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RESEARCH ARTICLE

GLYCEMIC VARIABILITY INDICATORS BY CONTINUOUS GLUCOSE MONITORING AND HYPOGLYCEMIA RISK IN CHILDREN AND YOUNG ADULTS WITH TYPE 1 DIABETES

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ABSTRACT

Background: Hypoglycemia is the main barrier to optimizing insulin treatment in people with type 1 diabetes, different risk factors have been studied and one of the mechanisms involved is glycemic variability.

Aims: To assess hypoglycemia risk showed by the glycemic variability metrics: coefficient of variation (CV), continuous overlapping net glycemic action (CONGA), low blood glucose index (LBGI) and lability index (LI) in a group of children, adolescents, and young adults with type 1 diabetes.

Methods: A group of 31 subjects with type 1 diabetes under 25 years were evaluated, data from professional continuous glucose monitoring records were studied, glycemic variability metrics, including CV, CONGA24, LBGI, and LI, were calculated. Correlation with percentage time of hypoglycemia under 54mg% was assessed. Multiple linear regression models were generated, univariate and multivariate analysis was also performed, area under curve of glycemic variability metrics was obtain from ROC curves analysis, the optimal cutoff points were calculated.

Results: The average age was 14.5 years with a range of 5 to 24 years. The mean duration of diabetes was 6.6 ± 3.7 years, and the glycated hemoglobin mean value was 8.2% ± 2.1%. The average percentage of time for hypoglycemia alert was 4.23% (0.2 to 13%), while for clinically significant hypoglycemia was 4.55% (0 to 17.1%). LBGI with R= 0.913 and CV with R= 0.735 ($p < 0.0001$) expressed the highest degree of correlation with percentage of time in hypoglycemia, furthermore, after multivariate analysis, they showed the highest predictive load. CV expressed an AUC of 0.97, while LBGI was 0.95, both statistically significant ($p<0.0005$). The cut-off point for CV of 38% had sensitivity of 93% and specificity of 74% in detection of time in hypoglycemia under 54mg/dl, and the cut-off point for LBGI of 5.4 expressed sensitivity of 87% and specificity of 94%.

Conclusions: Glycemic variability metrics studied outperformed the clinical variables as indicators of risk of hypoglycemia, and those with the greatest predictive power of hypoglycemia risk were LBGI and CV above 38%.

Keywords: hypoglycemia risk, glycemic variability, type 1 diabetes.

Introduction

Hypoglycemia is the main barrier to optimizing insulin treatment in people with type 1 diabetes, hence its prevention is one of the most critical issues in the management of these patients[1,2].

A history of hypoglycemia decreases the plasma glucose threshold for both autonomic and cognitive responses, altering the detection and response systems[3]. Repeated hypoglycemia can affect spatial intelligence and memory in children and adolescents[4]. On the other hand, severe hypoglycemia can be lethal and is the cause of death in 4–10% of children and adolescents with type 1 diabetes[2].

Glycated hemoglobin (HbA1c) is not a predictable value for severe hypoglycemia[2] or glycemic variability (GV)[5], so more reliable predictive indicators are required. Exaggerated glucose fluctuations are associated with an enhanced risk of adverse cardiovascular outcomes due primarily to hypoglycemia, increased glucose variability is consistently associated with mortality in the intensive care unit and is a consistent predictor of hypoglycemia both in prospective studies and randomized clinical trials, therefore the assessment of glycemic variability is a parameter to consider in the evaluation of patients with diabetes[6,7].

In search of improving the evaluation of glycemic control, different metrics have been developed, first using self-monitoring of capillary blood glucose (SMBG) and then the data obtained from continuous glucose monitoring (CGM)[6].

Coefficient of variation (CV), which is the SD divided by the mean, has the advantage of being a metric relative to the mean, which makes it more descriptive of hypoglycemic excursions than the SD alone, CV have been considered the primary measure of variability. Stable glucose levels are defined as a CV <36%, and unstable glucose levels are defined as CV ≥36%[7-9].

