ANALYSIS OF CHRONIC KIDNEY DISEASE – ASOCIATED GLYCEMIC VARIABILITY IN PATIENTS WITH TYPE 2 DIABETES USING CONTINUOUS GLUCOSE MONITORING SYSTEM

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Abstract

Background and Aims. *In diabetic patients, chronic kidney disease (CKD) requires special attention due to the multitude of factors that determine glycemic variability. We aimed to assess glycemic variability in patients with CKD and type 2 diabetes mellitus (T2DM) using a continuous glucose monitoring system (CGMS) and identify the predictive value of inter-day and intra-day glycemic variability indices for metabolic imbalance.* ***Material and method.*** *We included 20 diabetic patients (10 CKD patients/10 patients without CKD) and 10 healthy volunteers. Anthropometric parameters, glycated hemoglobin (HbA1c), and glycemic variability indices on CGMS readings were registered.* ***Results.*** *CKD diabetic patients presented significantly higher inter-day and intra-day glycemic variability compared to the diabetic patients without CKD. HbA1c was not significantly different between diabetic subjects with/without CKD. ROC curves indicated that just some CGMS parameters had higher predictive value for metabolic imbalance (HbA1c≥6.5%) but only the percentage of time with glucose values>180 mg/dl (p=0.024) was an independent predictor for HbA1c≥6.5%.* ***Conclusions.*** *Subjects with CKD and T2DM had poor glycemic control and significantly higher glycemic variability comparative to those without CKD, and especially to healthy volunteers. Assessment of glycemic variability indices is more accurate than HbA1c for the quantification of glycemic control in CKD diabetic patients.*

key words: *glycemic variability, HbA1c, chronic kidney disease, type 2 diabetes mellitus, continuous glucose monitoring system*

Background and Aims

Diabetes is no doubt one of the most difficult health problems of the 21st century. In 2012 more than 371 million people have diabetes [1]. It is the fourth or fifth leading cause of death in most high-income countries and there is substantial evidence for us to say that diabetes has become a pandemic disease [1,2]. The National Health and Nutrition Examination Survey (NHANES V) data (2005-2008) show that 8.1% of the U.S. population has diabetes and 14.5% has chronic kidney disease (CKD) [3]. In developed countries, diabetes is the

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leading cause of chronic kidney disease and in the following years that same thing is expected to happen in developing countries as a result of overall increase of type 2 diabetes mellitus (T2DM) and obesity [4]. In our country, diabetes occupies first place (14.8%) among the diseases that lead to end stage renal disease [5].

Several studies indicated that glycemic variability seems to be an independent cardiovascular risk factor and has more deleterious effects on endothelial function compared to sustained hyperglycemia, especially due to oxidative stress activation [6-9].

Glycated hemoglobin (HbA1c) is considered the gold standard for the assessment of glycemic control. In CKD patients there are many factors which could lead to false and misleading values of HbA1c [9]. Among the factors that lead to falsely low HbA1c values are: reduce erythrocytes lifespan, hemolysis, iron deficiency, repeated transfusions, erythropoiesis stimulating agents [10]. Falsely high HbA1c levels are induced by hemoglobin carbamylation [11,12]. Also HbA1c is not able to identify glycemic variability. Therefore it is necessary to identify methods to assess glycemic excursions in CKD patients [13].

Continuous glucose monitoring system may represent an useful tool that allows glycemic variability quantification and also efficient discrimination between the sustained chronic hyperglycemia and acute glucose fluctuation [8,14].

We hypothesize that the assessment of glycemic variability using CGMS recordings may provide a more accurate evaluation of the metabolic status in patients with CKD. In order to test this hypothesis, we assessed the glycemic variability indices estimated on 72 hours CGMS readings in 30 subjects stratified according to the presence of CKD and diabetes. We also attempted to identify the predictive value of inter-day and intra-day glycemic variability

indices for the poor glycemic control (HbA1c≥6,5%) in analyzed subjects.

Material and method

Subjects

In this cross –sectional study we included 20 diabetic patients (10 patients with CKD and 10 patients without CKD) and 10 healthy volunteers. Normal kidney function was defined as estimated glomerular filtration rate (eGFR) > 90 mL/min per 1.73 m^2 and no albuminuria (urine albumin-creatinine ratio <30 mg/g). CKD stage 2-4 was defined as eGFR = 90-15 mL/min per 1.73 m^2. The patients were recruited consecutively from the patients routinely visiting the Nephrology Ambulatory for CKD patients and, respectively, the Diabetes Ambulatory for diabetic patients.

