# Evaluating glucose control with a novel Composite Continuous Glucose Monitoring Index (COGI)

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## ABSTRACT

### *Objective*

To describe a novel composite continuous glucose monitoring index (COGI) and to evaluate its utility, in adults with type 1 diabetes, during hybrid closed-loop (HCL) therapy and multiple daily injections (MDI) therapy combined with real-time continuous glucose monitoring (CGM).

### *Methods*

COGI consists of three key components of glucose control as assessed by CGM: Time in range (TIR), time below range (TBR) and glucose variability (GV) (weighted by 50%, 35% and 15%). COGI ranges from 0 to 100, where 1% increase of time <3.9 mmol/L (<70 mg/dl) is equivalent to 4.7% reduction of TIR between 3.9 to 10 mmol/L (70 to 180 mg/dl), and 0.5 mmol/L (9 mg/dl) increase in standard deviation is equivalent to 3% reduction in TIR.

### *Results*

Continuous subcutaneous insulin infusion (CSII) users with HbA1c >7.5% to 10%, had significantly higher COGI during 12 weeks of HCL compared to sensor-augmented pump therapy (mean (SD), 69.5 (6.9) vs 60.3 (8.6), p<0.001). Similarly, in CSII users with HbA1c <7.5%, HCL improved COGI from 59.9 (11.2) to 74.8 (6.6), p<0.001. In MDI users with HbA1c >7.5% to 9.9%, use of real-time CGM led to improved COGI, 49.8 (14.2) vs 58.2 (9.1) p<0.0001. In MDI users with impaired awareness of hypoglycaemia, use of real-time CGM led to improved COGI, 66.7 (11.1) vs 53.4 (12.2), p<0.001.

***Conclusions***

COGI summarises three key aspects of CGM data into a concise metric that could be utilised to evaluate the quality of glucose control and to demonstrate the incremental benefit of wide range of treatment modalities.

**Keywords**: continuous glucose monitoring, type 1 diabetes, closed-loop insulin delivery

Real-time continuous glucose monitoring (CGM) and intermittently viewed continuous glucose monitoring has transformed the management of type 1 diabetes (1) and paved the way to novel therapeutic interventions such as automated insulin delivery (2). Usage of real-time CGM by multiple daily injection (MDI) users has been shown to improve HbA1c (3) and reduce the burden of hypoglycaemia (4). There is increasing recognition of the limitations of HbA1c as the sole measure of glycaemic control, as it provides little or no information on clinically relevant outcomes such as hypoglycaemia or glucose variability (5-6). In contrast, continuous glucose monitoring (CGM) data provide detailed information about multiple aspects of glucose control such as time spent in the target glucose range (TIR), time spent in hypo and hyperglycaemia as well as glucose variability (GV). An international panel of experts has recently agreed on reporting of various CGM based metrics under research and clinical care setting (7).

Given the limitation of HbA1c and the greater appreciation of CGM-derived glycaemic outcomes, there is a growing interest to develop composite CGM indices (8). Such composite indices may provide adjuvant information related to dysglycaemia in people living with type 1 diabetes and may provide a tool to assess the therapeutic response to novel interventions such as automated insulin delivery or other therapies incorporating CGM (9). Composite indices are widely used in other clinical specialities to complement decision-making, for example in intensive care medicine (APACHE score), neonatology (APGAR score) and stroke medicine (Glasgow Coma Scale). Previous attempts at summarising CGM data include "Glucose Pentagon Model" (8) and “Q score”(10).

Here we describe a novel, easier to calculate and interpret, composite continuous glucose monitoring index (COGI) encompassing three vital elements of CGM-derived glucose control. We then use data from four recently published randomised controlled trials (RCTs) to demonstrate the utility of COGI index. We hypothesised that COGI might reveal important glycaemic benefits of novel treatment modalities such automated insulin delivery with hybrid closed-loop and addition of real-time CGM to those using MDI therapy, beyond merely reporting changes in HbA1c.

**Methods**

We constructed the COGI from three key elements of CGM representing euglycaemia, hypoglycaemia, and glucose variability: “Time in Range” (TIR) between 3.9 to 10mM (70 to 180mg/dl) and “Time below Range” <3.9 mmol/L (70mg/dl) (TBR) were used as measures for euglycaemia and hypoglycaemia, respectively (Table 1). Standard deviation (SD) of overall glucose was used as a measure of glucose variability (GV). The relative contributions from these components where TIR, TBR and GV contributed 50%, 35% and 15% to the total COGI were pragmatically based on investigator consensus.