Continuous overlapping net glycemic action (CONGA) is a metric that calculates the difference between current blood glucose (BG) reading, and a reading taken (n) hours earlier and later[10]. Thereby, it integrates the duration and degree of glucose excursions[6].

The low blood glucose index (LBGI) is designed to calculate the risk for hypoglycemia, measure of frequency and extent of hypoglycemia, amplify hypoglycemic excursions and ignore hyperglycemia, initially calculated by SMBG[7,10]. For some authors, LBGI calculations based on CGM data tend to slightly underestimate risk, particularly in the low-risk range[7]; however, others account well for the risk of hypoglycemic excursions[11].

The lability index (LI) is calculated as the sum of all the squared differences in consecutive glucose readings divided by the time interval between the readings, based on the change in glucose levels over time[12]. This metric gives a good measure of glycemic lability when it is compared with the clinical assessment[13].

There is a limited group of trials that evaluate these metrics in patients under 25 years of age[14], and they have different methodological framework.

The purpose of this work was to assess the risk of hypoglycemia showed by the glycemic variability indicators: CV, CONGA, LBGI and LI in a group of children, adolescents, and young adults with type 1 diabetes.

METHODS

This cross-sectional study included a total of 31 subjects with type 1 diabetes, under 25 years and was conducted at Unidad de Diabetes y Enfermedades Metabólicas La Sagrada Familia in Maracaibo, Venezuela, these patients underwent professional CGM Ipro2® from Medtronic for 3 to 6 days. Clinical records were consulted to collect information related to sex, age of diagnosis, age at which monitoring was performed, body mass index (BMI), HbA1c, insulin dose, whether carb counting method was used, and modality insulin treatment (continuous subcutaneous insulin infusion [CSII] or multiple daily injections [MDI]).

Raw data from CGM records were entered into the EasyGV software, available free for noncommercial use at (www.phc.ox.ac.uk/research/technologyoutputs/easygv), glycemic metrics, including CV, CONGA24, LBGI, and LI, were calculated.

For descriptive analysis, continuous variables are expressed as mean and SD. Categorical variables are expressed as count and percentage. Spearman's correlation was used to assess the correlation between the GV metrics and the percentage time of hypoglycemia. Multiple linear regression models were generated, in a univariate analysis, the potential risk factors associated with hypoglycemia and the different metrics used to determine the GV were evaluated. A multivariate analysis was also performed, variables that were not statistically significant were excluded, and those with collinearity and confusion variables were deleted progressively from the model to obtain a reduced model with the best set of predictors.

The area under curve (AUC) of GV metrics was obtained from ROC curves analysis, the optimal cutoff points were generated using the Liu method[15]. Statistical significance was considered for variables with a $P < 0.05$. SPSS version 26 was used for the analysis.

RESULTS

Characteristics of the patients are listed in table 1. Most of the patients were female. The average age was 14.5 years with a range of 5 to 24 years. The mean duration of diabetes was 6.6 ± 3.7 years and the mean HbA1c value was 8.2% ± 2.1%. 20 participants (64.5%) were treated with MDI, whereas 11(35.5%) used CSII. Data of 142 days of CGM was recorded, with an average of 4.5 days per patient and 1287 ± 307 measures of tissular glycaemia. A total of 177 events (<54 mg/dl) were documented in 22 patients (8 events/patient). The average percentage of time for hypoglycemia alert (55 to 69 mg/dl) was 4.23% (0.2 to 13%), while for clinically significant hypoglycemia (<54 mg/dl), was 4.55% (0 to 17.1%).

