Partial clinical remission in type 1 diabetes: a comparison of the accuracy of total daily dose of insulin of <0.3 units/kg/day to the gold standard insulin-dose adjusted hemoglobin A1c of ≤9 for the detection of partial clinical remission

Abstract

Background: It is unclear whether the gold standard test for the detection of partial clinical remission (PCR) in new-onset type 1 diabetes (T1D), the insulin-dose adjusted Hemoglobin A1c (IDAA1c) of ≤9, is superior to a new tool, total daily dose of insulin (TDD) of <0.3 units/kg/day. The aim of the study was to test the superiority of IDAA1c over TDD of <0.3 units/kg/day for the detection of PCR.

Methods: A retrospective analysis of 204 subjects of ages 2–14 years, mean age 7.9±3.2 years, (male 78±3.4 years, [n = 98]; female 7.9±3.0 years, [n = 106], p = 0.816) with new-onset T1D. Anthropometric and biochemical data were collected for the first 36 months of disease. PCR was defined by both IDAA1c <9 criterion, and 82 (40.2%) remitters (age 9.1±3.0 years; male 57%) remitters by IDAA1c <9 criterion, and 82 (40.2%) remitters (age 7.3±2.8 years) by TDD of <0.3 units/kg/day criterion (p = 0.655). The duration of PCR was 10.0±6.1 months using TDD <0.3 units/kg/day, and 9.2±5.5 months using IDAA1c (p = 0.379). Subjects in PCR as denoted by TDD <0.3 units/kg/day had 1.44 times increased probability of entering PCR than those denoted by IDAA1c <9, after adjusting for BMI, bicarbonate, and HbA1c:OR = 1.44, 95% CI [1.03–2.00], p = 0.033). Peak prevalence for PCR was at 6–12 months by either definition; more subjects were in PCR at 6 months by IDAA1c <9: 62/86 (72.1%) than by TDD <0.3 units/kg/day: 43/82 (52.4%), (p = 0.011).

Conclusions: There were no significant differences in the number of remitters, duration of PCR, or the time of peak remission defined by IDAA1c <9 or TDD of <0.3 units/kg/day.

Keywords: bicarbonate; children and adolescents; hemoglobin A1c; honeymoon period; insulin; type 1 diabetes.

Introduction

More than 50% of children and adolescents with new-onset type 1 diabetes (T1D) will not experience partial clinical remission (PCR), also known as the honeymoon phase [1–4]. These non-remitters have been shown to have poorer short- and long-term diabetes outcome compared to those who entered PCR [5–8]. A recent long-term study found a significantly reduced risk for chronic microvascular complications at 7-year follow-up in patients who entered PCR [9]. Thus, patients who undergo PCR, also known as remitters, have an overall prognostic advantage over non-remitters, but there is no consensus on a simple and easily usable tool for the detection and monitoring of PCR in children and adolescents.

The IDAA1c, which integrates HbA1c and total daily dose (TDD), is considered the gold standard for detection of PCR, and its validation in multiple cohort studies [10, 11] is helpful for the characterization of PCR in clinical studies. Despite its strength as a surrogate marker of serum C-peptide, IDAA1c has been criticized for its various shortcomings; for example, age, a major determinant of PCR, is not included in its formula [12]. Additionally, IDAA1c underestimates PCR in younger children with new-onset TID who often have lower serum C-peptide levels; because it was optimized using a higher C-peptide cut-off value of 300 pmol/L, instead of the 200 pmol/L validated by the Diabetes Control and Complications
Subjects and methods

Ethics statement

This study protocol was approved by the Institutional Review Board of the University of Massachusetts. All subjects’ records were anonymized and de-identified prior to analysis.

