INSULIN PUMP THERAPY REDUCES THE SEASONAL HBA1C DRIFT IN CHILDREN WITH TYPE 1 DIABETES

Irina Bojoga[1,2], Elisabeta Malinici[1,2*], S. Ioacara[1,2], Amalia Arhire[3], Rebeca Armat[2], Simona Fica[1,2]
"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
1. Endocrinology and Diabetes Department
"Elias" University Emergency Hospital, Bucharest, Romania
2. Endocrinology and Diabetes Department
3. "Kilostop Junior", Bucharest, Romania
[*]Corresponding author. E-mail: drelisabetasava@yahoo.com

INSULIN PUMP THERAPY REDUCES THE SEASONAL HBA1C DRIFT IN CHILDREN WITH TYPE 1 DIABETES (Abstract): Glycated hemoglobin A1c (HbA1c) levels are known to fluctuate seasonally in children with Type 1 Diabetes (T1D), typically decreasing during warmer months and increasing during colder months. Given that continuous subcutaneous insulin infusion (CSII) may lower HbA1c by approximately 0.3% (3 mmol/mol) relative to multiple daily insulin injections (MDI), the well-documented seasonal drift might offset the immediate benefits of initiating CSII in warm seasons. This study examines how CSII and MDI each modulate the expected rise in HbA1c from warmer to colder weather. **Materials and methods**: A total of 504 T1D patients under 18 years old attending the pediatric diabetes department of a major university hospital were evaluated. Exclusion criteria included disease duration under 1 year, lack of continuous glucose monitoring (CGM) access, fewer than 6 months on CSII, or incomplete data. Propensity score matching was used to yield two groups (CSII versus MDI), matched by age, HbA1c, body mass index, and calendar month (n=65 in each group). Follow-up visits occurred at 180±90 days after baseline. **Results:** Follow-up time was comparable in both groups (174±35 days for CSII *vs.* 169±38 days for MDI, p=0.44). Children in the CSII group demonstrated no significant change in HbA1c between baseline and follow-up. Conversely, the MDI group exhibited a statistically significant increase in HbA1c at follow-up (7.58±1.0%; p=0.01 *vs.* baseline). Among adolescents, the same pattern emerged, indicating a stable HbA1c level in the CSII group and a marked rise in MDI users (p=0.01). **Conclusions:** Children receiving MDI experienced the expected seasonal HbA1c increase, whereas CSII users did not demonstrate significant changes. These findings highlight the potential buffering role of CSII on seasonal HbA1c drift, even when follow-up conditions and baseline characteristics are comparable. **Keywords:** PEDIATRIC DIABETES, INSULIN PUMP, HBA1C SEASONALITY.

INTRODUCTION

Diabetes mellitus continues to be a significant public health problem, although diabetes-associated mortality rates seem to be declining in recent years (1). Despite the increasing recent recognition of time in

range importance, glycated hemoglobin A1c (HbA1c) is still the pillar of glycemic control evaluation in type 1 diabetes mellitus (T1D) in children. In many temperate regions worldwide, HbA1c levels exhibit seasonal variations, with lower values observed in the second and third quarters compared to the rest of the year (2-8). In addition, HbA1c variability tends to be greater in countries that experience a more prominent contrast in temperatures between winter and summer (5,9).

As costs and access improve, continuous subcutaneous insulin infusion (CSII) using an insulin pump may become the primary treatment option for children with T1D. Compared with multiple daily insulin (MDI) treatment, its advantage on HbA1c of approximative 0.3% (3 mmol/mol) is strikingly similar to the average differences in HbA1c induced by seasonality (2,10). Consequently, initiating CSII in summer might not translate into an immediate HbA1c benefit simply because of the known summer-winter HbA1c inherent drift. CSII appears to ameliorate HbA1c seasonality, but a direct comparison with MDI on this aspect is still missing (7).