Table 1. Characteristics of included participants

Variable	n =31
Sex female, *n* (%)	19 (61%)
Age, years, mean (SD)	14.5 (5.6)
BMI, Kg/m^2, mean (SD)	20.7 (3.8)
Duration of diabetes, years, mean (SD)	6.6 (3.7)
HbA1c (%), mean (SD)	8.2 (2.1)
Carbs Counting, n (%)	25 (80.6%)
Number of patients with episodes of severe hypoglycemia in the last year, n (%)	9 (29%)
Modality of treatment	
Continuous *subcutaneous insulin* infusion (CSII), n (%)	11 (35.5%)
Multiple daily injections (MDI), n (%)	20 (64,5%)
Basal insulin type, n (%)	
Glargine	13 (41.9%)
Detemir	8 (25.8%)
Prandial insulin type, n (%)	
Lispro	2 (6.5%)
Aspart	22 (71%)
Glulisine	3 (9.7%)
Regular	4 (12.9%)
TDDI, mean (SD)	42.7 (25.4)
TDDI, U/kg, mean (SD)	0.87 (0.38)
Proportion of Basal/bolus (%)	47.9/52.0

SD: standard deviation, BMI: body mass index, TDDI: total daily dose of insulin.

Correlation analysis were performed between clinical and anthropometric variables with the percentage of time in clinically significant hypoglycemia (< 54mg%) and it was observed positive correlation between the duration of diabetes and a greater percentage of time in hypoglycemia, although not statistically significant (p = 0.070). The other variables such as daily dose of insulin, nutritional status (expressed by BMI) and even the HbA1c level did not show any correlation with the percentage of time in hypoglycemia. (Figure 1)

