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Glycemic Variability and Type 2 Diabetes Mellitus

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Abstract
Aim: The purpose of the present study was to quantify glucose variability in type 2 diabetic patients and establishing relationship with cardiometabolic parameters and type of glucose-lowering treatment. *Material and Methods*: Continuous glucose monitoring (CGM) was used in 373 type 2 diabetic patients. Glycemic variability (GV) was evaluated by many indices based on CGM data such as mean amplitude of glycemic excursions (MAGE), standard deviation (SD), nMAGE (calculating MAGE from glucose monitoring data using the algorithm proposed by Baghurst) and mean interstitial glucose values (MG). *Results*: GV increases significantly from diet to insulin group (p=0.001) and from oral therapy to insulin therapy (p=0.001) by MAGE, SD and nMAGE indices and less powerful for MG (p=0.042 and 0.003 respectively). All GV indices are correlated with each other, the strong relationship being shown between MAGE, SD and nMAGE (p=0.0001). *Conclusions*: There exists a progressive alteration of GV from diet to insulin therapy in individuals with type 2 diabetes mellitus. The simple standard deviation of CGM (continuous glucose monitoring) readings appears to be the best practical pathway to quantify glucose variability.

Keywords: Type 2 diabetes mellitus; Continuous glucose monitoring (CGM); Glycemic variability (GB).

Introduction

Optimal glycemic control represents the cornerstone in reduction of diabetes-specific microvascular and macrovascular complications, and there is very strong evidence to support this claim [1-4]. The impact of hyperglycemia on cardiovascular disease is also supported by numerous clinical studies [5-7], diabetes mellitus being an independent risk factor for coronary heart disease [8]. Leading cause of death in type 2 diabetes mellitus (T2DM) is represented by cardiovascular diseases and their sequelae. Over 70% of adults with diabetes die due to macrovascular complications [9]. Cardiovascular mortality risk among people with type 2 diabetes is more than double compared to people of the same age who do not associate diabetes [10].

Assessment of glycemic control in people with T2DM has been and continues to be a challenge. It is currently based on three parameters, named: glycated hemoglobin A1c (HbA1c), fasting plasma glucose and postprandial glucose [11]. But recent data suggest that these parameters do not provide enough information for a complete picture of glycemic imbalance and thus a fourth parameter, glycemic variability will address this shortcoming [12-14]. Numerous studies suggest the possibility that glycemic variability contributes to the risk of diabetes-related complications [15-19], while others say that would be an independent risk factor for long-term vascular complications [20]. The

mechanism by which glycemic variability (glycemic excursions) contribute to the genesis of vascular complications is activation of oxidative stress leading to endothelial dysfunction [21, 22]. Convincingly, endothelial dysfunction contributes to the development of cardiovascular diseases [23]. Recent studies strongly suggest that daily periods of glucose fluctuations represent a more specific triggering effect on oxidative stress that chronic sustained hyperglycemia [13, 24]. The fact is that the role of glucose variability in diabetes-related complications is not fully established, but continues to be a subject to controversy and remains an open field of research [25-29]. To date, many indices of quantifying glycemic variability (GV) have been proposed [11, 30, 31]; however, it is note that there is no universally accepted "gold standard" for measuring glycemic variability. Indices based on continuous glucose monitoring are considered more accurate; thus, MAGE (Mean Amplitude of Glycemic Excursions) index is a classic measure of variability being considered almost a "gold standard" [13].

The aim of the present study was to quantify glucose variability in people with T2DM and establishing relationship with cardiometabolic parameters and type of glucose-lowering treatment.

Material and Method

We have performed a cross-sectional study including persons with T2DM who consecutively attended to "Unirea" Medical Center Cluj-Napoca between 2007 and 2010. The study protocol has been approved by our institution's ethics committee. Informed consent was obtained from all participants. The following inclusion criteria were used for the study: subjects with known or newly diagnosed T2DM (defined according to American Diabetes Association [32]), aged ≥ 18 years, accessibility of continuous interstitial glucose monitoring for at least 48 hours and availability of subject characteristics. Persons with severe concomitant diseases, including kidney, liver, cardiovascular disease, severe uncontrolled hypertension (blood pressure ≥200/100 mmHg) or recent acute illness or psychiatric disease were excluded. At the beginning of the study, after a complete clinic exam, the following data were evaluated: demographic characteristics (age, gender), duration of the disease, current glucose-lowering therapies with indication of the class of drug, anthropometric parameters (body mass index, waist circumference), blood pressure, smoking status; blood was extracted to measure basic glycosylated hemoglobin A1c, lipids. Body mass index (BMI) was calculated as weight/height^2; waist circumference (WC) was measured at the midpoint between the lower border of the rib cage and the iliac crest at the end of a normal expiration. Blood pressure (BP) was measured after 5 minutes of rest in a sitting posture using a standard sphygmomanometer or an automatic oscillometric blood pressure recorder. HbA1c was measured with turbidimetric immunoassay; triglycerides, total and HDL cholesterol were determined by standard analytical methods; LDL cholesterol was calculated according to the Friedewald formula [33] and subjects with triglycerides ≥400 mg/dl were excluded. The estimated absolute 10 year coronary heart disease (CHD) risk was calculated using the UK Prospective Diabetes Study risk engine [34].