The inclusion criteria were: signing of inform consent for participation in the study, CKD stage 2-4 for the CKD group and diagnosis of T2DM for the diabetes group.

Exclusion criteria were all conditions that can increase glycemic variability: acute diseases (infections, surgery, myocardial infarction, stroke, etc.,); chronic consumptive diseases (chronic hepatitis, tuberculosis, human immunodeficiency virus infection, malignancies, etc) that decrease appetite thus modifying carbohydrates intake; pregnancy and lactation (hormonal profile influence glucose metabolism) and mental illnesses (difficulty in CGMS monitoring). The study was performed according to the Helsinki declaration and the good clinical practice guidelines and the study was approved by the Ethics Committee of University of Medicine and Pharmacy Craiova.

Study protocol

The CGMS sensor (DexCom SEVENPLUS) was subcutaneously inserted for 72 hours, allowing interstitial glucose measurement every 5 minutes. The CGMS calibration was

performed by recording at least 4 self-monitoring capillary blood glucose with a glucose meter. All the subjects had the same carbohydrates intake according to nutritionist's recommendation.

The following data were recorded: demographic characteristics, medical history (type 2 DM duration, current therapy), anthropometric parameters. HbA1c was measured in all subjects.

The next glycemic variability indices were assessed on CGM readings using the GlyCulator application [15,16]:

- **Mean level of 24 h interstitial glucose value** (MIG) and **its standard deviation** (SD)
- **Mean amplitude of glycemic excursion** (MAGE) calculated based on mean of differences between consecutive glucose values picks and nadirs, only for differences greater than SD. MAGE provides a measure of intra-day, high amplitude, glucose variability [17].
- **Fractal dimensions** (FD) calculated based on Higuchi algorithm. FD describes glucose variability of small amplitude and high frequency [18,19].
- **Mean of daily differences** (MODD) calculated as the mean of absolute differences between glucose values at corresponding time points of consecutive days. MODD allows the estimation of inter-day glucose variability [20].
- **Continuous overall net glycemic action** (CONGA) **at 1, 2, 4 and 6 hours** - glycemic variability within a predetermined time window)
- **Percentage coefficient of variation** (%CV) - the ratio of standard deviation to mean
- **Percentage of time with glucose values above 180 mg/dl** (% above 180mg/dl) and **bellow 70 mg/dl** (% below 70mg/dl).

Statistical analysis

Continuous variables are expressed as means ± standard deviation; categorical variables are expressed as percentages. The variables were tested for normal distribution using the Kolmogorov-Smirnov test. Comparisons between different groups were performed using parametric or nonparametric tests, depending of the variables distribution.

Receiver operating characteristic (ROC) curves were used to determine the predictive utility of glycemic parameters in identifying poor glycemic control quantified by HbA1c≥6.5%. Multiple stepwise regression was assessed in order to establish the independent predictors for glycemic imbalance. Values of $p < 0.05$ were considered significant. SPSS19.0 software was used for analysis.

Results

The subjects included in the present study were stratified in 3 groups, according to the presence of CKD and diabetes: CKD diabetic patients (T2DM+/CKD+), diabetic patients without CKD (T2DM+/CKD-) and healthy volunteers subjects (T2DM-/CKD-). There were 10 patients in group T2DM+/CKD+ (3M/7F; age 66.8±9.8 years; BMI 27.2±2.7kg/m^2; T2DM duration 9.5±2.1 years), 10 patients in the T2DM+/CKD- group (4M/6F; age 60.4±6.8 years; BMI 26.5±1.9kg/m^2; T2DM duration 9.2±1.5 years) and 10 subjects in the T2DM-/CKD- group (2M/8F; age 30.2±3.8 years; BMI 22.2±1.8kg/m^2).

Glycemic variability indices distribution in the study groups is presented in Table 1.

The CKD diabetic patients presented inter-day variability (quantified by MODD) and intra-day glycemic variability (quantified by MAGE, % CV, CONGA at 1, 2, 4 and 6 h) significantly higher compared to the diabetic patients without CKD. Likewise MIG was higher in the CKD diabetic patients, compared to the diabetic patients without CKD (Table 1, Figure 1, 2, 3).

