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Predicting progression to diabetes in islet autoantibody positive children

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ABSTRACT

While full oral glucose tolerance test (OGTT) helps improve prediction, it requires intravenous access with 6 sample collections for glucose and C-peptide. The objective of this study was to explore less costly and less time-consuming options. All children being prospectively followed by the Diabetes Autoimmunity Study in the Young (DAISY) who had a complete baseline OGTT and at least one confirmed islet autoantibody (Ab+) were included in this study (n = 68). Of 68 Ab+ subjects with a baseline OGTT, 25 developed diabetes after a mean follow-up 5.7 yrs, at a mean age of 12.4 yrs. Univariate proportional hazards (PH) models suggested that age at seroconversion, number of Ab+, IA-2A levels, HbA1c and metabolic variables from the OGTT predicted progression to diabetes, while HLA DR3/4, BMI, levels of IAA or GADA did not. Five multivariate PH predictive models were similar (p = 0.32). All five models included age at seroconversion, number of Ab+, IA-2A levels and HbA1c, and in addition included: model 1 - 1 h glucose and 1 h C-peptide; model 2 - 2 h glucose and 2 h C-peptide; model 3 - glucose sum and C-peptide sum; model 4 - glucose AUC and C-peptide AUC; and model 5: index 60. A model containing age at seroconversion, number of Ab+, IA-2A levels, HbA1c, 1 h glucose and 1 h C-peptide was as predictive for type 1 diabetes progression as models including all sum or AUC values for glucose and C-peptide from full OGTT. The performance of this model should be confirmed in an independent population of Ab+ children.

1. Introduction

Prospective, longitudinal studies following individuals at high risk for type 1 diabetes, determined by genetic risk markers or family history, have elucidated the typical disease progression prior to the onset of clinical symptoms [1–5]. The American Diabetes Association, the Juvenile Diabetes Research Foundation and the Endocrine Society published a joint statement in 2015 that describes distinct stages of type 1 diabetes [6]. In Stage 1, a person is euglycemic with no symptoms but positive for multiple islet autoantibodies. Stage 2 occurs when a person with multiple autoantibodies begins to have metabolic abnormalities (dysglycemia) but remains clinically asymptomatic. In Stage 3, a patient has classical diabetes symptoms in the presence of significant dysglycemia and therefore meets standard clinical diagnostic criteria for diagnosis of diabetes.

Dysglycemia precedes clinical diagnosis of diabetes by months or years and has gained interest as a distinct stage of pre-diabetes and a potential window for therapeutic intervention. The ability to reliably identify the dysglycemic period and implement prevention may have important implications for preservation of endogenous insulin secretion. The oral glucose tolerance test (OGTT) has value in predicting progression from islet autoimmunity to type 1 diabetes [7,8], is performed in prospective studies to monitor subjects' risk of progression, as entry criteria into prevention trials and/or to confirm the diagnosis of diabetes. While full OGTT helps improve prediction, it requires intravenous access with 6 sample collections for glucose and C-peptide, and repeated OGTTs are poorly accepted by children and families.

The objective of this study was to explore whether less costly and less time-consuming options are as accurate as a full OGTT for

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prediction of type 1 diabetes in children known to be at high genetic risk and positive for islet autoantibodies. We found that a model containing age at seroconversion, number of Ab+, IA-2A levels, HbA1c, 1 h glucose and 1 h C-peptide was as predictive for type 1 diabetes progression as models including all sum or area under the curve (AUC) values for glucose and C-peptide from a full OGTT.

2. Material and methods

2.1. Study population

Since 1993, DAISY has followed two cohorts of young children at increased risk of type 1 diabetes (total N = 2542): a cohort of relatives of type 1 diabetes patients (siblings and offspring), and the general population newborn cohort. The latter consists of children with type 1 diabetes susceptibility HLA-DR/DQ genotypes identified through screening of over 31,000 newborns at St. Joseph Hospital in Denver, Colorado. Recruitment began in 1993 and ended in 2004. The details of screening and follow-up have been previously published [9]. DAISY children with at least one confirmed Ab+ on two consecutive visits are offered an OGTT. Only DAISY children who had a complete baseline OGTT were included in this study (N = 68). Onset of diabetes was defined according to ADA criteria. Informed consent was obtained from the parents of each study subject. The Colorado Multiple Institutional Review Board approved all study protocols.

2.2. Islet autoantibodies

Measurement of islet autoantibodies to insulin, GAD65 and IA-2 was performed in the Clinical Immunology Laboratory at the Barbara Davis Center, the core immunology laboratory for TrialNet study antibody testing, using radio-immunoassays as previously described [10–12]. In addition, all available samples from children ever positive for any of the above autoantibodies or who developed type 1 diabetes were tested for autoantibodies to ZnT8 as previously described [13]. In the 2015 IASP Workshop, sensitivities and specificities were 52% and 100% respectively for mIAA, 82% and 99% respectively for GADA, 72% and 100% respectively for IA-2A, and 70% and 97% respectively for ZnT8A.

