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ORIGINAL ARTICLES

Computing the Risk of Postprandial Hypo- and Hyperglycemia in Type 1 Diabetes Mellitus Considering Intrapatient Variability and Other Sources of Uncertainty

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Abstract

Objective:

The objective of this article was to develop a methodology to quantify the risk of suffering different grades of hypo- and hyperglycemia episodes in the postprandial state.

Methods:

Interval predictions of patient postprandial glucose were performed during a 5-hour period after a meal for a set of 3315 scenarios. Uncertainty in the patient's insulin sensitivities and carbohydrate (CHO) contents of the planned meal was considered. A normalized area under the curve of the worst-case predicted glucose excursion for severe and mild hypo- and hyperglycemia glucose ranges was obtained and weighted accordingly to their importance. As a result, a comprehensive risk measure was obtained. A reference model of preprandial glucose values representing the behavior in different ranges was chosen by a χ^2 test. The relationship between the computed risk index and the probability of occurrence of events was analyzed for these reference models through 19,500 Monte Carlo simulations.

Results:

The obtained reference models for each preprandial glucose range were 100, 160, and 220 mg/dl. A relationship between the risk index ranges <10, 10–60, 60–120, and >120 and the probability of occurrence of mild and severe postprandial hyper- and hypoglycemia can be derived.

Conclusions:

When intrapatient variability and uncertainty in the CHO content of the meal are considered, a safer prediction of possible hyper- and hypoglycemia episodes induced by the tested insulin therapy can be calculated.

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Abbreviations: (CHO) carbohydrates, (MIA) modal interval analysis, (RI) risk index, (T1DM) type 1 diabetes mellitus

Keywords: blood glucose, glucose variability, interval analysis, simulation, type 1 diabetes mellitus

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Introduction

The intensive insulin therapy required to achieve the glucose control objectives in type 1 diabetes mellitus (T1DM) patients is based on the administration of basal and bolus insulin to "emulate" its physiological secretion. The frequency and size of the dosage depend on each individual patient's weight, physical activity, consumed carbohydrates (CHO), insulin sensitivity, disease history, etc. Before each meal, patients normally measure their preprandial blood glucose level and then calculate the adjusted insulin dose in relation to the planned CHO intake according to rules prescribed by the physician in the therapy plan. If the dose is too high there is the risk of severe hypoglycemia with all its consequences.

So far no gold standard method has been devised to analyze the risk of suffering hypoglycemia and hyperglycemia events in the postprandial state. Among the possible methods used are M-value,[1] mean amplitude of glycemia excursions,[2] mean of daily differences,[3] and mean absolute difference.[4] Recently, other methods, such as continuous overall net glycemic action,[5] daily average of risk range,[6] lability,[7] and the glycemic penalty index,[8] have appeared. A probabilistic model for predicting hypoglycemia was also presented elsewhere.[9]

Any attempt to predict the risk of postprandial hypo- or hyperglycemia should consider the different sources of uncertainty and patient's variability so that it is reliable enough to be used in any insulin dosage advisory system. However, none of the aforementioned methods can deal with this problem.

Interval simulation of glucose prediction models can provide valuable information about postprandial glucose responses in the presence of intraindividual variability and uncertain food intake, for instance.

In this article, all possible postprandial glucose responses of a patient for a given insulin therapy and uncertainty in insulin sensitivities and food intake were computed using interval predictive models. This interval prediction was used to develop a method to quantify the risk of suffering different grades of hypo- and hyperglycemia episodes.

Finally, the relationship between the risk index (RI) and the probability of occurrence of hypo- and hyperglycemia events was evaluated through Monte Carlo simulation.

Methods

Computing Glucose Trajectories under Uncertainty

Calculating a risk index unavoidably requires evaluation of the bolus insulin and food intake impact on postprandial glucose, thus implying accurate enough short-time postprandial glycemia predictions. The use of dynamical models provides valuable information about the postprandial glucose excursions. However, one of the main challenges that must be taken into account lies in the large intraindividual variability of the patients. Also, an important source of uncertainty is food intake, as it is not possible to measure precisely the CHO contents of a mixed meal in daily-life situations. These factors make it necessary to develop prediction tools able to consider different sources of uncertainty (inputs, parameters, initial state). Then, a worst-case approach can be introduced to calculate the RI.

