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Increased glycemic variability in type 2 diabetes patients treated with insulin - a real-life clinical practice, continuous glucose monitoring (CGM) study

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Abstract

Chronic hyperglycemia is an important cause for the development of chronic complications of diabetes, but glycemic variability has emerged in recent years as an independent contributor to diabetes-related complications. Our objective was to evaluate glycemic variability in patients with T2DM treated with insulin compared with other antidiabetic drugs. In this retrospective study, we collected 24-hour continuous glucose monitoring (CGM) recording data from 95 patients with T2DM, of which 27 treated with insulin and 68 with non-insulin treatment. We calculated and compared 16 glucose variability parameters in the insulin-treated and non-insulin treated groups. Insulin treated patients had significantly higher values of parameters describing the amplitude of glucose value fluctuations (standard deviation of glucose values, percentage coefficient of variation [%CV], and mean amplitude of glycemic excursion [MAGE], p <0.05) and time-dependent glucose variability (percentage of time with glycemic values below 70 mg/dl and continuous overall net glycemic action [CONGA] at 2, 4 and 6 hours, p <0.05). In conclusion, insulin therapy in T2DM is correlated with significantly higher glycemic variability.

Keywords*: glycemic variability, insulin therapy, type 2 diabetes, continuous glucose monitoring*

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Introduction

Data published by the International Federation of Diabetes showed that in 2017 worldwide there were 425 million people living with diabetes, of which type 2 diabetes (T2DM) represented up to 90% of cases (1). Uncontrolled hyperglycemia has been shown to be associated with acute and chronic diabetes complications and with impaired quality of life and decreased life expectation, being the leading cause of blindness, amputation, and kidney failure (2). The classic parameters used to evaluate glycemic control are HbA1c, pre-prandial and/or post-prandial and nocturnal glycemic values (so-called glycemic profiles) (3). Recent studies have showed that glycemic variability is a HbA1c-independent risk factor (4) for diabetes chronic complications (5-6) and is associated with increased mortality in elderly patients with T2DM (7). Currently, there

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is no golden standard for the evaluation of glycemic variability. This can be evaluated as intra-day or inter-day variation of glucose values measured using glucometers, as variation of glycaemia between visits to medical surgeries, or HbA1c value variation measured every 3 months. Recently, the use of continuous glucose monitoring systems (CGMS) made possible a more complete analysis of intra-day variability using 288 glucose values recorded during 24 hours, tens of parameters being proposed so far (8).

Glycemic control in T2DM can be achieved using lifestyle optimization and pharmacotherapy (9). Insulin therapy in T2DM is used to obtain a better glycemic control, with proved powerful reduction of HbA1c, but with side-effects such as weight gain and hypoglycemia (10). Its effect on glycemic variability (GV) compared with non-insulin agents using data obtained from continuous glucose monitoring systems is not so well-studied. In our study, we compared the effect of insulin administration with non-insulin therapy on parameters of glycemic variability using CGMS data, in patients with T2DM.

Methods

Study design and study patients

We enrolled 95 patients in this retrospective study, previously diagnosed with T2DM, of which 27 were treated with insulin and 68 with non-insulin treatment, with a complete CGM recording available (first 24 hours of recording starting from the midnight after insertion with no pause in recorded values). The CGM was performed using the iPRO™ device (Medtronic, Northridge, CA) over a 3 to 7-day-interval, in a blinded manner. The iPRO was placed on and removed from the abdominal area of the patient by a trained member of the medical staff, on the left or right part of the abdominal region, depending on patient preferences, in recumbent position, at distance from the sites used for insulin injection. The patients' data were retrospectively collected from their medical charts. The study was conducted according to the World Medical Association Declaration of Helsinki and national legislation regarding the conduct of retrospective clinical trials. A previous written Inform Consent was provided by every patient for the CGM procedure as required by Standard Operating Procedures of the clinic.

