C-peptide assay was 6.9% in a reference pool with relatively high values and 7.8% in a reference pool with relatively low values.

Statistical analysis

The progression to diagnosis was analyzed for two periods, from 30 to 6 months before diagnosis and from 6 months before diagnosis to diagnosis, so that earlier and later progression could be examined separately.

Student's *t* tests were utilized for comparisons of continuous variables between groups, while χ^2 tests were utilized for comparisons of dichotomous variables between groups. Multiple regression analyses were performed for certain comparisons, with BMI, age, insulin intervention, and sex included as covariates.

For the examination of progression from 30 to 6 months before diagnosis, slopes of the glucose and C-peptide indexes were calculated for each participant from the values obtained at the visits between −30 and −6 months inclusively. The slopes were then averaged and tested for significance. *P* values were determined by calculating *t* statistics for the slopes. Differences were calculated for the glucose and C-peptide indexes between a visit and its preceding visit with *P* values determined from paired *t* tests.

For the analysis of glucose intolerance with progression to type 1 diabetes, impaired fasting glucose (IFG) was defined as a fasting glucose of 100–125 mg/dl, while impaired glucose tolerance (IGT) was defined as a 2-h glucose of 140–199 mg/dl.

For the examination of progression from 6 months before diagnosis to diagnosis, differences were calculated for the glucose and C-peptide indexes between the −6-month visit and the visit at diagnosis, with *P* values determined from paired *t* tests. All *P* values are two sided.

RESULTS

From 30 to 6 months before diagnosis (earlier in the course of progression)

The earlier course of progression was studied in 54 DPT-1 participants, 22 in the parenteral insulin trial and 32 in the DPT-1 oral insulin trial, who were followed for 24 months up to the visit before diagnosis (approximately −30 to −6 months before diagnosis). At the baseline of the trials there were no statistically significant differences between the parenteral and oral groups for age (10.7 ± 7.6 vs. 10.5 ± 6.4 years), sex (55 vs. 72% were male), and those who had received insulin (50 vs. 59%). The parenteral group tended to have lower BMI values (17.0 ± 3.3 vs. 19.0 ± 3.6 kg/m^2, $P = 0.05$, with $n = 19$ and $n = 31$ due to missing values).

Baseline characteristics of the progressors to type 1 diabetes who were in-

Table 1—*Slopes (per month) of glucose (mg/dl) and C-peptide (ng/ml) indexes from OGTTs at visits from 30 to 6 months before diagnosis*

	Parenteral		Oral	
	Insulin	No insulin	Insulin	No insulin
n	11	11	19	13
Fasting glucose	0.35 ± 0.37*	0.41 ± 0.51*	0.47 ± 0.47‡	0.27 ± 0.62
2-h glucose	2.68 ± 2.54†	1.43 ± 2.25	1.92 ± 1.63‡	2.31 ± 1.86‡
AUC glucose	168 ± 106‡	99 ± 157	204 ± 192‡	181 ± 138‡
Fasting C-peptide	−0.00 ± 0.04	−0.00 ± 0.02	0.01 ± 0.02*	−0.01 ± 0.04
Peak C-peptide	−0.03 ± 0.06	−0.00 ± 0.04	−0.01 ± 0.06	−0.04 ± 0.07
AUC C-Peptide	−2.50 ± 7.57	0.02 ± 4.04	−2.07 ± 5.51	−4.16 ± 7.30
Fasting C-peptide–to–glucose ratio ($\times 10^3$)	−0.1 ± 0.4	−0.1 ± 0.3	0.1 ± 0.3	−0.2 ± 0.3
Peak C-peptide–to–2-h glucose ratio ($\times 10^3$)	−0.6 ± 0.5†	−0.4 ± 0.6	−0.7 ± 0.9†	−0.7 ± 0.8†
AUC C-peptide–to–glucose ratio ($\times 10^3$)	−0.3 ± 0.4*	−0.1 ± 0.2	−0.4 ± 0.4‡	−0.4 ± 0.4†

Data are means ± SD. *P* values are for differences from 0. *$P < 0.05$; †$P < 0.01$; ‡$P < 0.001$.

cluded in the analyses below and those of progressors who did not meet inclusion criteria were compared. For the parenteral trial, there were no significant differences between the progressors included ($n = 22$) and excluded ($n = 138$) for age, sex, and insulin intervention, although BMI values of the excluded progressors ($n = 121$ due to missing values of that measurement) were somewhat higher (18.6 ± 3.9 vs 17.0 ± 3.3 kg/m^2, $P = 0.08$). For the oral trial, there were no significant differences in age and insulin intervention between included ($n = 32$) and excluded ($n = 63$) progressors. However, BMI values of the excluded progressors ($n = 61$ due to missing values) were higher (20.9 ± 5.2 vs. 19.0 ± 3.6 kg/m^2, $P = 0.04$) and a higher proportion were female (51 vs. 28%, $P = 0.04$).

