

Incident Dysglycemia and the Progression to Type 1 Diabetes among Participants in the Diabetes Prevention Trial-Type 1

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Objective: We studied the incidence of dysglycemia and its prediction of the development of type 1 diabetes (T1D) in islet cell autoantibody (ICA)-positive individuals. In addition, we assessed whether dysglycemia was sustained.

Methods: Participants (n=515) in the Diabetes Prevention Trial-Type 1 (DPT-1) with normal glucose tolerance who underwent periodic oral glucose tolerance tests (OGTTs) were followed for incident dysglycemia (impaired fasting glucose, impaired glucose tolerance, and/or high glucose levels at intermediate time points of OGTTs). Incident dysglycemia at the 6-month visit was assessed for T1D prediction.

Results: Of 515 participants with a normal baseline OGTT, 310 (60%) had at least one episode of dysglycemia over a maximum follow-up of 7.0 years. Dysglycemia at the 6-month visit was highly predictive of the development of T1D, both in those <13 years ($p<0.001$) and those ≥ 13 years ($p<0.01$). Those <13 years with dysglycemia at the 6-month visit had a high cumulative incidence (94% estimate by 5 years). Among those who developed T1D after a dysglycemic OGTT and who had at least two OGTTs following the dysglycemic OGTT, 33/64 (52%) reverted back to a normal OGTT. However, 26 (79%) of the 33 then had another dysglycemic OGTT prior to diagnosis.

Conclusion: ICA positive individuals with normal glucose tolerance had a high incidence of dysglycemia. Incident dysglycemia in those ICA-positive is strongly predictive of T1D. Children with incident dysglycemia are at an especially high risk. Fluctuations in and out of the dysglycemic state are not uncommon prior to the onset of T1D.

There is increasing evidence that impaired glucose tolerance (IGT) is a predictor and common precursor of type 1 diabetes (1-3). Still, little is known about the incidence of IGT and other forms of dysglycemia in individuals who have pancreatic autoantibodies with normal glucose tolerance. Also, there is no information about the risk of T1D when dysglycemia occurs in those individuals. Moreover, it is not known whether dysglycemia is sustained once it occurs.

We have utilized data from the Diabetes Prevention Trial-Type 1 (DPT-1) (4,5) to examine these questions. In addition to IGT, impaired fasting glucose (IFG) and high glucose values at intermediate times (between fasting and two hours) during oral glucose tolerance tests (OGTTs), termed indeterminate glycemia (INDET), were included as other forms of dysglycemia in the analyses. Glucose levels at intermediate times have been shown to be predictive of T1D (6,7).

Information regarding the incidence of these various forms of dysglycemia and their prediction of T1D should be helpful for understanding the pathogenesis and natural history of T1D. Also, such information should be useful for improving T1D prevention trials.

RESEARCH DESIGN AND METHODS

Subjects: There was a total of 711 participants in the parenteral (n=339) and oral (n=372) insulin DPT-1 trials. All were islet cell autoantibody (ICA)-positive relatives of T1D patients. Greater than a 50% 5-year risk was required for eligibility for the parenteral insulin trial. Individuals were deemed to be at greater than a 50% 5-year risk if the first-phase insulin response (FPIR) on an intravenous glucose tolerance test (IVGTT) was below a defined threshold and/or there were OGTT abnormalities (IFG, INDET or IGT). Those without metabolic criteria but

positive for insulin autoantibodies were considered to be at 26-50% 5-year risk and eligible for the oral insulin trial. There was no overall treatment effect in either trial. The analyses included 515 participants of the parenteral (n=168) and oral trials (n=347). All had normal OGTTs prior to trial entry, at least one non-diabetic OGTT after randomization, and no missing values (n=6). Those excluded were somewhat older (15.4 ± 10.6 years vs 13.3 ± 9.1 years, $p < 0.01$). There was almost no difference in gender (excluded: 58%; included 56%).

