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BRIEF REPORT

Individuals with Type 1 and Type 2 Diabetes Mellitus Trade Increased Hyperglycemia for Decreased Hypoglycemia When Glycemic Variability is not Improved

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ABSTRACT

Introduction: Glycemic variability refers to oscillations in blood glucose within a day and differences in blood glucose at the same time on different days. Glycemic variability is linked to hypoglycemia and hyperglycemia. The relationship among these three important metrics is examined here, specifically to show how reduction in both hypo- and hyperglycemia risk is dependent on changes in variability.
Methods: To understand the importance of glycemic variability in the simultaneous reduction of hypoglycemia and hyperglycemia risk, we introduce the glycemic risk plot-estimated HbA1c % (eA1c) vs. minutes below 70 mg/dl (MB70) with constant variability contours for predicting post-intervention risks in the absence of a change in glycemic variability.
Results: The glycemic risk plot illustrates that individuals who do not reduce glycemic variability improve one of the two metrics (hypoglycemia risk or hyperglycemia risk) at the cost of the other. It is important to reduce variability to improve both risks. These results were confirmed by data collected in a randomized controlled trial consisting of individuals with type 1 and type 2 diabetes on insulin therapy. For type 1, a total of 28 individuals out of 35 (80%) showed improvement in at least one of the risks (hypo and/or hyper) during the 100-day course of the study. Seven individuals (20%) showed improvement in both. Similar data were observed for type 2 where a total of 36 individuals out of 43 (84%) showed improvement in at least one risk and 8 individuals (19%) showed improvement in both. All individuals in the study who showed improvement in both hypoglycemia and hyperglycemia risk also showed a reduction in variability.
Conclusion: Therapy changes intended to improve an individual's hypoglycemia or hyperglycemia risk often result in the reduction of one risk at the expense of another. It is important to improve glucose variability to reduce both risks or at least maintain one risk while reducing the other.
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Keywords: Glycemic Risk Plot; Hyperglycemia; Hypoglycemia; Variability

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INTRODUCTION

Glycemic variability (GV) refers to swings in blood glucose levels that occur throughout the

day, including hypoglycemic periods, postprandial increases, as well as blood glucose fluctuations that occur at the same time on different days. The broad definition of GV considers the intraday glycemic excursions, including episodes of hyperglycemia and hypoglycemia.

Glycemic variability is linked to hypoglycemia and hyperglycemia. The relationship among these three important metrics is examined here specifically to show how reduction in both hypo- and hyperglycemia risks is dependent on changes in variability. For example, improvement in hyperglycemia risk is often accompanied by an increase in hypoglycemia including episodes of severe hypoglycemia [1]. In addition, glycemic variability has previously been identified to be associated with increased hypoglycemia [2, 3].

The role of glycemic variability in achieving better glucose control without having to trade-off one glycemic risk for another is an important topic. Dunn et al. [4] developed a clinical report that presents all three metrics: hypoglycemia risk, hyperglycemia risk, and glycemic variability. The purpose of the report is to underscore the importance of addressing variability when both hypoglycemia and hyperglycemia are high. Here we attempt to demonstrate the underlying mathematical relationship among the three measures in a graphical fashion.

We introduce the glycemic risk plot, which shows all three measures of glycemic control in one plot, namely:

1. Hypoglycemia risk: average minutes below 70 mg/dl per day (MB70).
2. Hyperglycemia risk: estimated HbA1c (eA1c).
3. Glycemic variability: difference between the median and the 10th percentile [4].

Similar to the plot by Rodbard [5], the glycemic risk plot displays hyperglycemia risk vs. hypoglycemia risk but with key differences including:

1. The usage of constant variability contours as opposed to time-in-target contours.
2. The metrics used for hypoglycemia and hyperglycemia risk.

The goal of the plot is to help clinicians understand the magnitude of variability improvement needed to safely address hypoglycemia without introducing additional hyperglycemia risk and vice versa.

We analyzed data from a continuous glucose-monitoring (CGM) study [6] to look for relationships between the glycemic risks and variability and to look for patterns of trade-offs between hypoglycemia and hyperglycemia when variability is improved, unchanged, or worsened.

METHODS

Study Design

Data from a randomized controlled trial were used for this analysis. The details of the study are described in [6]. Briefly, the study consisted of type 1 and type 2 individuals on insulin therapy with two arms: (1) the intervention group utilized a continuous glucose monitor (CGM) to assess daily glucose levels and (2) the control group relied on capillary glucose testing. After an initial 14-day masked CGM baseline period, the diabetes management intervention period was 85 days, with a masked 14-day CGM wear at the end of the study for the control group. The control and intervention groups had a total of 25 (10 T1DM, 15 T2DM) and 53 (25 T1DM, 28 T2DM) participants, respectively.