We allocated 0 points to 0% TIR and 100 points where TIR between 3.9 to 10mM (70 to 180mg/dl) is 100%. For TBR, 100 points were allocated if the TBR <3.9 mmol/L (<70mg/dl) was 0% and 0 points if TBR 15% and above. GV as measured by SD was scaled from 1 to 6 mmol/L (18 to 108mg/dl) where SD of 1 mmol/L (18mg/dl) and below is given 100 points, and SD of 6 mmol/L (108mg/dl) and above is given 0 points. For each of these elements, points were linearly interpolated between their boundaries.

The total index ranges from 0 to 100. The above allocation of scoring means, one percent increase in time <3.9 mmol/L (<70mg/dl) is equivalent to 4.7% decrease in time in range (TIR) (penalty for time below range), and 0.5 mmol/L (9mg/dl) increase in standard deviation of glucose is equivalent to 3% decrease in TIR (penalty of higher variability). It also means one percent increase in time <3.9 mmol/L (<70mg/dl) will decrease COGI by 2.3 points, whereas an increase of TIR by 1 percentage point will increase the COGI by 0.5 points. A healthy individual without

diabetes who spent 2% time below 3.9 mmol/L (70mg/dl) will have a COGI of 90.6 while if the time spent below 3.9 mmol/L is zero will have maximum COGI of 100 (based on reference 13).

The total and individual components of COGI were calculated in adults with type 1 diabetes treated with multiple daily injection therapy (MDI) or continuous subcutaneous insulin infusion (CSII) from 4 previously published RCTs (3,4,11,12). Study design and methods of these studies have been published and described in detail elsewhere. Summaries of these studies are shown in Table 2.

Briefly, AP@home04 phase 1 study (11) evaluated the safety and effectiveness of hybrid closed-loop in comparison to sensor-augmented pump therapy in adults with type 1 diabetes and HbA1c between 7.5% to 10% (58 to 86 mmol/mol) for 12 weeks, while AP@home04 phase 2 study (12) evaluated the safety and effectiveness of hybrid closed-loop in comparison to insulin pump therapy with or without real-time CGM in adults with type 1 diabetes and HbA1c < 7.5% (<58 mmol/mol) for 4 weeks.

DIAMOND study (3) evaluated the effectiveness of real-time CGM in adults with type 1 diabetes and HbA1c levels between 7.5% (58 mmol/mol) to 9.9% (85 mmol/mol) treated with MDI where participants were allocated 2:1 to either real-time CGM (Dexcom G4 Platinum system, Dexcom Inc, CA, USA) or usual care group for 24 weeks. HypoDE study (4) evaluated the effectiveness of real-time CGM (Dexcom G5, Dexcom Inc, CA, USA) in avoidance of hypoglycaemia in adults with type 1 diabetes treated with MDI and history of impaired awareness of hypoglycaemia or severe hypoglycaemia and HbA1c ≤9.0% (75 mmol/mol).

*Data and statistical analysis*

We calculated TIR between 70 to 180 mg/dl, TBR <70 mg/dl and GV as measured by the SD for each study participant. We then calculated the individual and total components of the COGI score using Microsoft Excel. SD are reported for means and interquartile ranges (IQRs) for medians where applicable. We used SPSS (v.22) or SAS (version 9.3) for statistical analysis. Either paired samples t-tests or analysis of covariance (ANOVA) were performed for comparison of treatment groups. In case of skewed data, either Wilcoxon signed rank tests or covariance models based on ranks with van der Waerden scores were used. Each analysis was tested at a two-sided significance levels of 0.05.

**Results**

Twelve-week of hybrid closed-loop by type 1 diabetes adults with HbA1c >7.5% (11) led to a significant improvement in COGI index (Table 3). Although all three components of COGI improved, the highest contribution came from TIR. HbA1c and COGI improvement by hybrid closed-loop use in the whole cohort was -0.3%(0.6) (p=0.002) and +10% (p<0.005, 95% confidence interval (CI) 7 to 11%) respectively. Sub-group analysis in those without HbA1c improvement (n=15) showed that total and individual COGI components improved with hybrid closed-loop use (total COGI, CL vs. SAP, 71(6) vs. 60 (10), p<0.001, TIR 36(5) vs. 33(6), p=0.003, TBR 26 (4) vs. 19 (9), p=0.001 and GV 9(2) vs. 8(2), p=0.029). Four-week hybrid closed-loop use by type 1 diabetes adults with HbA1c <7.5% (12) also showed significant improvements in total and all three components of the COGI index (Table 3).

