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The correlation of dawn phenomenon with glycemic variability parameters in type 2 diabetes mellitus

Corelații ale fenomenului dawn cu parametrii de variabilitate glicemică în diabetul zaharat

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Abstract

Introduction. Dawn phenomenon could have deleterious effect on overall glycemic control. Glycemic variability may be an independent risk factor for the development of diabetes chronic complications. The study aimed to evaluate any correlations between the dawn phenomenon and parameters of glycemic variability in a cohort of type 2 diabetes patients (T2DM). *Material and methods.* This retrospective observational study included 131 T2DM patients. Continuous glucose monitoring (CGM) has been performed. Data from the first 24h of full recording were used for analysis of glycemic variability indices: mean level of 24h interstitial glucose value and standard deviation; % coefficient of variation; J index; mean amplitude of glycemic excursion - MAGE; continuous overall net glycemic action (CONGA) at 1, 2, 4 and 6 hours; mean of daily differences (MODD) index. *Results.* Mean age was 56.04 ± 9.91 years, 35.9% women, 17.6% on diet, 53.4% on oral therapy and 29% on insulin. Dawn phenomenon was more frequent in patients below 60 years (70%) and in oral therapy group (72.85%). Significant correlations between the dawn phenomenon and j-index, MAGE, CONGA-4 and CONGA-6 have been found in T2DM patients on diet therapy alone. The amplitude of dawn phenomenon was 46.10 ± 24.40 mg/dl and significantly correlated ($p < 0.05$) after adjustment for age, gender and treatment with % CV, MAGE, CONGA-1, CONGA-2, CONGA-4, CONGA-6 and MODD. *Conclusions.* The dawn phenomenon significantly increases the glycemic variability parameters in drug-naive T2DM patients, with no impact in T2DM on oral or insulin therapy.

Keywords: dawn phenomenon, glycemic variability, continuous glucose monitoring

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Rezumat

Introducere. Fenomenul "dawn" poate asocia alterarea controlului glicemic. Variabilitatea glicemică poate fi un factor de risc independent pentru complicațiile cronice în diabet. Obiectivul studiului a fost evaluarea posibilelor corelații între fenomenul "dawn" și parametrii variabilității glicemice la pacienții cu diabet zaharat tip 2 (DZ2). Materiale și metode. Studiul retrospectiv, observațional, a inclus 131 pacienți cu DZ2, la care s-a efectuat monitorizarea continuă de glucoză. Datele rezultate din primele 24 ore de înregistrare continuă au fost analizate. Parametrii de variabilitate glicemică utilizați: valoarea medie a glucozei interstițiale / 24 ore și deviația standard; % coeficient de variație (%CV); J index; amplitudinea medie a excursiilor glicemice (MAGE); acțiunea continuă globală a glicemiei (CONGA) la 1, 2, 4 și 6 ore; media diferenței zilnice (MODD). Rezultate. Vârsta medie a fost de 56.04 ± 9.91 ani, 35.9% au fost de gen feminin, 17.6% cu dietă, 53.4% cu terapie orală și 29% insulinotratați. Fenomenul "dawn" a fost mai frecvent la pacienții cu vârsta < 60 ani (70%) și în grupul cu terapie orală (72.85%). Corelații semnificative între fenomenul "dawn" și parametrii J-index, MAGE, CONGA-4 și CONGA-6 au rezultat în grupul tratat cu dietă. Amplitudinea fenomenului "dawn" a fost de 46.10 ± 24.40 mg/dl, corelat semnificativ cu %CV, MAGE, CONGA-1, CONGA-2, CONGA-4, CONGA-6 și MODD, după ajustarea pentru vârstă, gen și tratament. Concluzii. Fenomenul "dawn" crește semnificativ parametrii de variabilitate glicemică la pacienții cu DZ2 cu dietă, fără impact semnificativ în grupurile cu terapie orală sau insulinoterapie.

Cuvinte cheie: fenomenul „dawn”, variabilitate glicemică, monitorizare continuă a glucozei

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Introduction

Dawn phenomenon was described by Bright et al. in 1980 (1) as an abrupt increase in fasting plasma glucose, insulin requirements or both in early morning between 05:00 and 09:00, without antecedent hypoglycemia in patients with type 1 diabetes. In 1984 Bolli and Gerich (2) demonstrated that this phenomenon is present in both type 1 and type 2 diabetes patients. Later, the dawn phenomenon or dawn effect was considered to be an abnormal increase in blood glucose that occurs usually between 02:00 and 08:00 in people with diabetes and between 04:00 and 08:00 in people without diabetes (3). In present, there are three definitions of dawn phenomenon: 1) an absolute dawn increase in glucose level above 10 mg/dl or the increase in insulin requirement should be at least 20% from the overnight nadir; 2) an absolute dawn increase in glucose level above 20 mg/dl and 3) a relative increase of glucose level during night with more than 6.9% (4-6).