Then a sensor was inserted in the abdominal subcutaneous tissue and interstitial glucose was recorded every 5 minutes for at least 2 days (CGMS System Gold, Medtronic Minimed, Medtronic Diabetes, Northridge, CA, USA or Guardian System, Medtronic Minimed, Medtronic Diabetes, Northridge, CA, USA). Subjects were asked to record at least 4 fingerstick measurements daily to calibrate the continuous glucose monitoring system (CGMS). Patients carried on with their normal ambulatory life, followed their normal treatment. A glucose time series was obtained from each subject. From this series we extracted a 24-hour long series (from 00.00 AM on day 2 to 00.00 AM on day 3) for study. We selected day 2 to avoid the stressing influences of insertion and laboratory exam. Patients were trained in the use of CGMS and meters as appropriate.

Assessment of glycemic variability was made by the standard deviation (SD) from 24-h continuous interstitial glucose measurement data; mean amplitude of glycemic excursions defined as the average of all interstitial glucose excursions of more than 1 SD of the 24-hour mean interstitial glucose value [35-37]; nMAGE (calculating MAGE from glucose monitoring data using the algorithm proposed by Baghurst [38]); mean interstitial glucose values on 24-hours identified by CGMS (MG).

Statistical Analyses

For statistical analyses, the SPSS software, version 16.0 (Statistical Package for Social Science, Inc., Chicago, IL, USA) was used. Descriptive statistics were summarized by mean and SD for normally distributed continuous variables or proportion for qualitative variables. Skewed variables were compared using Mann-Whitney *U* test. Kolmogorov-Smirnov test was used to test normal distribution of the variables. Nonparametric analysis was done by determining the Spearman correlation coefficient (ϱ). A test result with p-value <0.05 was considered statistically significant.

Results

A total of 373 persons with T2DM out of 467 met the inclusion criteria. The mean age of study population was 54.46 years (range from 23 years to 83 years), 272 were male and 101 women. The mean duration of diabetes was 5.71 years (Table 1). The mean HbA1c was 8.42 % (range from 4.6% to 23.2%). Regarding glucose-lowering therapy, 21.45 % of study group were treated with diet alone; oral therapy was observed in more than half of individuals (51.74%) and insulin (alone or in association with oral agents) was given in 26.8%. Our research group was obese (mean BMI=30.46 kg/m^2) predominating abdominal obesity (mean WC = 107.34 cm). The estimated 10-years mean CHD risk was 20.3%.

Table 1. Characteristics of T2DM patients

Characteristics	Mean ± SD
Age (years)	54.46±10.46
Male gender (%)	72.92
Diabetes duration (years)	5.71±6.32
Weight (kg)	91.15±18.90
BMI (kg/m^2)	30.46±5.75
Waist circumference (cm)	107.34±13.68
Total cholesterol (mg/dl)	192.85±49.90
HDL cholesterol (mg/dl)	43.19±12.70
Triglycerides (mg/dl)	207.36±136.46
LDL cholesterol (mg/dl)	112.09±42.66
A1C (%)	8.42±1.99
Systolic BP (mmHg)	139.85±19.84
Diastolic BP (mmHg)	83.94±12.75
Current smoker (%)	27.34
Ex smoker (%)	36.73
CHD risk (%)	20.3±14.3
Fatal CHD risk (%)	13.3±12.6

Data presented are mean (±SD) or proportion (%)
BMI = body mass index; LDL = low density lipoprotein;
HDL = high density lipoprotein; TG = triglycerides;
A1c = glycated hemoglobin A1c; BP = blood pressure;
CHD = coronary heart disease

Glycemic Variability and Glucose-Lowering Therapy

The greater GV was observed in insulin-treated group compared with diet and oral therapy groups (Table 2). Applying Mann-Whitney U test, GV increases significantly from diet to insulin group (p=0.001) and from oral therapy to insulin therapy (p=0.001) by MAGE, SD and nMAGE indices and less powerful for MG (p=0.042 and 0.003 respectively) (data are not presented). From diet to oral therapy, an increase in GV is not statistically significant for neither indices (p= 0.169, 0.184, 0.845 and 0.134 for MAGE, SD, MG and nMAGE respectively using Mann-Whitney U test).