Subjects

Study subjects were pediatric patients of ages 2–14 years with a confirmed diagnosis of T1D from January 1, 2006 through September 30, 2015 from the Children’s Medical Center Database of the UMass Memorial Medical Center, Worcester, MA, USA. As detailed in Nwosu and Maranda [21], the diagnosis of T1D was established using any of the following glycomic parameters: a fasting blood glucose of ≥7 mmol/L (126 mg/dL), and/or 2-h postprandial glucose of ≥11.1 mmol/L (200 mg/dL), and/or random blood glucose of ≥11.1 mmol/L (200 mg/dL) with symptoms of polyuria and/or polydipsia. In addition, all participants were positive for one or more diabetes-associated auto-antibodies, namely insulin autoantibodies, islet cell cytoplasmic autoantibodies, glutamic acid decarboxylase antibodies, and/or insulinoma-associated-2 (IA-2A) autoantibodies. Subjects with other forms of diabetes mellitus were excluded from the study.

Following the diagnosis of diabetes mellitus, all patients had blood drawn for routine diagnostic testing to confirm the diagnosis of T1D and to assess for acidosis. Patients that were not in diabetic ketoacidosis (DKA) were started on a standard basal-bolus insulin regimen, consisting of injections of once-daily long-acting insulin and pre-meal short-acting insulin. Patients in DKA were started on an insulin drip at 0.05 units/kg/h, which was titrated to maintain glycemia until the resolution of acidosis. All patients were discharged from the hospital on a basal-bolus insulin regimen.

Ongoing data collection for anthropometric, clinical (HbA1c, TDD of insulin), and biochemical parameters were conducted at baseline (at diagnosis), every 3 months for the first year, and every 3–6 months until 36 months. Missing data were accounted for in the statistical analysis using linear mixed models. DKA was defined by pH < 7.35, blood glucose >200 mg/dL, and serum bicarbonate <15 mg/dL [22]. PCR was defined by both a TDD of <0.3 units/kg/day, and by the gold-standard methodology, IDAA1c ≤ 9 [10, 12]. The formula for IDAA1c is HbA1c (%) + (4 X TDD of insulin [units/kg/24 h]).

Anthropometry

As described in detail previously [23, 24], weight was measured to the nearest 0.1 kg using an upright scale. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer that was calibrated daily. BMI was calculated from the formula: weight/height² (kg/m²), and expressed as standard deviation score (SDS) for age and sex, based on National Center for Health Statistics (NCHS) data [25]. Overweight was defined as BMI of ≥85th but <95th percentile, and obesity was defined as BMI of ≥95th percentile for age and gender.
Assays

Assays for laboratory chemistries have been previously described [23, 24]. Briefly, serum 25(OH)D concentration was analyzed using 25-hydroxy cholecalciferol immunoassay (DiaSorin Läisänen; Stillwater, MN, USA), which measures total serum 25(OH)D content by detecting both metabolites of 25(OH)D: 25(OH)D$_2$ and 25(OH)D$_3$. It has intra- and inter-assay coefficients of variation of 5% and 8.2%, respectively, and a functional sensitivity of 10 nmol/L. Hemoglobin A\textsubscript{1c} was measured by DCA 2000 + Analyzer (Bayer, Inc., Tarrytown, NY, USA) based on Diabetes Control and Complications Trial standards [26]. Serum bicarbonate was measured at the University of Massachusetts Medical School Clinical Laboratory by total carbon dioxide (CO$_2$) estimation using Beckman Coulter AU system CO$_2$ reagent according to the method of Forrester et al. [27]. Diabetes-associated autoantibodies were measured by Quest Diagnostics, Chantilly, VA, USA. GAD-65 assay was performed using enzyme-linked immunosorbent assay, and IA2A and IAA assays were performed using radio-binding assay.

Statistical analyses

Means and standard deviations (SD) were calculated for descriptive summary statistics and biochemical parameters. Linear mixed models were used to compare the means of continuous covariates between the remitters and non-remitters. Student’s t-test was used to make the comparison between the groups for non-anthropometric continuous variables namely, TDD of insulin, and HbA\textsubscript{1c} [13]; and Fisher exact test was used for categorical variables. These variables were compared using both definitions for PCR (IDAA\textsubscript{1c} criterion, but was similar from diagnosis through 36 months of disease in remitters; HbA\textsubscript{1c} was significantly lower in the remitters at 24 months by TDD <0.3 units/kg/day criterion, (0.2±0.8 vs. 0.3±1.1, p=0.797) or the IDAA\textsubscript{1c} criterion (0.2±1.0 vs. 0.3±1.0, p=0.348). Weight SDS was significantly lower in the remitters at 24 months by TDD <0.3 units/kg/day criterion (0.3±0.9 vs. 0.7±1.0, p=0.02) but was similar between remitters and non-remitters throughout the study by IDAA\textsubscript{1c} criterion (0.5±0.9 vs. 0.7±0.8, p=0.412).

