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Short Report

Glycemia Risk Index (GRI) and international glucose targets before and 6 months after initiation of hybrid closed loop system in the CIRDIA, a French multisite out-of-hospital center

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ABSTRACT

Aims: To analyze in a population of persons with type 1 diabetes (PwT1D) ambulatory glucose profile (AGP) parameters – including glycemia risk index (GRI) – for six months after hybrid closed loop (HCL) initiation in a multisite out-of-hospital French center (CIRDIA). We calculated the percentage of people reaching glucose targets and determined a GRI threshold that could identify patients reaching targets.

Methods: This was a retrospective study conducted in the CIRDIA, a multisite (n=7) out-of-hospital HCL initiation center. AGP metrics for the 14 previous days were manually extracted from HCL platforms at initiation (M0), 3 ± 1 months (M3) and 6 ± 1 months (M6). PwT1D were considered as reaching efficacy and safety targets (EST) if time-in-range was > 70 %, GMI was < 7 %, time-below-range (TBR)$^{<70}$ was < 4 % and TBR$^{<54}$ was < 1 %. GRI was calculated and ROC analyses were performed to set a GRI threshold that could identify patients reaching EST.

Results: Six-month data were available for 136 persons. The percentage of PwT1D reaching glucose targets at respectively M0, M3 and M6 were for EST: 6.6 %, 40.4 % and 39.7 %. GRI decreased from 56.0 ± 20.9 to 30.1 ± 14.1 and 30.6 ± 13.8. ROC analyses showed that the best GRI value to detect patients who reached EST was GRI <26. A threshold set at this level had very good specificity (92 %) and negative predictive value (93 %) to identify those who do need further intensive support with HCL.

Conclusion: Setting a GRI threshold at 26 could be helpful to detect with a single number, potentially automatically calculated by CGM platforms, PwT1D who require further support.

Introduction

We have extensive evidence that hybrid closed loop (HCL) systems improve ambulatory glucose profile (AGP) parameters in persons living with type 1 diabetes (PwT1D) [1] with more people reaching glucose metric targets that have been defined in a consensus of international experts [2]. Recently, new glucose parameters have been described including the glycemia risk index (GRI) that better characterizes the risk

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of hypoglycemia and hyperglycemia with a single number ranging from 0 (minimal risk) to 100 (maximal risk) [3]. GRI can be reported on a grid showing both hypo- and hyperglycemic components with a risk categorized in five GRI zones ranging from A (GRI 0–20, lowest risk) to E (81–100, highest risk). In this study, we report real-life data for glucose metrics including GRI over a 6-month period after HCL initiation in the CIRDIA, a multisite out-of-hospital center, and we define a GRI threshold that could easily identify most of the patients who do not reach glucose targets and need further support with their HCL system.

Methods

This was a rolling retrospective study conducted in the Inter-Regional Center for Automatized Insulin in Diabetes (CIRDIA), a multisite (n=7) out-of-hospital HCL initiation center. A new concept of healthcare organization for PwT1D in France, CIRDIA involves highly trained, mostly private practice, diabetologists. All the investigators had completed a university degree on HCL systems and the structure is based on the French-speaking Diabetes Society (SFD) recommendations [4].

Consecutive non-pregnant adult PwT1D who had HCL initiation in a CIRDIA center between May 1, 2023, and April 30, 2024, were included after they had signed an informed consent form. No ethic committee approval was necessary, as this was a retrospective study on an ongoing basis. AGP metrics for the 14 previous days were manually extracted from HCL platforms at initiation and then at 3 ± 1 months (M3) and 6 ± 1 months (M6). No difference was made between systems, noting that at the time of study, only three systems were available and reimbursed in France: Medtronic 780G with G4 sensors (780G), Control-IQ with Tandem TSlimX2 pump (Tandem) and Dexcom G6 sensors (CIQ), CamAPS with Ypsopump (Ypsomed) and Dexcom G6 sensors (CamAPS). At the time of the study, CIQ and CamAPS systems were reimbursed only when HbA1c was at or above 8 %.