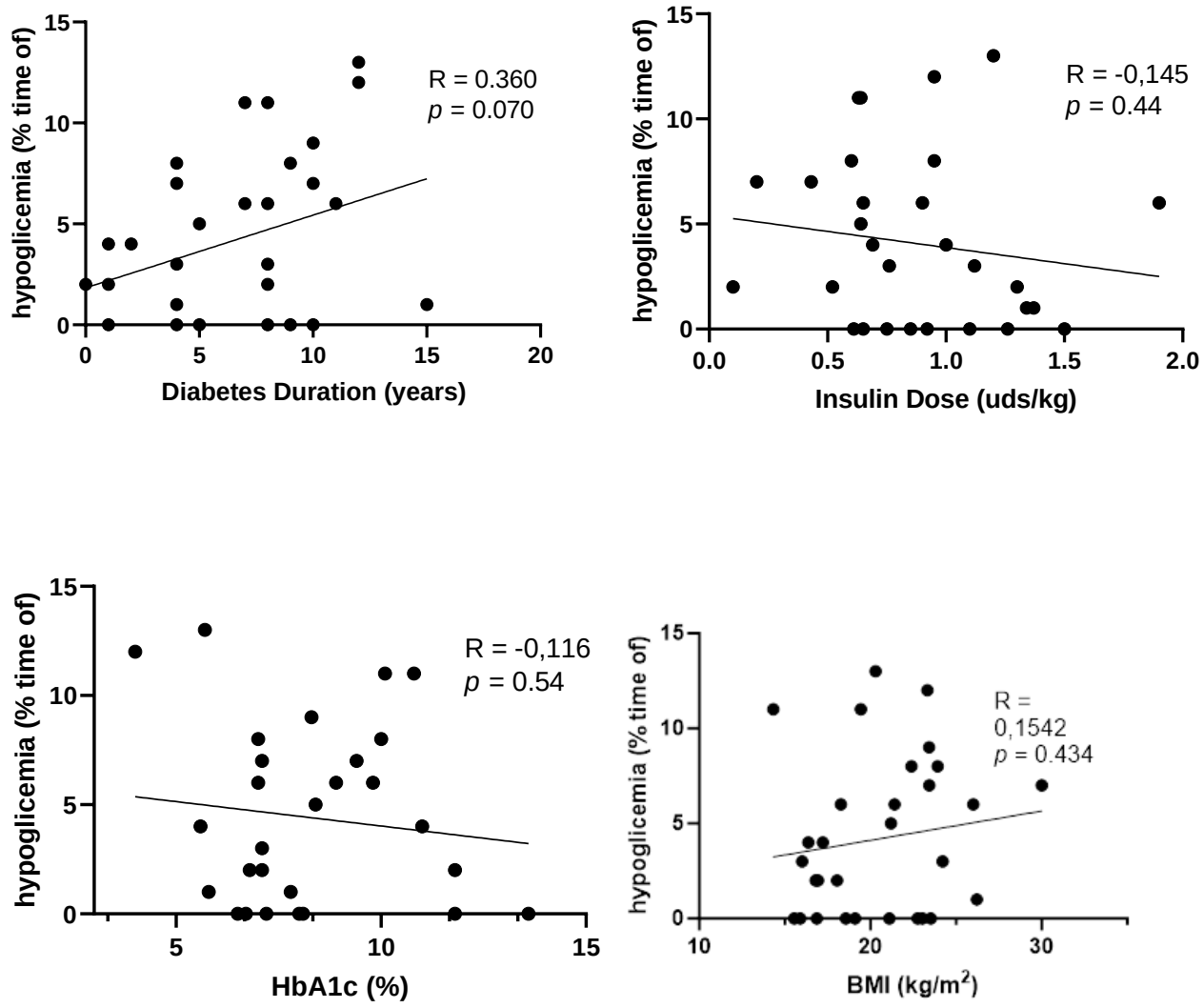

Figure 1. Correlation analysis among percentage of time clinically significant hypoglycemia (<54 mg/dL), and diabetes duration, insulin doses, HbA1c and BMI.

On the other hand, when analyzing the correlation between indicators of glycemic variability and the percentage of time in hypoglycemia, LBGI with R= 0.913 and CV with R= 0.735 ($p < 0.0001$) expressed the highest degree of correlation (Spearman's coefficient), while CONGA and IL had a lower degree of correlation, R= -0.509 and 0.495 respectively. (Figure 2)

