



## Research letter



# Glycemic Risk Index (GRI) variability in type 1 diabetes adults with HbA1c $\leq 7\%$ : Insights for clinical evaluation and intervention

The glycemic risk index (GRI) is a new composite indicator derived from continuous glucose monitoring (CGM) data that assesses glycemic control quality by weighting hypoglycemic events more heavily than hyperglycemia and extreme hypo/hyperglycemia [1].

The ambulatory glucose profile (AGP) provides percentages of time spent in 70–180 mg/dl range (TIR),  $< 54$  mg/dm (very low glucose hypoglycemia; VLow), 54 to  $< 70$  mg/dl (low glucose hypoglycemia; Low),  $< 70$  mg/dl (time below range (TBR)  $< 70$  mg/dl; VLow + Low),

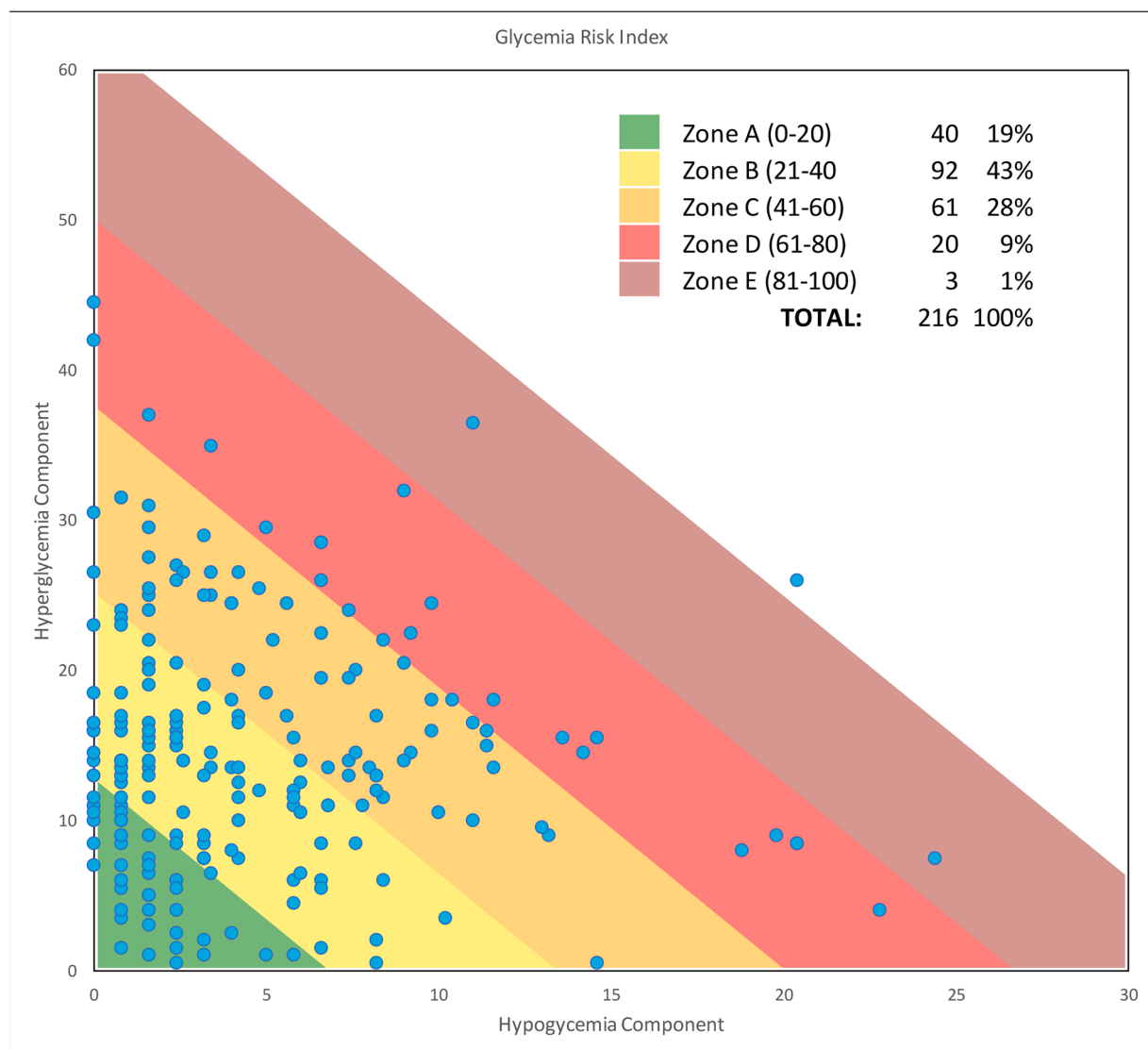


Fig. 1. - GRI (Glycemic Risk Index) grid for 216 is-CGM tracings in T1DM patients with HbA1c  $< 7.0\%$ .