BMI-SDS was significantly lower in remitters at 24 months (0.4±0.8 vs. 0.7±0.9, p=0.032) and 36 months (0.4±0.9 vs. 0.9±0.7, p=0.040) by TDD <0.3 units/kg/day criterion, but was similar from diagnosis through 36 months by IDAA\textsubscript{1c} criterion (0.6±0.9 vs. 0.6±0.9, p=0.593).

Results

Baseline analysis

Anthropometry

Two hundred and four children and adolescents, ages 2–14 years with a mean age of 7.9±3.2 years, (male 78.3±4.3 years, [n = 98]; female 79.3±3.0 [n = 106], p = 0.816) with new-onset T1D were analyzed. When PCR was defined by a TDD insulin <0.3 units/kg/day, there were 82 remitters (age 7.3±2.8 years, male 50%) and 123 non-remitters (age 8.2±3.4 years, male 53.7%). The prevalence of remission was 40.2%, with the peak period of remission occurring between 6 and 12 months (Table 1).

When PCR was defined by IDAA\textsubscript{1c} ≤9, there were 86 remitters (age 9.1±3.0 years, male 57%), and 118 non-remitters (age 7.0±3.1 years; male 40.7%). The prevalence of remission using IDAA\textsubscript{1c} was 42.2%, and the peak period of remission was between 6 and 12 months.

A sub-analysis of the two groups that focused on direct comparison of the remitters as designated by IDAA\textsubscript{1c} vs. TDD <0.3 units/kg/day showed that subjects in remission as defined by TDD insulin <0.3 units/kg/day were younger (p<0.001), and required a lower TDD of insulin at baseline (p=0.006), and at 6 months (p=0.02) (Table 1). Table 2 shows that hemoglobin A\textsubscript{1c} values were lower at 6, 9, and 24 months in subjects in whom PCR was defined by IDAA\textsubscript{1c} ≤9.

At baseline, remitters were significantly younger than non-remitters by the TDD <0.3 units/kg/day criterion, (7.3±2.8 vs. 8.2±3.4 years, p=0.038), but were significantly older than the non-remitters by the IDAA\textsubscript{1c} criterion (9.1±3.0 vs. 7.0±3.1 years, p<0.001). Height SDS was similar at baseline between the remitters and non-remitters by either the TDD <0.3 units/kg/day criterion, (0.2±0.8 vs. 0.3±1.1, p=0.797) or the IDAA\textsubscript{1c} criterion (0.2±1.0 vs. 0.3±1.0, p=0.348). Height SDS was significantly lower in the remitters at 24 months by TDD <0.3 units/kg/day criterion (0.3±0.9 vs. 0.7±1.0, p=0.02) but was similar between remitters and non-remitters throughout the study by IDAA\textsubscript{1c} criterion (0.5±0.9 vs. 0.7±0.8, p=0.412).

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Biochemical parameters

Serum bicarbonate (HCO$_3$) was significantly higher in remitters than in non-remitters using IDAA\textsubscript{1c} criterion; a trend that was also present, although non-significant, using TDD <0.3 units/kg/day. Using the HbA\textsubscript{1c}-defined IDAA\textsubscript{1c} to identify PCR, HbA\textsubscript{1c} was significantly lower in the first 3–18 months of disease in remitters; HbA\textsubscript{1c} was significantly lower only at 3 months of disease using the TDD <0.3 units/kg/day definition of PCR (Table 1, Figure 1). Serum 25(OH)D concentration was similar between the remitters and non-remitters by either criterion.