The parenteral and oral groups were compared for the glucose and C-peptide indexes at the −30-month visit (Table 1 of online appendix [available at http://diabetes.diabetesjournals.org]). As expected, due to the different selection criteria between the trials, the parenteral group tended to have higher glucose levels ($P < 0.01$ for area under the curve [AUC] glucose) and lower peak C-peptide–to–2-h glucose and AUC C-peptide–to–AUC glucose ratio values ($P < 0.01$ for both). However, in a multivariate analysis that included age, BMI, sex, and insulin intervention, only the AUC glucose difference remained significant.

Table 1 shows mean ± SD values for the slopes of the metabolic indexes from 30 to 6 months before diagnosis according to the trial and whether there was an insulin intervention. The means of the slopes were statistically significantly positive ($P < 0.05$) for all glucose indexes in all groups except for the fasting glucose in the oral trial nonintervention group, and for the 2-h glucose and AUC glucose in the parenteral trial nonintervention group ($P = 0.06$ for both of the latter). None of the means of the slopes was significant for any of the C-peptide indexes except for the positive trend of the fasting C-peptide in the oral intervention group ($P = 0.04$). The means of the slopes for both of the stimulated C-peptide–to–glucose ratios were significantly negative in all groups except in the parenteral trial nonintervention group, whereas the mean slope for the fasting C-peptide–to–fasting glucose ratio was nonsignificant in all groups.

Figure 1 displays the trends of the metabolic indexes over the interval from 30 to 6 months before diagnosis by trial. (There were no significant differences in the slopes between the intervention and the nonintervention groups for any of the metabolic indexes except for the fasting C-peptide [$P < 0.05$] and the fasting C-peptide–to–fasting glucose ratio [$P < 0.05$] in the oral trial.) Glucose levels tended to be higher and C-peptide levels lower in the parenteral group throughout the 24 months, but the patterns of change were similar.

Fig. 1*A–C* shows a gradual increase over the period of follow-up for all of the glucose indexes. The pattern of increase was more consistent in the oral trial group. This is particularly evident for the AUC glucose levels of that group, which increased at each consecutive visit (range of *P* values from visit to visit: <0.10 to <0.01). Fig. 1*D–F* shows little change over the interval for the C-peptide indexes. Fig. 1*G–I* shows declines in the stimulated C-peptide–to–glucose ratio values and little change in the fasting ratio values.

Percentages of those with glucose tolerance abnormalities (IFG, IGT, or a glucose level in the diabetic range that was not confirmed upon repeat testing) at each visit by trial can be viewed in Fig. 1 of the online appendix. Both the parenteral and oral groups had appreciable percentages of individuals with abnormal glucose tolerance 30 months before diagnosis (45 and 22%, respectively). There was a consistent increase in the percentage of those with abnormalities as the time to diagnosis decreased in the oral group (84% at 6 months before diagnosis). The percentage of those with abnormalities in the parenteral group fell from 30 to 24 months before diagnosis, but then rose gradually thereafter (82% at 6 months before diagnosis).

From 6 months before diagnosis to diagnosis (later in the course of progression)

The later course of progression was studied in 47 individuals, 21 of the 22 parenteral group participants and 26 of the 32 oral group participants, who were followed from 30 months before diagnosis and who were diagnosed at a routine visit with an OGTT. Those not included in this part of the analysis were diagnosed clinically before the routine visit; thus they did not have OGTTs performed at diagnosis.