Evaluated parameters

Age, gender, diabetes duration, and information about diabetes treatment were collected from the patients' charts. The parameters of glycemic variability were calculated using the method described by Czerwoniuk D et al. (11). The glycemic values recorded by the iPRO device during the first 24 hours of full recording (288 glucose values – between 00:00 and 23:59 of the day following the day of the device insertion) were used for the calculation of the parameters (11). We did not use the values recorded immediately after the insertion because current sensors are generally less accurate during this time-period due to local tissue inflammation following tissue trauma associated with sensor insertion (12). The patients were also instructed to avoid administration of acetaminophen or vitamin C during the recording period in order to avoid bias (13).

The glycemic variability indices calculated by GlyCulator based on CGM readings were (11):

Standard deviation (SD of the glucose values) - an index of the dispersion of data around mean blood glucose over a 24-hour recording (14).

Percentage coefficient of variation (%CV) - the ratio between the SD of the glucose values and the mean glucose values. This parameter describes the variation within sample values (15).

M100 - provides a measure of stability of the glycemic values in comparison with an arbitrarily assigned glucose value, initially set to 100 mg/dl (16).

J index is a measurement of the quality of glycemic control based on the combination of information from the mean and SD calculated as 0.001 × (mean + SD) (17).

Mean amplitude of glycemic excursion (MAGE) - represents the "mean of differences between consecutive peaks and nadirs of differences greater than one SD of mean glycemia". (11) The small variations are excluded. MAGE provides a measurement of intra-day, high amplitude, glucose variability (18).

Fractal Dimension (FD) – "describes glucose variability of high frequency and small amplitude" (11).

Continuous overall net glycemic action (CONGA) at 1, 2, 4 and 6 hours (CONGA -1, -2, -4, -6) - shows the glycemic variability within 1 hours, 2 hours, 4 hours or 6 hours' time window. It is an indicator of intra-day glucose variability (19).

Other parameters measured were mean glucose value, median glucose value and percentage of glucose values above or below a given threshold measured as the percentage of glycemic levels over 126 mg/dl and 180 mg/dl (percentage of hyperglycemia) and percentage of glycemic levels below 70 mg/dl and 54 mg/dl (percentage of hypoglycemia).

The body composition analysis was performed using InBody 720 device (Biospace Co., Korea) according to the recommendation provided in the user manual (20). This analysis is derived from the 4-compartment model, which divides body composition into 4 components: total body water, protein, mineral, and body fat mass.

The HbA1c was measured by high-performance liquid chromatography (Cobas Integra 400Plus, Roche Diagnostics).

Statistical analysis

The statistical analysis was performed using SPSS software v 21.0. Distribution of variables was tested with Kolmogorov-Smirnov test and evaluating the skewness and the kurtosis of the variable. Variables are presented as the mean ± standard deviation (SD) for normally-distributed variables, median (1st quartile; 3rd quartile) for variables with abnormal distribution and percentage for categorical variables. Student t-test was used to compare variables with normal distribution, and Mann-Whitney U test for variables with abnormal distribution. The correlation between variables was assessed by Pearson correlation coefficient for variables with normal distribution and Spearman correlation coefficient for variables with abnormal distribution. The level of significance was set at 0.05.

Results

We included in our analysis 95 patients with T2DM and a complete CGM recording available from the first 24 hours of full recording: 27 patients treated with insulin and 68 patients with non-insulin treatment. Patients' clinical and anthropometric characteristics are displayed in Table 1. The mean dose of insulin used in the first group was 51.37±28.95 units/day. Thirteen out of 27 patients (48.15%) were treated only with basal insulin, 8 patients (29.63%) received basal-bolus therapy, 5 patients were treated with premixed analogs of insulin (18.52%) and one patient (3.70%) received rapid-acting insulin. In the group of non-insulin treated patients, 29 (42.64%) did not receive pharmacotherapy at the time of the CGMS recording (being newly diagnosed or the patient did not take the recommended therapy), 30 patients (44.11%) received metformin, 20 (29.41%) had sulphonylureas in their therapeutic plan, and 11 patients (16.17%) received incretins (the percentage is above 100 because one patient could take more than one class of drug). Nine insulin-treated patients (33.33%) presented hypoglycemia during CGM recording, with median percentage of time spent with gly-