Uncertainty will be represented here by means of an interval model, i.e., a model in which the parameters, inputs, and/or initial states take interval values. The results of a simulation in the case of a real-valued model are the trajectories of the system variables across time. When the quantities involved in the simulation take values inside intervals of variation, the set of trajectories determines a manifold bounded by two envelopes, representing the set of all possible responses, as depicted in **Figure 1**.

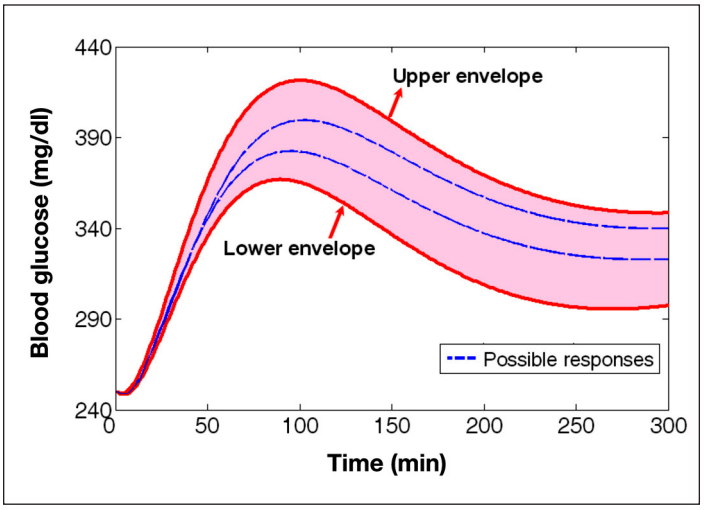

Figure 1. Output of an interval dynamical model: upper and lower envelopes of the manifold of possible system responses (shared area).

When applied to the prediction of postprandial glycemia, models for subcutaneous insulin absorption, CHO digestion and absorption, insulin pharmacokinetics and pharmacodynamics, and glucose metabolism must be considered. In this work, the Tarín model[10] for subcutaneous insulin absorption and the Hovorka model[11,12] for the rest of the components of the model were combined to represent the glucoregulatory model.[13]

Uncertainty in the patient's hepatic and peripheral insulin sensitivities[11] was considered: S_{IT} (distribution/transport) with 11% variation, S_{ID} (disposal) with 8% variation, and S_{IE} (endogenous glucose production) with 2% variation according to the standard deviation presented in the Hovorka model.[11] An uncertainty of 5% in the CHO content of the planned meal was also considered. With regard to this, it is well known that diabetic patients tend to underestimate the carbohydrate content of their meal consistently. When the RI is applied to a specific patient, this deviation is taken into account in the process of adjusting the model with a correction of the bias in the patient's CHO estimation. The 5% uncertainty considered here thus represents the deviation with respect to this bias-corrected estimation.

Interval simulations[13] of the model were performed during a 5-hour period after a meal. Upper and lower envelopes of all possible glucose responses were estimated using modal interval analysis (MIA),[14] yielding a tight (sometimes exact) enclosure of the envelope that includes all possible behaviors of the system. In the case under consideration, a change of variables allowed computation of the exact enclosure of the envelope by means of the coercion theorems[14] from MIA. These computations were carried out using the C++ modal interval library IvalDb.

Hyper- and Hypoglycemia Risk Index

The risk index was computed from a quantification of the excursions, provided by the glucoregulatory model with uncertainty described earlier, in the mild and severe hypo- and hyperglycemic ranges and its relative importance. The following considerations were taken into account.

1. Glucose ranges corresponding to severe (H_s) and mild (H_m) hyperglycemia and to severe (h_s) and mild (h_m) hypoglycemia are those depicted in **Figure 2** with thresholds $h_s = 36$, $h_m = 70$, $H_m = 150$, and $H_s = 250$ mg/dl.

2. A weighting function $\gamma(t)$ was established for the time occurrence of hyperglycemia (mild and severe). Major relevancy was given to zones far from meal-time to take into account long-term hyperglycemia (see **Figure 2**).

3. Weights were established for quantifying the relative importance of mild and severe hypo- and hyperglycemia events (α_{hs}, α_{hm}, α_{Hm}, and α_{Hs}). They were adjusted to the following values: for mild and severe hypoglycemia, $\alpha_{hs} = \alpha_{hm} = 1$; for mild hyperglycemia, $\alpha_{Hm} = 0.0625$; and for severe hyperglycemia, $\alpha_{Hs} = 0.25$.

