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Continuous glucose monitoring reduces pubertal hyperglycemia of type 1 diabetes

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Abstract

Background: Physiologic hyperglycemia of puberty is a major contributor to poor glycemic control in youth with type 1 diabetes (T1D). This study's aim was to determine the effectiveness of continuous glucose monitoring (CGM) to improve glycemic control in pubertal youth with T1D compared to a non-CGM cohort after controlling for age, sex, BMI, duration, and insulin delivery methodology. The hypothesis is that consistent CGM use in puberty improves compliance with diabetes management, leading to increased percentage (%) time in range (TIR^{70–180 mg/dL}) of glycemia, and lowering of HbA1c.

Methods: A longitudinal, retrospective, case-controlled study of 105 subjects consisting of 51 T1D controls (60.8% male) age 11.5 ± 3.8 y; and 54 T1D subjects (48.1% male) age 11.1 ± 5.0 y with confirmed CGM use for 12 months. Pubertal status was determined by Tanner staging. Results were adjusted for baseline HbA1c and diabetes duration.

Results: HbA1c was similar between the controls and the CGM group at baseline: $8.2 \pm 1.1\%$ vs $8.3 \pm 1.2\%$, $p=0.48$ respectively; but was significantly lower in the CGM group

12 months later, $8.2 \pm 1.1\%$ vs. $8.7 \pm 1.4\%$, $p=0.035$. Longitudinal change in HbA1c was similar in the prepubertal cohort between the control- and CGM groups: $-0.17 \pm 0.98\%$ vs. $0.38 \pm 1.5\%$, $p=0.17$. In contrast, HbA1c increased with advancing age and pubertal status in the pubertal controls but not in the pubertal CGM group: 0.55 ± 1.4 vs $-0.22 \pm 1.1\%$, $p=0.020$. Percent TIR was inversely related to HbA1c in the CGM group, $r=-0.6$, $p=0.0004$, for both prepubertal and pubertal subjects.

Conclusions: CGM use significantly improved glycemic control in pubertal youth with T1D compared to non-CGM users.

Keywords: children; continuous glucose monitoring; hemoglobin A1c; puberty; type 1 diabetes.

Introduction

The goal of attaining persistent euglycemia in children and adolescents with type 1 diabetes (T1D) remains elusive [1, 2]. Current estimates indicate that <21% of youth with T1D meet the American Diabetes Association (ADA) goal of hemoglobin A1c (HbA1c) concentration of 7.5% for children [1, 3]. Puberty is marked by a state of physiologic insulin resistance (IR) [4, 5], which in non-diabetic children represents a normal physiologic regulator of the pubertal growth spurt that is achieved via glucose-specific effects of IR and hyperinsulinemia that result in an adaptive, growth promoting, anabolic effect during puberty [4, 6]. In contrast, in youth with T1D, this evolutionary adaptive response becomes exaggerated and maladaptive, resulting in uncontrolled hyperglycemia [4–8]. This phenomenon, called physiologic hyperglycemia of puberty (PHOP), is a major contributor to persistent poor glycemic control in youth with T1D [4–10], and has been reported in landmarks studies such as the Diabetes Control and Complications Trial (DCCT) [11] and the T1D Exchange studies [1–13]. The pathophysiology of PHOP was investigated by Amiel et al., using a euglycemic insulin-clamp study [9]. The investigators reported a 30% decrease in glucose response to insulin in pubertal youth with T1D compared to their

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prepubertal peers. This study [9] also found that the insulin response in these children was inversely correlated with mean growth hormone (GH) concentration; suggesting that the physiologically increased secretion of GH during puberty induces an anti-insulin effect leading to impaired insulin-stimulated glucose metabolism, and consequent poor glycemic control and hyperglycemia in youth with T1D. Along with PHOP, psychosocial stressors and noncompliance with diabetes care also contribute to deterioration in metabolic control [4].

Recent improvements in continuous glucose monitors (CGM) technology has led to the increased adoption of newer-generation CGM by children and adolescents with T1D [1, 14], such that mixed population studies in children and adults report improved glycemic outcomes in a combined group of children and adults of 14–75 years using hybrid closed-loop therapy [15, 16], as well as in subjects using CGM only [17]. However, the effect of CGM use on the persistent hyperglycemia of puberty is not fully studied [18].