Time and duration of PCR

The mean duration of PCR was 10.0±6.1 months using TDD <0.3 units/kg/day, compared to 9.2±5.5 months...
Table 1: Comparison of the anthropometric and biochemical characteristics of (A) remitters and non-remitters, and (B) remitters only, by using both insulin dose-adjusted hemoglobin A$_1c$ of ≤9 and total daily dose of <0.3 units/kg/day to define partial clinical remission in patients with new-onset type 1 diabetes.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Remitters (n=86)</th>
<th>Non-remitters (n=118)</th>
<th>p-Value</th>
<th>Remitters (n=82)</th>
<th>Non-remitters (n=123)</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>9.1 ± 3.0</td>
<td>7.0 ± 3.1</td>
<td>&lt;0.001</td>
<td>7.3 ± 2.8</td>
<td>8.2 ± 3.4</td>
<td>0.038</td>
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<td>Age (categorized)</td>
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<td></td>
</tr>
<tr>
<td>0–4 years</td>
<td>9 (11%)</td>
<td>36 (31%)</td>
<td></td>
<td>21 (26%)</td>
<td>24 (20%)</td>
<td></td>
</tr>
<tr>
<td>5–10 years</td>
<td>38 (44%)</td>
<td>58 (49%)</td>
<td></td>
<td>42 (51%)</td>
<td>55 (46%)</td>
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<td>11–14 years</td>
<td>39 (45%)</td>
<td>24 (20%)</td>
<td></td>
<td>19 (23%)</td>
<td>44 (36%)</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td>0.02</td>
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<td></td>
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</tr>
<tr>
<td>Male</td>
<td>49 (57%)</td>
<td>48 (41%)</td>
<td></td>
<td>41 (50%)</td>
<td>57 (46%)</td>
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</tr>
<tr>
<td>Female</td>
<td>37 (43%)</td>
<td>70 (59%)</td>
<td></td>
<td>41 (50%)</td>
<td>66 (54%)</td>
<td>0.36</td>
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<tr>
<td>Height SDS$^*$</td>
<td>0.2 ± 0.1</td>
<td>0.3 ± 0.1</td>
<td>0.35</td>
<td>0.2 ± 0.8</td>
<td>0.3 ± 1.1</td>
<td>0.80</td>
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<tr>
<td>Weight SDS$^*$</td>
<td>0.5 ± 1.0</td>
<td>0.4 ± 0.9</td>
<td>0.59</td>
<td>0.6 ± 0.8</td>
<td>0.4 ± 1.0</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI-SDS$^*$</td>
<td>0.6 ± 1.0</td>
<td>0.5 ± 1.0</td>
<td>0.14</td>
<td>0.6 ± 0.9</td>
<td>0.4 ± 1.1</td>
<td>0.009</td>
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<tr>
<td>25-hydroxyvitamin D, nmol/L</td>
<td>67.5 ± 28.4</td>
<td>66.1 ± 19.4</td>
<td>0.72</td>
<td>69.1 ± 26.5</td>
<td>65.2 ± 21.4</td>
<td>0.32</td>
</tr>
<tr>
<td>HCO$_3$ at diagnosis, mmol/L</td>
<td>21.4 ± 5.9</td>
<td>18.3 ± 8.3</td>
<td>0.006</td>
<td>20.7 ± 6.9</td>
<td>18.8 ± 7.9</td>
<td>0.09</td>
</tr>
<tr>
<td>Duration of PCR, months</td>
<td>9.2 ± 5.5</td>
<td>0.1 ± 1.1</td>
<td>&lt;0.001</td>
<td>10.0 ± 6.1</td>
<td>0.0 ± 0.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDD at diagnosis, units/kg/day</td>
<td>0.5 ± 0.3</td>
<td>0.5 ± 0.2</td>
<td>0.33</td>
<td>0.4 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDD at 6 months</td>
<td>0.3 ± 0.2</td>
<td>0.5 ± 0.2</td>
<td>&lt;0.001</td>
<td>0.2 ± 0.2</td>
<td>0.6 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDD at 18 months</td>
<td>0.5 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>&lt;0.001</td>
<td>0.5 ± 0.2</td>
<td>0.7 ± 0.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDD at 24 months</td>
<td>0.5 ± 0.3</td>
<td>0.7 ± 0.3</td>
<td>&lt;0.001</td>
<td>0.6 ± 0.2</td>
<td>0.7 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>TDD at 36 months</td>
<td>0.7 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>0.17</td>
<td>0.7 ± 0.3</td>
<td>0.8 ± 0.3</td>
<td>0.44</td>
</tr>
</tbody>
</table>

