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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

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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 A_{1c} of ≤9 for the detection of partial clinical remission

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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 A_{1c} ($IDAA_{1c}$) 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 $IDAA_{1c}$ 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 7.8 ± 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 $IDAA_{1c}$ ≤ 9 and TDD < 0.3 units/kg/day.

Results: There were 86 (42.2%) (age 9.1 ± 3.0 years; male 57%) remitters by $IDAA_{1c}$ ≤ 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 $IDAA_{1c}$ (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 $IDAA_{1c}$ of ≤9, after adjusting for BMI, bicarbonate, and HbA_{1c}:(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 $IDAA_{1c}$ ≤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 $IDAA_{1c}$ of ≤9 or TDD of <0.3 units/kg/day.

Keywords: bicarbonate; children and adolescents; hemoglobin A_{1c}; honeymoon period; insulin; type 1 diabetes.

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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 $IDAA_{1c}$, which integrates HbA_{1c} 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, $IDAA_{1c}$ has been criticized for its various shortcomings; for example, age, a major determinant of PCR, is not included in its formula [12]. Additionally, $IDAA_{1c}$ underestimates PCR in younger children with new-onset T1D 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

Trial [12, 13]. $IDAA_{1c}$ also underestimates the prevalence of PCR in older girls who are more insulin resistant, since $IDAA_{1c}$ cannot discriminate between insulin sensitivity and insulin secretion [13]. Cengiz et al. [13] recently reported that $IDAA_{1c}$ was not a sensitive measure of the risk for severe hypoglycemia in patients with newly diagnosed T1D. $IDAA_{1c}$ was derived from a cohort of European and Japanese subjects, who may have different diabetes characteristics from the general US population [13]. Finally, although the components are readily accessible, calculating the $IDAA_{1c}$ may represent a barrier to time-strapped clinicians, a factor that prevents widespread use. In a recent multi-center study, Nagl et al. [11] called for additional research to clarify the usefulness and performance of $IDAA_{1c}$ in clinical practice, with an emphasis on determining age- and sex-specific $IDAA_{1c}$ limits for the definition of PCR based on the serial determination of serum C-peptide concentration.

$IDAA_{1c}$ has been extensively compared to previous definitions of PCR [1, 3, 12, 14–19], such as $HbA_{1c} \leq 7.5\%$, TDD of insulin ≤0.5 units/kg/day [14], or a combination of $HbA_{1c} \leq 7.5\%$ and TDD ≤ 0.5 units/kg/day [19]. $IDAA_{1c}$ was found to be less sensitive than TDD < 0.5 units/kg/day for the early detection of PCR following the diagnosis of T1D, but was more specific for PCR between 6 and 12 months [12]. These comparisons further showed that $IDAA_{1c}$ has a stronger correlation with stimulated C-peptide concentration than previous definitions [12]; and that the use of either TDD of ≤0.5 units/kg/day, or HbA_{1c} of <7.5% could overestimate the prevalence of PCR; while the use of a combination of TDD of ≤0.5 units/kg/day and HbA_{1c} of <7.5% could underestimate PCR [12].

However, $IDAA_{1c}$ has not been compared to TDD of insulin <0.3 units/kg/day, which is another sensitive tool for the detection of PCR [20]. It has been hypothesized that TDD of <0.3 units/kg/day may fall in an intermediate position between TDD of ≤0.5 units/kg/day [14] and the combination of HbA_{1c} of <7.5% and TDD of ≤0.5 units/kg/day [19]. Furthermore, the calculation of TDD is already being performed by endocrinologists during routine clinic visits. Therefore, in a busy outpatient clinic, TDD of <0.3 units/kg/day may serve as a more practical tool for early detection and monitoring of PCR in children and adolescents with new-onset T1D than the $IDAA_{1c}$.

We designed this study to investigate whether $IDAA_{1c}$ of ≤9 is superior to TDD < 0.3 units/kg/day in detecting PCR in children and adolescents with new-onset T1D. We hypothesized that there would be no significant difference in the number of remitters identified by either definition, suggesting TDD < 0.3 may be an adequate test for PCR for clinical use.

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 glycemic 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 (HbA_{1c}, 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 ng/mL [22]. PCR was defined by both a TDD of <0.3 units/kg/day, and by the gold-standard methodology, $IDAA_{1c} \leq 9$ [10, 12]. The formula for $IDAA_{1c}$ is HbA_{1c} (%) +(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/height^2 (kg/m^2), 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 chemiluminescent immunoassay (DiaSorin Liaison; 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_{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 IA-2A 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_{1c} [13]; and Fisher exact test was used for categorical variables. These variables were compared using both definitions for PCR ($IDAA_{1c}$ of ≤9 and TDD < 0.3 units/kg/day). Cox's proportional hazard models were used to investigate the adjusted associations between the duration of remission and covariates of interest. The duration of PCR was calculated as the interval between the first and last documented time points with $IDAA_{1c}$ value of ≤9. The analysis was performed using SPSS Predictive Analytics Software v.23 (IBM Corporation, Armonk, NY, USA).