During sleep, many hormonal changes take place in the human body, changes that have been

postulated to play a role in the occurrence of dawn phenomenon: in the middle of the night, growth hormone increases, followed by an increase in cortisol and catecholamine, which leads to increased glucose production in the liver to prepare the body for daytime activity after a period of fasting. In individuals without diabetes, these processes are attenuated by increased insulin secretion and therefore blood glucose levels remain relatively stable within normal ranges. Plasma glucagon level tends to decrease or remains unchanged during nighttime (7). The main hormones implicated in glucose homeostasis are insulin and glucagon that work in opposition to each other. Insulin regulates glucose metabolism by decreasing gluconeogenesis and glycogenolysis, thus reducing the hepatic glucose output, by facilitating the transport of glucose into the cells and by inhibiting glucagon secretion. In opposition, glucagon counteracts hypoglycemia by stimulating hepatic glucose production. In the diabetic status, defects in pancreatic insulin secretion and peripheral insulin action, hepatic insulin resistance and, to some extent, dysregulated glucagon secretion and inadequate suppression

of glucagon production, impair glucose homeostasis leading to hyperglycemia (8). Thereby, in people with diabetes, changes in glucose metabolism during sleep can have a profound effect on morning blood glucose levels (3).

The contribution of dawn phenomenon to maximum blood glucose in type 1 diabetes patients was observed by Schmidt et al. more than 30 years ago (7). In a study published in 2013 by Monnier et al. it was shown that the presence of dawn phenomenon in type 2 diabetes patients leads to an increase in HbA1c of 0.4%, and the effect cannot be eliminated by any of the currently available oral antidiabetes agents (9).

In the recent years the role of glycemic variability in the development of diabetic complications was extensively discussed. Monier et al., analyzing the data resulted from continuous glucose monitoring system in relation to the level of oxidative stress, have elegantly demonstrated that glycemic variability seems to have a more specific triggering effect on oxidative stress than chronic hyperglycemia (9). Thus, glycemic disorders should be considered in the context of at least two dimensions: chronic hyperglycemia, identified by glycated hemoglobin (Hb) A1c, and acute glycemic fluctuations, which may independently contribute to diabetes-related complications (10-15). Therefore, addressing both chronic hyperglycemia and acute glucose variability should be important target for metabolic control and prevention of chronic complications.

After the emergence of continuous glucose monitoring systems (CGMS) in medical practice we had the possibility to evaluate more precisely the glycemic increment during nighttime and to calculate more parameters in order to have a complete image about within-day and inter-day glucose variability. Using CGMS, glucose levels from the interstitial fluid can accurately be measured at every 5 minutes with a disposable glucose sensor which is approved for up to seven days of use. CGMS data provides informa-

tion about the direction, magnitude, duration and frequency of fluctuations in blood glucose levels (16). No golden standard has been established for glycemic variability evaluation. Several tens of different indices for glycemic variability quantification have been proposed in the recent years.

Our objective in the present study was to evaluate the possible correlations between the dawn phenomenon and the main parameters of glycemic variability as defined and used in previous studies (mean level of 24h interstitial glucose value and standard deviation, percentage coefficient of variation, average of glucose values, J index, mean amplitude of glycemic excursion, continuous overall net glycemic action and the mean of daily differences) calculated from CGMS data in a cohort of type 2 diabetes patients.

Material and methods

Study design and study participants

In this retrospective observational study performed in an outpatient clinic from Cluj-Napoca, Romania, we enrolled 131 patients with type 2 diabetes who consequently had a complete CGM recording available (first 24 hours of recording starting from the midnight after insertion, with no pause in recorded values) and with no nocturnal hypoglycemia during first full day of recording. In the above setting, the CGM represents a routine method frequently used to explore the glycemic profile in uncontrolled patients with diabetes. All the patients consent the procedure. To continuously monitor the glucose values, the iPRO™ device (*Medtronic*, Northridge, CA) has been used over a 3-7 day interval, in a blinded manner. The iPRO was placed on and removed from the patient by a trained member of the medical staff, in the abdominal area, left or right part, depending on patient preferences, in recumbent position, at distance from the sites used for in-

sulin injection (although recent data support the idea that insulin infusion near sensor insertion do not influence glycemic values) (17). CGM data were downloaded from our clinic's database stored on iPRO (Medtronic) Carelink site and the patients' data were collected from their medical charts.