Table 1. Comparative evaluation of glycemic variability indices between the study groups.

| PARAMETERS	T2DM+/CKD+ n=10	T2DM+/CKD- n=10	T2DM-/CKD- n=10
HbA1c	7.2±0.9	6.7±1.7	4.8±0.4#§
MIG	187.1 ±56.3	138.6±38.8*	96.7±10.2#
% above 180mg/dl	49.5±6.5	19.6±7.8	0#
% below 70mg/dl	1.2±0.6	1±0.1	0.9±0.4
%CV	26.8±6.6	18.8±6.6*	10.6±3.1#
MAGE	145±60	82.3±41*	34.6±10.7#
FD	1.3±0.1	1.2±0.07	1.1±0.1#
MODD	47.1±11.2	23.8±11.1*	10.8±2.9#
CONGA1h	38.8±11.7	26±12.9*	11.5±3.6#
CONGA2h	55.1± 21.8	33.6±18.1*	12±3.6#
CONGA4h	69.4±29	41.2±24.9*	13.5±4.3#
CONGA6h	72.7±28.5	44.4±27.8*	14±4.4#
# P<0,05 T2DM+/CKD+ vs T2DM-/CKD- *** P<0,05 T2DM+/CKD+ vs T2DM+/CKD-** **§ P<0.05 T2DM+/CKD- vs T2DM-/CKD-**			
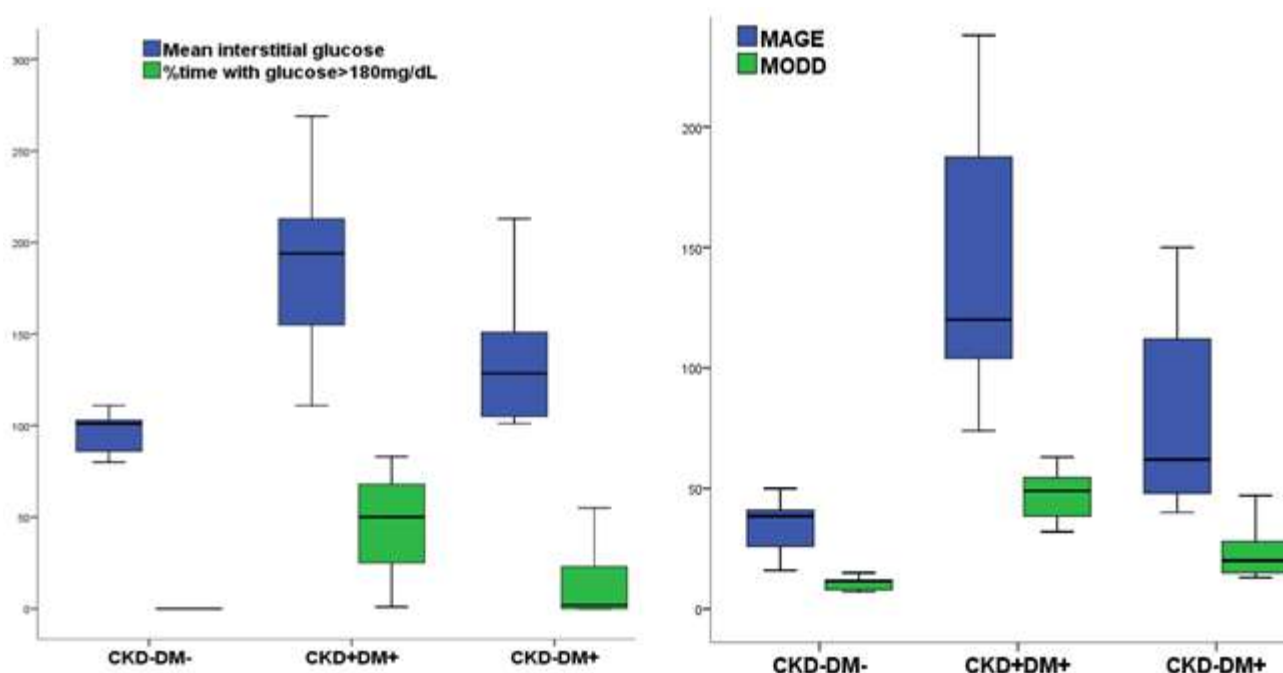
Figure 1. Box Plot indicating the glycemic parameters distribution of MIG and % above 180mg/dl (left), MAGE, MODD (right), according to CKD and T2DM presence.