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**Table 1**Characteristics of individuals and Continuous Glucose Monitoring Metrics according to GRI zones category ( $n = 216$ ).

| Baseline characteristics of individuals with T1D by GRI zone                                                              |                                                       |             |                 |                                                              |              |                                |  |
|---------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------|-------------|-----------------|--------------------------------------------------------------|--------------|--------------------------------|--|
|                                                                                                                           | All zones<br>means $\pm$ SD with [95 %CI], n or n (%) |             | Zones A-B       | Zones C-d-E                                                  |              | Zones C-d-E vs A-B<br><i>P</i> |  |
| N                                                                                                                         | 216                                                   |             | 132 (61)        | 84 (39)                                                      |              |                                |  |
| Age (years)                                                                                                               | 56.9 $\pm$ 18.5                                       | 54.4 - 59.3 | 61.9 $\pm$ 17.2 | 49.1 $\pm$ 17.8                                              |              | < 0.0001                       |  |
| Male                                                                                                                      | 129 (59.7)                                            | -           | 73 (55.3)       | 56 (66.7)                                                    |              |                                |  |
| Female                                                                                                                    | 87 (40.3)                                             | -           | 59 (44.7)       | 28 (33.3)                                                    |              |                                |  |
| BMI (kg/m <sup>2</sup> )                                                                                                  | 27.6 $\pm$ 6                                          | 26.8 - 28.4 | 28.5 $\pm$ 6.6  | 26.1 $\pm$ 4.5                                               |              | 0.004                          |  |
| Insulin therapy:                                                                                                          |                                                       |             |                 |                                                              |              |                                |  |
| -Multiple daily injections (n (%))                                                                                        | 203 (94)                                              | -           | 124 (93.9)      | 79 (94)                                                      |              |                                |  |
| -Insulin pump therapy (n (%))                                                                                             | 8 (3.7)                                               | -           | 3 (2.3)         | 5 (6)                                                        |              |                                |  |
| -Hybrid closed-loop insulin delivery (n (%))                                                                              | 5 (2.3)                                               | -           | 5 (3.8)         | 0                                                            |              |                                |  |
| Diabetes duration (years)                                                                                                 | 23.9 $\pm$ 15                                         | 21.9 - 25.9 | 23.07 $\pm$ 15  | 25.3 $\pm$ 14.3                                              |              | 0.27                           |  |
| Characteristics of 90-day ambulatory glucose profile and A1C measurements in overall GRI zones, A-B zones and C-d-E zones |                                                       |             |                 |                                                              |              |                                |  |
| GRI zones                                                                                                                 | All zones<br>means $\pm$ SD or n (%)                  | Zones A-B   | Zones C-d-E     | Zones C-d-E versus A-B<br>Difference between means $\pm$ SEM | [95 %CI]     | <i>P</i>                       |  |
| HbA1c (%)                                                                                                                 | 6.6 (0.4)                                             | 6.6 (0.4)   | 6.6 (0.3)       | 0.05 $\pm$ 0.05                                              | -0.05; 0.16  | 0.33                           |  |
| HbA1c (mmol/mol)                                                                                                          | 48.4 (4.14)                                           | 48.4 (4.14) | 48.7 (3.6)      |                                                              |              |                                |  |
| Duration FSL2 sensor active (%)                                                                                           | 90.7 (9.3)                                            | 90.8 (9.6)  | 90.6 (8.7)      | -0.2 $\pm$ 1.3                                               | -2.7; 2.3    | 0.89                           |  |
| Average scans/day (n)                                                                                                     | 9.5 (5.2)                                             | 9.5 (5.4)   | 9.5 (4.9)       | 0.08 $\pm$ 0.7                                               | -1.4; 1.5    | 0.91                           |  |
| Coefficient of variation (%)                                                                                              | 37 (7.1)                                              | 33 (4.7)    | 43.1 (5.8)      | 10.1 $\pm$ 0.7                                               | 8.7; 11.5    | < 0.0001                       |  |
| Individuals with coefficient of variation $\leq$ 36 % (n)                                                                 | 101 (46.7)                                            | 93 (70.4)   | 8 (9.5)         |                                                              |              | < 0.0001                       |  |
| Mean glucose (mg/dl)                                                                                                      | 145 (19)                                              | 140 (15)    | 153 (22)        | 13.0 $\pm$ 2.5                                               | 8.2; 18.2    | < 0.0001                       |  |
| GMI (%)                                                                                                                   | 6.7 (0.5)                                             | 6.6 (0.3)   | 7.0 (0.5)       | 0.4 $\pm$ 0.06                                               | 0.2; 0.4     | < 0.0001                       |  |
| Standard CGM metrics:                                                                                                     |                                                       |             |                 |                                                              |              |                                |  |
| % of time below range:                                                                                                    |                                                       |             |                 |                                                              |              |                                |  |
| Very Low (< 54 mg/dl; < 3.0 mmol/l)                                                                                       | 1.0 (2.0)                                             | 0.3 (0.6)   | 2.0 (3.0)       | 1.7 $\pm$ 0.2                                                | 1.2; 2.3     | <sup>a</sup>                   |  |
| Low (54- < 70 mg/dl; 3.0- < 3.9 mmol/l)                                                                                   | 4.4 (4)                                               | 3 (2.2)     | 7.0 (4.0)       | 4.0 $\pm$ 0.4                                                | 3.3; 5.1     | <sup>a</sup>                   |  |
| % of time In range (70-180 mg/dl; 3.9-10.0 mmol/l)                                                                        | 71 (12)                                               | 78 (8.1)    | 60 (7.8)        | -18.0 $\pm$ 1.1                                              | -20.6; -16.2 | <sup>a</sup>                   |  |
| % of time above range:                                                                                                    |                                                       |             |                 |                                                              |              |                                |  |
| Very High (> 250 mg/dl; > 13.9 mmol/l)                                                                                    | 5.5 (5.3)                                             | 3 (2.5)     | 10.0 (6)        | 7. $\pm$ 0.6                                                 | 5.6; 7.9     | <sup>a</sup>                   |  |
| High (> 180-250 mg/dl; > 10.0-13.9 mmol/l)                                                                                | 18 (7.3)                                              | 16 (6.8)    | 21.0 (7.0)      | 5.0 $\pm$ 0.9                                                | 3.6; 7.4     | <sup>a</sup>                   |  |
| HypoComponent                                                                                                             | 4.6 (4.6)                                             | 3 (2.2)     | 8.0 (6)         | 5.0 $\pm$ 0.54                                               | 4.1; 6.2     | <sup>a</sup>                   |  |
| HyperComponent                                                                                                            | 14.5 (8.2)                                            | 11 (5.4)    | 20 (9)          | 9 $\pm$ 0.9                                                  | 7.6; 11.4    | <sup>a</sup>                   |  |
| Glycemia risk index                                                                                                       | 37 (18)                                               | 25 (8.9)    | 56 (12)         | 31 $\pm$ 1.4                                                 | 28.0; 33.6   | <sup>a</sup>                   |  |