Researchers should carefully consider these aspects when using descriptive data from real-world registries. Therefore, we tried to contribute data to the general knowledge about the impact of CSII and MDI on the HbA1c expected increase from warm to cold seasons. The primary outcome of the current study was to assess short-term (six months) changes in HbA1c starting from the second and third trimester of the year in T1D children treated with either CSII or MDI. Secondary outcomes included changes in the total daily insulin dose, the prandial-to-total insulin ratio, and the units of insulin per kilogram of body weight.

MATERIALS AND METHODS

Study population. This retrospective observational cohort study compared the short-term metabolic control in type 1 diabetes children on either CSII therapy or MDI. All patients attending the pediatric diabetes department of a major university hospital from 2019 to 2024 were eligible for this study (n=504). This major pediatric diabetes center serves a large urban area and its surroundings within a 300 Km radius. As part of the larger SWEET Project (www.sweet-project.org), the local pediatric diabetes registry contained information on anthropometrics, biochemistry, and therapy, including data before 2019. As continuous glucose monitoring (CGM) was known to impact metabolic control significantly, patients were required to have continuous CGM access to be eligible for this study. Other exclusion criteria at baseline were age 18 or more, diabetes duration under one year, and time since CSII initiation less than 180 days.

The study has been conducted in accordance with all the relevant national regulations and institutional policies and with the tenets of the Helsinki Declaration, and the local Ethics Committee has approved it. Informed consent was obtained from all legal guardians of individuals included in this study.

Baseline. The baseline was defined as the first available recording, in which the age was less than 18 years, the diabetes duration was 365 days or more, CGM was used, and the date of visit was in the second or third trimester of the year. Propen-

sity score matching was used to control differences in age, diabetes duration, HbA1c, BMI and calendar month at baseline in a 1: 1 group ratio. The final cohort retained 130 subjects, split into a CSII (n=65) and an MDI group (n=65) based on the baseline insulin delivery method (see fig. 1). The MDI group was formed using the remaining patient pool after constructing the CSII group. The treatment option at baseline had to remain unchanged at the follow-up visit.

Follow-up visits occurring at 180 ± 90 days after baseline were eligible for this study. Where multiple follow-up visits were available, only the one closest to 180 days was retained in the primary analysis. Patients without at least one follow-up visit were excluded (n=52) (fig. 1).

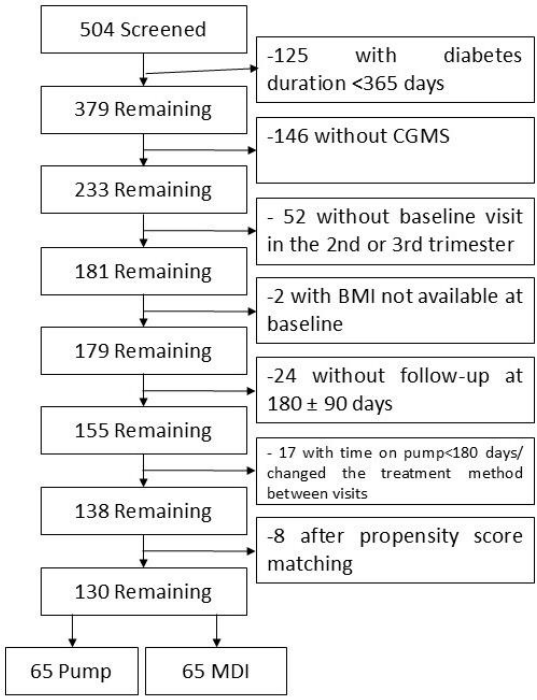

Fig. 1. Flowchart of patient attrition in the study. (CGMS: continuous glucose monitoring system, BMI: body mass index, MDI: multiple daily injections)

Statistical analysis was performed using *SPSS version 29.0.1.0*. A 2-sided p-value less than 0.05 was considered statistically significant. Propensity score matching used the multivariable logistic regression model. Only patients with baseline and follow-up data were retained when individual variables were analyzed. Primary outcome variables were available in all study subjects. The primary outcome was supplementary checked in a sensitivity analysis, using all available follow-up visits at

180 ± 90 days after the baseline. This analysis was performed to check the reliability of the main results.

