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Identification of individuals with diabetes who are eligible for continuous glucose monitoring forecasting

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ABSTRACT

Background and objectives: Predicting glucose levels in individuals with diabetes offers potential improvements in glucose control. However, not all patients exhibit predictable glucose dynamics, which may lead to ineffective treatment strategies. We sought to investigate the efficacy of a 7-day blinded screening test in identifying diabetes patients suitable for glucose forecasting.

Methods: Participants with type 1 diabetes (T1D) were stratified into high and low initial error groups based on screening results (eligible and non-eligible). Long-term glucose predictions (30/60 min lead time) were evaluated among 334 individuals who underwent continuous glucose monitoring (CGM) over a total of 64,460,560 min.

Results: A strong correlation was observed between screening accuracy and long-term mean absolute relative difference (MARD) (0.661–0.736; $p < 0.001$), suggesting significant predictability between screening and long-term errors. Group analysis revealed a notable reduction in predictions falling within zone D of the Clark Error Grid by a factor of three and in zone C by a factor of two.

Conclusions: The identification of eligible patients for glucose prediction through screening represents a practical and effective strategy. Implementation of this approach could lead to a decrease in adverse glucose predictions.

1. Introduction

More than 20 million people in the United States have been diagnosed with diabetes, and approximately 5–10% of people with diabetes have insulin-dependent Type 1 Diabetes (T1D) [1]. Complications related to diabetes are a burden for patients and a serious economic burden for the healthcare sector [1]. Adequate control of blood glucose levels is a key component in the prevention and delay of diabetes-associated long- and short-term complications [2]. The standard approach to diabetes management requires patients to take blood glucose measurements several times throughout the day with a finger prick test. The introduction of continuous glucose monitoring (CGM) devices allows for improved sampling of glucose measurements, which enables patients to adhere to stricter glycemic control. CGMs have proven successful at reducing glycosylated hemoglobin (HbA1c) levels as well as reducing time in hypo- and hyperglycemia [3–5].

Additional improvements in glycemic control could be achieved through forecasting blood glucose [6]. This approach allows patients to take timely action to minimize the incidence of adverse glycemic events [7]. The challenges associated with glucose forecasting are related to the large inter- and intra-variability in factors that impact glycemic variability [8]. These factors are associated with disease progression, medicine, infections, physical activity, smoking, ingested food, and physiological stress [9–11]. In particular, the high variability between subjects could lead to imprecise glucose forecasting for some patients with diabetes, even though they are monitored under similar conditions [7,12,13].

We recently published two studies demonstrating how neural network models could be used to forecast glucose dynamics in a heterogeneous cohort [14,15]. As seen in these two studies, as well as other studies related to individual or generalized glucose prediction [7,12,13], the algorithms work inadequately for a proportion of the participants. For these participants, the use of glucose forecasting could lead to deterioration in treatment rather than improvements. Hence, identifying these patients before such an algorithm is activated and used to make changes to the treatment is highly relevant. One interesting novel approach could be to blind test the precision of the forecasting approach for each patient for a short duration before unblinding the forecast.

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However, this approach has not yet been evaluated, and there is uncertainty regarding the correlation between the precision of the test and long-term usage.

Therefore, the aim of this study was to investigate whether it is feasible to identify individuals with diabetes who respond with high or low accuracy to continuous glucose monitoring forecasting.

2. Subjects, materials and methods

To investigate whether a blinded screening test could help identify diabetes patients who have glucose dynamics eligible for glucose forecasting, this study combined participants with type 1 diabetes from two earlier studies with CGM data. The methods and results of the two studies for which data were used in the current analyses have been published [16–18]. The first study (Replace Blood glucose, REPLACE-BG [16]) aimed to determine whether the use of CGM without confirmatory blood glucose monitoring measurements is safe and effective in adults with well-controlled T1D. The second study (Wireless Innovations for Seniors with Diabetes Mellitus,WISDM [18]) had the objective of determining whether CGM is effective at reducing hypoglycemia compared with standard blood glucose monitoring in older adults with T1D.

For this study, the inclusion criterion was a suitable CGM wear period for a minimum of 30 days with a successful CGM worn≥80%. We included a total of 334 participants from the studies (REPLACE-BG, n = 135; WISDM, n = 199). The purpose of using these study cohorts was to pool a large heterogeneous cohort that could better reflect the differences in the general population of T1D patients.

