ORIGINAL ARTICLE

WILEY

Clinical evaluation of a decision support system for glucose infusion in hypoglycaemic clamp experiments

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Abstract

Aim: To provide a preliminary evaluation of the accuracy and safety of Gluclas decision support system suggestions in a hypoglycaemic clamp study.

Methods: This analysis was performed using data from 32 participants (four groups with different glucose-insulin regulation: post Roux-en-Y gastric bypass with and without postprandial hypoglycaemia syndrome, postsleeve gastrectomy and non-operated controls) undergoing Gluclas-assisted hypoglycaemic clamps (target: 2.5 mmol/L for 20 minutes at 150 minutes after oral glucose ingestion). Gluclas provided glucose infusion rate suggestions upon manual entry of blood glucose values (every 5 minutes), which were either followed or overruled by investigators after critical review. Accuracy and safety were evaluated by mean absolute error (MAE), mean absolute percentage error (MAPE), average glucose level, coefficient of variation (CV) and minimal glucose level during the 20-minute hypoglycaemic period.

Results: Investigators accepted 84% of suggestions, with a mean deviation of 30.33 mg/min. During the hypoglycaemic period, the MAE was 0.16 (0.12-0.24) (median [interquartile range]) mmol/L and the MAPE was 6.12% (4.80%-9.29%). CV was 4.90% (3.58%-7.27%), with 5% considered the threshold for sufficient quality. The minimal glucose level was 2.40 (2.30-2.50) mmol/L.

Conclusions: Gluclas achieved sufficiently high accuracy with minimal safety risks in a population with differences in glucose-insulin dynamics, underscoring its applicability to various patient groups.

KEYWORDS
bariatric surgery, clinical trial, glycaemic control, hypoglycaemia

1 | INTRODUCTION

The glucose clamp (GC) is an experimental technique that is frequently used to investigate several aspects of human physiology and the pharmacodynamic actions of glucose-lowering medications. The key concept is to clamp plasma glucose to a predefined level and/or trajectory. This is achieved by a variable intravenous glucose infusion according to frequently sampled glucose values. For simplicity, the insulin infusion is most commonly kept constant after an initial priming dose.

The two types of GC that are most commonly used are the hyperglycaemic GC,[1-3] for the quantification of beta-cell sensitivity to

glucose, and the euglycaemic GC,[1,4,5] which is used to estimate whole body insulin sensitivity. Other examples include the hypoglycaemic GC, to evaluate counter-regulatory responses.[6,7] Pharmacodynamic responses of insulin formulation are usually quantified using euglycaemic GC experiments that are required by regulatory guidelines.

The GC method is supposed to be a standardized and reproducible experimental procedure. However, even minor deviations from the target glycaemic level can induce spurious fluctuations in the outcome, and the quality of these experiments relies heavily on how tightly glycaemia is controlled around the target.

In manual GCs, the investigators perform blood glucose (BG) measurements and manually adjust the glucose infusion rates (GIRs) every 3-10 minutes. Unfortunately, this task is not trivial and is highly dependent on the investigators' skills. Consequently, manual GC experiments are characterized by substantial interoperator and intraoperator variability, which challenges comparability between tests. To minimize potential bias and inaccuracies of GC experiments, adjustments of GIRs can be automated by a glucose control algorithm. In a fully automated GC experiment, such dosing algorithms are coupled with continuous glucose monitoring and infusion systems by means of dedicated devices, thereby obviating the need for manual entries by the investigator.[8–10] Such systems are dependent on interoperability between components, are considered high-risk medical devices and require regulatory approval. As a further complication, these fully automated GC devices are outdated (e.g. controller logic was not updated to modern insulin analogues),[11] not on the market, not accessible to academic researchers and may require highly invasive devices.