The primary outcome was further explored in the adolescents' group, defined as age at baseline between 10 and 17 years (n=79). Preadolescents could not be investigated due to the limited number of patients in this age category.

Secondary outcomes were investigated in a subgroup of patients (n=53 CSII and n=58 MDI) due to missing information in some patients. The number of sick days over the last three months was available in a limited patient sample (n=27) containing a mixture of CSII and MDI patients. Due to the limited number of cases, the Wilcoxon matched-pairs signed-ranks test was used in this subset of data.

RESULTS

Primary outcome. The final cohort retained 130 subjects, respecting all the inclusion and none of the exclusion criteria. Mean age was 10.7 ± 3.5 years, with a diabetes duration of 4.5 ± 2.8 years. In the CSII group, the baseline mean time since pump initiation was 858 ± 491 days (range 193-2327 days). Propensity score matching was responsible for the similar results at baseline for age and HbA1c among pump users (n=65, mean age 10.7±3.7 years, HbA1c 7.28 ± 0.9%) and MDI users (n=65, mean age 10.7±3.4 years, HbA1c 7.35 ± 1%; all p>0.05 *vs.* CSII), (tab. I).

HbA1c at baseline was also similar between the two groups in adolescents (7.23 ± 0.9 CSII *vs.* 7.32 ± 1 MDI).

The mean follow-up was similar in the CSII (174 ± 35 days) and the MDI group (169 ± 38 days, p=0.44). HbA1c at the follow-up visit was similar to baseline in the CSII group. However, the MDI group experienced a statistically significant rise in HbA1c at the follow-up visit (7.58 ± 1%, p= 0.01 *vs.* baseline) (tab I). The supplementary sensitivity analysis using all available follow-up visits occurring 180 ± 90 days after the baseline did not change these results.

Adolescent restricted analysis showed the same pattern: no significant changes from baseline in the CSII group (7.23 ± 0.9% *vs.* 7.4 ± 0.8 %, p=0.93), but a significant rise in the MDI users (7.32 ±1.0% *vs.* 7.63 ± 1.1%, p=0.01).

Secondary outcomes. The total daily insulin dose at follow-up increased significantly in both CSII (+4.5U, 95%CI 1.7-7.3, p=0.02) and MDI group (+3.5U, 95%CI 1.4-5.5, p<0.001), see Tab I. During the follow-up, the prandial to basal ratio remained relatively unchanged (p>0.05). MDI group had a significantly higher prandial to basal ratio as compared with pump users at baseline (p<0.01), but not at the follow-up visit (p=0.173). During the follow-up, the CSII group showed a significant increase in insulin per body weight (p=0.02), accompanied by significant increases in BMI (p=0.006), weight (+2.2Kg, 95%CI 1.5-2.8, p<0.001), and height (+2.4 cm, 95%CI 1.9-2.9, p<0.001). The MDI group experienced an increase in insulin per body weight (p=0.041), weight (+2.1 Kg, 95%CI 1.5-2.7, p<0.001) and height (+3.2 cm, 95%CI 2.4-4, p<0.001), but not BMI (p=0.131).

There was a significant rise in the number of sick days from baseline (1.2, 95%CI 0.2-2.4) to follow-up visit (7.1, 95%CI 3.7-11.3, p=0.005). Data could not be further detailed by the treatment group.

TABLE I.