2.1. Prediction model

To forecast future glucose values, we used an artificial neural network (ANN) with input from CGM and a lead time prediction horizon (PH) of 30 or 60 min. The full details on the network have recently been published [15]. The ANN was implemented in MATLAB R2020b (The MathWorks, Inc., Natick, Massachusetts) using the Levenberg–Marquardt algorithm. The ANN was constructed with error weights. The weights were constructed such that a false prediction error <100 mg/dL glucose would be penalized 5/1 and an error in the hypoglycemic range <70 mg/dL would be penalized 10/1. The motivation for penalizing bias in lower ranges was based on the clinical relevance of the precise prediction of low glucose levels. The error weights were implemented using the mean square error (MSE) performance function used to train the network. Each squared error contributes an equal amount, based on the individual error weight w_i^e, to the performance function; see equation (1).

$$F = MSE = \frac{1}{N}\sum_{i=1}^{N} w_i^e (Y_i - \widehat{Y}_i)^2 \quad \text{Equation 1}$$

Features for the ANN model were retrospectively obtained in a 120-min sliding window for each forecast. The features were presented to the ANN as a matrix of readings in the timely order of measurement:

$$Features = \left[f_{i=-23} ; f_{i=-23} ; \ldots f_{i=0;} \right]$$

The results from a previously reported study [15] showed that the penalty-weighted ANN had favorable clinical relevance for forecasting compared to several other approaches. However, the reporting also highlighted that a small percentage of predictions would still be in zone C-D according to consensus error grid analysis [19,20]. These predictions could lead to late or incorrect treatment in some patients. Hence, it is highly relevant to assess whether the approach with a blinded screening test could be used to identify patients eligible for using the ANN.

2.2. Screening approach

For each patient, the first seven days of CGM use were used to estimate the screening performance of the ANN for the individual patient. The remaining weeks to month of CGM data for each patient were used to calculate a long-term performance estimate of the ANN forecast. The approach is illustrated in Fig. 1. Metrics from the screening period were used to divide the patients into two groups: one potentially eligible for screening and one noneligible. Metrics from the remaining data were used to evaluate whether there was a long-term clinically relevant difference in performance between the groups.

2.3. Performance metrics

We calculated common performance metrics such as the root mean square error (RMSE) and mean absolute relative difference (MARD) – equations (2)–(4).

$$RMSE = \sqrt{\frac{1}{N}\sum_{i=1}^{N} (Y_i - \widehat{Y}_i)^2} \quad \text{Equation 2}$$

$$ARD = 100\frac{|Y_i - \widehat{Y}_i|}{Y_i} \quad \text{Equation 3}$$

$$MARD = \frac{1}{N}\sum_{i=1}^{N} ARD_i \quad \text{Equation 4}$$

Common performance metrics (RMSE and MARD) concerning glucose forecasting and prediction are frequently reported in studies, and these metrics assess the general performance and fit of models. Nevertheless, these metrics do not assess performance with a focus on clinical relevance. Therefore, we used consensus error grid analysis (CEGA) [19,20] to evaluate the performance of the screening approach.

CEGA can be used to evaluate the precision of glucose forecasting compared to a reference standard (the CGM value measured in this study). The analysis labels the predicted values into five zones, A, B, C, D, or E, depending on the clinical threat of forecasting a glucose value in the zone. In brief, forecasting in zone A is considered clinically accurate, forecasting in zone B is a benign error, predictions in zone C are characterized as having the potential for overcorrection of treatment, forecasting in zone D describes the potential for delayed treatment, and forecasting in zone E presents clinical errors.

We investigated which of the metrics from the screening period were the best for identifying diabetes patients with glucose dynamics suitable for glucose forecasting. Pearson's correlation coefficient between the screening metric and the full period was calculated. Furthermore, the 75th percentile of each metric (MARD, RMSE or percentage in zones A + B) was chosen as a potential cutoff between eligible and noneligible patients according to the CGM algorithm.

3. Results

A total of 334 participants were included in the analysis cohort. From the WISDM study, 199 participants were included; 51% were male, the median [25; 75 percentile] age was 68 [64; 70], and the median duration of diabetes was 36.8 [26; 49]. From the REPLACE-BG study, 135 participants were included; 50% were male, the median [25; 75 percentile] age was 38.8 [30; 51], and the median duration of diabetes was 18.9 [13; 29]. A total of 64,460,560 min of CGM among the 334 patients were analyzed in this study. This corresponds to an average of 134 days of CGM for each patient.

Table 1 shows the correlation coefficients between the screening and the full period for the three metrics. In general, there is a strong to moderate correlation between the metric from screening and the metric obtained from the full period. The MARD and RMSE seemed to have