Table 2. Indices of glucose variability in all/different glucose-lowering treatment groups

	Total	Diet	Oral therapy	Insulin therapy
N	373	80	193	100
MAGE	61.45±35.67	51.28 ±27.18	56.74±30.05	78.77±44.86
SD	33.93±17.11	28.83±14.10	31.23±15.27	43.27±19.14
MG	164.69±49.37	160.98±47.73	158.79±46.56	179.06±53.40
nMAGE	66.55±37.01	56.09±32.15	61.11±32.80	85.49±41.56

N=number; MAGE = Mean Amplitude of Glycemic Excursions; SD = standard deviation; MG = mean interstitial glucose measurements by CGMS; nMAGE = MAGE according to the algorithm proposed by Baghurst

Glycemic Variability and Cardiometabolic Parameters

Spearman's correlation coefficients were calculated to assess the association between glucose variability and other variables (Table 3 and Table 4).

Table 3. Glucose variability and different variables

		Age	Diabetes duration	Weight	BMI	WC
MAGE	Correlation Coefficient	0.196**	0.204**	-0.375**	-0.244**	-0.289**
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
SD	Correlation Coefficient	0.193**	0.273**	-0.351**	-0.238**	-0.253**
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
MG	Correlation Coefficient	0.112*	0.129*	-0.107*	-0.045	-0.002
	p	0.031	0.013	0.039	0.386	0.965
nMAGE	Correlation Coefficient	0.183**	0.244**	-0.352**	-0.239**	-0.264**
	p	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001

**. Correlation is significant at the 0.01 level (2-tailed).
*. Correlation is significant at the 0.05 level (2-tailed).
MAGE = Mean Amplitude of Glycemic Excursions; SD = standard deviation; MG = mean interstitial glucose measurements by CGMS; nMAGE = MAGE according to the algorithm proposed by Baghurst; BMI = body mass index; WC = waist circumference

We found that MAGE, nMAGE and SD have a weak but statistically significant correlation with HbA1c; a more powerful correlation was observed between MG and HbA1c (Table 4) ($p<0.0001$). A negatively significant correlation was found between these three indices and weight, BMI and WC but not for MG except with weight (Table 3)($p=0.039$). No correlation between MAGE, nMAGE and SD and lipid profiles was observed (Table 4). MG correlates weak but significantly with cholesterol, triglycerides and negatively with HDL. Regarding age and diabetes duration there is a weak, but statistically significant correlation with all GV indices (Table 3).

Table 4. Glucose variability and different variables

		Chol	HDL	TG	A1C	LDL
MAGE	Correlation Coefficient	0.041	0.080	0.030	0.263**	0.002
	p	0.426	0.124	0.568	0.000	0.966
SD	Correlation Coefficient	0.008	0.031	0.056	0.320**	-0.046
	p	0.882	0.553	0.279	<0.0001	0.384
MG	Correlation Coefficient	0.116*	-0.074	0.223**	0.517**	0.060
	p	0.024	0.154	<0.0001	<0.0001	0.256
nMAGE	Correlation Coefficient	0.021	0.033	0.039	0.274**	-0.017
	p	0.683	0.523	0.458	<0.0001	0.753

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).
MAGE = Mean Amplitude of Glycemic Excursions; SD = standard deviation; MG = mean interstitial glucose measurements by CGMS; nMAGE = MAGE according to the algorithm proposed by Baghurst; Chol = total cholesterol; TG = triglycerides; LDL = low density lipoprotein; HDL = high density lipoprotein; A1c = glycated hemoglobin A1c

GV and estimated 10-year risk for both CHD and fatal CHD is associated significant but in a weak manner; from all indices of GV, MG had a stronger correlation with CHD and fatal CHD (see Table 5).

One the other hand, all GV indices are correlated with each other, the powerful relationship being shown between MAGE, SD and nMAGE (Table 5) (Spearman test; p=0.0001).