Procedures: Participants in the parenteral insulin trial intervention group received recombinant human ultralente insulin, while those in the oral insulin trial intervention group received recombinant human insulin crystals. OGTTs were performed at 6-month (± 3 months) intervals in both trials. The dose of oral glucose was 1.75 g per kilogram (maximum, 75 g of carbohydrate). Blood samples were obtained for plasma glucose in the fasting state and at 30, 60, 90 and 120 minutes. Most individuals were diagnosed with T1D at routine visits. Those with OGTTs in the diabetic range were asked to return for confirmation by another OGTT unless this was clinically contraindicated. If the second OGTT was not confirmatory, participants continued to be followed at 6-month intervals.

Laboratory **Measures:** Methodologies for assessing autoantibody positivity in DPT-1 have been described (8). ICAs were determined by indirect immunofluorescence and insulin autoantibodies were measured by competitive fluid-phase radioassay. Plasma glucose levels were measured by the glucose oxidase method. Insulin was measured by radioimmunoassay.

Data Analysis: The t-test and chi-square test were utilized for simple comparisons, and the log-rank test was used to compare the distributions of event-times

between groups. The Cox Proportional Hazards regression model was utilized for assessing T1D associations over time. Kaplan-Meier curves were used to obtain cumulative incidence estimates of T1D over time. Incident dysglycemia was defined as the first dysglycemic OGTT that occurred.

Glucose tolerance abnormalities were defined as: IFG=fasting glucose value 100-125 mg/dl; INDET=30, 60, and/or 90-minute glucose value ≥ 200 mg/dl; IGT=2-hr glucose value 140-199 mg/dl. The thresholds for diabetes were a fasting glucose value ≥ 126 mg/dl and/or a 2-hr glucose value ≥ 200 mg/dl. Unconfirmed OGTTs in the diabetic range were excluded [n=81 (2.8%) of all OGTTs performed during follow-up] from the analysis. The FPIR was defined as the sum of insulin levels at the 1st and 3rd minutes of the IVGTT. An FPIR less than the 10th percentile according to age norms was considered below threshold. Of those analyzed, 35% were below this threshold.

The SAS 9.1.3 version was used for the analyses. All p-values are 2-sided.

RESULTS

Of the 515 DPT-1 participants with normal glucose tolerance at baseline who were studied, 56% were male. The mean \pm SD age at baseline was 13.3 \pm 9.1 years.

Over a maximum follow-up of 7.0 years (mean \pm SD: 2.3 \pm 1.6 years), dysglycemia occurred in 310 (60%) of the 515 participants, with 2- and 5-year estimates of approximately 41% and 73%. In proportional hazards models there were no associations of dysglycemia with either age or gender. Dysglycemia occurred in 199/330 (60%) of those <13 years, with 2- and 5-year estimates of 44% and 73% respectively. Of those ≥ 13 years, 111/185 (60%) developed dysglycemia, with 2- and 5-year estimates of 36% and 72% respectively. There was no significant difference between the curves. In a proportional hazards model, there was no

association between incident dysglycemia and a FPIR below threshold.

Distributions of the specific abnormalities for the first occurrence of dysglycemia are shown in Table 1, overall and according to <13 and ≥ 13 age categories. Overall, IGT alone (43%) occurred much more frequently than either IFG alone (16%) or INDET alone (17%). A high percentage developed IGT alone or in combination (65%). There were no significant differences in the proportions of IFG, INDET, and IGT between those <13 and ≥ 13 . Whereas the proportions of IFG and INDET were similar between females and males (IFG: 24% vs. 25%; INDET: 34% vs. 41%, respectively), the proportion of IGT was higher in females (75% vs. 58%, $p < 0.01$).

The risk for the development of subsequent T1D after the occurrence of dysglycemia was examined among those individuals (n=484) who had a non-diabetic OGTT at the 6-month visit (6 \pm 3 months). Over a maximum follow-up of 6.7 years (mean \pm SD: 2.9 \pm 1.6 years) from the 6-month visit, 131 (27%) developed T1D. In proportional hazards models (Table 2), those with a dysglycemic OGTT at the 6-month visit were at much greater risk for subsequently developing T1D than those with a normal OGTT (53/97 vs. 78/387; $p < 0.001$). When the data were stratified according to age <13 and ≥ 13 , the association between T1D and dysglycemia at 6 months was apparent in both groups ($p < 0.001$ for <13 and $p < 0.01$ for ≥ 13). The increased progression to T1D among those with dysglycemia at the 6-month visit is evident in the cumulative incidence curves in Figure 1. When IGT was used as a marker, 40/63 (63%) developed T1D. The 4-year estimate for IGT was 72%, whereas that for dysglycemia was 65%.