Glycemic Risk Plot

The glycemic risk plot shows the relationship between estimated HbA1c % (eA1c) and minutes below 70 mg/dl (MB70) with superimposed constant-variability contours. While several measures of variability have been reported [7], variability here is defined as the difference between the median and 10th percentile of glucose values. A gamma distribution is obtained as per [4] for a range of glucose median and variability values. Dunn et al. used data from the JDRF-CGM trial to generate the gamma distribution parameters for various

combinations of median and variability values [8]. The contours were then calculated by holding the variability constant and determining the gamma distribution at various values of median glucose using these parameters. Once the glucose distribution is obtained for a given variability value, the MB70 values can be calculated by multiplying the number of minutes in a day by the probability of glucose < 70 mg/dl defined by the distribution. The median goal is then converted to eA1c using the equation derived from [9]. A single contour for each variability value is then generated by plotting the corresponding eA1c and MB70 pairs. An example of the plot is shown below in Fig. 1.

The plot is divided into four zones, as shown in Fig. 1:

1. Hyper only: eA1c above 7% with MB70 below 84 min.
2. In target: eA1c below 7% with MB70 below 84 min.
3. Hyper and hypo: eA1c above 7% with MB70 above 84 min.
4. Hypo only: eA1c below 7% with MB70 above 84 min.

The gray contours illustrate how hypoglycemia risk varies with hyperglycemia risk if variability is held constant. The hypoglycemia and hyperglycemia metrics chosen here align with those reported by [4]. A similar plot can be generated with different measures for hypoglycemia risk, hyperglycemia risk, and glycemic variability without changing the underlying relationship.

Each vector on the plot represents data from a single individual with the arrow end representing post-intervention risk and the tail end representing the pre-intervention risk.

Generally, movement towards the *in target* zone indicates improvement in hyperglycemia and hypoglycemia risk.

The sample vectors shown in Fig. 1 illustrate how glycemic risks are dependent on variability. Examples 2 and 3 show that if variability is not improved, individuals are likely to trade-off one glycemic risk for the other. Example 1 shows that if variability is improved, it is possible to achieve improvement in hypoglycemia and hyperglycemia risk, or at least achieve improvements in one risk while maintaining the other constant. The plot also provides other valuable insights; for example, as the individual moves closer to the *in target* zone, a larger change in variability is needed to not increase the risk of hypoglycemia as is illustrated by the distance between the contours, which increases near the in target zone.

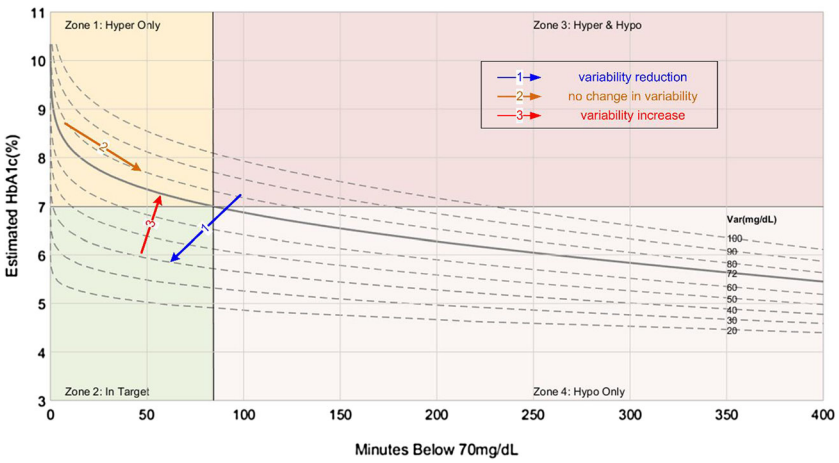

Fig. 1 Glycemic risk plot with glycemic variability (Var) contours. Each contour on the plot represents a fixed variability value. The plot is divided into four zones based on risk of hypoglycemia and hyperglycemia. Vectors 1, 2, and 3 show examples of individuals with (1) improving variability, (2) no change in variability, and (3) worsening variability

Data Analysis

To verify the predictions of the glycemic risk plot, data were analyzed from a randomized control trial for evaluation of the Navigator QS Continuous Glucose Monitor combined with prototype informatics software used for clinical visits [6]. As described above, the study enrolled individuals with type 1 and type 2 diabetes who were on insulin therapy. Data from the intervention and control groups were pooled for this analysis, and comparisons were made between the baseline and final periods of the study.