To assist researchers who cannot access fully automated solutions, our group developed Gluclas, a decision-support software for managing GC experiments. Gluclas is based on a proportional derivative integrative (PID) controller to suggest suitable GIRs through a simple-to-use graphical user interface (GUI) and was developed to support any GC protocol, including euglycaemic, hyperglycaemic and hypoglycaemic clamps.

To date, Gluclas has been validated in silico on 100 virtual subjects on different GC protocols.[12] In this work, we evaluate the performance of Gluclas-supported hypoglycaemic clamp experiments that were performed within the framework of a clinical trial involving 32 participants belonging to four different groups, matched for age, body mass index (BMI) and sex, but with differences in glucose-insulin dynamics.[13] Performance evaluation focused on control accuracy and patient safety, as well as acceptance and trust by the medical staff.

2 | MATERIALS AND METHODS

2.1 | Gluclas software

Gluclas is computer software that aims to assist researchers with modulation of the GIR during GC experiments. GIR suggestions are based on BG measurements, which are manually inserted by the user into the GUI. Gluclas employs a closed-loop control algorithm based on PID control to compute GIR suggestions to track a desired glycaemic reference signal. A detailed description of the software, including the underlying control algorithm and tuning of its parameters, can be found elsewhere.[12] The software can be downloaded at.[14] The source code is open-source and made available under creative common licence at[15] to permit customization, for example, to change the GUI or to create customized glycaemic reference profiles.

2.2 | Experimental data

The data considered in this work were collected within a clinical study conducted at the University Hospital of Bern (CH). The study was approved by the local ethic committee and registered with ClinicalTrials.gov under the number NCT04334161. The main objective of the study was to evaluate endocrine and metabolic counter-regulation to hypoglycaemia in postbariatric surgery individuals and non-operated controls by means of hypoglycaemic GC experiments. During these experiments, investigators were assisted by Gluclas for the GIR modulation. For a detailed presentation of the study and its main findings, we refer the reader to Tripyla et al.[13] In the current work, we instead focus on the effectiveness of the GC achieved by the study team with the assistance of Gluclas. In the following, those aspects of the study that were relevant for evaluating the performance of Gluclas are reviewed.

2.2.1 | Study population

Thirty-two adults participated in the study and were divided into four subgroups (with eight in each): individuals who underwent a Roux-en-Y gastric bypass and developed postbariatric hypoglycaemia (the PBH group); individuals who underwent gastric bypass but showed no evidence of PBH (the GB non-PBH group); individuals who underwent sleeve gastrectomy (the SG group); and individuals who had no surgery (the control group). The groups were matched for age, sex and BMI.

2.2.2 | Clinical procedures related to the GC

Participants were received at the clinical research unit after an overnight fast and withdrawal from strenuous physical activity, alcohol and caffeine for 48 hours. Blood withdrawal, insulin infusion and glucose infusion were performed via intravenous catheters in the forearms. At time t_0 of the experiment, participants consumed 15 g of glucose (Roquette Frères SA, Lestrem, France) dissolved in 200 mL of water (ingested within 5 minutes in an upright sitting position). From t_{75} (i.e. 75 minutes after glucose ingestion) onwards, venous blood was sampled every 5 minutes and glucose concentration was measured using an Accu-Check Inform II Meter (Roche Diagnostics GmbH, Mannheim, Germany). Continuous infusion of insulin aspart (NOVORAPID, Novo Nordisk A/S, Bagsvaerd, Denmark) started at

time t_{90} of the experiment with a rate of 0.0623 U/kg/h per subject's body weight. From this moment, the infusion of glucose (Glucose Bioren, Sintetica SA, Mendrisio, Switzerland, concentration of 20%) was modulated to keep subjects' BG levels close to the glycaemic reference.

The reference signal smoothly decreased towards the hypoglycaemic target, starting from t_{115}. The target hypoglycaemic period of the GC experiment was considered from t_{150} and set at 2.5 mmol/L for 20 minutes. At t_{170}, the GC was considered to be complete, insulin infusion rate was stopped and the GIR increased to rapidly restore euglycaemia.