Among those who also had a normal OGTT at 6 months, there was still a strong association between T1D and dysglycemia occurring at 1 year (19/43 vs. 48/291,

$p < 0.001$), even with the shorter follow-up (maximum: 5.5 years). Gender was not predictive of T1D both at 6 months and at 1 year.

In an analysis limited to only those individuals with dysglycemia at 6 months, T1D was inversely related to age ($p < 0.001$) in a proportional hazards model. This is evident in Figure 2, in which the risk estimate for T1D was much higher for those < 13 (94% vs. 40% by five years). The hazard ratio was 3.3 (95% Confidence Interval: 1.6, 6.7; $p = 0.001$). There were 24 participants < 13 years with incident dysglycemia at 6 months that persisted at 1 year. Of these, 18 developed T1D (75%) with a maximum follow-up of 4.5 years. Of the 15 children < 13 years with incident IGT that persisted at one year, 14 (93%) developed T1D.

There were 136 individuals among the 515 studied who developed T1D. Of the 136, 78 (57%) had a minimum of three visits prior to diagnosis. Of those 78, 74 (95%) had at least one dysglycemic OGTT. Among the 275 participants with a minimum of three visits who did not develop T1D, 152 (55%) had at least one dysglycemic OGTT.

The occurrence of a single glucose tolerance abnormality at 6 months was assessed for the prediction of T1D. T1D did not occur significantly more frequently in individuals with IFG (5/15, $p = 0.216$) when they were compared with those who had a normal OGTT at the 6-month visit (78/387). However, in a proportional hazards model with age included as a covariate, IFG was predictive ($p = 0.009$). T1D occurred significantly more frequently in individuals with INDET alone (8/17, $p = 0.008$) or with IGT alone (19/36, $p < 0.001$) at the 6-month visit when they were compared to those with normal OGTTs. In proportional hazards models with age as a covariate, the associations persisted ($p = 0.002$ for INDET; $p < 0.001$ for IGT).

To assess whether dysglycemia was sustained once it occurred, we studied 64 participants who developed T1D after dysglycemia had occurred and who had at least two OGTTs after the dysglycemic OGTT. Of these, 33 (52%) reverted back to a normal OGTT. However, 26 of the 33 (79%) then had another dysglycemic OGTT prior to diagnosis.

CONCLUSIONS

This study is unique in that it examined the occurrence of dysglycemia in autoantibody positive individuals who had pre-existing normal glucose tolerance. The incidence of dysglycemia was very high both in the younger and older age groups. The distribution of the forms of dysglycemia was similar between the age groups and IGT was the most common type. The data also showed that incident dysglycemia was strongly predictive of T1D, both in younger and older individuals.

There is no prior information available regarding the incidence of dysglycemia and its prediction of T1D in autoantibody positive individuals with antecedent normal glucose tolerance. However, IGT has been found to be a predictor and precursor of T1D (1-3). Also, fasting glucose levels and glucose levels at various OGTT time points have also been found to be predictive of T1D (7, 9).

The data in this report indicate that among autoantibody positive individuals there is a high likelihood of dysglycemia occurring at some point prior to the onset of T1D. The occurrence of at least one episode of dysglycemia in those who developed T1D was very high. Although the occurrence of dysglycemia was much lower among those who did not develop T1D, it was still substantial. This suggests that some of the latter could have developed T1D with more extended follow-up.

IGT occurring alone appears to be highly predictive of T1D. Although the extent

to which either IFG or INDET occurring alone predict T1D is difficult to gauge due to the small numbers, each of those dysglycemia abnormalities occurring singly at 6 months was predictive of T1D with age as a covariate. The data suggest that INDET can indeed be used as a predictor of T1D in addition to the more traditional indicators of dysglycemia.