In the 6-month study of real-time CGM use among MDI users with sub-optimal control (DIAMOND study) (3), a significant improvement of all three components of COGI was shown (Table 4). During the HypoDE study, which included individuals with impaired awareness of hypoglycaemia, as expected the most noticeable improvements were noted in the hypoglycaemia component. The between-group HbA1c difference in the study involving type 1 diabetes individuals with impaired awareness of hypoglycaemia (HypoDE study) was non-significant at 0.03% (p=0.66) (4), however a significant improvement in the total COGI index was observed notably within the hypoglycaemia component, highlighting the utility of COGI beyond HbA1c.

## Discussion

The multiple glucometric data provided by CGM present an excellent opportunity to define a composite index which can be utilised in clinical and research settings. Here we present such a novel composite CGM index, encompassing three key aspects of CGM-based assessment of glucose control: time spent in normal glucose, hypoglycaemia and glucose variability. These are aspects of glucose control which are arguably most important for people living with type 1 diabetes. We show that by using COGI, the incremental benefits of hybrid closed-loop use on glucose control can be demonstrated even in those individuals with very good HbA1c. Furthermore, COGI demonstrates the additional benefit of real-time CGM use even without apparent HbA1c improvements.

The original Glucose Pentagon Model described by Thomas et. al in 2009 (8) included five metrics: mean glucose, SD of the mean glucose, amount of time per day in which hyperglycaemic values (>160mg/dl) were recorded, the area below the curve of hyperglycaemic values (>160mg/dl), and HbA1c. Each parameter formed a single axis of a five-sided figure. By taking the area within the glucose pentagon of a given individual with diabetes and normalising it to the standard area of a healthy individual without diabetes, a Glycaemic Risk Parameter (GRP) was defined. Subsequently, authors re-analysed a sub-set of data from the JDRF real-time CGM study showing a more substantial percentage improvement of GRP than HbA1c improvement with real-time CGM (9).

Hypoglycaemia is one of the most significant barriers to achieving near-normal glucose control for people living with diabetes and their caregivers (13). One of the

limitations of the original glucose pentagon may be the non-inclusion of a measure of hypoglycaemia. In 2017, Vigersky et al. presented the comprehensive glucose pentagon (CGP) which included several changes to the original pentagon model (14). In the CGP, HbA1c axis was eliminated, and glycaemic variability was measured with CV rather than SD. New aspects included time outside range and intensity of hypo and hyperglycaemia.

Q-score is another novel concept in analysing CGM profiles presented by Augustein et al. in 2015 (10). Authors identified four key factors using 1,562 historic CGM profiles in people with type 1 and type 2 diabetes. These four factors were; central tendency and hyperglycaemia, intra-day variability, hypoglycaemia and inter-day variability. They choose mean glucose, time spent above the target range, the range of glucose, time spent below target range and mean of daily difference (MODD) in calculating the Q score. They used Q-score to categorise the quality of glucose control ranging from poor to very good.

One potential limitation of glucose pentagon models and Q score is the need for relatively complex mathematical formulas to calculate the pentagon area and Q score and difficulty in interpreting values obtained with these methods under day-to-day clinical practice conditions. On the other hand, a single index expressed as a score from 100 (where 100 reaches the glucose profile of people without diabetes) would be easier to understand and interpret. A previous real-time CGM study looking at the characterisation of interstitial glucose levels in individuals without diabetes have shown that virtually all glucose levels were <140mg/dl (<7.8mM) and that 0.6 to 2.9% of real-time CGM glucose levels could be below 70mg/dl (<3.9mM) (15). In that

study, glucose variability measured with SD was below 18mg/dl (<1 mmol/L) in all age groups.

COGI summarises CGM data into a single index ranging from 0 to 100. It is easy to interpret, i.e. those with COGI close to 100 have a glucose profile similar to somebody without diabetes while COGI of 50 indicates that quality of glucose control is 50% of that in a healthy individual without diabetes. COGI can be calculated using three widely available CGM metrics. As shown by variety of recently published studies, COGI could be easily applied in a wide number of study design and settings using CGM to assess study outcomes. Due to its cumulative effects, it may generate higher statistical power over individual components of CGM or HbA1c. Serial COGI scores could also be used as a relatively convenient and understandable method by people living with type 1 diabetes and caregivers to assess the progress of treatment during routine care.