To address this knowledge gap, we designed this 12-month case-control study to determine the effect of CGM use during puberty in youth with T1D compared to controls. The study's aim was to determine the effectiveness of CGM to improve glycemic control in pubertal youth with T1D compared to a non-CGM cohort after controlling for age, sex, BMI, duration of diabetes, and the use of insulin pump. The hypothesis is that consistent CGM use in puberty will improve patients' compliance with diabetes management, leading to increased percentage (%) time in range ($TIR^{70-180 \text{ mg/dL}}$) of glycemia, and a lowering of HbA1c.

Methods

Ethics Statement

The Institutional Review Board of the University of Massachusetts Medical School approved the study protocol and the waiver of authorization to review subjects' retrospective records under Docket # H00015061. Subjects' data were de-identified and anonymized prior to analysis in compliance with the World Medical Association Declaration of Helsinki.

Subjects

The patient population for this retrospective, case-control study consisted of 105 pediatric patients from the Children's Medical Center Database of the UMassMemorial

Medical Center, Worcester, Massachusetts, USA (Table 1). Patients in the CGM group had a diagnosis of T1D by the American Diabetes Association (ADA) criteria [19], and had evidence of consistent use of CGM for >80% of the time for at least one year. Consistent CGM use was confirmed by review of serial CGM cloud-based Dexcom Clarity[®] downloads in the Diabetes Mellitus Database of the electronic medical record system. Serial HbA1c data for the CGM group were obtained from the time of initiation of CGM and every 3 months for 12 months; while similarly timed HbA1c data for the T1D controls were obtained in patients naïve to CGM who have had T1D for > 1 year.

The pediatric endocrinology clinic treats approximately 500 patients with T1D, of whom about 40% (200) use the CGM either as a stand-alone device or in combination with an insulin pump. Of these, about 90 subjects are on stand-alone Dexcom G5 device. All study subjects were <21 years, of Tanner stages I–V, and had HbA1c data spanning a period of >12 months following the introduction of Dexcom G5 stand-alone CGM. 15 subjects with T1D were excluded from the analysis due to lack of data on HbA1c and Tanner staging; and eight subjects were excluded due to insufficient CGM usage as shown in the study inclusion Flow Chart (Appendix 1). To exclude the confounding effect of variations in Tanner staging by different providers, we based the Tanner staging for this retrospective study on the age of the subjects: with prepubertal status, Tanner I, designated at <10 years; and pubertal status, Tanner II–V, as ≥10 years according to a recent population-based study on the timing of puberty [20]. In the sub-analysis, subjects of ages 10–12 year were designated as Tanner II, ages 13–14 years as Tanner III; ages 15–16 years as Tanner IV, and >17 years as Tanner V for this age-based Tanner staging.

The standard procedure for starting a patient on a CGM device at our institution is to conduct a CGM trial for one week after a patient expresses interest in using a CGM device at any point in the course of the disease. This allows the patient to familiarize himself/herself with the device. If the patient decides to adopt the CGM, then a request is sent to his/her insurance company for an approval to use the device. Most commercial insurance plans would waive the need for a CGM trial.

The controls consisted of age- and sex-matched children and adolescents who have had T1D for >12 months, were naïve to CGM, and had serial HbA1c data for 12 months from the point of their inclusion in the study. The criteria for the diagnosis of T1D has been previously described in detail [21–23] and was based on glycemic and diabetes-associated antibody profiles as recommended by the ADA [19]. Individuals diagnosed with other forms of

Table 1: Anthropometric and Biochemical Characteristics of Subjects and Controls.