The diabetic patients with CKD had important inter-day and intra-day glycemic variability and also, statistically significant higher percentage of time with interstitial glucose above 180 mg/dl and FD, compared to the healthy subjects (Table 1, Figure 1, 2, 3).

HbA1c levels were significantly higher in the diabetic subjects compared to healthy subjects, regardless to the presence of CKD (Table 1, Figure 3). However there were no significant differences in HbA1c between diabetic subjects with or without CKD.
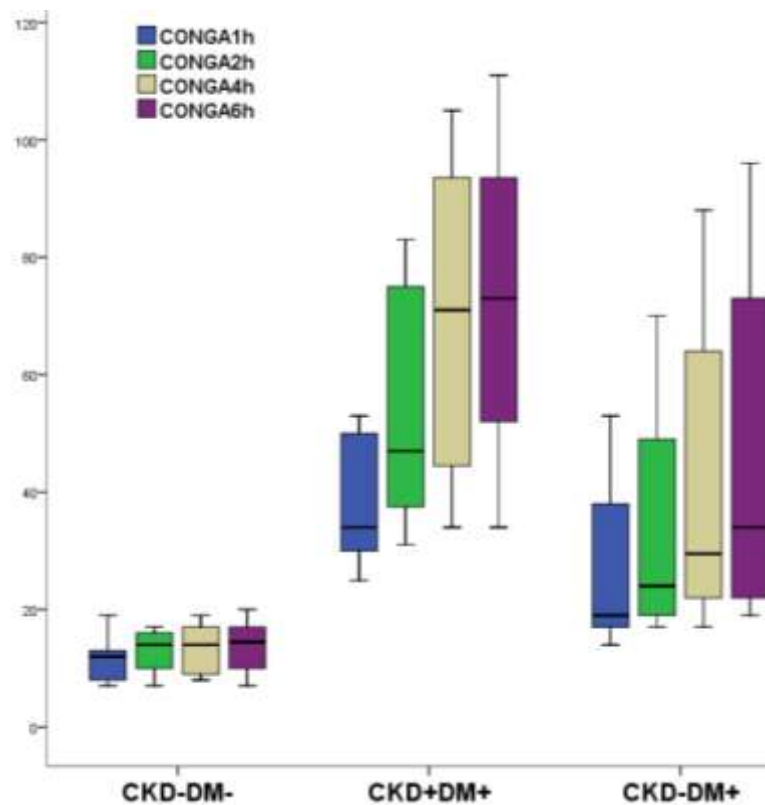
Figure 2. Box Plot indicating the glycemic parameters distribution of CONGA
at 1h, 2h, 4h and 6h, according to CKD and T2DM presence.
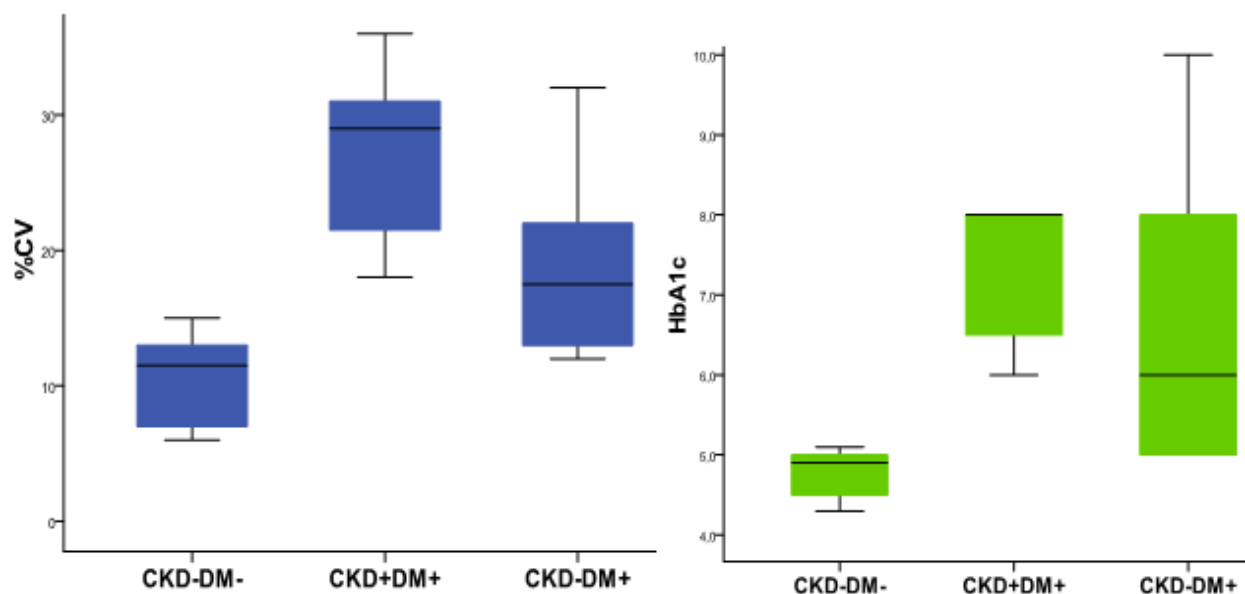
Figure 3. Box Plot indicating the glycemic parameters distribution of %CV (left)
and HbA1c (right), according to CKD and T2DM presence.