Parameters evaluated

Age, sex and diabetes treatment were collected from the charts. The parameters of glycemic variability were calculated with GlyCulator, a software designed mainly for research purposes, that allows the conversion of several parameters of glycemic variability based on CGM recordings (www.pediatria.umed.pl/team/glyculator). For the present analysis we have used 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) (18). 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 (19).

The glycemic variability indices assessed on CGM readings were (18):

- *Mean level of 24h interstitial glucose value (MG) and standard deviation (SD)* - an index of the dispersion of data around mean blood glucose;
- *Percentage coefficient of variation (%CV)* is the ratio of SD of the glucose values to mean of the glucose values. This parameter describes the magnitude sample values and the variation within them;
- *M100-weighted average of glucose values* provides a measure of stability of glycemia in comparison with an arbitrary assigned glucose value, initially set to 100 mg/dl;
- *J index* is a measure of quality of glycemic

control based on the combination of information from the mean and SD calculated as $0.001 \times (\text{mean} + \text{SD})$;

- Percentage of glucose values above or below a given threshold measured as the percentage of hyperglycemia (levels over 126 mg/dl and 180 mg/dl) and hypoglycemia (levels below 70 mg/dl and 54 mg/dl);
- *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. The small variations are excluded. MAGE provides a measure of intra-day, high amplitude, glucose variability;
- *Fractal Dimension (FD)* - an experimental method based on the works of Higuchi (20) and adapted by the authors of GlyCulator (18) that describes glucose variability of high frequency and small amplitude;
- *Continuous overall net glycemic action (CONGA) at 1, 2, 4 and 6 hours* (CONGA -1, -2, -4, -6) which shows glycemic variability within a predetermined time window. It is an indicator of within-day glucose variability;
- The mean of daily differences (MODD) index provides an estimation of interday glycemic variability. This parameter is calculated as the mean of absolute differences between glucose values at corresponding time points of consecutive days.

The dawn phenomenon was considered to be present if the difference between pre-breakfast glucose value and glucose nadir from the nighttime was more or equal with 20 mg/dl (21). We excluded from the beginning the patients with nocturnal hypoglycemia.

The study was conducted according to the World Medical Association Declaration of Helsinki, revised in 2000, Edinburgh and to European directives that require no approval from an

ethics committee for a non-interventional study, after each subject had given oral informed consent to use the data resulted from CGMS (22).

Statistical analysis

Statistical analysis was carried out using SPSS-PC 15.0 software (SPSS Inc., Chicago, IL, USA). Distribution of variables was tested with Kolmogorov-Smirnov test. Statistical data is presented as mean ± standard deviation (SD) for normally-distributed variables, median (1st quartile; 3rd quartile) for variables with abnormal distribution and percentage for categorical variables. Z-test was used to compare percent of dawn phenomenon according to age categories. Student’s 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 (r) for variables with normal distribution and Spearman correlation coefficient (ρ) for variables with abnormal distribution. The level of significance was set at 0.05.

Results

We included in our analysis 131 patients with type 2 diabetes and a complete CGM available from 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) and with no nocturnal hypoglycemia during first night after the insertion of CGMS. Patients’ characteristics are displayed in Table 1.

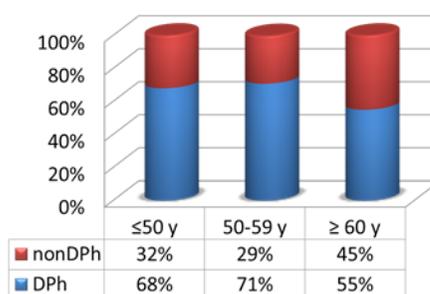
The proportion of patients with dawn phenomenon according to age is represented in Figure 1. In the category of age below 60 years, almost 70 % of the patients presented dawn phenomenon, and after the age of 60 years the proportion decreased to 55%.