The values for the glucose and C-peptide indexes are shown at the −6-month and diagnosis visits in Table 2. From the −6-month visit to the diagnosis visit, glucose indexes increased substantially in both groups ($P < 0.01$ or $P < 0.001$ for all). There were significant declines in the values of the AUC C-peptide

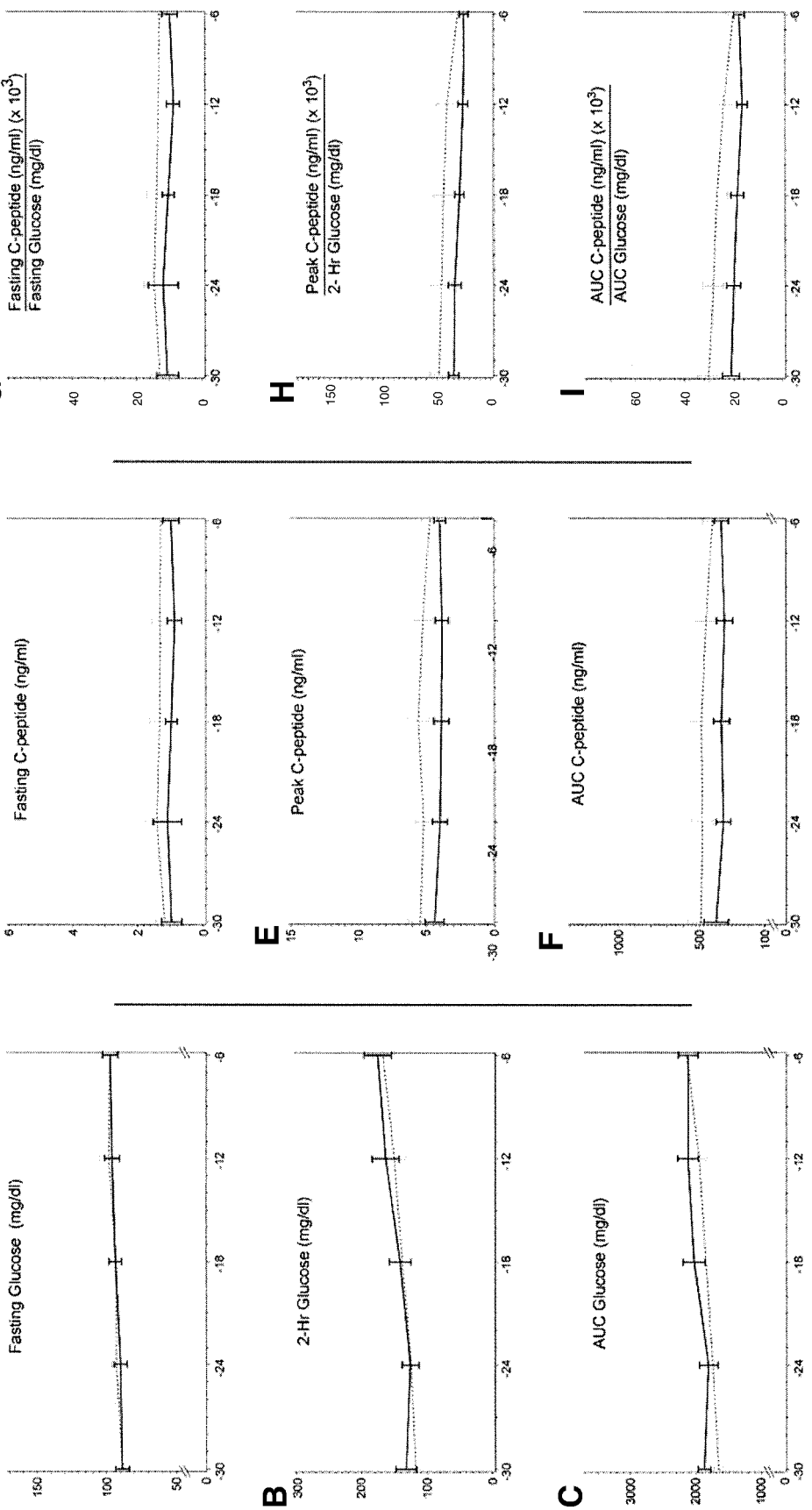

Figure 1—*Patterns of progression for the parenteral and oral insulin trials from the visit 30 months before diagnosis to the visit 6 months before diagnosis. A–C: Mean ± SD slopes for the glucose (mg/dl) indexes. A: Fasting glucose 0.38 ± 0.44, P < 0.001 (parenteral); 0.39 ± 0.54, P < 0.001 (oral). B: Two-hour glucose 2.05 ± 2.43, P < 0.001 (parenteral); 2.08 ± 1.71, P < 0.001 (oral). C: AUC glucose 133 ± 135, P < 0.001 (parenteral); 194 ± 170, P < 0.001 (oral). Gradual increases are apparent in all glucose indexes. D–F: Mean ± SD slopes for the C-peptide (ng/ml) indexes. D: Fasting C-peptide −0.00 ± 0.03, NS (parenteral); 0.00 ± 0.03, NS (oral). E: Peak C-peptide −0.02 ± 0.05, NS (parenteral); −0.02 ± 0.07, NS (oral). F: AUC C-peptide −1.24 ± 6.06, NS (parenteral); −2.92 ± 6.27, P < 0.05 (oral). There was no change in the fasting C-peptide; stimulated C-peptide indexes declined slightly. G–I: Mean ± SD slopes (×10³) for the C-peptide–to–glucose (mg/dl) ratio indexes. G: Fasting C-peptide–to–fasting glucose ratio −0.1 ± 0.3, NS (parenteral); −0.0 ± 0.3, NS (oral). H: Peak C-peptide–to–2-h glucose ratio −0.5 ± 0.6, P < 0.001 (parenteral); −0.7 ± 0.8, P < 0.001 (oral). I: AUC C-peptide–to–AUC glucose ratio −0.2 ± 0.3, NS (parenteral); −0.4 ± 0.4, P < 0.001 (oral). The stimulated ratios declined; the fasting ratio held constant.*

Table 2—*Glucose (mg/dl) and C-peptide (ng/ml) values from OGTTs at visits 6 months before diagnosis and at diagnosis*

	Parenteral (n = 21)		Oral (n = 26)	
	−6 months	Diagnosis	−6 months	Diagnosis
Fasting glucose	97 ± 13	110 ± 22*	98 ± 14	120 ± 25†
2-h glucose	176 ± 50	279 ± 74†	162 ± 43	274 ± 78†
AUC glucose	21,149 ± 3,608	28,400 ± 5,025†	21,343 ± 3,730	29,320 ± 5,835†
Fasting C-peptide	0.99 ± 0.58	1.15 ± 0.64	1.33 ± 0.74	1.80 ± 1.17*
Peak C-peptide	4.04 ± 1.01	3.41 ± 1.47	4.91 ± 1.79	4.22 ± 2.38‡
AUC C-peptide	371 ± 100	306 ± 108‡	441 ± 179	397 ± 212
Fasting C-peptide–to–glucose ratio ($\times 10^3$)	10 ± 6	10 ± 5	14 ± 7	15 ± 10