The data were analyzed by using two methods: (1) the glycemic risk plot and (2) modified glycemic risk plot. The modified glycemic risk plot (Fig. 1) shows change in MB70 and eA1c between two study periods using a single plot marker. Each point on the plot is one individual, and the size of the plot marker is proportional to the variability change between the study periods, with the color magenta indicating a variability increase and cyan indicating a variability decrease. The data are stratified (annotated using zone numbers) by the starting glycemic condition for any individual based on the zones shown in Fig. 1.

Compliance with Ethics Guidelines

This article does not contain any new studies with human or animal subjects performed by any of the authors.

RESULTS

Glycemic Risk Plot Analysis of CGM Data

Individual performance of participants in the study starting with a high risk of hypoglycemia is shown in Fig. 2 below with each vector on the glycemic risk plot representing one individual. A majority of individuals in both type 1 and type 2 groups showed a significant reduction in MB70. However, most did so at the cost of worsening estimated HbA1c because few showed variability reduction.

Individuals who improve variability (and both hypo- and hyperglycemia risk) move across variability contours towards the lower variability contours, while individuals who worsen variability move across variability lines towards the higher variability contours. Individuals who show no change in variability stay on the same variability contour at the start and finish of the study. The variability contours illustrate the risk trade-off if therapy changes are made to address hypoglycemia risk or hyperglycemia risk without improving variability, which is typically attained by self-care behavior changes. This observation suggests that the availability of CGM data enables people to address hypoglycemia. However, if an effort is not made to reduce variability, this improvement in hypoglycemia risk will only result in increased hyperglycemia risk. Other tools may be needed to augment CGM to reduce glycemic variability by addressing self-care behaviors.

Modified Glycemic Risk Plot Analysis of CGM Data

Modified glycemic risk plots for type 1 and type 2 individuals are shown in Fig. 3. The modified glycemic risk plot shows change in MB70 and estimated HbA1c pre- and post-intervention using a single plot marker. Each point on the plot is one individual, and the size of the plot marker is proportional to the variability change between the study periods, with the color magenta indicating a variability increase and cyan indicating a variability decrease. The data are stratified (annotated using zone numbers) by the starting glycemic condition for any individual based on the zones shown in Fig. 3.

For type 1 individuals (upper panel), a total of 28 individuals out of 35 (80%) showed at least one glycemic risk improvement during the course of the study. Twelve individuals showed an improvement in eA1c (from $8.0 \pm 1.1\%$ to $7.4 \pm 1.1\%$, $p < 0.05$), while 24 individuals showed an improvement in MB70 (from 118 ± 100 min to 51 ± 42 min, $p = 0.0006$). Of these, seven individuals (20%) showed

