Continuous Glucose Monitoring (CGM) Reveals Undertreated Hypoglycemia in Patients with Congenital Hyperinsulinism

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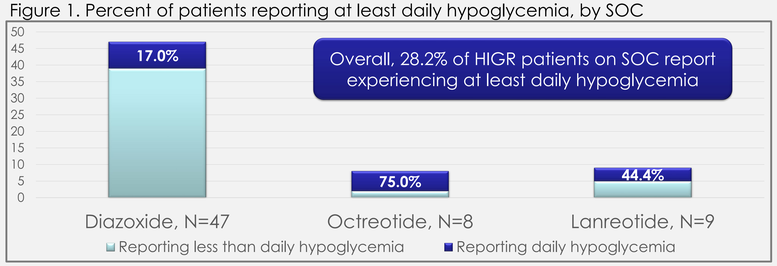
INTRODUCTION & BACKGROUND

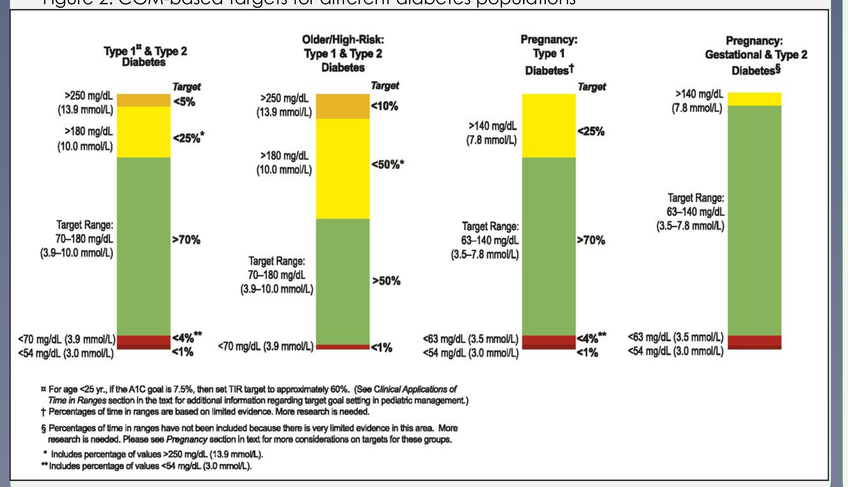
Congenital Hyperinsulinism (HI) is the most frequent cause of severe, persistent hypoglycemia in children (Lord & De León, Monogenic hyperinsulinemic hypoglycemia: current insights into the pathogenesis and management, 2013). Patients experience a high prevalence of neurodevelopmental abnormalities (26–48%) regardless of the duration of the hyperinsulinism or treatment modality (Lord & De León-Crutchlow, Neurodevelopmental Outcomes, 2019). Despite the use of currently available treatments, 28% of patients (Figure 1) report continued daily hypoglycemia according to the HI Global Registry 2020 Annual Report (Hood, et al., 2020).

Figure 1. Percent of patients reporting at least daily hypoglycemia, by SOC



Patients with Type 1 diabetes mellitus (T1DM) also experience adverse neurocognitive outcomes as a result of hypoglycemia; therefore, the interventional goals for T1DM may be viewed as a useful and robustly-studied analog to congenital HI. The Advanced Technologies and Treatments for Diabetes (ATTD) expert panel provided consensus guidelines for recommended time in range using CGM (Figure 1), notably a target time in hypoglycemia (< 70 mg/dL (3.9 mmol/L) of <4%, or an average of less than one hour per day (Battelino & et.al., 2019).

Figure 2. CGM-based targets for different diabetes populations



‡ For age <25 yr., if the A1C goal is 7.5%, then set TIR target to approximately 60%. (See *Clinical Applications of Time in Ranges* section in the text for additional information regarding target goal setting in pediatric management.)
† Percentages of time in ranges are based on limited evidence. More research is needed.
§ Percentages of time in ranges have not been included because there is very limited evidence in this area. More research is needed. Please see *Pregnancy* section in text for more considerations on targets for these groups.
* Includes percentage of values >250 mg/dL (13.9 mmol/L).
** Includes percentage of values <54 mg/dL (3.0 mmol/L).

INTRODUCTION & BACKGROUND, CONT'D

There is a lack of analogous published literature and guidelines in congenital HI. Utilizing analogs such as T1DM, additional research is needed to further characterize and to quantify hypoglycemia in patients with congenital HI in order to guide goals of care and future therapy development.

METHODS

A two-week observational study was conducted in congenital HI patients ages two years and older, recruited randomly from the Congenital Hyperinsulinism International community, using CGM (Dexcom G4®). Hypoglycemic thresholds in this study were defined as <70 mg/dL (3.9mmol/L), <60mg/dL (3.3 mmol/L), or <50mg/dL (2.8 mmol/L).