Future iterations of COGI may include replacing components of COGI with alternative metrics. There is currently no consensus on the optimal metric for assessing GV. Standard deviation, which correlates with mean glucose, was used to measure GV in our analysis. As COGI does not include mean glucose, use of SD may be acceptable or advantageous. It is thus possible to replace SD with the coefficient of variation with the appropriate scale as the metric choice of variability. Similarly, time spent below 54mg/dl could be used instead of 70mg/dl. Reporting on COGI outcomes could potentially be incorporated into clinical software programmes such as Medtronic Carelink, Dexcom Clarity or Freestyle Libreview, as part of type 1 diabetes management.

A limitation of COGI is the pragmatic decision related to the weight of the three components: TIR 50%, TBR 35% and GV 15%. We allocated the most substantial weight to the time in range with 50% contribution to the index as this is likely to be the parameter most likely to relate to HbA1c and hence to capture the risk of long-term complications. We allocated 35% of weight to time below range, more than the 15% weight for GV to account for the importance of avoiding hypoglycemia as it remains one of the biggest barriers to achieving near normal glucose control. Other potential limitations include the use of SD instead of CV (see above) and use of 70 mg/dl as a cut off for time below range. HbA1c remains to date the only clinically validated prognostic marker of diabetes complications, and at present, no studies have linked CGM-based metrics with long-term clinical outcomes. There is a need to evaluate whether COGI can provide prognostic indications for future risk of macro and microvascular complications. Future studies will also need to evaluate the utility of COGI in type 2 diabetes or hospitalised patients and the relationship between COGI and patient-reported outcomes such as diabetes distress or low mood.

In conclusion, we have presented a novel composite CGM index consisting of three clinically meaningful parameters of glucose control representing euglycaemia, hypoglycaemia and glucose variability. We demonstrated, using four randomised studies involving adults with type 1 diabetes in diverse settings, that COGI may be utilised as an index of quality of glucose control specifically in the context of novel technology using CGM. Future studies evaluating its impact on real world data as well as clinical and patient-related outcomes are needed.

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*Author contributions:*

LL, HT and RH conceptualised the COGI index. HT, MEW, LB, JKM, TRB, CB, SA, LL, MLE and RH were involved in the planning and conduct of the two closed-loop studies. TJ analysed the data from the DIAMOND study. LL, HT and RH analysed data from other studies apart from DIAMOND study. LH and NH are lead investigators of the HypoDE study and provided data from that study. All authors critically evaluated the manuscript.

*Conflict of interest disclosures:* RH reports having received speaker honoraria from Minimed Medtronic, LifeScan, Eli Lilly, BBraun, and Novo Nordisk, serving on advisory panel for Animas, Minimed Medtronic, and Eli Lilly, receiving license fees from BBraun and Beckton Dickinson; and having served as a consultant to Beckton Dickinson, BBraun, Sanofi, and Profil. MLE reports having received speaker honoraria from Abbott Diabetes Care, Animas, NovoNordisk and Eli Lilly and serving on advisory boards for Medtronic, Roche, Cellnovo and NovoNordisk. MEW has received license fees from Becton Dickinson and has served as a consultant to Beckton Dickinson. RH and MEW report patent applications. LH is partner and consultant of Profil Institut für Stoffwechselforschung, Neuss, Germany and ProSciento Institute, San Diego, USA. He is a consultant for a number of companies that are developing novel diagnostic and therapeutic options. JKM is a member in the advisory board of Sanofi, Eli Lilly and Boehringer Ingelheim, and received speaker honoraria from Abbott Diabetes Care, Astra Zeneca, Eli Lilly, Nintamed, NovoNordisk A/S, Roche Diabetes Care, Servier and Takeda and is shareholders of decide

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## References


1. Tauschmann M, Hovorka R: Technology in the management of type 1 diabetes mellitus - current status and future prospects. Nat Rev Endocrinol 2018;14:464-475

2. Bekiari E, Kitsios K, Thabit H, Tauschmann M, Athanasiadou E, Karagiannis T, Haidich AB, Hovorka R, Tsapas A: Artificial pancreas treatment for outpatients with type 1 diabetes: systematic review and meta-analysis. BMJ 2018;361:k1310

3. Beck RW, Riddlesworth T, Ruedy K, Ahmann A, Bergenstal R, Haller S, Kollman C, Kruger D, McGill JB, Polonsky W, Toschi E, Wolpert H, Price D, Group DS: Effect of Continuous Glucose Monitoring on Glycemic Control in Adults With Type 1 Diabetes Using Insulin Injections: The DIAMOND Randomized Clinical Trial. JAMA 2017;317:371-378

4. Heinemann L, Freckmann G, Ehrmann D, Faber-Heinemann G, Guerra S, Waldenmaier D, Hermanns N: Real-time continuous glucose monitoring in adults with type 1 diabetes and impaired hypoglycaemia awareness or severe hypoglycaemia treated with multiple daily insulin injections (HypoDE): a multicentre, randomised controlled trial. Lancet 2018;391:1367-1377