In the CGM group included in the analysis, 84 (64.12%) out of 131 patients presented dawn

Table 1. The characteristics of the patients included in the analysis

Parameter	CGMS group N=131
Age ± SD, years	56.04 ± 9.91
Women, n (%)	47 (35.9)
Diabetes therapy	
Diet, n (%)	23 (17.6)
Oral anti-hyperglycemic agents, n (%)	70 (53.4)
Insulin, n (%)	38 (29.0)
Dawn phenomenon, n (%)	84 (64.12)
Diet, n (%)	12 (57.17%)
Oral anti-hyperglycemic agents, n (%)	51 (72.85%)
Insulin, n (%)	21 (52.63%)

n, number; %, percentage



p>0.05 for the frequency of dawn phenomenon in each age categories

Figure 1. The frequency of dawn phenomenon (DPh) according to category of age.

phenomenon. The comparisons of different variables between the group with dawn phenomenon and the group without dawn phenomenon are presented in Table 2.

None of the parameters of glycemic variability were significantly influenced by the presence of dawn phenomenon. If we analyse separately the groups defined according to diabetes treatment (diet, oral therapy and insulin), significant correlations between the dawn phenomenon and some of the parameters of glycemic variability have been found in the group of patients on diet therapy alone, as shown in Table 3. Patients with dawn phenomenon had a higher % over 126

Table 2. Comparison between parameters of glycemic variability according to the presence of dawn phenomenon

Parameter	Group without DPh N=47	Group with DPh N=84	p-value
Age (years)	57.57±12.19	55.18±8.33	0.186
Mean glucose (mg/dl)	171.50±56.23	167.14±47.42	0.638
SD (mg/dl)	27.69 (5.45-94.32)	29.36 (10.11-102.92)	0.436
% CV	15.37 (3.42-44.64)	17.40 (8.58-53.27)	0.126
M100	8.23 (0.13-94.40)	9.74 (0.42-145.99)	0.741
J index	45.41±28.77	43.39±26.77	0.687
% over 126 mg/dl	68.86±33.90	73.02±26.53	0.438
% over 180 mg/dl	38.51±40.94	31.67±32.91	0.299
% below 70 mg/dl	0 (0-34.38)	0 (0-13.54)	0.170
% below 54 mg/dl	0 (0-8.68)	0 (0-3.12)	0.059
FD	1.06±0.03	1.05±0.02	0.438
MAGE	82.43 (16.26-240.79)	89.66 (31.99-306.93)	0.373
CONGA-1	22.01 (6.98-55.89)	23.99 (7.09-72.73)	0.311
CONGA-2	32.23 (9.40-82.90)	35.41 (10.43-125.95)	0.334
CONGA-4	40.75 (10.36-100.34)	43.30 (14.26-167.93)	0.282
CONGA-6	40.89 (11.11-121.84)	41.59 (14.46-164.67)	0.228
MODD	27.88 (8.54-89.48)	27.43 (9.19-88.75)	0.746

(Variables with normal distribution are presented as mean±SD and variables with abnormal distribution are presented as median and interval) SD - standard deviation; %CV -percentage coefficient of variation; M100 - weighted average of glucose values; 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, MODD-the mean of daily differences.

and 180 mg/dl, j-index, MAGE, CONGA-4 and CONGA-6. The presence of dawn phenomenon showed no significant influence on glucose variability parameters in groups of patients with diabetes treated with oral therapy or insulin.

Next, we wanted to evaluate if the amplitude of dawn phenomenon is correlated with parameters of glycemic variability. The general amplitude of dawn phenomenon was 46.10 ± 24.40 mg/dl and was significantly correlated after adjustment for age, gender and treatment with % CV ($\rho=0.534$; $p<0.001$), MAGE ($\rho=0.519$; $p<0.001$), CONGA-1 ($\rho=0.479$; $p<0.001$), CONGA-2 ($\rho=0.448$; $p<0.001$), CONGA-4 ($\rho=0.495$; $p<0.001$), CONGA-6 ($\rho=0.533$; $p<0.001$) and MODD ($\rho=0.411$; $p<0.001$).