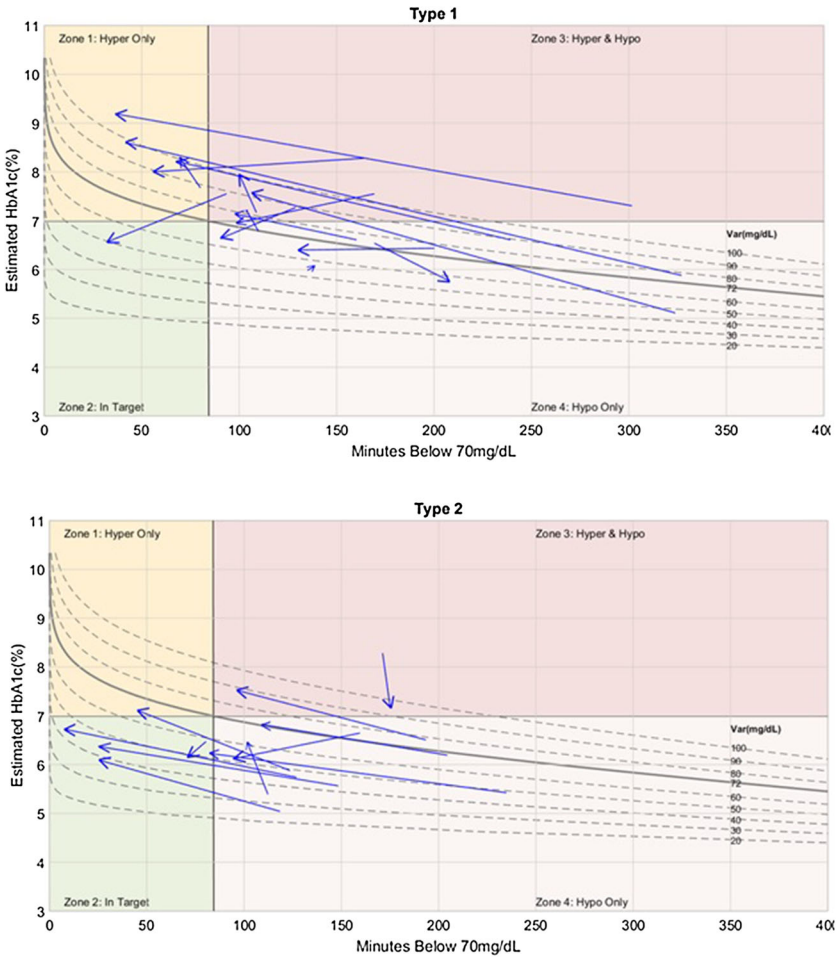

Fig. 2 Glycemic risk plot for type 1 and type 2 individuals who have a high pre-intervention risk for hypoglycemia. The arrow end represents post-intervention risk, while the tail end represents pre-intervention risk of hypo- and hyperglycemia. Most of these individuals improve their risk of hypoglycemia but at the expense of increased hyperglycemia

improvement in both estimated HbA1c and MB70. Similarly, for type 2 individuals (lower panel), a total of 36 individuals out of 43 (84%) showed improvement during the course of the study. Twenty-four individuals showed an improvement in eA1c (from $8.2 \pm 1.6\%$ to $7.1 \pm 1.1\%$, $p < 0.05$), while 20 individuals showed an improvement in MB70 (from 88 ± 73 min to 38 ± 39 min, $p = 0.0002$). Of these, eight individuals (19%) showed improvement in both estimated HbA1c and MB70. All of the individuals who showed improvement in both parameters also showed an improvement in variability. This can be observed in Fig. 3 where the blue plot markers accumulate in the improved hypo and hyper quadrant.[1]

It was also observed that most individuals who showed an increase in variability also showed an increase in estimated HbA1c. This was observed for both type 1 and type 2 individuals. This can be seen in Fig. 3 where for both T1 and T2 the magenta dots tend to

[1] One type 1 individual who showed an increase in variability (ΔVariability = + 1 mg/dl) showed a significant reduction in eA1c (− 0.7%) and a negligible reduction in MB70 (− 1.5 min). This individual had a starting MB70 of 1.5 min and ending MB70 of 0 min. Due to negligible starting hypoglycemia and variability change, this person was not counted as having shown an improvement in both metrics.