Parameters	CGM Users (n=54)	Controls (n=51)	p value
Age (years) at baseline	11.07 ± 5.03	11.54 ± 3.81	0.60
Sex			
Male: n (%)	26 (48.1%)	31 (60.8%)	0.19
Female: n (%)	28 (51.9%)	20 (39.2%)	
Race			
White: n (%)	50 (92.6%)	44 (86.3%)	0.29
Non-white: n (%)	4 (7.4%)	7 (13.7%)	
Pubertal Status at baseline			
Tanner I: n (%)	24 (44.4%)	16 (31.4%)	0.17
Tanner II-V: n (%)	30 (55.6%)	35 (68.6%)	
BMI Status in percentile at baseline			
Normal-weight (<85th) n (%)	38 (70.4%)	23 (45.1%)	0.01
Overweight/obese (≥85th) n (%)	16 (29.6%)	28 (54.9%)	
Height z-score at baseline	0.16 ± 0.89	-0.95 ± 0.98	0.16
Weight z-score at baseline	0.54 ± 1.11	0.37 ± 1.15	0.45
Body mass index (BMI) z-score	0.58 ± 1.0	0.78 ± 1.05	0.30
Systolic Blood Pressure (mm Hg)	107.0 ± 9.85	108 ± 11.6	0.66
Diastolic Blood Pressure (mm Hg)	69.4 ± 7.35	68.9 ± 7.54	0.73
Hemoglobin A1c (%) at 0 month	8.36 ± 1.11	8.17 ± 1.43	0.37
Hemoglobin A1c (%) at +12 months	8.16 ± 1.07	8.70 ± 1.43	0.033
Δ Hemoglobin A1c (%)	-0.20 ± 1.02	0.49 ± 1.43	0.006
Insulin pump users: n (%)	24 (49.0%)	26 (51%)	0.84
Multiple daily injections: n (%)	25 (51.0%)	25 (49%)	
Duration (years)	3.9 ± 3.6	2.35 ± 2.53	0.012
Range of duration (years)	0.2–16.2	1.0–10.5	
Total Daily Dose at 0 month (unit/kg/day)	0.72 ± 0.28	0.64 ± 0.30	0.017
Total Daily Dose at +12 months (unit/kg/day)	0.79 ± 0.24	0.77 ± 0.27	0.71

CGM: continuous glucose monitor

diabetes mellitus such as type 2 diabetes or cystic fibrosis related diabetes were excluded from the study.

Anthropometry

The methodology for anthropometry has been previously described in detail [22–25]. Briefly, height and weight were measured in the clinic by standard techniques, and Body mass index (BMI) was calculated from the formula: weight/height² (kg/m²). Height, weight, and BMI were expressed as z-scores for age and sex, based on National Center for Health Statistics data [26, 27]. Overweight was defined as BMI of ≥85th but <95th percentile, and obesity was defined as BMI of ≥95th percentile for age and gender. Sexual maturity rating was determined by Tanner staging, with Tanner I considered prepubertal status, and Tanner II-V denoting pubertal status.

Statistical Analyses

The continuous descriptive summary statistics and biochemical parameters were expressed as means and

standard deviations (SD). Two-sided Student's *t*-test was used to compare the two groups (Table 1). Proportions were calculated for the presence of overweight or obesity (BMI >85th percentile). Comparisons of binary variables (sex, race, and Tanner stage) between the two groups were performed using Pearson's chi-squared test. The p values for categorical variables were derived from chi-square statistics, while the p values for continuous variables were derived from ANOVA statistics. Non-parametric data were analyzed using Wilcoxon rank test. The relationship between percentage time in range (TIR^{70–180} mg/dL) and HbA1c was explored by Pearson product-moment correlation analysis. Analysis for outliers were performed by standard techniques and no outliers were removed from the analyses. All statistical analyses were performed using SAS 9.4 software (SAS Institute Inc, Cary, NC).

Results

This study analyzed the data of 105 subjects with T1D consisting of 54 subjects who used CGM for 12 months, and 51 T1D controls who were naïve to CGM. Table 1 shows the