Baseline and follow-up characteristics of children with type 1 diabetes

	Insulin pump		Multiple daily injections	
	Baseline	**Follow-up**	**Baseline**	**Follow-up**
Primary outcome				
N	65	65	65	65
Age (years)	10.7 ± 3.7	-	10.7 ± 3.4	-
Diabetes duration (years)	5.7 ± 2.8	-	3.3 ± 2.3	-
HbA1c (%)	7.28 ± 0.9	7.38 ± 0.8^{NS}	7.35 ± 1	7.58 ± 1*
Secondary outcomes				
N	53	53	58	58
Age (years)	10.8 ± 3.8	-	10.6 ± 3.5	-
Diabetes duration (years)	5.6 ± 2.8	-	3.3 ± 2.2	-
Total insulin (U)	34.6 ± 19.9	39.2 ± 22.5*	32.7 ± 17	36.2 ± 17.9**
P: B ratio	1.23 ± 0.62	1.39 ± 0.96^{NS}	1.65 ± 0.68	1.61 ± 0.65^{NS}
IBW (U/Kg)	0.77 ± 0.24	0.83 ± 0.23*	0.8 ± 0.19	0.84 ± 0.2*
BMI (Kg/m^2)	19.1 ± 3.5	19.5 ± 3.8**	18.6 ± 3.8	18.8 ± 3.9^{NS}

^{NS} not significant; * p<0.05; ** p<0.01 *vs.* baseline; P: B ratio - prandial to basal insulin ratio; IBW - insulin per body weight; BMI - body mass index

DISCUSSION

This observational study investigated the hypothesis that CSII (n=65), MDI (n=65), or both could change the natural rise of HbA1c from warm to cold seasons in children with T1D and uncovered three major findings. First, children on MDI treatment experienced the expected rise in HbA1c during follow-up. Second, the CSII group did not show a significant rise in HbA1c despite similar follow-up conditions. And third, BMI showed different dynamics in CSII compared with the MDI group.

Seasonal variation in HbA1c is an important concept, especially in older children with T1D from world regions with a high temperature contrast between winter and summer (5, 11, 12). Primary contributors to higher HbA1c in cold seasons might be increased susceptibility to viral infections, winter celebrations related to excessive eating, school stress, and decreased physical activity (3, 11, 13, 14). Parallel variation in blood pressure, lipid profile and insulin sensitivity might also contribute to some seasonal variations in HbA1c (12, 15, 16).

Moreover, some children have an acute recovery of insulin secretion a few days after insulin initiation following T1D onset. Insulin requirements may drop significantly, and sometimes the patients can live insulin-free for a limited amount of time. This partial or total remission may last for a couple of weeks or months but rarely exceeds one year in children. HbA1c levels and variability are exceptionally low during this period but sharply rise following its end. The current study enforced at least one year of diabetes duration at baseline, but most children had significantly more than that. The total number of sick days over the previous three months was used to proxy

for viral infection incidence. Although results could not be detailed by treatment group, this important parameter did rise significantly in the limited sample of patients investigated. No data was available for physical activity, but the authors' observation is that summer is associated with increased leisure-related physical activity compared with late autumn and winter.

Cold stress-related rise in mean glucose levels, asserted by HbA1c, might also be explained by increased glucagon, epinephrine, cortisol, growth hormone, and thyroid hormones plasma concentrations as a natural adaptation to the body's demand for heat production (17-19). Besides increased levels, resistance to glucocorticoid action was described as an adaptation to a cold environment (19). Increased counter-regulatory hormone concentrations translate into a parallel increase in insulin resistance during the cold seasons and, ultimately, in HbA1c variability (19).

The results from a retrospective observational study by Tanaka *et al*. indicate that insulin pump treatment may significantly reduce seasonal variation in HbA1c levels. The researchers examined the seasonal variation of HbA1c levels and how the COVID-19 pandemic and related restrictions affected this variation in a cohort of 52 adults with T1D. The study found that individuals using CSII and sensor-augmented pumps experienced the least seasonal variation in HbA1c levels. In contrast, greater variability was observed in groups using MDI without CGMS or with intermittently scanned continuous glucose monitoring. Notably, variability in HbA1c levels was present in 2019 but diminished in 2021 during the COVID-19 restrictions (20).