Data are presented as means  $\pm$  SD with [95 %CI] for continuous variables, and as numbers (%) for categorical variables. *P* value for chi-square or Student's *t*-test. *P* values < 0.05 considered significant. GRI: glycemic risk index, BMI: body mass index, HbA1c: hemoglobin A1c, GMI: glucose management indicator, FSL2: FreeStyle Libre 2.

<sup>a</sup> : *p*-values not determined for these items, as differences arise from patients' disposition to their respective groups as per study design.

>180 to 250 mg/dl (high glucose hyperglycemia; High), > 250 mg/dl (very high glucose hyperglycemia; VHigh) and >180 mg/dl (time above range (TAR) > 180 mg/dl; VHigh + High), mean glucose, glucose management indicator (GMI), and coefficient of variation of glucose.

From AGP data, the GRI and its hypoglycemia and hyperglycemia components were calculated as follows: hypoglycemia component = VLow + (0.8  $\times$  Low); hyperglycemia component = VHigh + (0.5  $\times$  High); and GRI = (3.0  $\times$  hypoglycemia component) + (1.6  $\times$  hyperglycemia component) or else GRI = (3.0  $\times$  VLow) + (2.4  $\times$  Low) + (1.6  $\times$  VHigh) + (0.8  $\times$  High). The GRI is then plotted on a graph (Fig. 1) divided into 5 glycaemia risk zones (called A-E) corresponding to the most favorable (1st-20th percentile) and most unfavorable (81st-100th percentile) quintiles for overall glycaemia quality.

Our study focused on GRIs of adults with well-controlled type 1 diabetes mellitus (T1DM), indicated by HbA1c levels of 7 % or less. We retrospectively analyzed T1DM patients using the FreeStyle Libre 2 CGM system, prioritizing those with over 70 % CGM usage in the past 90 days. Our inclusion criteria covered various insulin therapies, including multiple daily injections (MDI), insulin pump therapy, and hybrid closed-loop (HCL) systems, with a key focus on patients achieving optimal glycemic control. This approach aimed to provide insights into GRI of effectively-managed T1DM. Our analysis focused on evaluating 90-day CGM, specifically examining the GRI components of hypoglycemia and hyperglycemia (CHypo/CHyper).