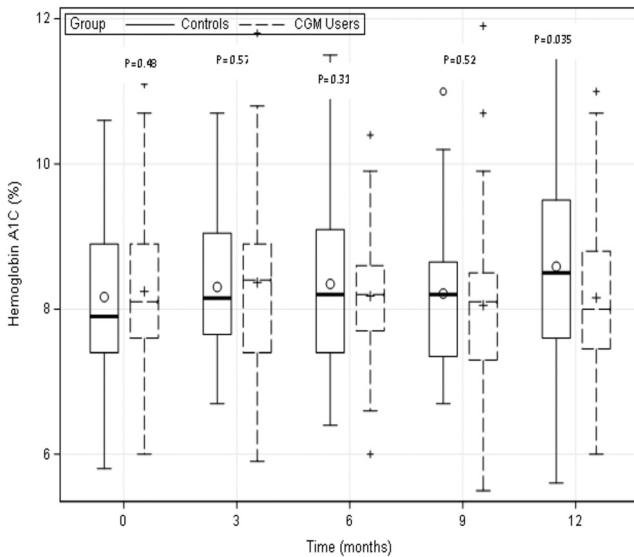


Figure 1: Box plots of the changes in mean hemoglobin A1c concentrations between the controls and the continuous glucose monitoring group during the 12 months of the study. Baseline HbA1c concentrations were not different between the groups but HbA1c was significantly lower in the CGM group at 12 months. The line in each box represents the median, while the ‘o’ and ‘+’ symbols represent the mean for the controls and CGM respectively.

baseline characteristics of the subjects and controls. The controls had better glycemic control at baseline, and a shorter duration of diabetes compared to the CGM group. There were no differences in age, sex, BMI, and methodology of insulin delivery, i.e., multiple daily injections (MDI) or insulin pump.

Figure 1 depicts a 12-month comparative analysis of mean HbA1c values between the CGM and control groups: Baseline HbA1c concentrations were not different between the controls and the CGM group: $8.2 \pm 1.1\%$ vs $8.3 \pm 1.2\%$, $p=0.48$ respectively; but HbA1c was significantly lower in the CGM group 12 months later, $8.2 \pm 1.1\%$ vs. $8.7 \pm 1.4\%$, $p=0.035$.

Further investigation explored whether the significant reduction in HbA1c in CGM users could be explained by the methodology of insulin administration, i. e., either by MDI or continuous subcutaneous insulin infusion (CSII). The results showed no significant difference in baseline-adjusted changes in HbA1c among the CGM users who administered their insulin by MDI or continuous subcutaneous insulin infusion.

Figure 2 shows the effect of age and pubertal status on serial HbA1c values in both the CGM users and controls. Among the prepubertal cohort, there was no significant difference in the changes in HbA1c between the CGM group and controls: $-0.17 \pm 0.98\%$ vs. $0.38 \pm 1.5\%$, $p=0.17$.

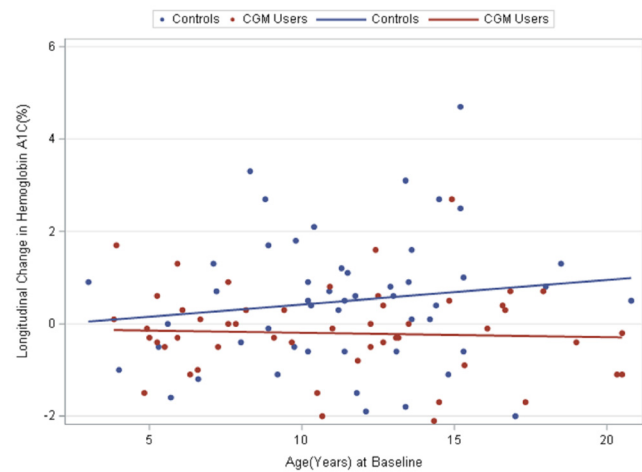


Figure 2: Graph of the baseline-adjusted hemoglobin A1c (HbA1c) showing the effect of advancing age and pubertal status on the serial HbA1c values in both the CGM users and controls. Among the prepubertal cohort, there was no significant difference in the changes in HbA1c between the CGM and controls: $-0.17 \pm 0.98\%$ vs. $0.38 \pm 1.5\%$, $p=0.17$. In contrast, HbA1c increased with age and pubertal status in the pubertal controls, $0.55 \pm 1.4\%$ compared to the CGM group, $-0.22 \pm 1.1\%$ vs, $p=0.020$.

Among the pubertal cohort, increasing age and pubertal status had no effect on HbA1c in the CGM group; in contrast, HbA1c increased with age and pubertal status in the pubertal control group: $-0.22 \pm 1.1\%$ vs $0.55 \pm 1.4\%$, $p=0.020$ (Figure 2). Thus, the CGM users had no change in HbA1c from young age through pubertal and older age range, whereas the controls experienced an increase in HbA1c concentrations with increasing age and pubertal status.