Peak C-peptide–to–2-h glucose ratio ($\times 10^3$)	25 ± 10	14 ± 8†	33 ± 15	17 ± 11†
AUC C-peptide–to–glucose ratio ($\times 10^3$)	18 ± 5	11 ± 5†	21 ± 9	15 ± 9†

Data are means ± SD. For difference from preceding visit: *$P < 0.01$; †$P < 0.001$; ‡$P < 0.05$.

in the parenteral group ($P < 0.05$) and the peak C-peptide ($P < 0.05$) in the oral group. The values of the postchallenge C-peptide–to–glucose ratios decreased markedly in both groups ($P < 0.001$ for all). However, fasting C-peptide levels increased in both groups ($P < 0.01$ for the oral group). Fasting C-peptide–to–fasting glucose ratio values remained constant.

CONCLUSIONS — This study provides the first systematic analyses of glucose and C-peptide trends in the period preceding the diagnosis of type 1 diabetes. Progression was broken into two intervals, from 30 to 6 months before diagnosis and from 6 months before diagnosis to diagnosis, so that the data from DPT-1 could be utilized to provide a more detailed picture of progression to type 1 diabetes. For the initial 24 months of follow-up, slopes of measurements across visits were utilized to assess changes, while for the last 6 months of follow-up differences between visits were utilized. The data indicate that the level of glycemia begins to increase at least 2 years before diagnosis, after which glucose levels continue to increase gradually until at least 6 months before diagnosis. Then within 6 months of diagnosis, there is a steeper rise in glucose levels.

As the level of glycemia increases, fasting C-peptide levels remain constant and are even increased at diagnosis. The consistency of the fasting C-peptide–to–fasting glucose ratio until diagnosis indicates that fasting C-peptide levels are maintained to a large extent, even relative to fasting glucose levels. Stimulated C-peptide levels tend to fall at a slow rate over an extended period of time and then fall more rapidly in the last 6 months before diagnosis. This pattern is more evident when stimulated C-peptide values are considered relative to glucose values. Thus, it appears that with progression to type 1 diabetes, fasting insulin secretion is preserved to a greater extent than glucose-stimulated insulin secretion. However, it should be noted that C-peptide levels may not fully correspond to insulin levels due to hepatic insulin extraction.