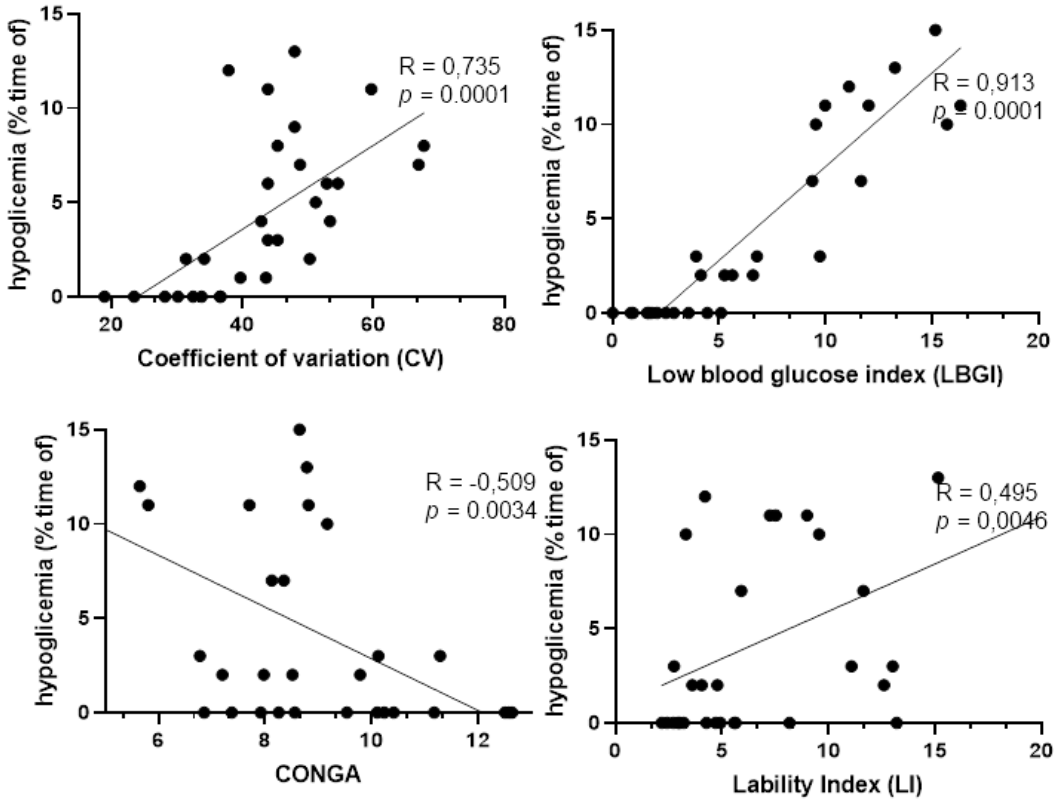

Figure 2. Correlation analysis among percentage of time clinically significant hypoglycemia (<54 mg/dL), and CV, LBGI, CONGA and LI.

Univariate and multivariate analysis of each GV metric, clinical and laboratory factors as identifiers of patients with a risk of hypoglycemia under 54 mg/dL, are presented in Table 2. Only CV, LBGI, and CONGA were significant as predictors of the percentage of time in hypoglycemia; though, when performing multivariate analysis, the ones that preserved its significance were the CV and LBGI, being the indicators with the highest predictive load.

Table 2. Linear logistic regression analysis

Independient Variables	*Univariate analysis*			*Multivariate analysis*		
	B (95% CI)	β	*p*	B (95% CI)	β	p
Duration of Diabetes	0.01 (-0.06 – 0.03)	0.117	0.53	-	-	-
Female Gender	0.29 (-0.07 – 0.67)	0.291	0.11	-	-	-
HbA1c	-0.46 (-0.04 – 0.13)	-0.198	0.30	-	-	-
BMI	0.03 (- 0.01 – 0.08)	0.244	0.18	-	-	-
CSII (Insuline Pump)	-0.32 (-0.70 – 0.04)	- 0.313	0.08	-	-	-
TDD	-0.29 (-0.79 – 0.20)	- 0.22	0.23	-	-	-
Carb Counting	-0.22 (-0.69 – 0.24)	-0.17	0.33	-	-	-
CV	0.03 (0.02 – 0.04)	0.753	0.00	0.03 (0.00 – 0.05)	0.707	0.01
LBGI	0.07 (0.05 – 0.10)	0.765	0.00	0.05 (0.04 – 0.09)	0.512	0.03
CONGA	-0.14 (-0.22 – -0.65)	-0.572	0.00	0.02 (- 0.08 – 0.01)	0.088	0.64
LI	0.02 (-0.00 – 0.60)	0.268	0.14	-	-	-

Finally, COR curve-type analyses were performed, where the CV expressed an AUC of 0.97, while LBGI was 0.95, both statistically significant (p<0.0005). The cut-off point for CV of 38% had sensitivity of 93% and specificity of 74% in detection of time in hypoglycemia under 54mg/dl, and the cut-off point for LBGI of 5.4 expressed sensitivity of 87% and specificity of 94%. (Figure 3)