IDAA$_{0.3}$, insulin-dose-adjusted hemoglobin A$_1c$; TDD, total daily dose; SDS, standard deviation score; BMI, body mass index; 25(OH)D, 25-hydroxyvitamin D; HCO$_3$, bicarbonate. *Comparison made by Linear mixed model adjusting for sex and age. For this study, partial clinical remission (PCR) was defined by both TDD of <0.3 units/kg/day; and also by IDAA$_{0.3}$, a two-dimensional definition that correlates insulin dose and measured HbA$_1c$ to residual β-cell function [10]. IDAA$_{0.3}$ has the best agreement with stimulated C-peptide definition of >300 pmol/L when compared to previous definitions [12]. The formula for IDAA$_{0.3}$ is: HbA$_1c$ (%) = [4 X insulin dose (units/kg/24 h)]. PCR was defined as IDAA$_{0.3}$ of ≤9 [20]. Significant p-values are bolded.

Table 2: Comparison of the hemoglobin A$_1c$ values of (A) remitters and non-remitters, and (B) remitters only, by using both insulin dose-adjusted hemoglobin A$_1c$ of ≤9 and total daily dose of <0.3 units/kg/day to define partial clinical remission in patients with new-onset type 1 diabetes.

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<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>HbA$_1c$ (%) at diagnosis</td>
<td>11.4 ± 2.4</td>
<td>11.5 ± 2.1</td>
<td>0.58</td>
<td>10.8 ± 2.2</td>
<td>11.9 ± 2.2</td>
<td>0.001</td>
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<td>HbA$_1c$ at 3 months</td>
<td>7.5 ± 1.0</td>
<td>8.6 ± 1.3</td>
<td>&lt;0.001</td>
<td>7.8 ± 1.3</td>
<td>8.3 ± 1.3</td>
<td>0.015</td>
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<tr>
<td>HbA$_1c$ at 6 months</td>
<td>7.3 ± 1.3</td>
<td>8.8 ± 1.3</td>
<td>&lt;0.001</td>
<td>7.9 ± 1.2</td>
<td>8.3 ± 1.7</td>
<td>0.06</td>
</tr>
<tr>
<td>HbA$_1c$ at 9 months</td>
<td>7.8 ± 1.0</td>
<td>8.7 ± 1.0</td>
<td>&lt;0.001</td>
<td>8.1 ± 0.9</td>
<td>8.4 ± 1.2</td>
<td>0.08</td>
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<td>HbA$_1c$ at 12 months</td>
<td>7.9 ± 1.1</td>
<td>8.7 ± 1.0</td>
<td>&lt;0.001</td>
<td>8.2 ± 1.0</td>
<td>8.5 ± 1.2</td>
<td>0.06</td>
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<tr>
<td>HbA$_1c$ at 15 months</td>
<td>8.1 ± 1.0</td>
<td>8.7 ± 0.9</td>
<td>&lt;0.001</td>
<td>8.3 ± 1.0</td>
<td>8.5 ± 1.0</td>
<td>0.18</td>
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<td>HbA$_1c$ at 18 months</td>
<td>8.2 ± 1.1</td>
<td>8.7 ± 1.2</td>
<td>0.008</td>
<td>8.5 ± 1.0</td>
<td>8.6 ± 1.3</td>
<td>0.73</td>
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<td>HbA$_1c$ at 21 months</td>
<td>8.4 ± 1.0</td>
<td>8.8 ± 1.1</td>
<td>0.09</td>
<td>8.5 ± 1.0</td>
<td>8.7 ± 1.2</td>
<td>0.31</td>
</tr>
<tr>
<td>HbA$_1c$ at 24 months</td>
<td>8.5 ± 1.1</td>
<td>8.8 ± 0.9</td>
<td>0.07</td>
<td>8.9 ± 1.1</td>
<td>8.6 ± 0.9</td>
<td>0.09</td>
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<tr>
<td>HbA$_1c$ at 27 months</td>
<td>8.5 ± 1.2</td>
<td>8.5 ± 1.4</td>
<td>0.82</td>
<td>8.6 ± 0.9</td>
<td>8.5 ± 1.5</td>
<td>0.79</td>
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<td>HbA$_1c$ at 30 months</td>
<td>8.5 ± 1.1</td>
<td>8.8 ± 1.0</td>
<td>0.13</td>
<td>8.5 ± 1.0</td>
<td>8.7 ± 1.1</td>
<td>0.39</td>
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<tr>
<td>HbA$_1c$ at 33 months</td>
<td>8.7 ± 1.4</td>
<td>8.6 ± 1.0</td>
<td>0.72</td>
<td>8.6 ± 1.0</td>
<td>8.7 ± 1.2</td>
<td>0.64</td>
</tr>
<tr>
<td>HbA$_1c$ at 36 months</td>
<td>8.4 ± 1.2</td>
<td>8.8 ± 1.0</td>
<td>0.09</td>
<td>8.6 ± 1.2</td>
<td>8.7 ± 1.0</td>
<td>0.68</td>
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</table>