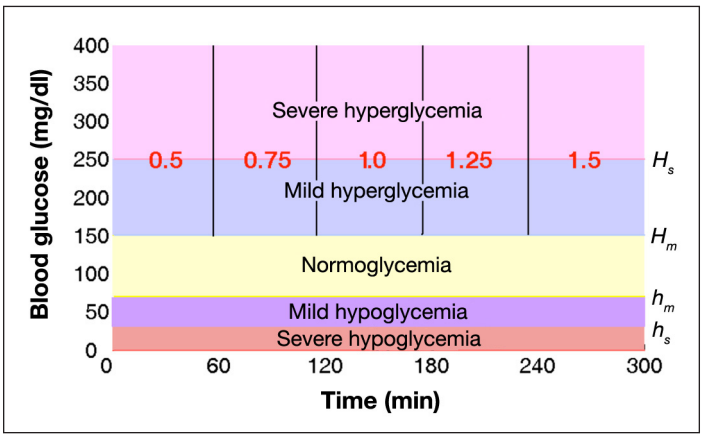

Figure 2. Grid of glucose ranges and hyperglycemia time weights (red numbers) used for risk index computation.

The RI was then computed as a weighted sum of the risk for each event, given by a normalized measure of the area under the curve in each glucose range:

$$J_{Hs} = \frac{\int_{T_{Hs}} \gamma(t)(G_{max}(t) - H_m)\,dt}{H_s - H_m} \qquad T_{Hs} = \{\, t / G_{max}(t) \geq H_s \,\}$$

$$J_{Hm} = \frac{\int_{T_{Hm}} \gamma(t)(G_{max}(t) - H_m)\,dt}{H_s - H_m} \qquad T_{Hm} = \{\, t / H_m \leq G_{max}(t) < H_s \,\}$$

$$J_{hs} = \frac{\int_{T_{hs}} (h_m - G_{min}(t))\,dt}{h_m - h_s} \qquad T_{hs} = \{\, t / G_{min}(t) \leq h_s \,\}$$

$$J_{hm} = \frac{\int_{T_{hm}} (h_m - G_{min}(t))\,dt}{h_m - h_s} \qquad T_{hm} = \{\, t / h_s < G_{min}(t) \leq h_m \,\}$$

$$J := \alpha_{Hs} J_{Hs} + \alpha_{Hm} J_{Hm} + \alpha_{hs} J_{hs} + \alpha_{hm} J_{hm}$$

where $G_{max}(t)$ and $G_{min}(t)$ are the upper and lower envelopes of the glucose excursions (see **Figure 3**).

An example of the risk index computation for one predicted manifold defined through its upper and lower

envelopes is depicted in **Figure 3**, where the areas m_i, s_i, i = 1,2,3 correspond to the area under the curve of normalized glucose with respect to each glucose range for the different episodes and time weights. The components of the RI corresponding to hyperglycemia are then calculated as $J_{Hm} = 0.5m_1 + 0.75m_2 + 1.5m_3$ and $J_{Hs} = 0.75s_1 + 1s_2 + 1.25s_3$. The same procedure is used to obtain J_{hm} and J_{hs} but in this case without time weights.

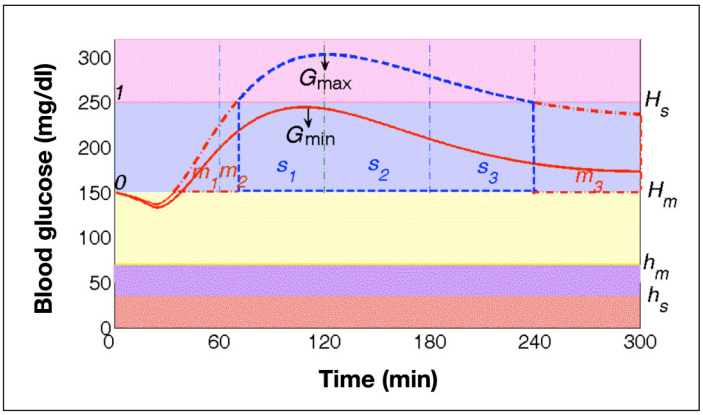

Figure 3. Example of risk index computation.