RESULTS

- Twenty-two patients ages 2-36 years old (Males:9, Females:13) with CHI of various genetic causes participated in this study.
- Fifteen patients were receiving at least one SOC therapy which included:
  - 11 (50%) on diazoxide,
  - 4 (18%) on octreotide,
  - 7 (32%) managed by other means (continuous enteral dextrose, glucagon, and/or diet).
  - 5 patients were also post-pancreatectomy (< 50% to > 95% removal).
- Time in hypoglycemia observed is outlined in Table 1
- The results equate to an average of:
  - Over 2.5 hours per day spent in hypoglycemia for all participants
  - Nearly 3.5 hours per day for those 2-6 years old.
- Patients taking SOC therapies experienced a similar magnitude of hypoglycemia.

Table 1. Time in hypoglycemia (< 70 mg/dL) by observation week.

		Week 1			Week 2		
Participants	N	Time in Hypoglycemia, minutes	SD	% monitored time*	Time in Hypoglycemia, minutes	SD	% monitored time*
ALL	22	1165	164	11.6%	1101	152	10.9%
Age 2-6 yr	12	1445	161	14.3%	1376	147	13.7%
Age 7-10 yr	4	770	567.1	7.6%	411.3	455.7	4.1%
Age 11-16 yr	2	1432.5	1417.8	14.2%	1267.5	1092.5	12.6%
Age 17+	4	1070	1194.8	10.6%	1292.5	1542	12.8%
Subgroup on SOC							
ALL	15	1269.3	973.6	12.6%	1104	963.2	11.0%
Age 2-6 yr	9	1455	1056.9	14.4%	1375.6	1005	13.6%
Age 7-10 yr	4	770	567.1	7.6%	411.3	455.7	4.1%
Age 11-16 yr	2	1432.5	1417.8	14.2%	1267.5	1092.5	12.6%
Age 17+	0	-	-	-	-	-	-
***calculated based on 10080 minutes/week**							

CONCLUSION & DISCUSSION

Persistent hypoglycemia places patients with congenital HI at risk for adverse clinical outcomes including development delays and permanent neurologic damage (Lord & De León-Crutchlow, Neurodevelopmental Outcomes, 2019). Current Pediatric Endocrine Society management guidelines for those diagnosed with congenital HI recommend maintenance of blood glucose > 70 mg/dL (Thornton, et al., 2015) to the extent possible. As evidenced by the CGM results of this study, patients with congenital HI, even on available SOC therapies, had substantial continued hypoglycemia, thus missing the recommended therapeutic goal. This was especially true for the younger patients in this study, who are also at the greatest risk of neurocognitive sequelae due to cumulative hypoglycemia. Yet, therapeutic goals for improvement of overall or cumulative hypoglycemia, based on the extent or duration of time below desired thresholds, are not specified in the published guidelines. This observational study demonstrates that while on the currently available standard of care, study participants experienced more than three times the hypoglycemia in a neurologically vulnerable age group than is recommended in the T1DM population. More effective treatments are needed to minimize hypoglycemia to achieve glucose normalization.

In the evaluation of potential new therapies or combination of therapies for congenital HI, better understanding of the baseline magnitude of time in glycemic ranges and a quantitative standard for clinically meaningful glycemic targets are needed. While the authors acknowledge historical device inaccuracy in the lower glucose ranges, significant technologic advancement in CGM and monitoring algorithms continue to be made. Qualitatively, the primary therapeutic goal for safe and effective glycemic management would be to increase the time-in-range while reducing the time-below-range as much as is achievable. Until standardized treatment goals are developed for congenital HI, it may be appropriate to extrapolate and utilize relative hypoglycemia improvements and treatment targets from clinical trials in diseases where hypoglycemia is common, such as T1DM. The results of this study documents residual hypoglycemia beyond what can be detected by intermittent measurement of blood glucose via point of care monitors, further demonstrating that CGM should have an important adjunctive role in the monitoring of congenital HI patients toward to-be-determined standardized glycemic targets.

References:

Battelino, T., & et.al. (2019). Clinical Targets for Continuous Glucose Montoring Data Interpretation: Recommendations From the International Consensus on Time in Range. *Diabetes Care*, 1593-1603.

Hood, D., Pasquini, T., Quinlan, L., Linsmeier, A., Chapel, S., Calderon, I., & Raskin, J. (2020). *Congenital Hyperinsulinism International HI Global Registry 2020 Annual Report.* Glen Ridge: Congenital Hyperinsulinism International. Retrieved from https://congenitalhi.org/wp-content/uploads/2020/06/IRB-Approved-HI-Global-Registry-2020-Annual-Report_06232020.pdf

Lord, K., & De León, D. (2013). Monogenic hyperinsulinemic hypoglycemia: current insights into the pathogenesis and management. *International Journal of Pediatric Endocrinology*(3). doi:10.1186/1687-9856-2013-3

Lord, K., & De León-Crutchlow, D. (2019). Neurodevelopmental Outcomes. In D. De León-Crutchlow, & C. Stanley, *Congenital Hyperinsulinism: A Practical Guide to Diagnosis and Management* (pp. 155-160). Cham: Humana Press, Cham. https://doi.org/10.1007/978-3-030-02961-6_14.

Thornton, P., Stanley, C., De Leon, D. D., Harris, D., Haymond, M., Hussain, K., . . . Wolfsdorf, J. (2015, August 1). Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. *The Journal of Pediatrics, 167*(2), 238-245.

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