Table 1. The characteristics of patients included in the analysis

Parameter	T2DM patients treated with insulin therapy N=27	T2DM patients treated with non-insulinic therapy N=68	p
Age(years)*	57.33±12.72	55.75±8.99	0.558
Women, n (%)	11 (40.74)	24 (35.29)	0.621
Duration of T2DM(years)**	8.5 (2;13)	4 (0;9)	0.028
BMI (kg/m^2)*	32.22±6.47	30.40±5.32	0.203
Weight (kg)*	93.75±22.46	89.31±18.26	0.367
PBF(%)*	32.68±11.40	33.67±8.38	0.688
VFA (cm^2) **	153.4 (130.8;220.5)	145.8 (118.5;170.5)	0.255
HbA1c (%)*	8.40±1.91	8.37±1.70	0.950

*variables have a normal distribution and are presented as mean±SD; **variables have an abnormal distribution and are presented as median (1st quartile; 3rd quartile); SD – standard deviation; T2DM – type 2 diabetes mellitus; BMI - body mass index; PBF – percent of body fat; VFA – visceral fat area

cemic values below 70 mg/dl of 4.17% (3.47; 11.11), versus six non-insulin treated patients (8.82%), with median percentage time spent in the hypoglycemic range of 1.04% (1.04; 6.60). Seven out of nine patients (77.78%) treated with insulin who presented hypoglycemia were treated with basal-bolus (5 patients) or premix insulin regimen (1 patient) or had sulfonylurea added to basal insulin (1 patient).

The HbA1c value was significantly and positively correlated with diabetes duration (rho=0.283, p=0.006), MAGE (rho=0.543, p<0.001), mean and median glucose value (r^2=0.749, p<0.001 and rho=0.735, p<0.001, respectively), standard deviation of the glycemic values (rho=0.572, p<0.001), M100 (rho=0.757, p<0.001), percentage of time spent above 126mg/dl and 180 mg/dl (rho=0.672, p<0.001 and rho=0.735, p<0.001, respectively), J index (rho=0.754, p<0.001) and CONGA 1hour, 2 hours, 4 hours and 6 hours (rho=0.488; 0.507; 0.537 and 0.565, respectively and p<0.001). After adjustment for insulin-therapy the correlation remained significant for all parameters of glycemic variability, but was not significant for the duration of diabetes (p=0.559).

The values of the parameters of glycemic variability and the statistical significance of the difference between groups are shown in Table 2. Although there was no significant difference between groups regarding the mean and median glucose values, there was a significant increase of the following parameters of GV in insulin-treated patients: the dispersion of data around mean glucose value, expressed as SD; the variation within sample values (%CV); high amplitude intra-day variability (MAGE), and glycemic variability within a time frame of 1, 2, 4 or 6 hours (CONGA). The glucose variability of high frequency and small amplitude (FD) was significantly smaller in the insulin-treated group (p=0.018). The percentage of time spent in hypoglycemia (measured as glucose values below 70 mg/dl) was significantly higher in insulin-treated T2DM patients.

The correlation between the use of insulin therapy and parameters of glycemic variability are displayed in Table 3. There was a positive significant correlation between the use of insulin therapy in patients with T2DM and SD, %CV, percentage of time spent in hypoglycemia (values below 70 mg/dl), MAGE, and all four time-interval CONGA. A significant negative correlation between insulin-therapy and FD was observed. There was no significant correlation between the number of units of insulin and the

Table 2. The comparison between parameters of glycemic variability according to the use of insulin therapy