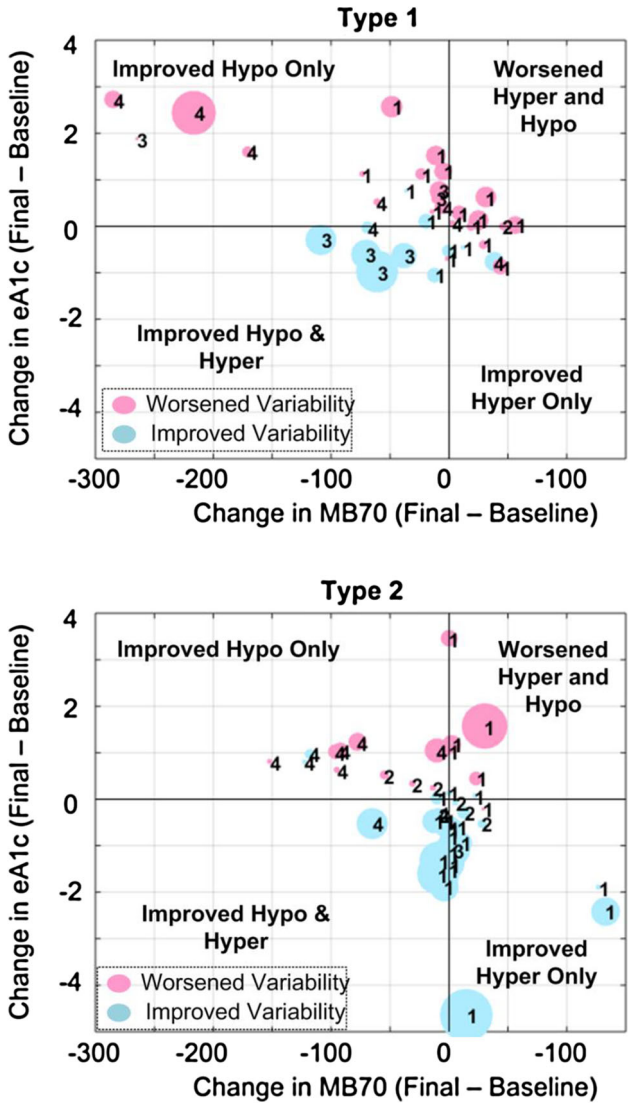

Fig. 3 Modified Glycemic risk plots. The size of the dots is proportional to the variability change (baseline to final). The number on the dot is the zone in which the individual started: (1) hyper only, (2) in target, (3) hyper and hypo, and (4) hypo only

accumulate in the upper left and upper right quadrants.

DISCUSSION

Understanding the relationship among hyperglycemia, hypoglycemia, and variability using tools such as the glycemic risk plot can be critical to educating patients about the importance of addressing glycemic variability. For example, type 2 individual 4713 (Fig. 4), who showed a large improvement in variability (by 52 mg/dl), had a corresponding large reduction in hyperglycemia, while only introducing a small amount of hypoglycemia risk.

On the other hand, as individuals get close to their target, the glycemic risk plot tells us that the variability improvement needs to be larger to prevent increasing the risk of hypoglycemia. This was observed for type 2 individual 5505, who improved variability (by 27 mg/dl) along with a corresponding reduction in hyperglycemia, but with a substantially increased risk

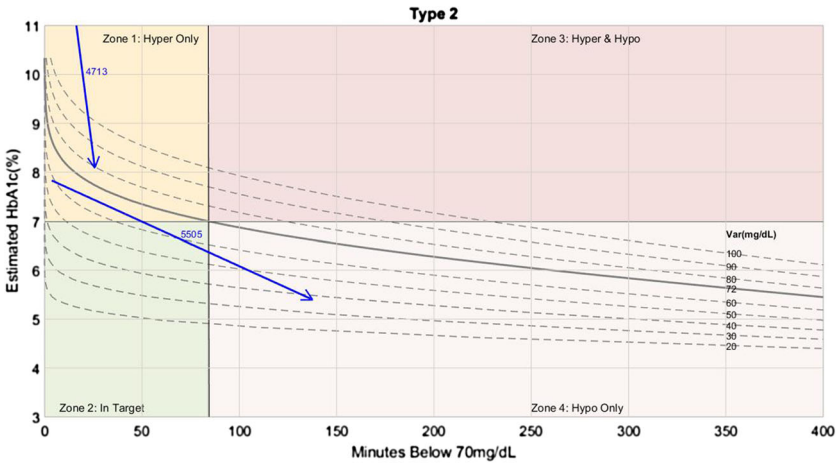

Fig. 4 Relationship among hyperglycemia, hypoglycemia, and glycemic variability is illustrated by the glycemic risk plot. The arrow end represents post-intervention risk, and the tail end represents pre-intervention risk. As individuals get closer to the target region, a larger reduction in variability is needed when attempting to reduce one risk (hyper- or hypoglycemia) without introducing the risk of the other

of hypoglycemia. For individual 5505 to maintain the same level of hypoglycemia risk and to achieve the decrease in estimated HbA1c desired, variability would need to be reduced by a larger amount. The individual's variability dropped to 38 mg/dl, but in order not to increase the risk of hypoglycemia, the variability would need to drop to 21 mg/dl as per the glycemic risk plot.

A limitation of this analysis is the relatively small sample size, so these findings need to be validated with larger cohorts in the future.

CONCLUSION

The above results emphasize the importance of addressing variability to attain tight glycemic control. The glycemic risk plot tells us that it is important to reduce variability if the risk of both hypo- and hyperglycemia is to be improved. Without addressing variability, there will be a trade-off of improving either the risk of hypo- or hyperglycemia at the expense of the other. Analysis of CGM data confirmed this prediction by showing that simultaneous improvement in hypoglycemia risk and hyperglycemia risk was strongly correlated with reduction in variability. Graphical tools such as the glycemic risk plot can be used to educate patients about the importance of addressing glycemic variability and the magnitude of variability improvement needed to improve eA1c without introducing the risk of hypoglycemia. Other tools are needed to help patients identify and address therapy management issues and lifestyle choices that contribute to glycemic variability.

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Compliance with Ethics Guidelines. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Data Availability. The data sets during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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