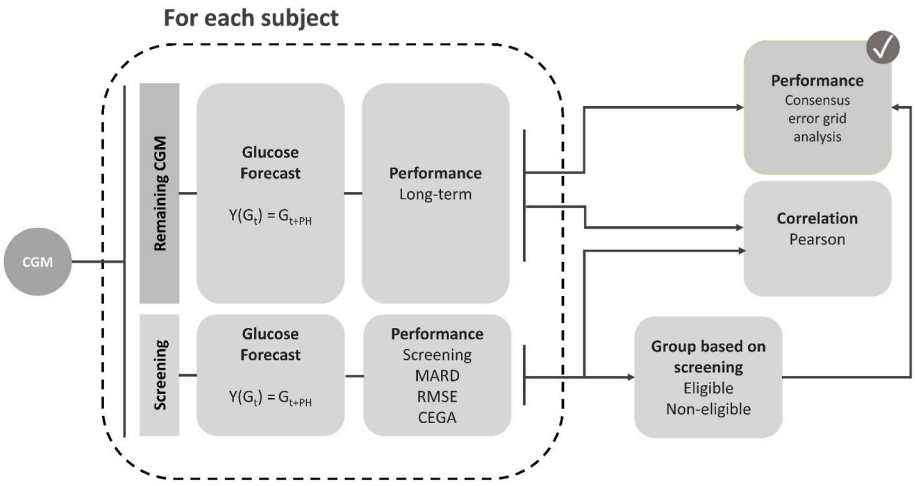

Fig. 1. Illustrates the approach used for screening. The performance metrics for each patient were calculated for the 7-day screening and for the adjacent long-term period. The prediction horizon (PH) is either 30 or 60 min. The performance is used to calculate the correlation between the screening and the long-term performance. The screening performance was also assessed by dividing the participants into groups of eligible and noneligible participants for prediction, and the groups were compared for performance on the basis of the long-term Continuous Glucose Monitoring (CGM) data.

Table 1
Correlations between the screening metrics from the 7-day screening and the long-termn metric. Abbreviations: Replace Blood Glucose study (REPLACE-BG); Wireless Innovations for Seniors with Diabetes Mellitus study (WISDM); Root Mean Square Error (RMSE); Consensus Error Grid Analysis (CEGA).

	Metrics					
	MARD-screening		RMSE-screening		CEGA A + B screening	
	Correlation Coefficient	p value	Correlation Coefficient	p value	Correlation Coefficient	p value
WISDM						
30-min forecasting	0.724	<0.001	0.731	<0.001	0.489	<0.001
60-min forecasting	0.736	<0.001	0.762	<0.001	0.651	<0.001
REPLACE-BG						
30-min forecasting	0.661	<0.001	0.656	<0.001	0.531	<0.001
60-min forecasting	0.736	<0.001	0.762	<0.001	0.651	<0.001

better correlations than did the CEGA A + B screening. All the correlations are significant, $p < 0.001$.

Table 2 shows the results from splitting the participants into CGM algorithm-eligible and noneligible patients based on the 75th percentile of each metric (MARD, RMSE or CEGA A + B screening). In general, all three metrics identified noneligible patients, who had a higher percentage of prediction in zone C or D according to the CEGA than did the eligible group. For both the analytic cohort (eligible and noneligible) and prediction lead time (30 or 60 min), MARD screening seemed to have slightly more clinically favorable results than did RMSE screening or CEGA A + B screening, e.g., higher percentages in zone A and lower percentages in zones C and D.

According to the MARD screening, the percentage of patients in zone C was approximately a factor of two; in zone D, there was an approximate factor of three between groups.

4. Discussion

In this study, we investigated the potential of screening the precision of a glucose forecasting algorithm. The results showed that there is a moderate to strong correlation between short-term performance and long-term performance. The results also indicate that utilizing this screening tool could be useful for selecting patients with type 1 diabetes who could benefit from using CGM enhanced with forecasting algorithms.

By identifying patients based on screening metrics, it was possible to find a group with substantially greater percentages of patients in zones C-D via consensus error grid analysis. Even though the absolute difference may seem small, this approach is clinically valuable. CGM was deployed 24 h a day, and sampling every 5 min produced 288 glucose readings each day. For example, as seen in this study, a difference in zone C of 0.192% (WISDM, 30-min prediction) would yield an additional forecast in zone C on average approximately every other day. For zone D, the difference is 0.006, which would yield an additional forecast in zone D on average approximately every other month. The difference is even greater if we look at the 60-min forecast. The clinical problem with forecasts in zones C-D is that they can lead to overcorrection or delay in treatment. These predictions are important for avoiding achieving the goal of supporting treatment for better glycemic control, including reducing glycemic variability, hypoglycemia, and hyperglycemia.

The clinical implication of using a forecasting algorithm could be in a closed-loop system where accurate glucose forecasting is important to deliver the ideal dosage of insulin at the optimal point in time [7]. A reliable glucose forecast could be used as an input to an insulin pump system that could initiate the suspension of insulin. Furthermore, reliable glucose forecasting is also important when considering CGM usage alone. Discontinuation of use is a challenge among CGM users due to the distress of false alarms and accuracy problems [21–23]. Additionally, reliable forecasts could facilitate the detection of hypoglycemia/hyperglycemia to initiate rapid treatment changes [12,24,25].