In this work, the Tarín and Hovorka models were used to show the feasibility of the risk index. However, this index can also be used with other glucoregulatory models representing the patient's behavior.

Index Validation

To validate the RI, a virtual patient with nominal parameters was considered. For this patient, a total of 3315 different scenarios were evaluated in order to compute the risk index; preprandial glucose was varied uniformly between 80 and 240 mg/dl. Food intake (40, 60, and 80 grams), bolus insulin (2 to 10 IU with a step size of 0.5 IU), and mealtimes (0, 15, 30, 45, and 60 minutes) were also varied. For each scenario, the RI was evaluated and classified into one of the following four types (**Figure 4**): low risk (index lower than 10), intermediate risk (index between 10 and 60), high risk (index between 60 and 120), and very high risk (index higher than 120). This classification was done based on observations of similar behaviors for indices in each of these ranges.

To analyze the relationship between the risk index range and the probability of occurrence of the different hypo- and hyperglycemia events, a Monte Carlo study was carried out. A reference model for a preprandial glucose value in the ranges 80–120 (range 1), 130–190 (range 2), and 200–240 (range 3) mg/dl (see **Figure 4**) was obtained to reduce the number of Monte Carlo simulations required. A χ^2 test with a nine degree of freedom distribution was used to test a reference model for each preprandial glucose range. The reference model was chosen to be the preprandial glucose that presented the lowest p value with respect to different preprandial glucose values in each range.

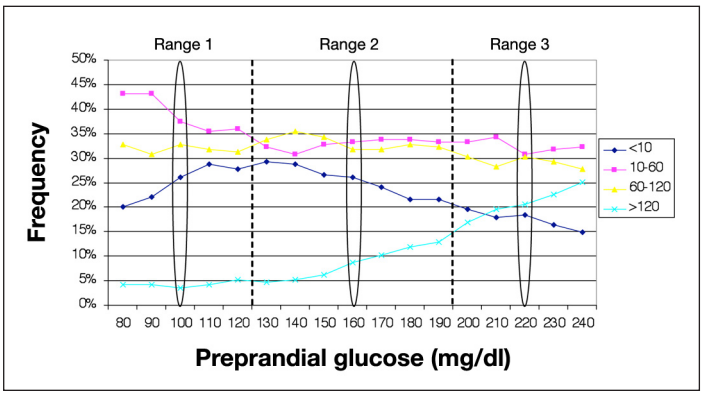

Figure 4. Risk index value distribution versus preprandial glucose. Preprandial glucose with less variation in each range is indicated by an ellipse.

Once a reference model was proposed, 19,500 Monte Carlo simulations for each preprandial glucose value were performed and the occurrence of hypo- and hyperglycemia events was computed, considering the same variation of food intake and bolus insulin as the previous scenarios. In the Monte Carlo simulation, parameter uncertainty was represented in terms of normal probability distributions. An event of severe hyperglycemia was considered to occur when the maximum glucose value was greater than 250 mg/dl and mild hyperglycemia when it was between 150 and 250 mg/dl. Severe hypoglycemia was considered to occur when the minimum glucose value was lower than 36 mg/dl and mild hypoglycemia when it was between 36 and 70 mg/dl.

Results

The obtained reference models for each preprandial glucose range were 100, 160, and 220 mg/dl, respectively, as indicated by each ellipse in **Figure 4**. The resulting p value was 0.210. The null hypothesis formulated was that $p > \alpha$. The significance level α was established as 0.05. This indicates that the distributions of RI values for the reference model and any preprandial glucose in the same range do not present variation. As p is greater than α, the null hypothesis was accepted.

Figure 5 shows the percentage of scenarios where hypo- and hyperglycemia events occurred in the Monte Carlo simulation carried out for each preprandial capillary glucose reference model (**Figures 5A**, **5B**, and **5C** for euglycemia, mild hyperglycemia, and severe hyperglycemia, respectively). These percentages were computed for the RI in the ranges <10, 10–60, 60–120, and >120.