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 7.8 ± 3.4 years, [n = 98]; female 7.9 ± 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 $IDDA_{1c}$ ≤ 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 $IDAA_{1c}$ 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 $IDAA_{1c}$ 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_{1c} values were lower at 6, 9, and 24 months in subjects in whom PCR was defined by $IDDA_{1c}$ ≤ 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 $IDAA_{1c}$ 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 $IDAA_{1c}$ 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 $IDAA_{1c}$ 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 $IDAA_{1c}$ criterion (0.6 ± 0.9 vs. 0.6 ± 0.9, p = 0.593).

Biochemical parameters

Serum bicarbonate (HCO_3) was significantly higher in remitters than in non-remitters using $IDAA_{1c}$ criterion; a trend that was also present, although non-significant, using TDD < 0.3 units/kg/day. Using the HbA_{1c}-defined $IDAA_{1c}$ to identify PCR, HbA_{1c} was significantly lower in the first 3–18 months of disease in remitters; HbA_{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.

Definition of PCR	$IDAA_{1c}$ ≤ 9			TDD < 0.3 units/kg/day			p-Value comparing remitters only
Parameter	Remitters (n = 86)	Non-remitters (n = 118)	p-Value	Remitters (n = 82)	Non-remitters (n = 123)	p-Value	
Age, years	9.1 ± 3.0	7.0 ± 3.1	**<0.001**	7.3 ± 2.8	8.2 ± 3.4	**0.038**	**<0.001**
Age (categorized)			**<0.001**			**0.15**	**0.002**
0–4 years	9 (11%)	36 (31%)		21 (26%)	24 (20%)		
5–10 years	38 (44%)	58 (49%)		42 (51%)	55 (44%)		
11–14 years	39 (45%)	24 (20%)		19 (23%)	44 (36%)		
Sex							
Male	49 (57%)	48 (41%)	**0.02**	41 (50%)	57 (46%)	0.61	0.36
Female	37 (43%)	70 (59%)		41 (50%)	66 (54%)		
Height SDS[a]	0.2 ± 1.0	0.3 ± 1.0	0.35	0.2 ± 0.8	0.3 ± 1.1	0.80	0.89
Weight SDS[a]	0.5 ± 1.0	0.4 ± 0.9	0.59	0.6 ± 0.8	0.4 ± 1.0	**0.04**	0.88
BMI-SDS[a]	0.6 ± 1.0	0.5 ± 1.0	0.14	0.6 ± 0.9	0.4 ± 1.1	**0.009**	0.52
25-hydroxyvitamin D, nmol/L	67.5 ± 28.4	66.1 ± 19.4	0.72	69.1 ± 26.5	65.2 ± 21.4	0.32	0.75
HCO_3 at diagnosis, mmol/L	21.4 ± 5.9	18.3 ± 8.3	**0.006**	20.7 ± 6.9	18.8 ± 7.9	0.09	0.58
Duration of PCR, months	9.2 ± 5.5	0.1 ± 1.1	**<0.001**	10.0 ± 6.1	0.0 ± 0.0	**<0.001**	0.379
TDD at diagnosis, units/kg/day	0.5 ± 0.3	0.5 ± 0.2	0.33	0.4 ± 0.2	0.6 ± 0.2	**<0.001**	**0.006**
TDD at 6 months	0.3 ± 0.2	0.5 ± 0.2	**<0.001**	0.2 ± 0.2	0.6 ± 0.2	**<0.001**	**0.02**
TDD at 18 months	0.5 ± 0.2	0.7 ± 0.2	**<0.001**	0.5 ± 0.2	0.7 ± 0.2	**<0.001**	0.10
TDD at 24 months	0.5 ± 0.3	0.7 ± 0.3	**<0.001**	0.6 ± 0.2	0.7 ± 0.3	**<0.001**	0.71
TDD at 36 months	0.7 ± 0.3	0.8 ± 0.3	0.17	0.7 ± 0.3	0.8 ± 0.3	0.44	0.68

$IDAA_{1c}$, 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. [a]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 $IDAA_{1c}$, a two-dimensional definition that correlates insulin dose and measured HbA_{1c} to residual β-cell function [10]. $IDAA_{1c}$ has the best agreement with stimulated C-peptide definition of >300 pmol/L when compared to previous definitions [12]. The formula for $IDAA_{1c}$ is: HbA_{1c} (%) + [4 X insulin dose (units/kg/24 h)]. PCR was defined as $IDAA_{1c}$ of ≤9 [10]. 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.