In an observational study on 454 T1D children, 231 on CSII and 223 on MDI, Fendler *et al.* found a significantly lower HbA1c variability in the CSII group compared with the MDI group (21). Although similar to results from the current study, they used a different approach to assess HbA1c variability, i.e., the mean standard deviations of the mean HbA1c during the mean three years follow-up. Also, they declared that only acute hospitalizations were considered during the follow-up, disregarding the scheduled hospital admissions. Adding the age imbalance at baseline, with the MDI group being around two years older than children on CSII, results might express the expected higher HbA1c variability in older T1D children when admitted to a hospital for an acute presentation. The current study used propensity score matching to control for age and other possible imbalances between groups. Results can also be interpreted for situations outside acute presentations in the hospital.

As strength points, this study used propensity score matching to control for important confounding variables. Besides enforced similar age, HbA1c, BMI and calendar month at baseline, the protocol excluded patients with no access to CGM, recognizing the importance of this confounding variable on HbA1c. The influence of partial remission phase was minimized by enforcing at least one-year duration of diabetes at baseline. HbA1c variability due to MDI to CSII switch was accounted for by including only patients with at least 180 days since insulin pump initiation.

As weak points, this study was performed in a single center, with a limited selection base (N=504). The number of cases retained in the final groups was also limited (n=65 each). Moreover, it did not

evaluate gender impact on HbA1c dynamic in studied groups. Although many girls (especially adolescents) seem to have slightly higher HbA1c levels than boys starting right from T1D onset, no gender differences were previously reported in studies investigating HbA1c variability (3, 11, 22). Information on physical activity and incidence of viral infections was not available. These parameters are part of the possible explanations of HbA1c variability. The number of sick days in a limited sample of patients from both investigated groups only offered limited compensation for this shortage. Although there is no obvious indicator that physical activity and viral infections differed substantially between the CSII and MDI groups, no direct systematic measurements were available.

CONCLUSIONS

In conclusion, children receiving MDI experienced the anticipated seasonal HbA1c increase, while CSII users exhibited no significant changes. These findings emphasize the potential buffering effect of CSII on seasonal HbA1c drift, even when follow-up conditions and baseline characteristics are similar. Pediatric endocrinologists and researchers should recognize the seasonal variability in HbA1c and the potential impact of CSII on modifying this phenomenon when used alongside CGM.

CONFLICT OF INTEREST AND FUNDING

The authors declare that there is no conflict of interest, and they received no specific funding.

ACKNOWLEDGMENTS

We acknowledge the support of the entire pediatric endocrinology and diabetes department.

REFERENCES

1. Ioacara S, Sava E, Georgescu O, Sirbu A, Fica S. Recent diabetes-related mortality trends in Romania. *Acta Diabetol.* 2018; 55(8): 821-826.
2. Hill NR, Peters CJ, Thompson RJ, Matthews DR, Hindmarsh PC. Cyclical variation in hba1c values during the year: Clinical and research implications. *Diabetes Care* 2013; 36(10): e175-176.
3. Mianowska B, Fendler W, Szadkowska A, *et al*. HbA1c levels in schoolchildren with type 1 diabetes are seasonally variable and dependent on weather conditions. *Diabetologia* 2011; 54(4): 749-756.
4. Sakura H, Tanaka Y, Iwamoto Y. Seasonal fluctuations of glycated hemoglobin levels in Japanese diabetic patients. *Diabetes Res Clin Pract* 2010; 88(1): 65-70.
5. Higgins T, Saw S, Sikaris K, *et al*. *Seasonal Variation in Hemoglobin A1c: Is It the Same in Both Hemispheres*? [Internet]. 2009. Available from: www.journalofdst.org
6. Gerstl EM, Rabl W, Rosenbauer J, *et al*. Metabolic control as reflected by HbA1c in children, adolescents and young adults with type-1 diabetes mellitus: combined longitudinal analysis including 27,035 patients from 207 centers in Germany and Austria during the last decade. *Eur J Pediatr* 2008; 167(4): 447-453.
7. Hathout EH, McClintock T, Sharkey J, *et al*. Glycemic, Auxologic, and Seasonal Aspects of Continuous Subcutaneous Insulin Infusion Therapy in Children and Young Adults with Type 1 Diabetes. *Diabetes Technol Ther* 2003; 5(2): 175-181.