From t_{90} to the end of the experiment, Gluclas provided suggestions for the modulation of GIR to the clinical team. The investigators were requested to critically review the suggestions before manually adjusting the desired GIR infusion on the infusion pump (Infusomat Space, B. Braun, Switzerland).

2.3 | Performance metrics

A first set of metrics assessed the quality of the clamp experiment in terms of control accuracy and patient safety. For each measured glucose level $g(t_k)$, we computed the tracking error, $e(t_k) = g(t_k) - r(t_k)$ (i.e. the deviation between the glucose level measured and the reference level desired at that time, $r(t_k)$), and we computed the percentage error, $pe(t_k) = 100 * e(t_k)/r(t_k)$, to quantify the relative deviation. Then we computed the mean absolute error (MAE) (called 'absolute control deviation' in other studies[8,11]) and the mean absolute percentage error (MAPE) (often referred to as mean absolute relative deviation) between t_{115} and t_{170}, which represent the mean absolute value of the error and percentage error (respectively) committed when tracking the reference profile during the descent to hypoglycaemia and its maintenance.

Moreover, following the recommendations of the European Medicine Agency,[16] we report the average glucose value, as well as the coefficient of variation (CV), the MAE and the MAPE of glucose concentration during the hypoglycaemic period (i.e. between t_{150} and t_{170}). Average glucose concentration should be close to the target value of 2.5 mmol/L. CV should be close to 0%, meaning that glycaemic variability is minimal during this period. In particular, a CV below 5% during the plateau period is broadly accepted as the threshold for an experiment of sufficient quality; hence, we considered this metric to be the primary outcome for this study. Lastly, participants' safety was evaluated by reporting the minimum glucose level measured in each subject and the total amount of glucose infused during the reference descent and the hypoglycaemic period.

A second set of metrics quantified the level of agreement between the suggestions provided by Gluclas and the investigators' execution. We report the number of times the team accepted the software's suggestions throughout the whole trial, as well as the percentage of accepted suggestions. Moreover, we computed the absolute and relative between the suggested and the delivered GIR. All metrics employed to evaluate the performance of the software are reported in Table 1.

TABLE 1 Summary of the metrics reported in this work.

	Metric	Time period considered
Control accuracy and safety	MAE during reference descent and hypoglycaemic period (mmol/L)	$(t_{115} - t_{170})$
	MAPE during reference descent and hypoglycaemic period (%)	$(t_{115} - t_{170})$
	MAE during hypoglycaemic period (mmol/L)	$(t_{150} - t_{170})$
	MAPE during hypoglycaemic period (%)	$(t_{150} - t_{170})$
	Mean glucose level during hypoglycaemic period (mmol/L)	$(t_{150} - t_{170})$
	CV of glucose during hypoglycaemic period (%)	$(t_{150} - t_{170})$
	Minimal glucose during reference descent and hypoglycaemic period (mmol/L)	$(t_{115} - t_{170})$
	Total glucose infused during reference descent and hypoglycaemic period (g)	$(t_{115} - t_{170})$
	Total glucose infused during hypoglycaemic period (g)	$(t_{150} - t_{170})$
Users' agreement with suggestions	Deviation from suggestion (mL/h)	$(t_{115} - t_{170})$
	Relative deviation from suggestion (%)	$(t_{115} - t_{170})$
	Number of deviations from suggestions	$(t_{115} - t_{170})$
	Percentage of deviations from suggestions (%)	$(t_{115} - t_{170})$

Abbreviations: CV, coefficient of variation; MAE, mean absolute error; MAPE, mean absolute percentage error.

2.4 | Statistical analysis

Safety and accuracy metrics were computed for each participant, and the results are reported as median (25th percentile-75th percentile) over the whole population and for the four groups. As a secondary analysis, we investigated whether differences in the clamp performance were observed between the four groups. This was carried out by running an analysis of variance test, with a significance level of 5%. Absolute and relative deviation between suggested and infused GIR are reported as median (25th percentile-75th percentile), computed over all data.