The risk for T1D at 4 years was somewhat higher for IGT than for dysglycemia. However, the number who developed dysglycemia at 6 months was much greater (97 vs. 63). In choosing criteria for entry into prevention trials, both of these findings need to be taken into account. It appears that the ultimate decision for the criteria to be used rests upon the nature of the specific prevention trial.

In the overall analyses there was a lack of influence of age on the occurrence of dysglycemia. However, among those with dysglycemia, age was a strong predictor of T1D. There is no previous information regarding these specific associations. Although the cutoff at age 13 was arbitrary, it served to demonstrate the influence of age.

The data indicate that even among those who ultimately develop T1D, dysglycemia is not necessarily sustained. Moreover, it appears that even after glucose levels normalize, dysglycemia tends to recur prior to diagnosis. This finding suggests that there are fluctuations at an undetermined frequency between the normal and dysglycemic states prior to the onset of T1D. The finding of recurrent dysglycemia suggests the possibility that dysglycemia could have occurred prior to study entry in some individuals.

Since this study was based on a population of ICA-positive relatives, some selected on the basis of a FPIR below threshold and some selected on the basis of IAA positivity, the findings may not necessarily fully generalize to other populations. Also, there was limited

information regarding IFG and INDET occurring alone.

The findings in this report have significant implications with regard to increasing the efficiency of prevention trials for T1D. Since the data show that dysglycemia will occur in an appreciable percentage of autoantibody positive individuals who initially screen negative for dysglycemia, repeating OGTTs in individuals with normal glucose tolerance should increase the yield of potential high risk participants. Moreover, since children less than 13 years of age with incident dysglycemia are at very high risk for T1D (94% 5-year estimate despite the variability of dysglycemia), dysglycemia could possibly be utilized as an early indicator of efficacy in prevention trials for those with normal glucose tolerance at baseline.

The pathogenetic development of T1D appears to be an ongoing process (10, 11) with an initial immunologic insult to β -cells followed by progressive metabolic deterioration prior to and following diagnosis (12-15). Therefore, from both clinical and research perspectives it may well be advantageous to identify individuals as early as possible in this process. The very high likelihood that autoantibody positive children will develop T1D within five years after the occurrence of dysglycemia suggests that the earlier identification of the disease is a distinct possibility.

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Table 1: The Distribution of Glucose Tolerance Abnormalities for the First Occurrence of Dysglycemia among Participants

Abnormality	All	<13 Years	≥13 Years
IFG Alone	50 (16.1)	27 (13.6)	23 (20.7)
INDET Alone	51 (16.5)	33 (16.6)	18 (16.2)
IGT Alone	133 (42.9)	87 (43.7)	46 (41.4)
IFG & INDET	7 (1.9)	5 (2.5)	2 (1.7)
IFG & IGT	9 (2.9)	8 (4.0)	1 (0.9)
IGT & INDET	49 (16.1)	35 (17.6)	14 (12.6)
IFG & IGT & INDET	11 (3.5)	4 (2.0)	7 (6.3)
Total	310	199	111

Percentage of total in parentheses

Table 2: Hazard Ratios with 95% Confidence Intervals for the Prediction of T1D According to Presence of Incident Dysglycemia at the 6-Month Visit

	n	T1D/Total		Hazard Ratio †
		Dysglycemic	Normal	
All	484	53/97	78/387	5.2 (3.7,7.5) ⁺⁺
< 13	312	44/67	60/245	5.4 (3.6,8.1) ⁺⁺
≥ 13	172	9/30	18/142	4.1 (1.8,9.3) ⁺

† With an adjustment for age

⁺p<0.01

⁺⁺p<0.001

Figure 1

Shown are cumulative incidence curves for the subsequent development of T1D according to whether dysglycemia occurred at the 6-month visit. The actual proportion of those developing T1D is shown for each curve. The cumulative incidence was significantly greater when dysglycemia occurred at the 6-month visit.

Figure 2

Shown are cumulative incidence curves for the development of T1D according to whether participants were <13 or ≥13 years of age among those who were dysglycemic at the 6-month visit. The cumulative incidence was significantly higher in the younger age group, with an estimate of 94% by 5 years in those individuals.