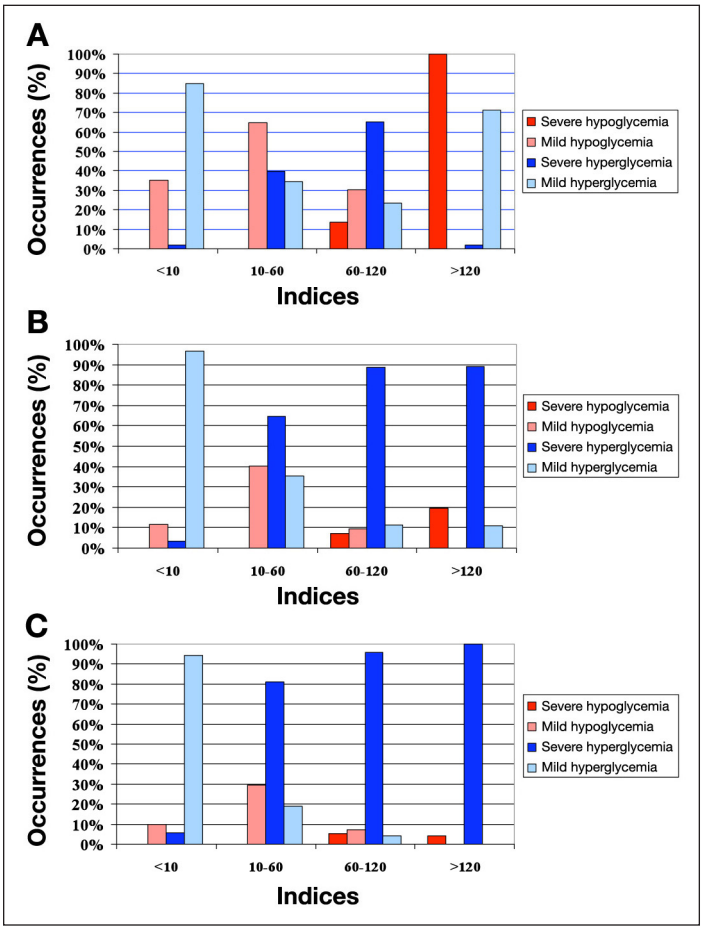

Figure 5. Percentage of scenarios where hypo- and hyperglycemia events can occur: **(A)** euglycemia, 110 mg/dl; **(B)** mild hyperglycemia, 160 mg/dl; and **(C)** severe hyperglycemia, 220 mg/dl.

Table 1 summarizes the probability of occurrence for mild and severe hypoglycemia and for mild and severe hyperglycemia. The probability was ranked according to very low (less than 10%), low (between 10 and 30%), moderate (between 30 and 50%), high (between 50 and 80%), or very high (higher than 80%).

Table 2 shows risk indices for different bolus insulin–mealtime pairs for each preprandial glucose range. Examples of blood glucose responses for selected bolus insulin–mealtime pairs from **Table 2** are shown in

Table 1.
Probability of Hypo- and Hyperglycemia Classified According to Preprandial Capillary Glucose and the Risk Index[a]

Preprandial glucose	Risk index	Hypoglycemia		Hyperglycemia	
		Mild	Severe	Mild	Severe
Euglycemia	<10				
	10–60				
	60–120				
	>120				
Mild hyperglycemia	<10				
	10–60				
	60–120				
	>120				
Severe hyperglycemia	<10				
	10–60				
	60–120				
	>120				

[a] Probability: Very Low - Low - Moderate - High - Very High

Figure 6. With these results, the different risks that can occur according to probabilities shown in **Table 1** can be observed.

Discussion

Risk Interpretation

Information contained in the RI is clearly dependent on preprandial glucose. For preprandial euglycemia (**Figure 5A**), there is an important risk of mild hypoglycemia for a RI between 10 and 60. For RI values greater than 60, the risk will translate into severe hypoglycemia. Values greater than 120 reflect an occurrence in 100% of the cases of severe hypoglycemia. Regarding hyperglycemia, mild events may happen for values in the lower and upper ranges, whereas a significant risk of severe hyperglycemia will be reflected in the intermediate ranges.

Thus, if an insulin therapy yields RI values less than 10, there will not be a risk of severe hyperglycemia or severe hypoglycemia. Values between 10 and 60 will indicate a risk of mild hypoglycemia or severe hyperglycemia. Values between 60 and 120 will predict an important risk of severe hyperglycemia. For RI values greater than 120, severe hypoglycemia will occur.