3 | RESULTS

A total of 35 participants were recruited for the study, three of whom were excluded because of incomplete data during the experiment. The remaining 32 participants were divided into four subgroups, which were matched in terms of age, sex distribution, BMI, body composition and HbA1c levels. In terms of median (interquartile range), age was 49.0 (31.4-54.2) years for the control group, 47.5 (30.6-48.9)

years for the PBH group, 45.2 (37.1-52.1) years for the GB non-PBH group and 49.2 (31.2-52.3) years for the SG group. BMI was 26.9 (24.8-31.6) kg/m^2 (control), 29.7 (24.1-32.0) kg/m^2 (PBH), 27.5 (24.2-31.0) kg/m^2 (GB non-PBH) and 30.2 (24.8-33.4) kg/m^2 (SG). Baseline HbA1c was 5.1% (4.7%-5.1%) (control), 5.0% (4.9%-5.2%) (PBH), 5.0% (4.9%-5.1%) (GB non-PBH) and 5.3% (5.1%-5.4%) (SG). The female-to-male ratio was 7:1 in each group. Further characteristics of the population (e.g. body composition) are available in Tripyla et al.[13]

Of the 32 total participants, two (both in the GB non-PBH group) showed BG levels above the reference for the entire duration of the experiment, with a minimal BG of 2.9 mmol/L (i.e. 0.4 mmol/L above the target level). In these subjects, the insulin dose (fixed by the study protocol) was insufficient to induce the desired hypoglycaemia and no glucose was infused throughout the entire experiment. For this reason, these participants were excluded from the present analysis.

Figure 1 displays the glycaemic trajectories (upper panel) and actuated GIR modulations (lower panel) for the remaining participants. BG and GIR are reported between t_{90} (i.e. start of insulin infusion) and t_{170} (i.e. end of the hypoglycaemic period).

Table 2 reports control accuracy and patient safety metrics, computed for the whole population and for each group separately. In the whole population, the MAE computed in the interval ($t_{115} - t_{170}$) was 0.23 (0.15-0.27) mmol/L and the MAPE for the same interval was 7.67% (5.13%-8.79%). When focusing on the hypoglycaemic period ($t_{150} - t_{170}$), the MAE resulted in 0.16 (0.12-0.24) mmol/L, while the MAPE was 6.12% (4.80%-9.29%) in the whole population. During

the hypoglycaemic period, the average BG was 2.55 (2.46-2.64) mmol/L and the CV was 4.90% (3.58%-7.22%).

Concerning safety, the minimal BG during the experiment was 2.40 (2.30-2.50) mmol/L in the whole population, corresponding to −0.10 (−0.20-0.00) mmol/L with respect to the desired glycaemic target of 2.5 mmol/L. The lowest BG recorded during the experiment was 2.10 mmol/L and it occurred in a SG subject. Median glucose administration among groups varied between 0.7 and 2.3 g during the hypoglycaemic period ($t_{150} - t_{170}$) and between 2.5 and 5.0 g when also considering the descent to hypoglycaemia ($t_{115} - t_{170}$). In most participants (27/30), euglycaemia was restored the end of the clamp experiment in less than 10 minutes with a median glucose administration of between 13.6 and 18.1 g. All the participants recovered from euglycaemia in less than 25 minutes.

For each subgroup, boxplots and scatterplots for the metrics related to control accuracy and safety are reported in Figure 2. No significant differences between the different groups in any of the considered metrics were observed.