5. Riddle MC, Gerstein HC, Cefalu WT: Maturation of rtCGM and Glycemic Measurements Beyond HbA1c-A Turning Point in Research and Clinical Decisions. Diabetes Care 2017;40:1611-1613

6. Agiostratidou G, Anhalt H, Ball D, Blonde L, Gourgari E, Harriman KN, Kowalski AJ, Madden P, McAuliffe-Fogarty AH, McElwee-Malloy M, Peters A, Raman S, Reifschneider K, Rubin K, Weinzimer SA: Standardizing Clinically Meaningful Outcome Measures Beyond HbA1c for Type 1 Diabetes: A Consensus Report of the American Association of Clinical Endocrinologists, the American Association of Diabetes Educators, the American Diabetes Association, the Endocrine Society, JDRF International, The Leona M. and Harry B. Helmsley Charitable Trust, the Pediatric Endocrine Society, and the type 1 diabetes Exchange. Diabetes Care 2017;40:1622-1630

7. Danne T, Nimri R, Battelino T, Bergenstal RM, Close KL, DeVries JH, Garg S, Heinemann L, Hirsch I, Amiel SA, Beck R, Bosi E, Buckingham B, Cobelli C, Dassau E, Doyle FJ, 3rd, Heller S, Hovorka R, Jia W, Jones T, Kordonouri O, Kovatchev B, Kowalski A, Laffel L, Maahs D, Murphy HR, Norgaard K, Parkin CG, Renard E, Saboo B, Scharf M, Tamborlane WV, Weinzimer SA, Phillip M: International Consensus on Use of Continuous Glucose Monitoring. Diabetes Care 2017;40:1631-1640

8. Thomas A, Schonauer M, Achermann F, Schnell O, Hanefeld M, Ziegelasch HJ, Mastrototaro J, Heinemann L: The "glucose pentagon": assessing glycemic control of patients with diabetes mellitus by a model integrating different parameters from glucose profiles. Diabetes Technol Ther 2009;11:399-409

9. Thomas A, Heinemann L: Prediction of the risk to develop diabetes-related late complications by means of the glucose pentagon model: analysis of data from the Juvenile Diabetes Research Foundation continuous glucose monitoring study. J Diabetes Sci Technol 2012;6:572-580

10. Augstein P, Heinke P, Vogt L, Vogt R, Rackow C, Kohnert KD, Salzsieder E: Q-Score: development of a new metric for continuous glucose monitoring that enables stratification of antihyperglycaemic therapies. BMC Endocr Disord 2015;15:22

11. Thabit H, Tauschmann M, Allen JM, Leelarathna L, Hartnell S, Wilinska ME, Acerini CL, Dellweg S, Benesch C, Heinemann L, Mader JK, Holzer M, Kojzar H, Exall J, Yong J, Pichierri J, Barnard KD, Kollman C, Cheng P, Hindmarsh PC, Campbell FM, Arnolds S, Pieber TR, Evans ML, Dunger DB, Hovorka R: Home Use of an Artificial Beta Cell in Type 1 Diabetes. N Engl J Med 2015;373:2129-2140

12. Bally L, Thabit H, Kojzar H, Mader JK, Qerimi-Hyseni J, Hartnell S, Tauschmann M, Allen JM, Wilinska ME, Pieber TR, Evans ML, Hovorka R: Day-and-night glycaemic control with closed-loop insulin delivery versus conventional insulin pump therapy in free-living adults with well controlled type 1 diabetes: an open-label, randomised, crossover study. Lancet Diabetes Endocrinol 2017;5:261-270

13. Seaquist ER, Anderson J, Childs B, Cryer P, Dagogo-Jack S, Fish L, Heller SR, Rodriguez H, Rosenzweig J, Vigersky R: Hypoglycaemia and diabetes: a report of a workgroup of the American Diabetes Association and the Endocrine Society. Diabetes Care 2013;36:1384-1395

14. Vigersky RA, Shin J, Jiang B, Siegmund T, McMahon C, Thomas A: The Comprehensive Glucose Pentagon: A Glucose-Centric Composite Metric for Assessing Glycemic Control in Persons With Diabetes. J Diabetes Sci Technol 2018;12:114-123

15. Fox LA, Beck RW, Xing D: Variation of interstitial glucose measurements assessed by continuous glucose monitors in healthy, nondiabetic individuals. Diabetes Care 2010;33:1297-1299