8. Nordfeldt S, Ludvigsson J. Seasonal Variation of HbA1c in Intensive Treatment of Children with Type 1 Diabetes. *Journal of Pediatric Endocrinology and Metabolism* 2000; 13(5): 529-535.
9. Tseng CL, Brimacombe M, Xie M, *et al*. Seasonal Patterns in Monthly Hemoglobin A1c Values. *Am J Epidemiol* 2005; 161(6): 565-574.
10. Pereira MTRP, Lira D, Bacelar C, Oliveira JC, De Carvalho AC. Seasonal variation of hemoglobin A1c in a Portuguese adult population. *Arch Endocrinol Metab* 2015; 59(3): 231-235.
11. Samuelsson U, Carstensen J, Löfman O, Nordfeldt S. Seasonal variation in the diagnosis of type 1 diabetes in south-east Sweden. *Diabetes Res Clin Pract* 2007; 76(1): 75-81.
12. Moltchanova E V, Schreier N, Lammi N, Karvonen M. Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide. *Diabetic Medicine* 2009; 26(7): 673-678.
13. Matthews CE, Freedson PS, Hebert JR, *et al*. Seasonal Variation in Household, Occupational, and Leisure Time Physical Activity: Longitudinal Analyses from the Seasonal Variation of Blood Cholesterol Study. *Am J Epidemiol* 2001; 153(2): 172-183.
14. Tucker P, Gilliland J. The effect of season and weather on physical activity: A systematic review. *Public Health* 2007; 121(12): 909-922.
15. Walker BR, Best R, Noon JP, Watt GCM, Webb DJ. Seasonal Variation in Glucocorticoid Activity in Healthy Men. *J Clin Endocrinol Metab* 1997; 82(12): 4015-4019.
16. Roche EF, Lewy H, Hoey HMCV, Laron Z. Differences Between Males and Females in the Seasonality of Birth and Month of Clinical Onset of Disease in Children with Type I Diabetes Mellitus in Ireland. *Journal of Pediatric Endocrinology and Metabolism* 2003; 16(5): 779-782.
17. Kristal-Boneh E, Froom P, Harari G, Malik M, Ribak J. Summer-Winter Differences in 24 h Variability of Heart Rate. *European Journal of Cardiovascular Risk.* 2000; 7(2): 141-146.
18. Bittel JH. Heat debt as an index for cold adaptation in men. *J Appl Physiol* 1987; 62(4): 1627-1634.
19. Hansen ÅM, Garde AH, Skovgaard LT, Christensen JM. Seasonal and biological variation of urinary epinephrine, norepinephrine, and cortisol in healthy women. *Clinica Chimica Acta* 2001; 309(1): 25-35.
20. Tanaka K, Meguro S, Itoh A, Kodani N, Itoh H. Impact of coronavirus disease 2019 in seasonal variation of hemoglobin A1c in adults with type 1 diabetes and the effect of the mode of treatment: a single-center retrospective study for 2019 and 2021 and analysis by the mode of treatment. *Endocr J* 2023; 70(8): 787-795.
21. Fendler W, Baranowska AI, Mianowska B, Szadkowska A, Mlynarski W. Three-year comparison of subcutaneous insulin pump treatment with multi-daily injections on HbA1c, its variability and hospital burden of children with type 1 diabetes. *Acta Diabetol* 2012; 49(5): 363-370.
22. Hanberger L, Åkesson K, Samuelsson U. Glycated hemoglobin variations in pediatric type 1 diabetes: The impact of season, gender and age. *Acta Paediatrica, International Journal of Paediatrics* 2014; 103(4): 398-403.