The clinical team accepted 279 of the 333 suggested GIR adjustments (84%). The median value and interquartile range of the deviation between suggested and executed GIR were equal to 0 (0-0) mL/h (equivalent to 0 [0-0] mg/min). The range (fifth percentile-95th percentile) of the deviation was 0.00-12.13 mL/h (i.e. 0.00-410 mg/min), indicating that 5% of the suggestions were increased by 12.13 mL/h or more. The mean deviation was 0.91 mL/h (i.e. 30.33 mg/min). Figure 3 presents a scatterplot representing all actuated versus suggested GIR modulations. The points are on the bisecting line when
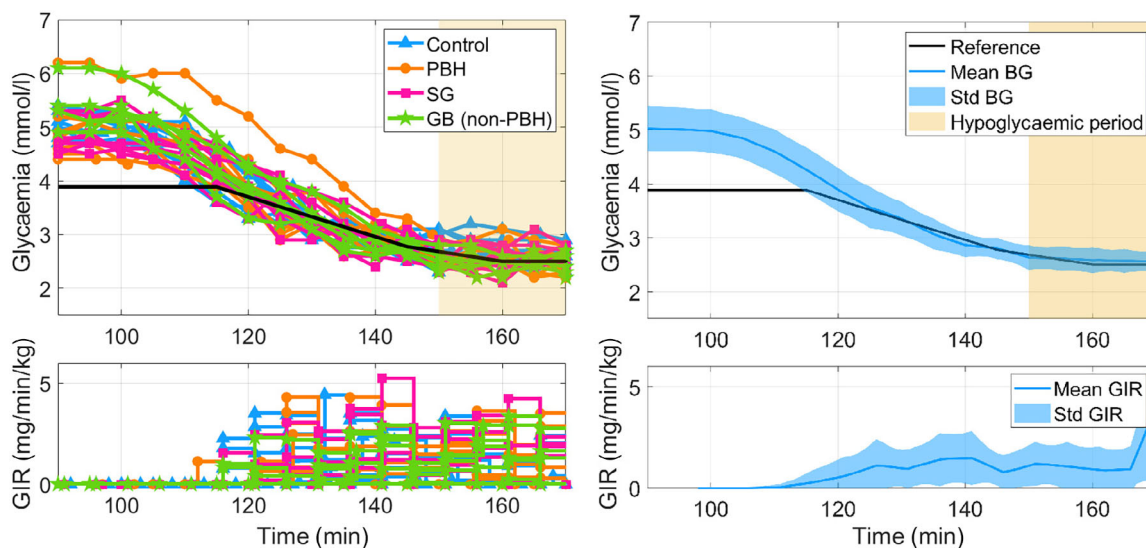

FIGURE 1 Trajectory of plasma glucose levels (upper panels) and GIR (lower panels) for the 30 participants. Individual trajectories are shown on the left, while mean ± SD trajectories are shown on the right. Blue lines with triangle markers represent the control group, orange lines with circle markers the PBH group, pink lines with square markers the SG group and green lines with star markers the GB (non-PBH) group. The black line is the reference signal tracked by the PID algorithm. The bold blue line represents the mean value and the light blue strip represents mean ± SD. To compute the mean and SD, the data underwent a linear interpolation. The black line is the reference signal tracked by the PID algorithm. The yellow region highlights the plateau period. GB, gastric bypass; GIR, glucose infusion rate; PBH, postbariatric hypoglycaemia; PID, proportional derivative integrative; SD, standard deviation; SG, sleeve gastrectomy.

TABLE 2 Results concerning control accuracy and patients' safety.