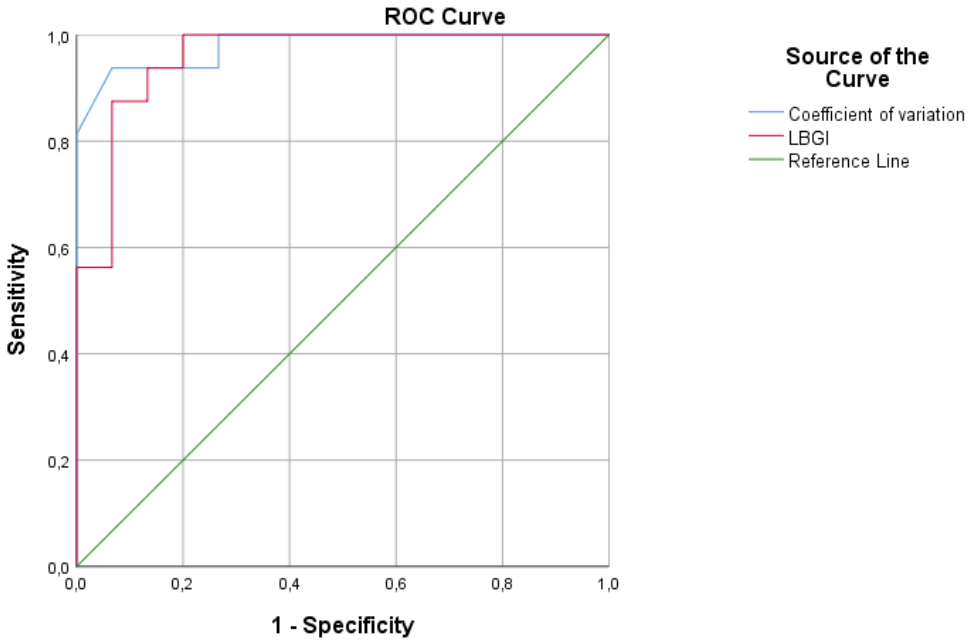

Figure 3. Area Under the Curve

Test Result Variable(s)	Area	Std. Error	Asymptotic Sig.	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
CV	0,979	0,021	0,000	0,939	1,000
LBGI	0,958	0,034	0,000	0,893	1,000

DISCUSSION

The development of technology applied to diabetes has marked a milestone in the evaluation and control of the patient. The use of CGM has shown evidence to reduce glycemic variability and the risk of hypoglycemia, helping to prevent the frequency of events due to its predictability capacity[16-17]. The Comisair Study showed that real-time CGM was superior to self-monitoring of blood glucose in reducing HbA1c and hypoglycemia in adults with type 1 diabetes, regardless of the method used to deliver insulin[18].

The data generated from the CGM has allowed a better knowledge of the behavior of diabetes and the response to different treatments[19]. When professional CGM is used, the patient is blinded to sensor glucose readings, and gave us unbiased glucose data, with subsequent analysis for possible adjustment of diabetes treatment[20-21].

We took the data from the professional CGM of 31 patients with type 1 diabetes under 25 years of age, to analyze some of the glycemic variability metrics related to hypoglycemia.

The search for predisposing factors for hypoglycemia continues to be a fundamental objective when optimizing intensive treatment

in diabetes[1-2], several studies have found risk factors such as: advanced age, duration of diabetes, presence of microvascular complications, lower HbA1c, and major hypoglycemic events in the last year[22-25]. Johansen, evaluating 3,320 children and adolescents with type 1 diabetes, found that the duration of diabetes and the management of the condition in centers with little experience, significantly increase the risk of hypoglycemia, while the use of insulin infusion pump and the greater bolus ratio vs. basal insulin confers protection[26]; Fredheim S. et al. described that the rate of hypoglycemia was lower among those who used more daily insulin bolus, a higher percentage of bolus in relation to basal insulin, and in those insulin pump users, however, they did not find differences in relation to hbA1c level or years of diabetes duration[27]. None of these studies used CGM data.

Now, when technology is used, the findings are different, Piona et al, using CGM data, collected from 805 children/adolescents with T1D, found that age, gender, BMI, duration of diabetes, type of CGM device, type of insulin therapy administration, and time in range percentage (%TIR) were not significant predictors of CV above 36%, indirectly relating this parameter with hypoglycemia risk[14]. These findings are similar to ours given that multivariate logistic regression analysis found no predictive capacity for hypoglycemic events due to any of these clinical and therapeutic variables. A trend towards a higher frequency of hypoglycemia with a longer duration of diabetes was observed, but without reaching statistical significance.