2.3. Oral glucose tolerance test (OGTT)

Participants were instructed to fast for 8 h prior to the study visit. The oral glucose tolerance test (OGTT) was conducted only if glucometer fasting glucose was below 200 mg/dl. A fasting blood sample was drawn for hemoglobin HbA1c, glucose and C-peptide. For the oral glucose tolerance test (OGTT), 1.75 g per kilogram glucose dose (maximum 75 g of carbohydrate) was ingested within 5 min and blood samples for glucose and C-peptide were collected at 6- time points (−10, 0, 30, 60, 90 and 120 min).

2.4. Statistical analysis

Statistical analyses were performed using the SAS software version 9.4. Autoantibody levels were converted to Z scores (SD units away from threshold) and log transformed for analyses. Because of negative values, 1 was added before log transformation and calculation of mean. Progression to diabetes from baseline OGTT visit was analyzed using univariate and multivariate Cox proportional hazard analyses. Follow-up time was defined as time from baseline OGTT to development of type 1 diabetes or last visit for those who did not develop diabetes. AUC was calculated according to the trapezoidal rule. Values from 30, 60, 90 and 120 min time points for glucose or C-peptide were combined for the glucose SUM and C-peptide SUM, respectively. Index60 combines log fasting C-peptide, 60-min C-peptide, and 60-min glucose values [14]. Receiver operating characteristic (ROC) curves were generated to compare AUC of five different predictive models. As we had incomplete data for ZnT8, ZnT8 was not included in multivariate models. A two-tailed p-value with an alpha level for significance was set at 0.05.

3. Results

The characteristics of study participants at baseline OGTT are shown in Table 1. DAISY Ab+ subjects who progressed to diabetes had a younger age at seroconversion (5.4 ± 2.9 vs 8.1 ± 4.1 yrs respectively, p = 0.005). As expected, follow-up time was shorter for those Ab+ subjects who progressed to type 1 diabetes. The percentage of subjects with a first-degree relative (FDR) with type 1 diabetes was high in both groups, and even higher in the Ab+ non-progressors (72% vs 48%, p = 0.047).

Univariate Cox proportional hazard (PH) models were performed to analyze factors involved in progression to diabetes in Ab+ subjects since baseline OGTT (Table 2). Age at seroconversion, number of Ab+, IA-2A and ZnT8A levels, HbA1c, 1 h glucose, 2 h glucose, glucose AUC, glucose sum, 1 h C-peptide, C-peptide AUC, C-peptide sum and index 60 predicted progression to type 1 diabetes. On the other hand, HLA DR3/4, BMI, FDR with diabetes, levels of IAA or GADA, fasting glucose, fasting C-peptide and 2 h C-peptide did not predict progression to diabetes.

Five multivariable Cox proportional hazards models predicting progression to diabetes were compared. All models contained the variables that were significant in univariate Cox PH models, i.e. age at seroconversion, number of Ab+, IA-2A levels and HbA1c (ZnT8 levels were not included in multivariate analyses due to incomplete data). In addition to these common variables, the model included significant metabolic variables from the OGTT: model 1: 1 h glucose and 1 h C-peptide; model 2: 2 h glucose and 2 h C-peptide; model 3: glucose sum and C-peptide sum; model 4: glucose AUC and C-peptide AUC; model 5: Index60 (Table 3). Factors that remained significantly associated with prediction to diabetes were: model 1: 1 h glucose and 1 h C-peptide; model 2: IA-2A and 2 h glucose; model 3: IA-2A and glucose SUM; model 4: IA-2A and glucose AUC; model 5: Index60

Receiver operating characteristic (ROC) curves were generated to compare area under the curve (AUC) of the five different predictive models. There were no significant differences in the ROC AUC of the five different models (Fig. 1, p = 0.316), suggesting that a simpler model such as model 1 (1 h glucose and 1 h C-peptide) was as predictive for type 1 diabetes progression as models including all sum or AUC values for glucose and C-peptide.

4. Discussion

To our knowledge, this is the first study to date to compare whether less costly and less time-consuming options are as accurate as a full OGTT for prediction of type 1 diabetes in children known to be at high genetic risk and positive for islet autoantibodies. Children with islet autoantibodies are at high risk for type 1 diabetes, but the individual risk varies. This study found that a model containing age at seroconversion, number of Ab+, IA-2A levels, HbA1c, 1 h glucose and 1 h C-peptide was as predictive for type 1 diabetes progression as models including all sum or AUC values for glucose and C-peptide from full OGTT.

Several risk scores for diabetes have been developed, including the Diabetes Prevention Trial-Type 1 Risk Score (DPTRS) [15,16] in order to predict risk for diabetes. The DPTRS(15) includes age, log

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