Metrics	All subjects (30)	Control (8)	PBH (8)	SG (8)	GB non-PBH (6)
MAE during reference descent and hypoglycaemic period (mmol/L)	0.23 (0.15-0.27)	0.21 (0.16-0.24)	0.25 (0.17-0.26)	0.26 (0.19-0.30)	0.19 (0.14-0.26)
MAPE during reference descent and hypoglycaemic period (%)	7.67 (5.13-8.79)	6.93 (5.18-8.02)	8.16 (5.64-8.77)	8.59 (6.24-9.56)	6.35 (4.59-7.77)
MAE during hypoglycaemic period (mmol/L)	0.16 (0.12-0.24)	0.15 (0.10-0.29)	0.16 (0.13-0.21)	0.21 (0.13-0.24)	0.13 (0.10-0.21)
MAPE during hypoglycaemic period (%)	6.12 (4.80-9.29)	5.82 (3.85-11.36)	6.12 (5.13-8.14)	8.03 (4.98-9.46)	5.03 (3.70-8.27)
Mean glucose level during hypoglycaemic period (mmol/L)	2.55 (2.46-2.64)	2.63 (2.57-2.80)	2.50 (2.45-2.58)	2.59 (2.45-2.72)	2.48 (2.42-2.54)
CV during hypoglycaemic period (%)	4.90 (3.58-7.27)	4.73 (3.86-7.73)	6.51 (4.45-7.80)	6.00 (3.09-6.92)	4.47 (3.58-4.56)
Minimal BG level during reference descent and hypoglycaemic period (mmol/L)	2.40 (2.30-2.50)	2.45 (2.35-2.70)	2.25 (2.20-2.45)	2.40 (2.30-2.55)	2.40 (2.20-2.40)
Total glucose infused during reference descent and hypoglycaemic period (g)	3.16 (1.37-7.79)	2.79 (0.55-6.75)	2.54 (1.51-7.01)	4.97 (1.88-7.64)	3.48 (3.20-7.79)
Total glucose infused during hypoglycaemic period (g)	0.94 (0.29-3.00)	0.72 (0.00-1.92)	1.45 (0.31-2.98)	1.71 (0.46-3.45)	2.26 (0.60-3.02)

Note: Metrics are reported for the whole population (30 subjects) and stratified for the four subgroups (control, PBH, SG and GB non-PBH) and are reported in terms of median (25th percentile-75th percentile).

Abbreviations: BG, blood glucose; CV, coefficient of variation; GB, gastric bypass; MAE, mean absolute error; MAPE, mean absolute percentage error; PBH, postbariatric hypoglycaemia; SG, sleeve gastrectomy.
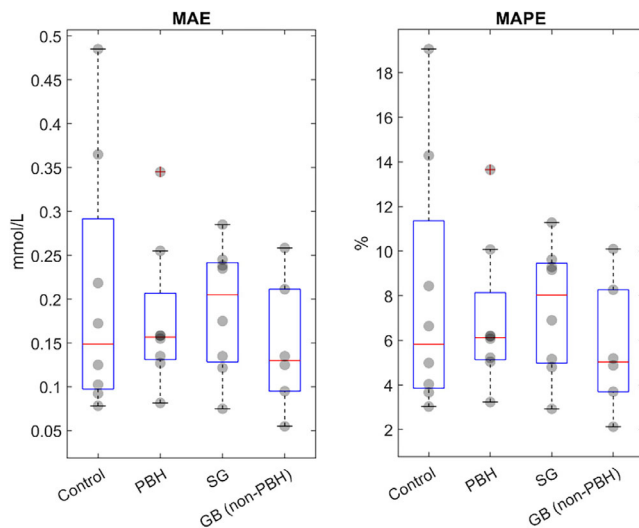

FIGURE 2 Boxplots and scatterplots of MAE and MAPE, computed during the period $t_{150} - t_{170}$ for the four subgroups. Each dot represents a participant. Red lines represent the median value for the subgroup, the boxes indicate the interquartile ranges and the whiskers delimit the interval (fifth-95th percentile). Outliers are indicated with a red cross. GB, gastric bypass; MAE, mean absolute error; MAPE, mean absolute percentage error; PBH, postbariatric hypoglycaemia; SG, sleeve gastrectomy.