We have elected to analyze the data separately for the two trials, since the criteria for inclusion differed. The metabolic inclusion criteria of IGT and IFG for parenteral trial participants somewhat complicate the interpretation of glucose data for that group, since regression toward the mean must be considered; this could explain at least in part the declines in the mean postchallenge glucose levels and in the percentage of those with glucose abnormalities from the −30-month visit to the −24-month visit.

The glucose tolerance data provide several insights. The appreciable proportion of those with abnormalities 30 months before diagnosis further confirms that the process of metabolic deterioration can be quite lengthy. The data also indicate that individuals can have substantial abnormalities and still not progress to diagnosis for years. Finally, the data strongly suggest that the vast majority of individuals pass through a phase of abnormal glucose tolerance before diagnosis.

Several studies have demonstrated that metabolic abnormalities are present before the onset of type 1 diabetes, including abnormal first-phase insulin secretion and impaired glucose tolerance (10–17). Moreover, an earlier report from DPT-1 has shown that type 1 diabetes can be diagnosed in asymptomatic individuals with a relatively mild degree of hyperglycemia (24). However, no studies have characterized the overall pattern of progression of glucose abnormalities over an extended time before diagnosis. Also, there are virtually no data pertaining to C-peptide levels and their relation to level of glycemia in both the fasting and postchallenge states over such a lengthy period before the diagnosis of type 1 diabetes.

The findings in this study may not be fully representative of other individuals who progress to type 1 diabetes, since the participants in DPT-1 were restricted to relatives of type 1 diabetic patients in whom islet cell autoantibodies were present. Also, the inclusion criteria for the analyses (which ensured that the same individuals would be studied from visit to visit) could have selected progressors who may have differed somewhat from the other progressors. Although the ages were similar between the progressors included and excluded in the analyses for both trials, BMI values at baseline tended to be somewhat higher in progressors excluded from the analyses.

Notwithstanding these considerations, the progression patterns of the individuals included in the analyses could well be representative of many of those who develop type 1 diabetes. The pathogenesis of sporadic cases of type 1 diabetes and of those with relatives who have type 1 diabetes may be the same, since their genetic and autoantibody characteristics appear to be similar (25,26). Also, the similarities in the progression patterns between the parenteral and oral groups suggest that they could be quite typical.

It is possible that the patterns of those in the intervention groups are less likely to reflect the true natural history of progression, although any direct metabolic effect of insulin intervention would be expected to be small. Oral insulin should have no such effect, and low doses of par-

enteral insulin were used. A lack of an insulin effect is supported by the consistency of the slopes between the intervention and control groups. It should be noted, however, that there is a possibility of type 2 errors in the comparisons due to small numbers.

The findings of increases in both fasting glucose levels and fasting C-peptide levels at diagnosis suggest the possibility that there may be some resistance to insulin action at this stage of pathogenesis. Although there is little evidence similar to our finding, there are some data that suggest that insulin resistance could play a role in the pathogenesis of type 1 diabetes (27–29).

C-peptide levels at diagnosis were much higher in our study participants than reported C-peptide levels of individuals at or soon after the clinical diagnosis (26,30,31). Since the differences were so substantial, it is doubtful that varying methodologies between DPT-1 and other studies could explain them. The higher C-peptide levels at diagnosis in DPT-1 almost certainly reflect an earlier diagnosis resulting from regular follow-up OGTTs. Studies suggest that type 1 diabetes is less severe at diagnosis when individuals at risk are followed before diagnosis (32).

The findings from this study indicate that a number of individuals at risk for type 1 diabetes have, on average, a prolonged, gradual metabolic deterioration with the persistence of substantial β-cell function until at least 6 months before type 1 diabetes occurs. This suggests that in individuals at risk for type 1 diabetes who are followed with OGTTs at regular intervals as in this study, even 6 months before diagnosis, an intervention to preserve β-cell function could have a long-term impact. Moreover, the appreciable remaining β-cell function at diagnosis in these individuals suggests the possibility that an intervention at diagnosis could still have a significant impact upon the maintenance of β-cell function and diabetes complications (33–35).

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