ROC curves indicated that MIG, MAGE, MODD and the percentage of time with blood glucose above 180 mg/dl had higher predictive value for metabolic imbalance assessed by HbA1c≥6.5% (Table 2, Figure 4).

Multiple stepwise linear regression showed that only the percentage of time with blood glucose above 180 mg/dl (p=0.024) was an independent predictor for HbA1c≥6.5% (Table 3).
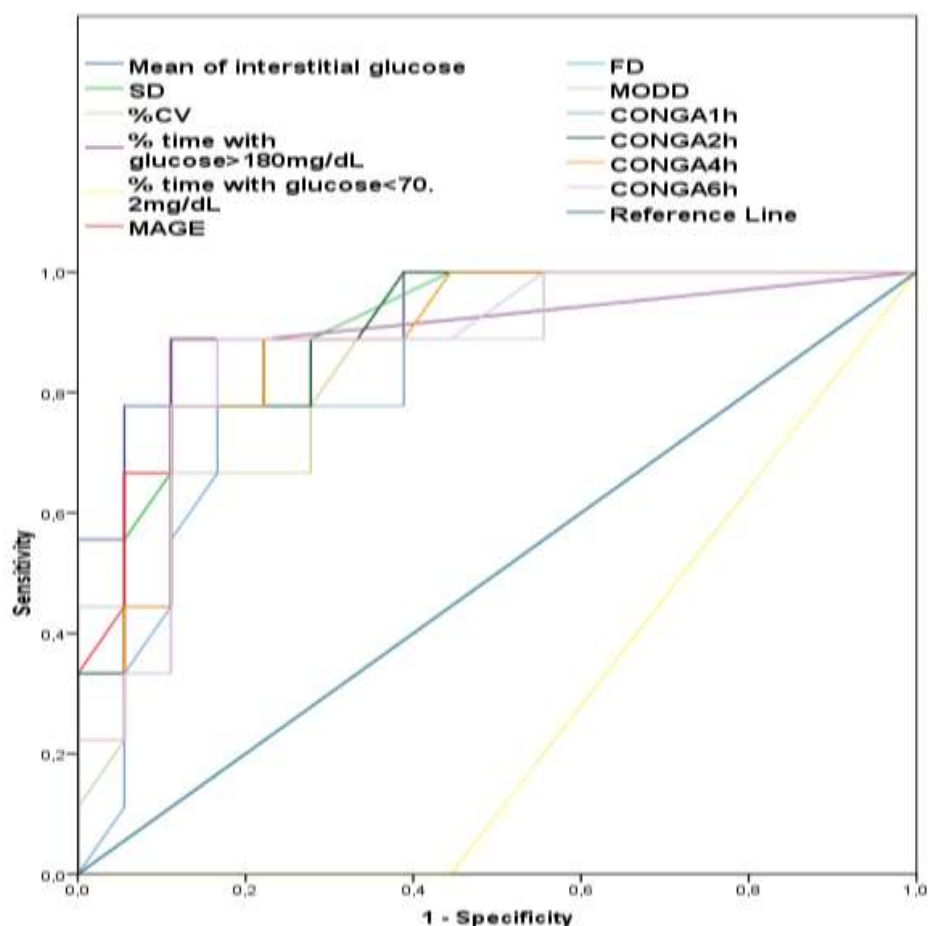
Figure 4. ROC curves indicating the predictors of poor glycemic control.