FIGURE 3 Deviation between computer-suggested GIR modulation (x-axis) and user-actuated GIR modulation (y-axis). Each dot represents a GIR modulation during the trial. GIR, glucose infusion rate.

there was no deviation with respect to suggestions. The inner region includes those deviations less than 25% (< 0.1 mg/kg/min for values of GIR < 0.5 mg/kg/min); the second inner region includes those deviations of less than 50% (< 0.25 mL/h for small values of GIR < 0.5 mL/h).
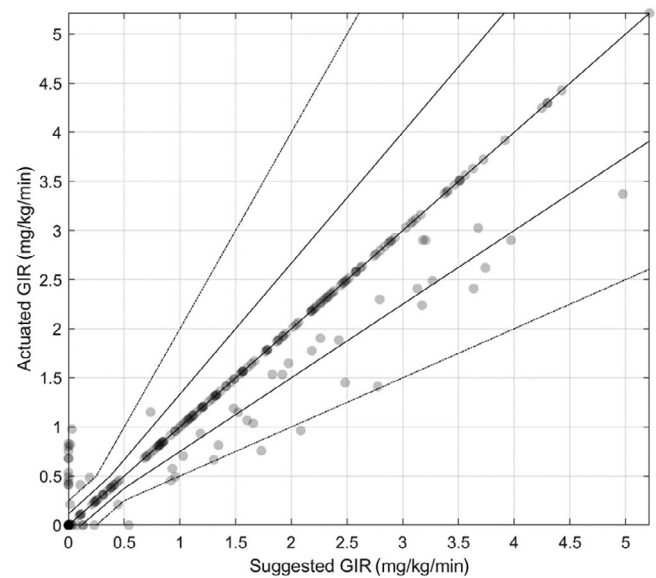
4 | DISCUSSION

Our study suggests that Gluclas is an effective tool to support researchers in high-quality performance of GC experiments. The software produced only minor deviations from the target glucose levels, with the MAPE during the hypoglycaemic period consistently less

than 10% in all groups (and MAE < 0.2 mmol/L). In the current experiment, the clinical team in charge of controlling the glucose infusion largely agreed with the suggestions provided by Gluclas (84% of suggestions were accepted). Furthermore, the median and interquartile range of deviation were 0 mL/h, indicating that most suggestions were deemed safe and effective.

The quality of GC experiment is evaluated based on the glycaemic variability during the plateau period. A CV of 5% during the plateau phase is generally considered the threshold for accurate control.[8] In the current experiment, the median CV was less than 5% for all four subgroups. In a recently published work reviewing the performance of 222 studies that used hypoglycaemic GC experiments,[17] the average CV during the hypoglycaemia period was 10% ± 9% (mean ± standard deviation). Of note, less than one-third (32.4%) of studies achieved a CV of less than 5%, highlighting existing unmet needs of those experiments.

Gluclas allowed for accurate GC during the hypoglycaemic period (the mean glucose level was 2.55 mmol/L for a target of 2.5 mmol/L and ranged from 2.48 to 2.63 mmol/L). Additionally, hypoglycaemic nadirs below the desired target were uncommon during the trial. The lowest nadir glucose value observed across the 30 participants was 2.1 mmol/L, indicating that the software's suggestions can be executed safely. We acknowledge that this positive result may have been favourably influenced by the slow approximation to the glycaemic target. The safety of experiments with more rapidly changing glucose targets remains to be evaluated. Similarly, our results are not directly applicable to protocols with differences in the insulin infusion protocol (e.g. higher dose or different administration schedule).

In standard GC experiments, the target is commonly reached by either tracking a single-step or multi-step glycaemic profile.[17] Gluclas allows tracking time-varying glycaemic trajectories of customizable shape depending on the research question. In the current study, a smooth decrease towards the hypoglycaemic target was chosen, resulting in standardized glycaemic trajectories (median MAPE in the reference descending phase is consistently < 10% for each subgroup, further increasing the standardization of the experiment.).

Finally, it should be noted that the accuracy achieved in vivo is consistent with the results observed in simulated tests on healthy individuals,[12] as well as with the results observed in a preliminary study in silico including both PBH individuals and non-operated controls.[18] This result supports the value of the simulation tool adopted for the tuning and the preclinical testing of Gluclas.