Patients were trained by the CIRDIA diabetologist (sometime with the help of a nurse and/or a dietician). Participants received written information on the management of hypo- and hyperglycemia crises and were provided with an emergency 24/7 phone number answered by a CIRDIA diabetologist – on call duty on a weekly basis. The role of the healthcare provider was limited to technical training (sensor insertion, pump training) and connectivity issues.

AGP parameters included time-in-range 70–180 mg/dl (TIR), time-below-range < 70 mg/dl ($TBR^{<70}$), time-below-range < 54 mg/dl ($TBR^{<54}$), time-above-range > 180 mg/dl ($TAR^{>180}$), time-above-range > 250 mg/dl ($TAR^{>250}$), glucose management index (GMI) and GRI that was calculated using an online electronic calculator [5]. We assessed the percentage of PwT1D reaching TIR > 70 %, GMI < 7 % and efficacy target (ET = TIR > 70 % and GMI < 7 %), the percentage of those reaching safety target (ST = $TBR^{<70}$ < 4 % and $TBR^{<54}$ < 1 %) and of those reaching combined efficacy and safety target (EST = TIR > 70 % and GMI < 7 % and $TBR^{<70}$ < 4 % and $TBR^{<54}$ < 1 %).

Results are expressed as mean ± SD or percentages. ROC analyses were performed using GraphPad Prism 9, GraphPad Software, LLC. The statistical changes in AGP parameters over time were calculated using Kruskal-Wallis's test. Differences in GRI's components were assessed with Mann-Whitney test.

Results

Six-month data were available for 136 PwT1D (55 % female, 45 % male). Mean age was 42.5 ± 14.3 years, diabetes duration was 23.1 ± 12.1 years, body mass index was 27.5 ± 5.1 kg/m^2. PwT1D used the following systems: 780G (76 %), CIQ (14 %) and CamAPS (10 %). Among participants, all had been on pump therapy for at least 6 months at the time of HCL initiation and 13 (9.6 %) had been on sensor-augmented pump therapy for more than 3 months. No serious event related to HCL treatment was reported. When considering AGP parameters at respectively M0, M3 and M6, TIR was 53.1 %, 72.9 % and 72.4 % (P for difference over time < 0.0001); $TBR^{<70}$ was 3.0 %, 2.0 % and 1.9 % (P = 0.04) including $TBR^{<54}$: 0.4 %, 0.3 % and 0.3 % (P = 0.82); $TAR^{>180}$ was 43.9 %, 25.0 % and 25.8 % (P < 0.0001) including $TAR^{>250}$: 17.2 %, 6.1 %, 6.6 % (P < 0.0001); GMI was: 7.7 %, 6.9 %, 7.0 % (P = 0.03) and GRI was 56.0 ± 20.9, 30.1 ± 14.1 and 30.6 ± 13.8 (P < 0.0001).

The percentage of PwT1D reaching glucose targets at respectively M0, M3 and M6 were for TIR >70 %: 14.7 %, 62.5 % and 61.8 %, for GMI < 7 %: 19.1 %, 59.6 % and 57.4 %, for ET: 14.7 %, 54.4 % and 55.1 %, for ST: 63.2 %, 73.5 % and 74.3 % and for EST: 6.6 %, 40.4 % and 39.7 %.

GRI components and distribution are shown in Fig. 1. Among participants in GRI zone A (0–20), almost all reached EST: 100 % at M0, 94.4 % at M3 and 93.3 % at M6. EST was reached by 20.8 %, 27.0 % and 31.3 % of participants from the GRI zone B (21–40) at M0, M3 and M6 respectively and by none of the PwT1D in the GRI zones C, D or E (>40) at any time. We performed ROC analyses that showed that the best GRI value to detect patients who reached EST was GRI <26. Noteworthily, while only 5 % of the participants had a GRI <26 at M0, almost half of the participants had a GRI <26 at M3 (42 %) and M6 (43 %).