Table 2. Area under the ROC curves indicating the predictors of poor glycemic control.

PARAMETERS	Area under the curve	SE	p
MIG	0.932	0.050	<0.001
% above 180mg/dl	0.889	0.076	0.001
% below 70mg/dl	0.278	0.096	NS
%CV	0.849	0.073	0.004
MAGE	0.904	0.058	0.001
FD	0.500	0.120	NS
MODD	0.877	0.071	0.002
CONGA1h	0.843	0.076	0.004
CONGA2h	0.886	0.063	0.001
CONGA4h	0.880	0.066	0.002

Table 3. Independent predictors for poor glycemic control (Multiple stepwise linear regression).

Coefficients[a]					
Model	Unstandardized Coefficients		Standardized Coefficients	t	Sig.
	B	Std. Error	Beta		
1 (Constant)	6.179	0.434		14.222	0.000
% above 180mg/dl	0.022	0.009	0.544	2.511	0.024
a. Dependent Variable: HbA1c					

Discussions

The outcomes observed in the actual study indicated that diabetic patients with CKD had statistic significantly higher inter-day (MODD) and intra-day (MAGE, %CV, CONGA 1h, 2h, 4h, 6h, MIG) glycemic variability comparative to diabetic and non-diabetic subjects with normal kidney function. The HbA1c was higher in CKD diabetic patients than in diabetic patients without CKD but the differences did not reach statistical significance. This data suggest that HbA1c is not a reliable marker of poor glycemic control in subjects with CKD, due to the multitude of factors that induce glycemic variability. Our findings are in accordance with other studies that show the lack of correlation between mean interstitial glucose assessed on CGMS recordings and HbA1c, indicating that CGMS could be more accurate in the evaluation of real-time glycemic control in this patients category [21-23].

Diabetic patients with CKD presented mean interstitial glucose and also interstitial glucose values above 180mg/dl and below 70mg/dl on longer time period comparative with diabetic subjects and non-diabetic subjects with normal kidney function. Only the differences between CKD diabetic patients and healthy volunteers regarding the percent of time with glucose above 180mg/dl were statistically significant. Fractal dimension was significantly higher in CKD diabetic subjects comparative to healthy volunteers, indicating that CKD is associated with high frequency low amplitude glycemic excursions. This data indicated that the presence of CKD induces important glycemic excursions. This could be justified by the presence of CKD–induced insulin resistance leading to hyperglycemia which coexists with risk of hypoglycemia due to malnutrition, an increased half-life of insulin and a reduced rate of gluconeogenesis [24].

To date there have been no studies examining the correlation between glycemic variability indices quantified on CGM readings and markers of glycaemic control to determine which biomarker most accurately characterizes the glycaemic control in diabetic patients with predialysis stages of CKD.

Analyzing the area under the ROC curves we observed that MAGE, MODD, MIG and % time with glucose above180mg/dl had predictive value for poor glycemic control (HbA1c ≥6.5%) but only the period of time spent with glucose above 180 mg/dl had an independent predictive value according to multiple stepwise regression.

This proof-of-principle study has limitations due to the sample size, the results from this sample data are strongly suggestive that a larger study on the glycemic variability in subjects with CKD should be encouraged and that the identification of glycemic variability indices using CGMS may be relevant to metabolic control of CKD patients. The lack of matching demographic and anthropometric characteristics of the study groups and the control group represents another limitation of this study.

Conclusions

In summary the current study provides evidence that subjects with CKD and T2DM had important metabolic imbalance and significant glycemic variability compared to diabetic patients without CKD. and especially to healthy subjects.

Since only the percentage of time with recorded blood glucose > 180 mg/dl was an independent predictor for HbA1c. our findings emphasize that HbA1c is not enough for metabolic imbalance assesment. the use of other glycemic variability indices being also useful.

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