Parameter	T2DM patients treated with insulin therapy N=27	T2DM patients treated with non-insulinic therapy N=68	p
Mean value, mg/dl	173.25 ± 66.24	178.08 ± 54.60	0.520
Median value, mg/dl	158.0 (116.0; 219.0)	165.3 (135.1; 203.5)	0.398
SD, mg/dl	42.71 (26.11; 50.07)	29.28 (22.33; 38.83)	0.022
% CV, %	24.2 (18.8; 30.2)	16.4 (14.4; 20.6)	<0.001
M100, mg/dl	13.8 (4.9; 47.7)	15.9(4.0; 45.1)	0.804
J index, mg/dl	40.3 (21.4; 76.8)	40.4 (24.4; 71.3)	0.921
% over 126 mg/dl, %	71.2 (32.9; 100.0)	84.6 (60.5; 100.0)	0.168
% over 180 mg/dl, %	34.4 (0.0; 64.6)	36.9(3.9; 74.9)	0.681
% below 70 mg/dl, %	0.0 (0.0; 3.47)	0.0 (0.0; 0.0)	0.002
% below 54 mg/dl, %	0.0 (0.0; 0.0)	0.0 (0.0; 0.0)	0.515
FD	1.04 (1.03; 1.06)	1.06 (1.04; 1.08)	0.018
MAGE, mg/dl	114.4 (75.9;149,8)	89.7 (64.5; 118.7)	0.022
CONGA-1, mg/dl	29.4 (20.5; 37.7)	23.89 (18.4; 29.7)	0.051
CONGA-2, mg/dl	45.6 (29.3; 61.0)	35.6 (24.9; 45.8)	0.035
CONGA-4, mg/dl	59.5 (37.7; 74.7)	41.2 (30.9; 57.3)	0.013
CONGA-6, mg/dl	65.8 (34.4; 77.1)	40.9 (32.1; 59.9)	0.017

T2DM – type 2 diabetes mellitus; SD - standard deviation; %CV -percentage coefficient of variation; M100 - weighted average of glucose values around 100 mg/dl; FD - fractal dimension; MAGE -mean amplitude of glucose excursions; CONGA-1, -2, -4,-6 - continuous overall net glycemic action at 1, 2, 4 and 6 hours.

parameters of GV after adjusting for age, gender, and diabetes duration, except for the percentage of time spent in hypoglycemia (correlation coefficient=0.571, p=0.004).

The parameters of glycemic control (HbA1c) or glycemic variability were not significantly different between patients treated only with basal insulin versus patients who received rapid-acting insulin (as a bolus or in premix formulation) - all p values were above 0.05. We also compared if the presence of metformin in insulin-treated patients had any impact on glycemic control or on glycemic variability parameters, but no value of p reached the threshold of statistical significance (13 patients without versus 14 patients with metformin added to insulin).

Table 3. Significant correlation of insulin therapy and other parameters

Parameter	Spearman's rho coefficient of correlation	p
SD, mg/dl	0.236	0.021
% CV, %	0.363	<0.001
% below 70 mg/dl, %	0.316	0.002
FD	-0.244	0.017
MAGE, mg/dl	0.236	0.021
CONGA-1, mg/dl	0.202	0.050
CONGA-2, mg/dl	0.217	0.034
CONGA-4, mg/dl	0.256	0.012
CONGA-6, mg/dl	0.247	0.016

SD - standard deviation; %CV -percentage coefficient of variation; FD - fractal dimension; MAGE -mean amplitude of glucose excursions; CONGA-1, -2, -4,-6 - continuous overall net glycemic action at 1, 2, 4 and 6 hours.

Discussion

The pharmacotherapy of T2DM includes non-insulin therapy or insulin administration in order to obtain glycemic control. Usually, pharmacological management of T2DM starts with metformin administration, adding new drugs as dual or triple therapy, as necessary to reach glycemic targets (21). New guidelines reconfirm that insulin therapy might be started at any stage during the management of diabetes, according to patient's comorbidities, glycemic targets and clinical presentation (22). In our study, the patients treated with insulin versus non-insulin therapy had no significant differences regarding age, gender distribution or anthropometric characteristics, but those treated with insulin had a significantly longer duration of diabetes. Insulin is the therapy with the higher power to reduce hyperglycemia, but also with the highest risk of hypoglycemia (23).