To our knowledge, this study is the first to investigate the potential of a screening phase to identify people with type 1 diabetes who could benefit from glucose forecasting algorithms. From a future perspective, it would be interesting to understand why the algorithm seems to

Table 2
Shows the consensus error grid analysis in relation to the use of the three screening methods (MARD, RMSE, and GEGA A + B). The table shows how the groups will perform in the long term based on the screening method. The data were further divided based on the forecasting lead time (30/60 min) and study cohort. Abbreviations: Replace Blood Glucose study (REPLACE-BG); Wireless Innovations for Seniors with Diabetes Mellitus study (WISDM); Root Mean Square Error (RMSE); Consensus Error Grid Analysis (CEGA).

	Metrics					
	MARD-screening		RMSE-screening		CEGA A + B screening	
	<75 centile	≥ 75 centile	<75 centile	≥ 75 centile	>25 centile	≤ 25 centile
WISDM						
30-min forecasting						
Consensus error grid						
Zone A + B	99.846	99.648	99.817	99.733	99.842	99.679
Zone A	89.718	86.766	89.495	87.432	89.668	87.21
Zone B	10.127	12.882	10.322	12.301	10.173	12.469
Zone C	0.152	0.344	0.179	0.263	0.156	0.315
Zone D	0.002	0.008	0.003	0.004	0.002	0.006
Zone E	0	0	0	0	0	0
60-min forecasting						
Consensus error grid						
Zone A + B	98.504	97.097	98.344	97.575	98.471	97.197
Zone A	71.864	66.663	71.172	68.725	71.587	67.49
Zone B	26.64	30.434	27.172	28.85	26.884	29.707
Zone C	1.457	2.787	1.601	2.358	1.491	2.686
Zone D	0.039	0.116	0.055	0.067	0.038	0.117
Zone E	0	0	0	0	0	0
REPLACE-BG						
30-min forecasting						
Consensus error grid						
Zone A + B	99.786	99.539	99.768	99.593	99.777	99.579
Zone A	88.746	84.335	88.345	85.527	88.464	85.355
Zone B	11.04	15.205	11.423	14.067	11.313	14.224
Zone C	0.209	0.446	0.227	0.392	0.218	0.407
Zone D	0.005	0.014	0.005	0.014	0.005	0.014
Zone E	0	0	0	0	0	0
60-min forecasting						
Consensus error grid						
Zone A + B	98.397	96.936	98.225	97.449	98.383	97.091
Zone A	71.379	65.044	70.597	67.366	71.315	65.726
Zone B	27.019	31.891	27.627	30.083	27.068	31.366
Zone C	1.551	2.916	1.707	2.451	1.562	2.774
Zone D	0.052	0.149	0.068	0.099	0.054	0.134
Zone E	0	0	0	0	0	0

perform worse for some patients. The cause could be multifactorial related to the progression of the disease and underlying pathophysiology, but it could also be related to the type of medicine/dosage or individual behavior that affects blood glucose. Understanding these contributing factors could aid in the development of such algorithms.

4.1. Limitations

This study has several limitations. We included participants from two large randomized controlled trials (RCTs), and these type 1 diabetes patients represented a wide section of the population. However, type 1 diabetes is a heterogeneous condition with high variability between patients. The results from this study need to be verified in other subpopulations before they can be fully transferred and applied. One clear limitation is that we cannot generalize the findings to all CGM sensors. Many new sensors (CGM) are emerging from various manufacturers. These sensors have different properties, precisions and built-in filters, which affect the ability of prediction algorithms. The sensors used in the included participants were Dexcom.

G4-G5. Finally, we showed how screening could affect the performance of one type of forecasting algorithm. In practice, many different algorithms can be utilized, and their properties can affect the results of screening.

5. Conclusion

In conclusion, we proposed and tested an approach for identifying individuals with diabetes who respond well to continuous glucose monitoring. The approach is feasible and easy to apply. From a future perspective, it would be relevant to investigate which factor contributes to reduced predictability in a proportion of patients.

Ethics

The data analyzed in this paper were obtained in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans, and informed consent was obtained for each subject.

Disclaimer

The source of the data is the T1D Exchange, but the analyses, content, and conclusions presented herein are solely the responsibility of the authors and have not been reviewed or approved by the T1D Exchange.

Author contributions

SLC had access to all of the data analyzed in this study. SLC takes responsibility for the integrity and accuracy of the study data analysis and results. SLC, MHJ, and OH were involved in the study design, concept, analysis, and interpretation of the data. SLC drafted the manuscript and performed the statistical analysis. MHJ and OH were involved in critical revision of the manuscript.

Conflict of interest

None to disclose.

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Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work the author(s) used AJE.com Curie in order to improve gramma and language. After using this tool/service, the author(s) reviewed and edited the content as needed and take(s) full responsibility for the content of the publication.

Declaration of competing interest

None to report.

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n/a.

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