The fact that no significant differences in accuracy and safety were observed when applying the software to postbariatric surgery individuals who have altered gastrointestinal anatomies and postprandial glucose metabolism supports that Gluclas can provide the necessary glycaemic stability and accuracy for successful GC experiments in a diverse population.

There are a number of limitations to be considered. First, this study reports the results of clamp experiments in which Gluclas suggestions could be modified by the study team. This introduces a confounding effect in evaluating Gluclas, as the contribution of Gluclas to the success of the clamps cannot be fully disentangled from the

contribution of the clinical team. On the other hand, this choice enabled testing Gluclas in a clinical trial designed for other purposes,[13] without exposing the patients to the risks associated with a trial exclusively dedicated to the evaluation of Glucas.

To investigate the extent of this confounding effect, we analysed the number and the magnitude of modifications performed by the study team to Glucas suggestions. Figure 3 presents a scatterplot of Glucas suggestions (x coordinate) versus user-actuated GIR modulations (y coordinate) during all the experiments. Encouragingly, the majority of the suggestions proposed by the software (∼ 84%) were accepted by the investigators without changes. In fact, most of the points in Figure 3 lie on the bisecting line, indicating no deviations from suggestions. In view of this, the performance observed cannot be imputed mostly to the study team intervention. The small fraction of modified suggestions lie mostly below the bisecting line, indicating that the user-actuated GIR modulations were lower than the ones suggested by the software and thus that Gluclas proposed a more conservative infusion than the one adopted by the clinical team, supporting the claim for the safety of Gluclas.

As a final comment, it should be noted that Gluclas is intended to be used in cooperation with investigators, and not as a replacement for human decisions, to increase the convenience, quality and safety of clamp experiments. Interestingly, our work considers precisely this cooperative setting. As such, the results reported are possibly more predictive of the performance achievable using Gluclas than the results produced by a 'manual clamp' versus 'automated clamps' head-to-head comparison.

A further limitation is that the performances could be different for other experimental set-ups, including euglycaemic and hyperglycaemic clamp experiments. Although no tests in vivo have been performed yet, the PID algorithm employed in Gluclas was extensively tested in simulation for these two GC protocols in.[12] We also believe that tracking a dynamic, hypoglycaemic glucose profile after a prandial stimulus, as we did in this study, represents one of the most challenging possible scenarios for validation of the software. The satisfactory performance achieved is therefore encouraging for less demanding conditions.

Lastly, broader applicability of the software should be corroborated with future research in more diverse populations, including different ranges of BMI, different age ranges and the use of different medications (e.g. glucocorticoids). Because the software has only been tested by one research group to date, further testing by other research groups is necessary to validate its usability.

5 | CONCLUSIONS

In conclusion, Gluclas appears to be a safe and effective tool to support academic researchers in conducting GC experiments that meet the required quality standards. Its free accessibility, ease of use and applicability to various experimental set-ups and populations provide further advantages for successful experiments.

This study paves the way for a more exhaustive validation of the software, under different experimental conditions and in more diverse populations, possibly through clinical trials solely designed for this purpose.

AUTHOR CONTRIBUTIONS

JP, SDF and CDM designed the software and underlying control algorithm. DH, AT and LB wrote the original study protocol and collected the data. JP analyzed the data. JP, SDF, DH, LB and CDM interpreted the results. JP, SDF, DH and LB wrote the manuscript. All the authors critically revised the manuscript.

ACKNOWLEDGEMENTS

CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/dom.15265.

DATA AVAILABILITY STATEMENT

Data available on request from the authors

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How to cite this article: Pavan J, Herzig D, Tripyla A, Dalla Man C, Bally L, Del Favero S. Clinical evaluation of a decision support system for glucose infusion in hypoglycaemic clamp experiments. *Diabetes Obes Metab*. 2023;1-7. doi:10.1111/dom.15265