We compared patients with GRI in high-risk areas, classified as areas C-d-E (41st to 100th percentiles), with those in lower-risk areas A-B (0th to 40th percentiles). This analysis aimed to assess the extent of glycemic variability among patients with HbA1c levels below 7 %. Informed

consent was not a prerequisite for this retrospective study. However, stringent measures for data confidentiality and security were implemented to ensure protection and anonymity of patients.

A total of 216 people with T1DM (age (mean  $\pm$  SD): 57  $\pm$  18.5 years) with a mean HbA1c of 6.6  $\pm$  0.3 % were studied. Patients' clinical characteristics are detailed in Table 1 and Fig. 1.

Individual GRIs were sorted into Zone A (0-20th;  $n = 40$ ), Zone B (21-40th;  $n = 92$ ), Zone C (41-60th;  $n = 61$ ), Zone D (61-80th;  $n = 20$ ), and Zone E (81-100th;  $n = 3$ ).

Patients in Zones C-d-E:  $n = 84$  (39 %; GRI 56  $\pm$  12) were compared with those in Zones A-B:  $n = 132$  (61 %; GRI 25  $\pm$  9). Zones C-d-E patients were younger (49  $\pm$  17.8 versus 62  $\pm$  17.2 years;  $P < 0.0001$ ), overweight (28.5  $\pm$  6.6 versus 26.1  $\pm$  4.5 kg/m<sup>2</sup>;  $P = 0.004$ ) with similar duration of diabetes (23.1  $\pm$  15.0 versus 25.3  $\pm$  14.3 years; ns). Mean interstitial glucose (153  $\pm$  22.4 versus 140  $\pm$  14.8 mg/dl) and glucose coefficient of variation (43.1  $\pm$  5.8 versus 33.0  $\pm$  4.7 %) were significantly higher among patients of Zones C-d-E, as were CHypo (8.0  $\pm$  6.0 versus 3.0  $\pm$  2.0) and CHyper (20  $\pm$  9 versus 11  $\pm$  5.0) ( $P < 0.0001$ ). TIR was also significantly lower among Zones C-d-E patients (60  $\pm$  8 % versus 78  $\pm$  8 % among Zones A-B patients).

## Conclusion

The management of T1DM is inherently complex, and our study underscores the emerging importance of GRI as a pivotal tool, complementing traditional metrics such as HbA1c and TIR. Our findings reveal that, even among T1DM patients who meet conventional criteria for optimal glycemic control, GRI assessment uncovered a significant

segment (39 %) whose inadequate glucose control was not obvious when based on standard parameters. This highlights a crucial gap in diabetes management: despite seemingly meeting satisfactory traditional indicators, many patients may still require tailored therapeutic adjustments for better diabetes control. To holistically evaluate glyce-mic control in T1DM, incorporating GRI assessment alongside routine metrics such as TIR, TBR, TAR, and GMI is recommended for a more nuanced and effective management strategy.

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## Author contributions

P.O., G.P conceptualized this work and drafted the protocol  
P.O., M.P.H., A.V., J.C.P and G.P. contributed to screening and data extraction.

P.O., M.P.H. and G.P. led the analysis and write-up of the work.

All authors reviewed and edited the manuscript. P.O. is the guarantor of this work and, as such, had full access to all data under review and takes responsibility for the integrity of the data and the accuracy of the data analysis.

## CRediT authorship contribution statement

**Philippe Oriot**: Conceptualization, Data curation, Formal analysis, Investigation, Methodology, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing. **Michel P Hermans**: Data curation, Investigation, Resources, Supervision, Validation, Visualization, Writing – original draft, Writing – review &

editing. **Antoine Vandelaer**: Data curation, Resources, Visualization. **Jean Christophe Philips**: Data curation, Supervision, Visualization. **Gaëtan Prévost**: Data curation, Investigation, Methodology, Supervision, Validation, Visualization, Writing – original draft, Writing – review & editing.

## Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Reference

- [1] Klonoff DC, Wang J, Rodbard D, Kohn MA, Li C, Liepmann D, et al. A Glycemia risk Index (GRI) of hypoglycemia and hyperglycemia for continuous glucose monitoring validated by clinician ratings. *J Diabetes Sci Technol* 2023;17:1226–42. <https://doi.org/10.1177/19322968221085273>.

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