Further sub-analysis explored the differences in A1c between the CGM group and controls at each Tanner stage. Figure 3 showed no statistically significant differences in A1c between the CGM and controls for each Tanner stage. This is most likely due to the small sample size of the subgroups (Table 2). For example, though the difference in A1c between the CGM group for Tanner stage IV ($n=5$) and the controls at Tanner IV ($n=4$) was clinically significant (a 2% difference in HbA1c), it was not statistically significant: $7.5 \pm 0.94\%$ vs $9.5 \pm 3.02\%$, $p=NS$.

Subsequent sub-analysis explored the differences in growth velocity between the two groups for each Tanner stage. Figure 4 showed no significant difference in growth velocity between the CGM and control groups at each Tanner stage. In contrast, growth velocity was significantly faster at Tanner II compared to Tanner stages III, IV and V ($p<0.05$), suggesting an earlier attainment of peak height velocity in our cohort. This could be due to the small subgroup sample size as the merging of both male and female

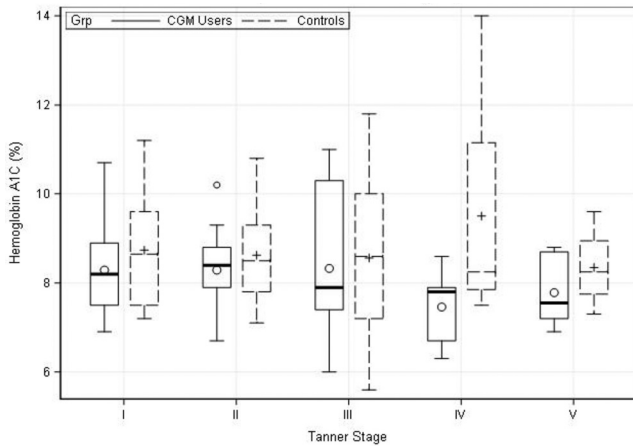


Figure 3: Box plots of the differences in HbA1c between the CGM group and controls at various age-based Tanner stages. There were no statistically significant differences in A1c between the CGM and controls for each Tanner stage. This could be due to the small sub-group sample size. For example, though the difference in A1c between the CGM group for Tanner stage IV (n=5) and the controls at Tanner IV (n=4) was clinically significant, it was not statistically significant: $7.5 \pm 0.94\%$ vs $9.5 \pm 3.02\%$, $p=NS$.

Table 2: The distribution of subjects by sex for each Tanner stage.

Tanner stage	I	II	III	IV	V
Female (n)	16	14	9	3	6
Male (n)	24	12	9	6	6

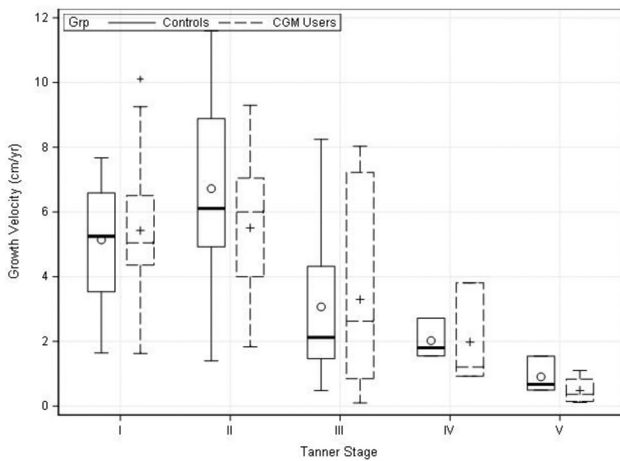


Figure 4: Box plots of the differences in growth velocity between the CGM group and the controls for each age-based Tanner stage. There was no significant difference in growth velocity between the CGM and control groups at each Tanner stage. In contrast, growth velocity was significantly faster at Tanner II compared to Tanner stages III, IV and V ($p<0.05$) which could be due to the higher number girls in the Tanner II category.

subjects for the age-based Tanner staging could easily result in an earlier Tanner stage designation for age, especially given that there were more girls than boys in the age-based Tanner stage II (Table 2).