Thus, we calculated the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of a GRI value < 26 to detect PwT1D reaching EST among all the AGPs at M0, M3 and M6 for the 136 participants (n= 408). GRI was < 26 for all profiles in zone A (n=70; 17.2 % of all profiles) and for 51 profiles with GRI 21–25 in zone B (12.5 % of all profiles). Among profiles reaching EST at any time (n = 118), GRI was < 26 for 98 profiles, giving a sensitivity of 83 %. Among profiles with a GRI < 26 (n=121), 98 met EST, giving a PPV of 81 %. GRI was < 26 in 23 of the 290 profiles that did not reach EST (specificity = 92 %) and 267 of the 287 profiles with a GRI ≥26 did not reach EST giving a NPV of 93 %.

In our population, 78 participants (57 %) did not reach a GRI value < 26 at M6. If we compare participants with a GRI ≥26 at M6 versus participants with a GRI < 26, those with a GRI score ≥26 were more often men (54 % versus 43 %), were younger (40.5 ± 13.5 versus 46.9 ± 13.6 years) with a quite comparable duration of diabetes (23.6 ± 11.5 versus 25.5 ± 12.6 years), and had a higher GRI value at baseline (M0) (63.9 versus 45.3, P < 0.0001) with a significantly higher hyperglycemia component (36.1 versus 22.9, P < 0.0001), while the hypoglycemia component was similar (2.2 versus 2.9, P = 0.70).

Discussion and conclusion

HCL has become the new standard of care in the treatment of PwT1D [6]. If we consider that 10 % of people living with diabetes have type 1 diabetes, it means that about 400,000 PwT1D are eligible to receive this therapy in France. However, it appears that much less than 10 % of them have been using HCL two years after its reimbursement. Hospitals cannot initiate and/or manage HCL follow-up for all PwT1D. Nevertheless, HCL initiation requires highly trained multiprofessional teams. This is the reason why we created the CIRDIA, a multisite HCL initiation center with highly trained diabetologists – mostly in private practice. We show here that this initiation center can achieve results that are very similar to those that had been reported in large populations.

If we compare our 6-month data to 1-year results in the large study (101,629 users of the 780G system in 34 countries) by Choudhary et al. [7], we report a TIR value at 72.4 % compared to the published 72.3 %; $TBR^{<70}$ was 1.9 % in our study versus 2.0 %; $TBR^{<54}$ was 0.3 % versus 0.4 % and GMI was 7.0 % versus 7.0 %. We report a percentage of patients reaching a TIR >70 % at 61.8 % versus 62.5 % and those reaching a GMI value < 7 % at 57.4 % versus 59.6 %. The percentage of patients PwT1D reaching EST was 39.7 % in our study versus 47.7 % in the large population.

Using HCL requires patient training and involvement, as it is still crucial for the system user to set activity mode when needed and to indicate carbohydrate intake before a meal. This can be hard to handle