Definition of PCR	$IDAA_{1c}$ ≤ 9			TDD < 0.3 units/kg/day			p-Value comparing remitters only
Parameter	Remitters (n = 86)	Non-remitters (n = 118)	p-Value	Remitters (n = 82)	Non-remitters (n = 123)	p-Value	
HbA_{1c} (%) at diagnosis	11.4 ± 2.4	11.5 ± 2.1	0.58	10.8 ± 2.2	11.9 ± 2.2	**0.001**	0.09
HbA_{1c} at 3 months	7.5 ± 1.0	8.6 ± 1.3	**<0.001**	7.8 ± 1.3	8.3 ± 1.3	**0.015**	0.10
HbA_{1c} at 6 months	7.3 ± 1.3	8.8 ± 1.3	**<0.001**	7.9 ± 1.2	8.3 ± 1.7	0.06	**0.002**
HbA_{1c} at 9 months	7.8 ± 1.0	8.7 ± 1.0	**<0.001**	8.1 ± 0.9	8.4 ± 1.2	0.08	**0.04**
HbA_{1c} at 12 months	7.9 ± 1.1	8.7 ± 1.0	**<0.001**	8.2 ± 1.0	8.5 ± 1.2	0.06	0.07
HbA_{1c} at 15 months	8.1 ± 1.0	8.7 ± 0.9	**<0.001**	8.3 ± 1.0	8.5 ± 1.0	0.18	0.20
HbA_{1c} at 18 months	8.2 ± 1.1	8.7 ± 1.2	**0.008**	8.5 ± 1.0	8.6 ± 1.3	0.71	0.07
HbA_{1c} at 21 months	8.4 ± 1.0	8.8 ± 1.1	0.09	8.5 ± 1.0	8.7 ± 1.2	0.31	0.52
HbA_{1c} at 24 months	8.5 ± 1.1	8.8 ± 0.9	0.07	8.9 ± 1.1	8.6 ± 0.9	0.09	**0.02**
HbA_{1c} at 27 months	8.5 ± 1.2	8.5 ± 1.4	0.82	8.6 ± 0.9	8.5 ± 1.5	0.79	0.54
HbA_{1c} at 30 months	8.5 ± 1.1	8.8 ± 1.0	0.13	8.5 ± 1.0	8.7 ± 1.1	0.39	1.00
HbA_{1c} at 33 months	8.7 ± 1.4	8.6 ± 1.0	0.72	8.6 ± 1.0	8.7 ± 1.2	0.64	0.59
HbA_{1c} at 36 months	8.4 ± 1.2	8.8 ± 1.0	0.09	8.6 ± 1.2	8.7 ± 1.0	0.68	0.25

$IDAA_{1c}$, insulin-dose adjusted hemoglobin A_{1c}; HbA_{1c}, hemoglobin A_{1c}. Significant p-values are bolded.