Comparisons of the glycemic metrics, percent time in range (%TIR), percent time above range (%TAR), percent time below range (%TBR) and percent glucose variability (%GV) obtained at 0, 6, and 12 months, within the CGM group between the prepubertal and pubertal cohort showed that the pubertal subjects had significantly higher %TBR compared to the prepubertal CGM cohort, $4.14 \pm 3.6\%$ vs $1.9 \pm 1.5\%$, $p=0.015$. Percent TIR was not different between the pubertal- and the prepubertal groups, $41.4\% \pm 15.8\%$ vs $38.3 \pm 12.5\%$, $p=0.49$ at 6 months; as well as 12 months, $42.2\% \pm 14.6\%$ vs $40.6 \pm 12.9\%$, $p=0.71$.

An exploration of the relationship between %TIR and HbA1c in the CGM group showed a strong, inverse relationship between %TIR and HbA1c, $r=-0.6$, $n=42$, $p=0.0004$ (Figure 5). This relationship was similar for both the prepubertal and pubertal cohorts. The %TIR^{70-180 mg/dL} accounted for about 30% of the variability in HbA1c values after controlling for time frame (0 mo, 6 mo, and 12 mo), and the interaction between timeframe and %TIR, $R^2 = 0.30$, $p<0.0001$. The %TBR had a weak inverse relationship with A1c, $R^2 = 0.09$, $p=0.005$; and accounted for only 9% of the variability in HbA1c. Percentage TAR was directly related to the A1c, $R^2 = 0.30$, $p<0.0001$; and accounted for 30% of variability in HbA1c.

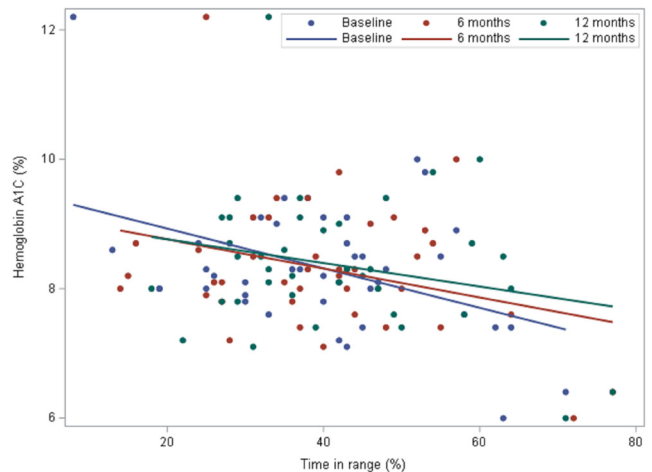


Figure 5: This scatterplot of the continuous glucose monitoring group shows a significant inverse relationship between hemoglobin A1c and percentage (%) time in range (TIR^{70-180 mg/dL}) of glycemia for three timepoints: baseline, 6 and 12 months, $r=-0.6$, $n=42$, $p=0.0004$.

Discussion

The primary finding from this study is that the use of CGM is associated with a significant reduction in HbA1c in pubertal youth compared to their non-CGM peers. This finding suggests that the behavioral changes occasioned by wearing a CGM and having access to real-time blood glucose data could lead to strategies to limit the magnitude of hyperglycemia of puberty. The pubertal subjects on GGM in this study had significantly higher %TBR than the prepubertal subjects on CGM, however, further analysis showed that %TBR accounted for only 9% of the variability in A1c. Thus, the significantly lower A1c in pubertal subjects compared to prepubertal subjects was not due to hypoglycemia. This real-time, glucose-data driven approach to diabetes management that is based on increasing the glycemic TIR while reducing glucose variability could provide the basis for a well calibrated insulin dosing regimen to reduce IR and reduce the magnitude of IR-mediated PHOP arising from physiologic increases in GH, free fatty acids, and sex steroids during puberty (1–13).