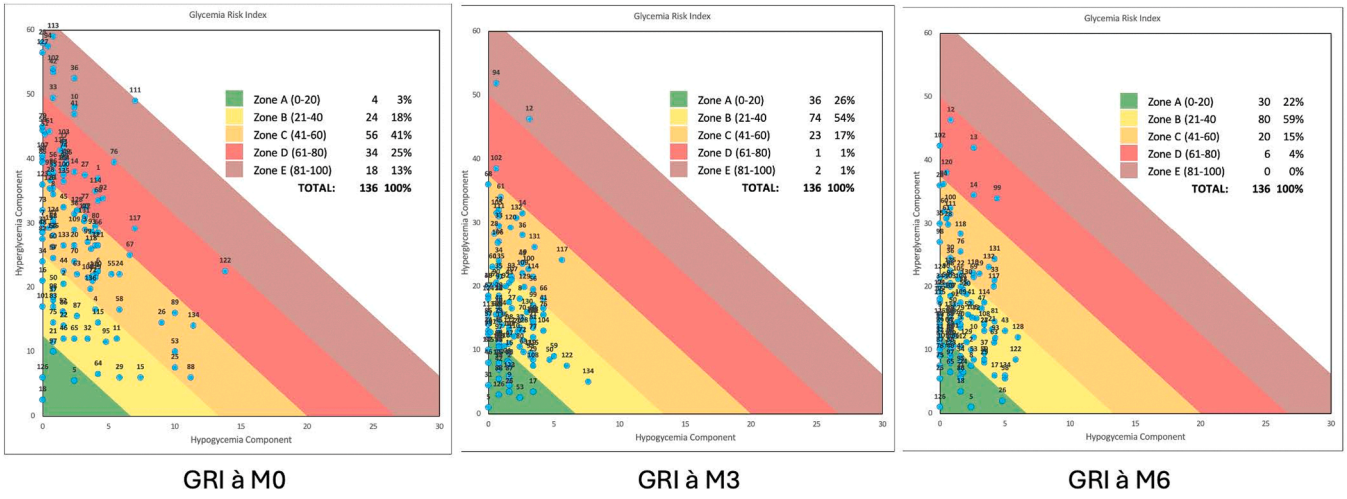

Fig. 1. GRI (= Glucose Risk Index) grids for the whole population (n=136) before hybrid closed loop initiation (M0), at 3 months (M3) and at 6 months (M6). Each grid is displayed with the number and the proportion of patients in the 5 GRI zones (A to E). Each patient is represented by a blue circle with an identification number (from 1 to 136).

for some patients and it is important to quickly identify those who struggle with their HCL system and need further support. It could be expected that people who reach EST as described above (a little less than half of our HCL users) are quite comfortable with their device and that attention should be focused on the other half. Many PwT1D using HCL are followed by telemedicine and a single number that could separate those who reach EST and those who do not, would help saving time and energy for those who need it most.

New glucose metrics have been described recently including GRI that accounts for both hypoglycemic and hyperglycemic risk and can be easily calculated using an electronic calculator. If GRI could be automatically calculated on CGM platforms, a single number with an automatic alert might help signaling those patients needing further support. Based on more than 400 AGP, we found that a GRI value < 26 would select most of the PwT1D who reach EST with 83 % sensitivity, 81 % PPV, 92 % specificity, and 93 % NPV. Thus, an alert on CGM platforms for GRI values at or above 26 – a little more than half of patients on HCL in our population – could help focusing on people who did not reach targets for further education. A threshold set at this level of GRI (< 26 versus ≥ 26) had very good specificity and NPV to identify those with a GRI ≥ 26 who do need further intensive support. As PPV was above 80 % and specificity above 90 %, we could consider it as a valid threshold.

Our study has some limitations. First, the population was quite limited and could have been "selected" as patients who are followed in private practice might be different from the general population of PwT1D. However, we found basically the same glucose metrics as Choudhary et al. [7] whose study included almost a thousand-fold more PwT1D as compared to our study. Furthermore, if we consider our GRI results at M6, we report a value close to the one reported by Resmini et al. [8] (30.6 in our study versus 27.6) although baseline AGP parameters were quite different (GRI at 56.0 in our study versus 37.5, TIR at 53.1 % versus 66.8 %). Second, HCL systems differed among patients and for a same person the sensor differed between before and after HCL initiation. We did not look at differences between systems or sensors as reimbursement conditions in France induced obvious differences between patients: the Medtronic 780G system was the first one covered by French national health insurance (in November 2022) and the only one that could be prescribed in PwT1D whatever baseline HbA1c. Nevertheless, this could have changed the evolution of glucose metrics between M0 and M3/M6 but not the relation between GRI value and EST achievement. Finally, it could be argued that our GRI calculation was based on only 14-day AGP measurements; however, this was shown as being the ideal sampling duration for GRI estimation [9].

Thus, for the first time, we showed here that multisite out-of-hospital initiation centers like the CIRDIA can achieve similar results to those reported in large cohorts. Moreover, we found that a GRI threshold at 26 could be useful to detect on a single number – potentially automatically calculated by CGM platforms – PwT1D who definitively require further support (those with a GRI ≥ 26). For PwT1D and a GRI < 26, it appears that those with a value at or below 20 (GRI zone A) almost always reach EST, whereas those with a GRI value ranging from 21 to 25 might need a specific analysis of their CGM metrics.

