EDITORIAL (SEE TRIOLO ET AL., P. 769)

Is It Time to Take a Different Approach to Screening People at High Risk for Type 1 Diabetes?

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It is generally believed that the onset of type 2 diabetes can be insidious and evade detection for prolonged time periods (1,2). Type 1 diabetes, however, often displays a sudden clinical onset due to the development of insufficient insulin secretory capacity following a pre-diabetic period characterized by the presence of pancreatic islet autoantibodies. Type 1 diabetes usually presents with symptoms, the most frequent being polyuria and polydipsia (97%) and weight loss (46%) in one recent study of newly diagnosed patients (3).

The article by Triolo et al. (4), in this issue of *Diabetes Care*, addresses the period in the development of type 1 diabetes between the onset of hyperglycemia that meets diagnostic criteria for diabetes and its clinical presentation. Triolo et al. present evidence that the onset of type 1 diabetes can occur without clinical symptoms and be difficult to detect with the current approach to diagnosis, which is based on fasting plasma glucose (FPG) measurement (5). These conclusions are based on the results of semiannual oral glucose tolerance tests for diabetes diagnosis among the Diabetes Prevention Trial–Type 1 (DPT-1) participants. The occurrence of asymptomatic type 1 diabetes in the DPT-1 population has been previously reported (6). The important additional findings are the value of A1C in the detection of diabetes and the comparatively low occurrence of diabetic ketoacidosis (DKA) at diagnosis of diabetes. The authors conclude by advising that "high-risk relatives may benefit from close attention or screening in order to prevent DKA at diagnosis" (4).

The potential for screening to benefit high-risk subjects such as those included in the DPT-1 requires further consideration. Of the 771 subjects included in this trial, 246 were diagnosed with diabetes during the course of the trial; of these, 167 were diagnosed by the OGTT, whereas the remaining cases were diagnosed by the FPG ($n = 29$) or random plasma glucose ($n = 42$) testing that was, presumably, performed because of a presence of symptoms or elevated home glucose readings. Only eight patients presented with DKA. Not all subjects were asymptomatic at the time of diagnosis. For the 218 subjects with available data on presence of symptoms, about one-third (36.7%) reported the presence of at least one symptom. If we assume that this proportion applies to all 246 subjects diagnosed with diabetes, then the number of individuals needing to be screened with a semiannual OGTT in order to detect one asymptomatic case of diabetes is $771/(246 \times 0.633)$, which is equal to five individuals. Although this number is quite low, the real benefit from semiannual screening would be the resulting decline in cases of DKA that otherwise would have occurred had screening not been in place. This number can only be estimated by comparing the DPT-1 experience with the literature, because there was no unscreened control group in the trial that would have allowed for estimation of the incidence of DKA in the absence of semiannual testing with the OGTT. Assuming that 20–40% of subjects who develop type 1 diabetes present with DKA, and accounting for the fact that 4% of new-onset cases in the DPT-1 presented with this condition despite semiannual OGTT screening, the incidence of potentially preventable DKA would range from 16–36% of cases (7). Using this estimate to perform the above equation for the number of individuals screened with a semiannual OGTT needed to detect one asymptomatic case of diabetes leads to a range of 20 [$771/(246 \times 0.16)$] to 9 [$771/(246 \times 0.36)$] people. By these estimates, 9–20 high-risk subjects would need to be screened semiannually by OGTT to prevent one case of DKA. These calculations probably represent significant underestimates, because it is highly likely that the DPT-1 participants have a greater level of diabetes awareness that would most likely translate into a lower risk of DKA, even in the absence of screening. In addition, other DPT-1 inclusion criteria may have led to a risk of DKA that differs significantly from subjects who were ineligible or declined participation. It has been shown that clinical trial participants usually fare better than nonparticipants (8). Confirmation of the potential benefit of OGTT screening in autoantibody-positive subjects at high risk for type 1 diabetes would require a clinical trial to assess the effects of screening on adverse outcomes. Such a trial could be of further value by assessing different frequencies of OGTT screening (e.g., semiannual vs. annual).