The study's findings are similar to published reports in the field [23–28]. The significantly lower HbA1c in CGM users versus controls is consistent with observational studies [28] and randomized control trials [16–31] that demonstrated improved glycemic control with adjunctive CGM therapy. These results are also similar to findings in mixed population of children and adults with T1D [1–32] who used the CGM device on a near-daily basis [33]. The inverse relationship between HbA1c and TIR^{70-180} mg/dL, as reported in this study, is similar to conclusions from recent studies in children and adults [16, 34, 35]. Foster et al. [1] from the T1D Exchange recently reported no improvement in serial HbA1c in their registry over a 5-year period despite an increase in the use of insulin pumps and CGM devices. Our results showed an inverse relationship between TIR and A1c for both pre-pubertal and pubertal subjects. However, significant reduction in A1c was seen only in the pubertal cohort, but not in the prepubertal cohort. Our findings of concurrent improvements in TIR and A1c in the pubertal CGM cohort are similar to reports by Brown et al. [16] on the effectiveness of control IQ technology in T1D which showed an increase in TIR with a reduction in A1c. These results are however different from the T1D Exchange data showing improvement in TIR, but not A1c.

The finding of a lack of a significant effect from the methodology of insulin delivery - use of insulin pump or MDI - on CGM-associated HbA1c reduction is consistent with a recent report from the T1D Exchange Registry [28]. The detection of a significant reduction in HbA1c in subjects who used the CGM consistently over a long period of

time is consistent with the findings of a recent meta-analysis [36] of randomized controlled trials of CGM and usual care that reported that the highest reduction in HbA1c concentrations occurred among CGM users on intensive insulin regimens who used the sensor on a near-daily basis. It is equally important to note that while behavioral intervention strategies such as motivational interviewing [37, 38] and the prevention of loss-to-follow-up using the care ambassador program [39], have resulted in HbA1c reduction among adolescents with T1D, it is noteworthy that the use of stand-alone CGM improved glycemic control and reduced HbA1c during the phase of persistent hyperglycemia of puberty in this traditionally non-compliant population.

Further exploration of the differences in glycemic control, expressed as A1c values, between the CGM group and controls at each Tanner stage; as well as the differences in growth velocity at each Tanner stage, were limited by the small sample size which prevented the detection of statistically significant differences in comparisons that otherwise showed clinically significant differences.

This study has several limitations that should be considered in the interpretation of the results. The retrospective nature of the study design precludes any inference to causality among the parameters studied. The inclusion of only subjects with confirmed record of consistent CGM use might represent a compliant population and may not accurately reflect the traditional pattern of CGM use by children and adolescents. As a result of the retrospective nature of this study, we did not have information on the conduct of real-time and retrospective CGM data review by the subjects, as well as any differences in the degree of communication between the diabetes management team and the patients wearing CGM compared to the controls. Lack of adequate data on the frequency and magnitude of hypoglycemic events in the controls prevented us from making a valid comparison of hypoglycemic episodes between the CGM and the controls. Tanner staging procedure for this study may not be exact as it was based on patients' age and not on patients' report or provider examination as there is a wide variation in the normal timing of the onset of puberty between boys and girls and even within the same sex. The shorter duration of T1D in the controls compared to the CGM group could have resulted in lower baseline HbA1c in the controls due to improved glycemia derived from residual endogenous beta-cell function. However, the results were adjusted for the duration of diabetes mellitus to control for the honeymoon period. Thus, it is notable that the baseline A1c in the controls worsened with time while A1c decreased in the CGM group.

Some of the strengths of this study included the inclusion of a well-matched control group to ensure the validity of the comparisons. All subjects in the CGM group used Dexcom G5 monitor which ensured a uniform exposure to the same intervention. The 12-month duration of study was long enough to observe significant changes in long-term glycemic markers, such as HbA1c, between the groups. The strong correlation between %TIR and A1c in the CGM group provided a verifiable basis for the reduction in HbA1c in the CGM group.

In conclusion, the use of CGM improves glycemic control in pubertal youth with T1D compared to non-CGM users. This reduction of the glycemic burden of PHOP is a critical step toward the goal of improved glycemic control in youth with T1D, which could translate to significant reductions in the magnitude and prevalence of the long-term complications of T1D. Randomized controlled trials are needed to confirm these findings.

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Competing interests: Authors state no conflict of interest.

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