CRediT authorship contribution statement

Sylvie Picard: Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Blandine Courbebaisse:** Validation, Investigation. **Joëlle Dupont:** Validation, Investigation. **Fabienne Amiot-Chapoutot:** Validation, Investigation. **Emmanuelle Lecornet-Sokol:** Validation, Investigation. **Estelle Personeni:** Validation, Investigation. **François Mougel:** Validation, Investigation. **Clara Bouché:** Validation. **Françoise Giroud:** Validation. **Sandrine Lablanche:** Validation. **Sophie Borot:** Validation, Supervision, Software, Methodology, Data curation.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Sylvie Picard reports a relationship with Abbott that includes: board membership, consulting or advisory, and speaking and lecture fees. Sylvie Picard reports a relationship with Insulet Corporation that includes: board membership. Sylvie Picard reports a relationship with Eli Lilly and Company that includes: consulting or advisory and speaking and lecture fees. Sylvie Picard reports a relationship with Medtronic that includes: speaking and lecture fees. Sylvie Picard reports a relationship with Novo Nordisk Inc that includes: consulting or advisory and speaking and lecture fees. Sylvie Picard reports a relationship with Sanofi that includes: speaking and lecture fees. Sylvie Picard reports a relationship with VitalAire France that includes: consulting or advisory, speaking and lecture fees, and travel reimbursement. Blandine Courbebaisse reports a relationship with Abbott that includes: speaking and lecture fees. Blandine Courbebaisse reports a relationship with Dexcom that includes: speaking and lecture fees. Blandine Courbebaisse reports a

relationship with Lilly France that includes: speaking and lecture fees. Blandine Courbebaisse reports a relationship with Novo Nordisk Inc that includes: speaking and lecture fees. Blandine Courbebaisse reports a relationship with Sanofi that includes: speaking and lecture fees. Blandine Courbebaisse reports a relationship with VitalAire France that includes: speaking and lecture fees. Joelle Dupont reports a relationship with Novo Nordisk Inc that includes: speaking and lecture fees. Emmanuelle Lecornet-Sokol reports a relationship with Abbott that includes: consulting or advisory and speaking and lecture fees. Emmanuelle Lecornet-Sokol reports a relationship with Dexcom that includes: speaking and lecture fees. Emmanuelle Lecornet-Sokol reports a relationship with Insulet Corporation that includes: board membership. Emmanuelle Lecornet-Sokol reports a relationship with LifeScan France SAS that includes: speaking and lecture fees. Emmanuelle Lecornet-Sokol reports a relationship with Novo Nordisk that includes: consulting or advisory and speaking and lecture fees. Emmanuelle Lecornet-Sokol reports a relationship with Lilly France that includes: speaking and lecture fees. Emmanuelle Lecornet-Sokol reports a relationship with Sanofi that includes: consulting or advisory and speaking and lecture fees. Estelle Personeni reports a relationship with Lilly France that includes: speaking and lecture fees. Francois Mougel reports a relationship with Lilly France that includes: speaking and lecture fees. Clara Bouche reports a relationship with Dexcom that includes: consulting or advisory and speaking and lecture fees. Clara Bouche reports a relationship with Lilly France that includes: consulting or advisory and speaking and lecture fees. Sandrine Lablanche reports a relationship with Abbott that includes: consulting or advisory and speaking and lecture fees. Sandrine Lablanche reports a relationship with Insulet Corporation that includes: consulting or advisory and speaking and lecture fees. Sandrine Lablanche reports a relationship with Medtronic that includes: consulting or advisory and speaking and lecture fees. Sandrine Lablanche reports a relationship with Dexcom that includes: consulting or advisory and speaking and lecture fees. Sophie Borot reports a relationship with Dexcom that includes: consulting or advisory and speaking and lecture fees. Sophie Borot reports a relationship with Insulet Corporation that includes: consulting or advisory and speaking and lecture fees. Sophie Borot reports a relationship with Lilly France that includes: consulting or advisory and speaking and lecture fees. Sophie Borot reports a relationship with Medtrum that includes: consulting or advisory and speaking and lecture fees. The CIRDIA is supported by a research grant from Clement-Drevon Foundation, Dijon and by donations from French Diabetic Association (Burgundy-Franche Comte), French Mutualite 39 and received an award from FENAREDIAM. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Disclosures

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