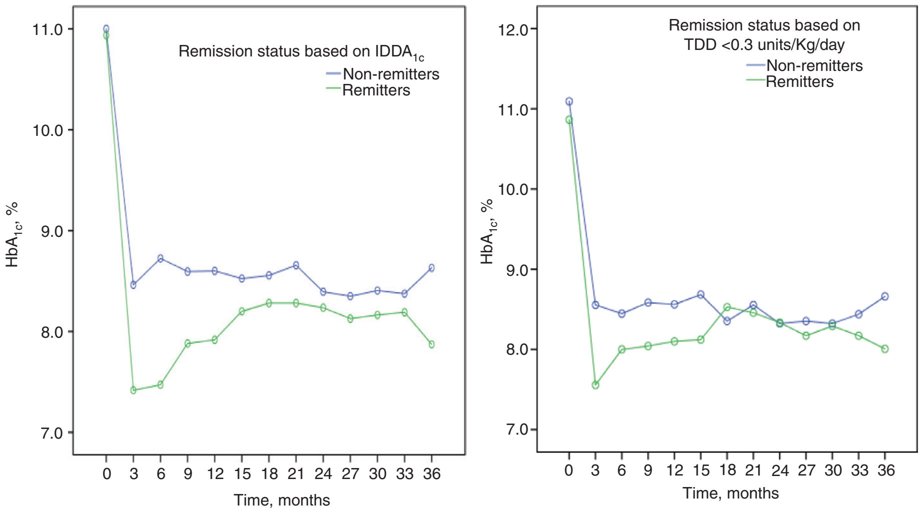

Figure 1: Graphical representation of the patterns of hemoglobin A$_{1c}$ (HbA$_{1c}$) trends in remitters and non-remitters in the first 36 months following the diagnosis of type 1 diabetes using either IDAA$_{1c}$ of ≤9 [10] (left panel) or TDD of <0.3 units/kg/day (right panel) to define PCR. Using TDD of <0.3 units/kg/day to define PCR, mean HbA$_{1c}$ level was significantly was lower in the remitters at diagnosis (10.8 ± 2.2 vs. 11.9 ± 2.2, p = 0.001), and at 3 months (7.8 ± 1.3 vs. 8.3 ± 1.3, p = 0.015), compared to the non-remitters, but remained non-significantly lower until the 15th month after diagnosis, when the mean HbA$_{1c}$ values became similar between the groups. Using the IDAA$_{1c}$ of ≤9 criterion, mean HbA$_{1c}$ was similar at diagnosis between the remitters and non-remitters (11.4 ± 2.4 vs. 11.5 ± 2.1%, p = 0.584), then became significantly lower in the remitters from 3 months (7.5 ± 1.0 vs. 8.6 ± 1.3%, p < 0.001), through 18 months (8.2 ± 1.1 vs. 8.7 ± 1.2%, p = 0.008), and was non-significantly lower in the remitters thereafter.

using IDAA$_{1c}$ 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$_{1c}$ ≤ 9 (p = 0.011).

Logistic regression analysis, adjusted for baseline BMI-SDS, HbA$_{1c}$, and serum bicarbonate, was performed to determine the likelihood of subjects entering PCR using either IDAA$_{1c}$ ≤ 9 and TDD < 0.3 units/kg/day to define PCR. HbA$_{1c}$ adjustment was necessary because the HbA$_{1c}$ 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$_{1c}$ criterion, after adjusting for BMI-SDS, serum bicarbonate, and baseline HbA$_{1c}$:(OR = 1.44, 95% CI [1.03–2.00], p = 0.033) (Figure 2).

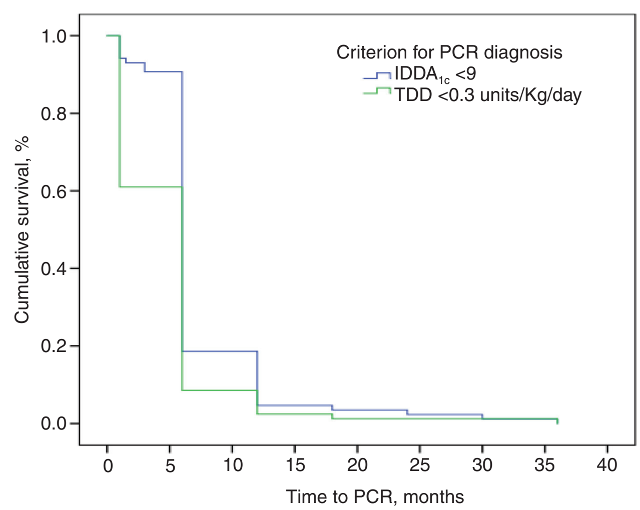

Figure 2: Kaplan-Meier survival curve showing the time to entering partial clinical remission (PCR) over time.
Only remitters are shown; the graph depicts the decay in survival without remission over time, comparing the two remission definitions. Remitters diagnosed using the TDD < 0.3 units/kg/day criterion were 1.44 times more likely to enter honeymoon in the first 4 months of disease than those diagnosed with IDAA$_{1c}$ criterion, after adjusting for confounders (OR = 1.44, 95% CI [1.03–2.00], p = 0.033).

Discussion

This is the first study to compare the gold standard formula for the detection of PCR detection, IDAA$_{1c}$, 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$_{1c}$ 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 $IDAA_{1c}$. However, there was a significantly higher proportion of patients in remission at 6 months by $IDAA_{1c}$ 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 $IDAA_{1c}$, 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 polyol 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 $IDAA_{1c}$ or TDD in this population. This study did not compare a combination of TDD of <0.3 units/kg/day plus HbA_{1c} of <7.5% to $IDAA_{1c}$ 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 HbA_{1c} < 7.5% 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 HbA_{1c} of <7.5%, 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 HbA_{1c} of <7.5% is similar to previously described underestimation of PCR by a combination of TDD of ≤0.5 units/kg/day and HbA_{1c} of <7.5% [12]. The high false-negative rates result from the exclusion of individuals who enter PCR as defined by $IDAA_{1c}$ and TDD < 0.3 units/kg/day but still have elevated HbA_{1c} levels, especially in the early phase of the disease when HbA_{1c} 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 HbA_{1c} 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 $IDAA_{1c}$ of ≤9 or TDD of <0.3 units/kg/day. TDD of <0.3 units/kg/day detected PCR earlier than $IDAA_{1c}$, while $IDAA_{1c}$ detected a higher proportion of remitters at 6 months. Thus, TDD of <0.3 units/kg/day was not inferior to $IDAA_{1c}$ for the detection of PCR and may be a simpler, user-friendly tool for routine clinical practice, while the $IDAA_{1c}$ will continue to be used for research purposes.

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