Table 2.
Examples of Risk Indices for Each Preprandial Glucose Value with Different Bolus Insulin and Mealtime Combinations

Preprandial glucose (mg/dl)	Bolus (IU)	Meal		Severe hypoglycemia index	Mild hypoglycemia index	Severe hyperglycemia index	Mild hyperglycemia index	Total index[a]
		Grams	Minutes					
100	4.5	40	45	0.00	0.15	0.00	0.23	0.38
	2.5	40	60	0.00	0.32	0.00	6.85	7.17
	4.5	60	15	0.00	0.00	3.96	6.49	10.45
	7.5	80	0	0.00	35.16	14.66	1.78	51.60
	3.5	60	60	0.00	2.32	63.29	1.07	66.68
	4.0	80	60	0.00	3.36	101.96	0.46	105.78
	9.0	80	0	85.44	29.44	6.79	1.59	123.26
	7.0	40	0	119.40	32.52	0.00	0.15	152.07
160	7.0	60	45	0.00	0.31	0.00	1.51	1.83
	3.0	40	30	0.00	0.00	0.00	8.59	8.59
	6.5	80	60	0.00	0.00	22.41	4.12	26.53
	7.0	60	0	0.00	50.00	8.00	1.93	59.93
	2.5	40	30	0.00	0.00	59.23	1.33	60.56
	9.0	80	15	27.54	49.19	6.72	2.00	85.45
	4.0	80	45	0.00	0.00	120.44	0.45	120.89
	10	80	0	138.52	21.24	11.83	1.24	172.83
220	9.0	80	60	0.00	1.50	0.00	2.62	4.12
	6.5	60	30	0.00	0.00	2.64	4.55	7.19
	5.5	40	0	0.00	3.42	9.92	2.08	15.42
	7.5	80	0	0.00	17.80	36.22	1.62	55.64
	4.5	60	15	0.00	0.00	57.35	4.62	61.97
	8.0	60	0	63.70	36.70	15.64	1.34	117.38
	9.5	80	15	75.36	29.11	13.88	1.75	120.10
	2.0	60	30	0.00	0.00	171.97	0.75	172.72

[a] See legend to **Figure 6**.

Regarding preprandial values in mild hyperglycemia (**Figure 5B**), a severe hyperglycemia risk will increase rapidly, with the index value reaching a probability of about 90% for RI values greater than 60. The risk of mild hypoglycemia will also increase, to a lesser extent, as the RI increases, yielding severe hypoglycemia when values greater than 60 are reached. Similar behavior is observed for preprandial values in the severe hyperglycemia range (**Figure 5C**).

Table 1 depicts graphically a grid with the obtained risk probabilities. White boxes indicate null risk; cyan boxes, very low risk; green boxes, low risk; golden boxes, moderate risk; brown boxes, high risk; and, finally, dark red boxes, very high risk.

As an illustration, **Figure 6** shows different scenarios for preprandial glucose values in euglycemia, mild hyperglycemia, and severe hyperglycemia. The red solid line corresponds to a scenario with a RI <10; the blue dashed line corresponds to a scenario with a RI in the 10–60 range; the green dotted line corresponds to a RI in the range 60–120; and the magenta dashed–dotted line corresponds to a RI >120 (see **Table 2**).