IDAA$_{0.3}$, insulin-dose-adjusted hemoglobin A$_1c$; HbA$_{0.3}$, hemoglobin A$_1c$. Significant p-values are bolded.
using IDAA<sub>1c</sub> of ≤9 (p = 0.379). Peak prevalence for PCR occurred at 6–12 months and the proportion of patients in PCR at 6 months was 43/82 (52.4%) using TDD < 0.3 units/kg/day; and 62/86 (72.1%) using IDAA<sub>1c</sub> ≤ 9 (p = 0.011).

Logistic regression analysis, adjusted for baseline BMI-SDS, HbA1c, and serum bicarbonate, was performed to determine the likelihood of subjects entering PCR using either IDAA<sub>1c</sub> ≤ 9 and TDD < 0.3 units/kg/day to define PCR. HbA1c adjustment was necessary because the HbA<sub>1c</sub> level at diagnosis is a reflection of the pre-diagnostic glycemia and initial insulin therapy, which could affect the validity of the definitions for PCR [12].

The results showed that among the remitters, those diagnosed using TDD < 0.3 units/kg/day criterion were 1.44 times more likely to enter honeymoon in the first 4 months than those diagnosed with IDAA<sub>1c</sub> criterion, after adjusting for BMI-SDS, serum bicarbonate, and baseline HbA1c (OR = 1.44, 95% CI [1.03–2.00], p = 0.033) (Figure 2).

**Discussion**

This is the first study to compare the gold standard formula for the detection of PCR detection, IDAA<sub>1c</sub>, to TDD < 0.3 units/kg/day to determine the accuracy of TDD < 0.3 units/kg/day to correctly identify patients in PCR. The results of this study, in a US population, showed that a similar proportion of patients entered PCR using either IDAA<sub>1c</sub> or TDD < 0.3 units/kg/day: 42.2% vs. 40.2%, respectively. Our findings are consistent with earlier reports of the occurrence
of PCR in 40%–70% of children diagnosed with new-onset T1D [11, 28]. Both definitions identified the peak prevalence of patients in remission between 6 and 12 months, with a majority of patients in remission at 6 months. Kaplan-Meier survival analysis showed an earlier detection of PCR by TDD < 0.3 units/kg/day, and a slightly increased probability of early remission by this definition compared to IDAA1c. However, there was a significantly higher proportion of patients in remission at 6 months by IDAA1c criterion compared to TDD < 0.3 units/kg/day. These findings are consistent with previous reports showing that the use of TDD alone as a definition of PCR identifies patients in remission sooner than IDAA1c, possibly due to the practice of starting patients on a relatively lower TDD of insulin at diagnosis [3, 12].