It is discouraging, but not surprising, that other measures of glycemia were not deemed helpful in diagnosis. The 2-h plasma glucose concentration generally captures more cases of type 2 diabetes than the FPG value in screening studies for this outcome (9). The A1C reflects nonenzymatic glycosylation of hemoglobin in erythrocytes and requires time before an elevation in this level occurs, with the midpoint between the starting level and the new steady-state level requiring 30–35 days (10). One would expect that the A1C would detect chronic hyperglycemia if it had been present for several months. This finding is confirmed by the results of the DPT-1: 49% of subjects had an A1C above the normal range of 6.2%. In addition, the area under the A1C receiver operating characteristic curve of 0.86 in Fig. 1*B* of the original article shows good ability to discriminate between patients with and without diabetes.

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A different A1C cut point may deserve further consideration as a marker for the detection of diabetes in high-risk subjects similar to those included in this study.

A high proportion of subjects diagnosed with diabetes had detectable C-peptide levels, which would indicate a potentially less complicated clinical course with fewer microvascular complications and less severe hypoglycemia based on results of the Diabetes Control and Complications Trial, where higher stimulated C-peptide levels were associated with a less severe clinical course (11). However, C-peptide concentration in the DPT-1 participants might have continued to fall despite earlier diagnosis, and it is not clear that detectable C-peptide concentrations were more likely to persist as a result of detection by OGTT screening. On the other hand, if a future clinical trial demonstrates that an intervention preserves the relatively high level of C-peptide found at diagnosis in the DPT-1, this intervention would be expected to have direct clinical benefit.

The study by Triolo et al. shows that periodic OGTT screening raises the potential for a reduction in disease severity at the time of type 1 diabetes onset. It is certainly possible that this practice would be acceptable and desirable to individuals at high risk for type 1 diabetes who are extremely motivated and willing to accept the inconvenience of regular testing. As the benefit of this testing has not been convincingly demonstrated, it cannot be recommended as standard clinical practice. Also, this report shows that the onset of type 1 diabetes may be asymptomatic and undetectable by FPG measurement, which runs counter to conventional wisdom. How much time it takes to progress from asymptomatic to symptomatic type 1 diabetes is a major unanswered question. Although not addressed by Triolo et al., A1C may hold promise in identifying the onset of type 1 diabetes, and further diagnostic cut points should be examined in this regard.

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References

1. Harris MI, Klein R, Welborn TA, Knuiman MW. Onset of NIDDM occurs at least 4–7 yr before clinical diagnosis. Diabetes Care 1992;15:815–819
2. Thompson TJ, Engelgau MM, Hegazy M, Ali MA, Sous ES, Badran A, Herman WH. The onset of NIDDM and its relationship to clinical diagnosis in Egyptian adults. Diabet Med 1996;13:337–340
3. Roche EF, Menon A, Gill D, Hoey H. Clinical presentation of type 1 diabetes. Pediatr Diabetes 2005;6:75–78
4. Triolo TM, Chase HP, Barker JM, the DPT-1 Study Group. Diabetic subjects diagnosed through the Diabetes Prevention Trial–Type 1 (DPT-1) are often asymptomatic with normal A1C at diabetes onset. Diabetes Care 2009;32:769–773
5. Expert Committee on the Diagnosis and Classification of Diabetes. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Diabetes Care 1997;20:1183–1197
6. Greenbaum CJ, Cuthbertson D, Krischer JP, the Diabetes Prevention Trial of Type 1 Diabetes Study Group. Type 1 diabetes manifested solely by 2-h oral glucose tolerance test criteria. Diabetes 2001;50:470–476
7. Haller MJ, Atkinson MA, Schatz D. Type 1 diabetes mellitus: etiology, presentation, and management. Pediatr Clin North Am 2005;52:1553–1578
8. Goss CH, Rubenfeld GD, Ramsey BW, Aitken ML. Clinical trial participants compared with nonparticipants in cystic fibrosis. Am J Respir Crit Care Med 2006;173:98–104
9. Wang W, Lee ET, Fabsitz R, Welty TK, Howard BV. Using HbA_{1c} to improve efficacy of the American Diabetes Association fasting plasma glucose criterion in screening for new type 2 diabetes in American Indians: the Strong Heart Study. Diabetes Care 2002;25:1365–1370
10. Goldstein DE, Little RR, Lorenz RA, Malone JI, Nathan D, Peterson CM, Sacks DB. Tests of glycemia in diabetes. Diabetes Care 2004;27:1761–1773
11. Steffes MW, Sibley S, Jackson M, Thomas W. β-Cell function and the development of diabetes-related complications in the diabetes control and complications trial. Diabetes Care 2003;26:832–836