Discussion

Similar with other data previously reported for type 2 diabetes patients, almost two-thirds (64.12%) of our patients presented dawn phenomenon (4, 23). The frequency of dawn phenomenon was higher in younger patients. This may be explained by the fact that aging is related to decreased secretion of hormones with hyperglycemic action. Similar trends were observed by Monnier et al. (23). In their study they reported a frequency of 52, 70, and 59% in groups ≤ 59 years, 60-69 years and ≥ 70 years, respectively. We also observed a higher prevalence of dawn phenomenon in patients treated with oral therapy. These observations may be explained by

Table 3. Comparison between the group with dawn phenomenon and the group without dawn phenomenon, according to treatment for diabetes

Parameter	DPh versus without DPh		
	p-value group with diet N=23	p-value group with OT N=70	p-value group with I N=38
% CV	0.260	0.538	0.121
M100	0.057	0.714	0.095
J index	0.013	0.863	0.170
% over 126 mg/dl	0.010	0.410	0.101
% over 180 mg/dl	0.012	0.908	0.044
% below 70 mg/dl	0.217	0.229	0.963
% below 54 mg/dl	0.217	0.799	0.742
FD	0.819	0.665	0.612
MAGE	0.023	0.917	0.243
CONGA-1	0.169	0.827	0.243
CONGA-2	0.091	0.766	0.223
CONGA-4	0.032	0.827	0.199
CONGA-6	0.011	0.911	0.199
MODD	0.288	0.276	0.816

DPh – dawn phenomenon; OT-oral therapy; I-insulin; SD - standard deviation; %CV -percentage coefficient of variation; M100 - weighted average of glucose values; 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, MODD-the mean of daily differences.

the fact that the fasting hyperglycemia worsens as a result of progressively impaired pancreatic beta-cell function accompanied with insulin resistance (24). None of the antihyperglycemic drugs have the possibility to attenuate the dawn phenomenon (9). Administration of basal insulin abolishes or reduces the dawn phenomenon by restraining hepatic glucose production and lipolysis during nighttime (25). In our study only 52.63% of patients treated with insulin presented dawn phenomenon, similarly with patients treated with diet (57.17%), compared to 72.85% of patients in group treated with oral therapy. It is important to mention that in our study the patients treated with diet were mainly newly-diagnosed type 2 diabetes patients.

In type 2 diabetes the presence of dawn phenomenon caused rises in overall glycemic value, with an impact on HbA1c of almost 0.4% (9). In

our study we observed no significant influence of dawn phenomenon on % above 126 and 180 mg/dl, respectively in patients with pharmacotherapy for diabetes, but we observed a significant influence in the group treated with diet (drug-naïve patients). These results may be explained by the fact that pharmacotherapy of type 2 diabetes (oral agents or insulin) reduces insulin resistance and/or the glucose output of the liver and/or improves insulin secretion, diminishing the effect of dawn phenomenon on glycemic variability parameters. In drug-naïve patients dawn phenomenon also induces significant increase in other parameters evaluating glucose variability as MAGE, j-index and CONGA-4 and CONGA-6. MAGE provides a measure of intra-day, high amplitude glucose variability and it is linked with activation of oxidative stress (18, 26). J-index is a measure of the quality of

glycemic control based on the combination of information from the mean and SD (18, 27). In the diet group J-index was significantly higher in the presence of dawn phenomenon. CONGA is similar to SD but shows glycemic variability within a predetermined time window (18, 28). It is an indicator of within-day glucose variability and in a time frame of 4h and 6h it was significantly higher in the presence of dawn phenomenon in diet group.

The presence of dawn phenomenon showed no influence in our cohort of type 2 diabetes patients, but the amplitude of dawn phenomenon was significantly correlated, after adjustment for age, gender and treatment, with % CV, MAGE, CONGA-1, CONGA-2, CONGA-4, CONGA-6, parameters that evaluate within-day glycemic variability. The mean of daily differences (MODD) index was the only parameter used by us to evaluate inter-day variability of glucose values. This parameter is calculated as the mean of absolute differences between glucose values at corresponding time points of consecutive days (18, 29). The amplitude of dawn phenomenon in the first day of CGM was significantly correlated with MODD after adjustment for age, gender and treatment. The analysis of the data have been made without considering the type and the action of pharmacotherapy, which might be a limitation. The strength of the study is the original analysis of the dawn phenomenon in correlation with different parameters of the glycemic variability. The findings of this study could be translated into clinical practice in selecting the optimal therapeutic intervention.

Conclusion

The presence of dawn phenomenon significantly increases % above 126 and 180 mg/dl, MAGE, j-index, CONGA-4 and CONGA-6 in drug-naive type 2 diabetes patients, but it has no impact on glycemic variability parameters in patients

treated with oral therapy or insulin. The amplitude of dawn phenomenon remains significantly correlated with some parameters of glycemic variability after adjustment for age, gender and treatment.

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