Severe hypoglycemia is a confirmed predictor for mortality in T2DM patients, but it is unclear if it is an associative or a causative factor (24). Takeishi S et al. identified hypoglycemia and increased glucose variability, rather than inflammatory markers or other clinical parameters, as factors associated with mortality in non-intensive care units of patients with diabetes and infectious diseases (25). The new basal insulin analogs have a lower risk of hypoglycemia than older NPH insulin (26). Although all the patients included in our study were treated with basal insulin analogs, one third presented hypoglycemia during CGM recording, due to the association with prandial insulin or sulfonylurea and the percentage of time spent in hypoglycemia was positively correlated with the number of insulin units used. Only 2 out of 13 patients treated only with basal insulin (15.38%) presented hypoglycemia, versus 6 out of 13 patients treated with basal-bolus or premixed insulin regimen (46.15%). A practical solution to avoid hypoglycemia in insulin treated patients with T2DM patients might be the association of a glucagon-like peptide-1 receptor agonist to basal insulin, as demonstrated by Bajaj HS et al. in a recently published study (27).

Glycemic variability refers to swings in blood glucose levels (28) and is associated with increased oxidative stress (29). The initial result of proof-of-concept FLAT-SUGAR trial (Fluctuation Reduction With Insulin and GLP-1 Added Together) showed that at week 26 the %CV, MAGE, weight, alanine transaminase, and serum amyloid were significantly higher in basal-bolus insulin-treated group versus the basal insulin plus exenatide group, but there was no significant difference between groups regarding glycemic control (HbA1c), hypoglycemic episodes, or other biomarkers (interleukin-6, high-sensitivity C-reactive protein, albuminuria or urinary isoprostanes) (30). It is difficult to perform a quantitative measurement of glycemic variability since it is dependent on amplitude and duration of the fluctuations of glycemic values (31). To date, there are tens of metrics proposed to measure glycemic variability. Some of them measure the amplitude of glycemic variability (e.g. SD, MAGE) and a few are developed to measure time-depended glucose variability (e.g. different time windows of CONGA). In a recently published study, Fabris C et al. showed that starting from a pool of 25 GV indices calculated from CGM recordings of T2DM patients, ten metrics are sufficient to describe 83% of the variance of the original pool (32). Monnier L et al. demonstrated that a %CV of 36% may distinguish between stable or unstable glucose values in T2DM because, especially in insulin-treated patients, the frequency of hypoglycemia increases significantly beyond this limit (33). In our study, the majority of glycemic variability parameters were higher in patients treated with insulin, despite the fact that there was no difference between mean and median glucose values between groups. In our study, there was no significant difference between groups regarding glycemic control (8.4±1.91% versus 8.37±1.70%) or anthropometric parameters (BMI< visceral fat

area or percentage of body fat), but there was a significant difference in time spent in hypoglycemia in patients treated with insulin (% of time below 70 mg/dl) and other parameters of glycemic variability calculated based on CGMS monitoring data. The MAGE was significantly higher in patients treated with insulin, which means that there were high amplitude variations of glycemic values (higher than the standard deviation), but the small amplitude and high-frequency variation of the glycemia (measured as FD) were significantly lower. FD is a new experimental parameter introduced by Czerwoniuk et al. (11) to measure glucose variability with high frequency but small amplitude, which is not captured by MAGE, but, to date, with no proved influence on oxidative stress or other health outcomes in patients with diabetes.

The originality of our work is that it is a real-life clinical practice study in which we compared the glycemic variability in T2DM patients treated with insulin and non-insulin therapy. The limitations of our study are the retrospective design and the relatively small number of patients treated with insulin.

Conclusion

The use of insulin therapy in T2DM is correlated with a significant difference in the majority of glycemic variability parameters, although there was no significant difference between HbA1c, anthropometric parameters or mean and median glucose values.

Conflict of interest disclosure

None of the authors has any conflict of interest to declare.

Abbreviations

T2DM – type 2 diabetes mellitus
CGMS – continuous glucose monitoring systems
SD – Standard deviation
%CV – Percentage coefficient of variation
MAGE – Mean amplitude of glycemic excursion
FD – Fractal Dimension
CONGA – Continuous overall net glycemic action

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