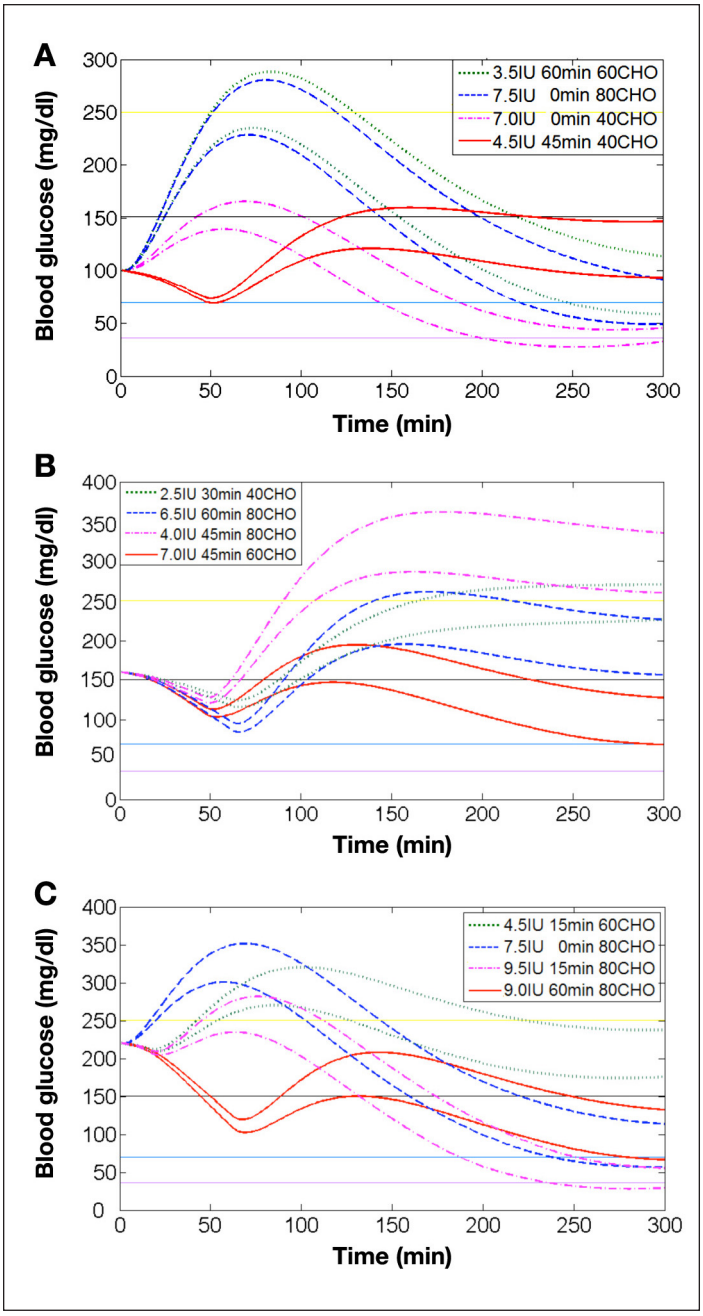

Figure 6. Blood glucose response for 5 hours considering preprandial glucose: **(A)** euglycemia, **(B)** mild hyperglycemia, and **(C)** severe hyperglycemia. The red solid line indicates indices less than 10, the blue dashed line represents indices between 10 and 60, the green dotted line represents indices between 60 and 120, and the magenta dashed–dotted line represents indices greater than 120.

With euglycemic preprandial glucose, a RI <10 corresponds to a bolus insulin–mealtime pair producing the envelope closest to euglycemia (red solid line in **Figure 6A**). When severe and mild hyperglycemia and/or mild hypoglycemia episodes occur during the simulation, an intermediate risk index value is generated (blue dashed line, **Figure 6A**). A high risk appears when sustained hyperglycemia is present and/or mild hypoglycemia is produced (green dotted line, **Figure 6A**). A RI >120 arises with severe hypoglycemia for a long time (magenta dashed–dotted line, **Figure 6A**).

Figure 6B illustrates scenarios with preprandial glucose values in 160 mg/dl. As observed, the risk index value is proportional to the presence of sustained hyperglycemia.

Figure 6C shows illustrative scenarios for a preprandial glucose value in 220 mg/dl. Similar conclusions are drawn. The lowest index indicates that the glucose trajectory will converge to euglycemia with lowest exposure to a hyperglycemic state. On the contrary, greatest risks are obtained when there is an excess (magenta dashed–dotted line) or lack (green dotted line) of insulin.

Conclusions

Modal interval analysis is a technique used to deal with uncertain variables and was applied here to predict postprandial glucose in patients with T1DM. By considering intrapatient variability and uncertainty in CHO, a safer prediction of possible hyper- and hypoglycemia episodes induced by the tested insulin therapy can be calculated.

The risk index proposed in this work is based on metrics that have been established according to the clinical relevance of each episode of hypo- and hyperglycemia. The relevance of these metrics can be appreciated clearly in the results.

An intensive study was carried out analyzing the relationship between different ranges for the value of the risk index and the occurrence of mild and severe hypoglycemia and hyperglycemia events.

The resulting risk index is apparently consistent with clinical judgment; however, a formal clinical validation is required. The authors are currently working on a way to integrate the RI into a decision support system.

In order to apply the methodology presented here in a patient-specific scenario, it is necessary to adjust the model to this patient. The model parameters would be estimated from measurements with a continuous glucose monitor for several days.

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