We could infer that when CGM data is used for the analysis, and not the data provided by the patient interview about hypoglycemia events, clinical and therapeutic variables lose weight in predicting the risk of hypoglycemia in front of glycemic variability metrics. This phenomenon could be explained because when interviewing the patient about hypoglycemic events, it is impossible to identify hypoglycemia unawareness, which is possible to detect with a CGM device.

Traditional glycemic targets are focused on HbA1c and are often used to assess the degree of hyperglycemia. In the case of hypoglycemia, their contribution is powerless, and it is usual that while trying to optimize HbA1c values, the frequency of hypoglycemia increases[25]. Rama Chandran[28] did not observe any relationship between HbA1c and indicators of hypoglycemia (measured by CGM and SMBG) in patients with type 1 diabetes, and only found a weak negative association in patients with type 2 diabetes ($r = -0.223$, $P = 0.03$). In our study, the association between these variables was not statistically significant ($r = -0.116$, $P = 0.54$), and we observed that hypoglycemic episodes were common in all HbA1c levels.

Coefficient of variation represents one of the most widely accepted indicators of glycemic variability and has been used to identify unstable patient[7,9]. In a study carried out in adults with long-standing type 1 diabetes (average duration 28 years), short-term glycemic variability (measured by %CV) explained more hypoglycemia than average glucose alone when the threshold limit is 54 mg/dl, thus they conclude that minimizing the risk of hypoglycemia requires CV below 34%[29]. Gomez[30], in a group of adults with type 1 diabetes, obtained the same cut-off point

(34%) to discriminate patients with events under 54 mg/dL. In another cohort of patients, CV above 36% significantly increases the frequency of hypoglycemia in patients with type 1 and type 2 diabetes, especially in those treated with insulin[9]. Rama Chandran identified in his cohort of patients with type 1 diabetes that a cut-off point above 41% expressed a sensitivity of 72% and a specificity of 96% in the prediction of hypoglycemia[28]. In our study using a cut-off point of 38%, CV expressed a positive correlation with the percentage of time in hypoglycemia and a very good predictive capacity in the ROC curve analysis. The differences in the cut-off points seem to be explained by inequalities in the demographic variables of the studied groups, especially age and diabetes type.

Another indicator of glycemic variability that expressed an excellent predictive capacity in the evaluation of hypoglycemia was the LBGI, our findings reveal an AUC of 0.95 (CI: 0.89-1) using a cut-off point of 5.4, sensitivity of 87% was observed and specificity of 94% in the detection of hypoglycemia (<54mg/dl). These results are compatible with those found by Gómez et al[30], who using a cut-off point of 3.9, obtained an AUC of 0.96 (CI: 0.92-0.99) in the detection of hypoglycemia.

These findings reaffirm what was expressed in previous works that glycemic variability is a parameter of metabolic control in patients with diabetes[5,9], in addition to the assertiveness of the international consensus to include %CV and LGBI as indicators to be present in the average glucose profile (AGP) from personal CGM reports. Such as reporting some authors[31], strategies to reduce GV should take account education on organized blood glucose testing, individualizing blood glucose goals, empowering self-management through education of carbohydrate counting with insulin dose adjustments, and superior accuracy in insulin dose delivery with the use of pump therapy and/or sensor-augmented pump therapy. The main strength of the study is age group included in whom GV has not been well assessed, by the other side, sample size is a limitation.

CONCLUSIONS

In a group of children and young adults, the glycemic variability metrics studied outperformed the clinical variables as indicators of risk of hypoglycemia, and those with the greatest predictive power were LBGI and CV above 38%. These results are similar to those reported by other authors in different age groups. The evaluation of glycemic status should go beyond HbA1c to incorporate GV and no traditional glycemic metrics to define both stable diabetes and optimal glycemic control.

Conflict of Interest Statement:

The authors have no conflicts of interest to declare.

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