The report that > 50% of children and adolescents with new-onset T1D do not experience PCR [1–4], and that these non-remitters have increased risk for both the short- and long-term diabetes complications [5–8] is of major concern. The recent report of a long-term study which found a significantly reduced risk for chronic microvascular complications at 7-year follow-up in patients who entered PCR [9] suggests that the primary mechanism for the endothelial dysfunction and vascular disease in non-remitters may be related to persistent hyperglycemia in the early phase of T1D. This is supported by recent findings suggesting that the underlying mechanism for the vascular damage in T1D is oxidative stress induced by several hyperglycemia-activated pathways such as the activated polyl and hexosamine pathways, activation of protein kinase C, increased production of advanced glycation end-products, and excessive production of growth factors, angiotensin II, and cytokines [29]. Both acute and chronic hyperglycemia work in concert to produce these complications as chronic hyperglycemia is reported to promote the onset and progression of microvascular complications [30], while acute hyperglycemia accelerates the progression of these complications [29]. This hyperglycemic effect is partly explained by the ‘hyperglycemic memory’ phenomenon, which proposes that prompt correction of dysglycemia in the early phase of T1D decreases the risk of its long-term complications [9]. Taken together, remitters have an overall prognostic advantage over non-remitters. Therefore, the introduction of a simpler definition for PCR such as TTD < 0.3 units/kg/day will enable early identification of non-remitters and the institution of targeted therapeutic regimens to prevent early dysglycemia in children and adolescents with T1D.

The limitations of this study include the fact that this was a retrospective cross-sectional study and thus no causality should be inferred from the relationships between the parameters studied. The lack of data on serum C-peptide limited our ability to test the reliability of the definition of PCR based on either IDAA1c, or TDD in this population. This study did not compare a combination of TDD of < 0.3 units/kg/day plus HbA1c of < 75% to IDAA1c because the aim of the study was to develop a simple, straightforward formula for an accurate detection of PCR. Equally, prior studies had shown that the combination of TDD < 0.5 units/kg/day with HbA1c < 75% lacked sensitivity. However, a cross-sectional analysis of our dataset at 6 months after the diagnosis of T1D showed that when PCR was defined by a combination of TDD < 0.3 units/kg/day and HbA1c < 75%, only 14.6% of subjects were in remission, and 41.7% of the patients were classified as false negatives. This underestimation of PCR by a combination of TDD < 0.3 units/kg/day and HbA1c < 75% is similar to previously described underestimation of PCR by a combination of TDD of < 0.5 units/kg/day and HbA1c < 75% [12]. The high false-negative rates result from the exclusion of individuals who enter PCR as defined by IDAA1c and TDD < 0.3 units/kg/day but still have elevated HbA1c levels, especially in the early phase of the disease when HbA1c is still dropping from the elevated values at diagnosis. The detection and monitoring accuracy of TDD < 0.3 units/kg/day could be improved by combining it with an automatic, blood glucose-driven insulin dose adjustment algorithm that removes provider bias while ensuring early normalization of HbA1c value. Strengths of this study include the use of a representative sample size, and extending data collection for up to 36 months. There was an adequate representation of age groups, sex, race, and current BMI status in this US cohort to allow for meaningful comparison between the remitters and non-remitters using either definition under study.

**Conclusions**

This study found no significant differences in the number of remitters, duration of PCR, or the time of peak remission detected by either IDAA1c of < 0.3 or TDD of < 0.3 units/kg/day. TDD of < 0.3 units/kg/day detected PCR earlier than IDAA1c, while IDAA1c detected a higher proportion of remitters at 6 months. Thus, TDD of < 0.3 units/kg/day was not inferior to IDAA1c for the detection of PCR and may be a simpler, user-friendly tool for routine clinical practice, while the IDAA1c will continue to be used for research purposes.

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