Table 5. Glycemic variability and 10-years risk for CHD

	Spearman test	MAGE	SD	MG	nMAGE
MAGE	Correlation Coefficient				
	p				
SD	Correlation Coefficient	0.913**			
	p	0.0001			
MG	Correlation Coefficient	0.499**	0.606**		
	p	0.0001	0.0001		
nMAGE	Correlation Coefficient	0.947**	0.932**	0.516**	
	p	0.0001	0.0001	0.0001	
CHD risk	Correlation Coefficient	0.147**	0.193**	0.334**	0.174**
	p	0.005	0.0001	0.0001	0.001
Fatal CHD risk	Correlation Coefficient	0.203**	0.254**	0.351**	0.228**
	p	0.0001	0.0001	0.0001	0.0001

**. Correlation is significant at the 0.01 level (2-tailed). *. Correlation is significant at the 0.05 level (2-tailed).

MAGE = Mean Amplitude of Glycemic Excursions; SD = standard deviation; MG = mean interstitial glucose measurements by CGMS; nMAGE = MAGE according to the algorithm proposed by Baghurst; CHD risk = 10-year absolute risk of coronary heart disease; Fatal CHD = 10-year absolute risk of fatal coronary heart disease

Discussion

HbA1c measurements usually evaluate the chronic variations of plasma glucose value and may not completely represent the risks that patients with diabetes are exposed to on a daily basis. HbA1c did not differentiate between glycemic excursions and thus did not offer information about GV. Patients with similar HbA1c levels and mean glucose values can have noticeably different daily glucose excursions. CGMS data provide information on continuous changes of acute glucose levels in daily life and come to complete the picture of glycemic disequilibrium along with HbA1c. This is confirmed on our findings by the fact that HbA1c had a weak correlation with indices of GV except MG (ρ= 0.517, p= 0.0001) which is in accordance with another researches [39, 40].

The best method to quantify GV is using the CGMS data that offer possibility to identify periods of glucose instability and variability that would otherwise remain undetected. In the present study we evaluated GV through a series of indices (MAGE, nMAGE, SD, MG) and found that MAGE, nMAGE and SD are highly correlated (p=0.0001 for all of them). This is in accordance with other studies conducted by Rodbard el al. [30, 41, 42]. Given the high correlation between MAGE and overall SD it may not be necessary to use the MAGE at all due to the fact that MAGE require a more complicated analysis of CGMS data and SD is easier to calculate and will generally be more precise and reproducible in accordance with Siegelaar et al. [18]. GV was noted irrespective of glucose-lowering therapy, even in individuals with diet alone (we considered the value $\geq$ 40 mg/dl to define the presence of glucose variability as demonstrated Monnier et al. [43] in their research). The greater GV was seen in insulin treated group and this is statistically significant when compared with diet and oral therapy. Our results confirm those found by Monnier et al. [44] that MAGE was significantly lower in oral therapy type 2 diabetic patients when compared with insulin-treated patients (type 1 and type 2 diabetic patients) and in accordance with Siegelaar [25] et al. who observed no amelioration of MAGE in group of type 2 diabetic individuals using inhaled mealtime insulin versus basal insulin treatment group.

We have shown that GV is weakly related to age and diabetes duration which is in contrast with data of Greven et al. [45] explained by a long asymptomatic period of T2DM until diagnosis is established.

The negative correlation of MAGE, SD and nMAGE with weight, BMI and WC suggests that obese individuals (especially having abdominal distribution of adiposity) could manifest a lower variability of glucose values being less insulinopenic by comparison with lean patients.

GV has been demonstrated to be independent risk factor for long-term vascular complications [20].

Di Flaviani et al. [46] observed that GV is associated with CHD even in well-controlled, uncomplicated type 2 diabetic patients. In the present study, there has been an association between CHD and indices of GV but in a weakly manner. From these indices, MG better correlates with CHD (ϱ=0.334, p= 0.0001).

Conclusions

Our results suggest that there exists a progressive alteration of GV from diet to insulin therapy in type 2 diabetic patients, the greater GV being observed in insulin treated group. Obese type 2 diabetic patients seem to be associated with less blood glucose excursions. No correlation between GV and lipid profiles was observed. GV and estimated 10-year risk for both CHD and fatal CHD was associated significant but in a weak manner. We suggest that simple SD of CGM readings appears to be the best practical pathway to quantify glucose variability.

Ethical Issues

The research was conducted in accordance with the guidelines in the Declaration of Helsinki and the medical ethical committee of the "Unirea" Medical Center Cluj Napoca approved the study protocol.

Conflict of Interest

The authors declare that they have no conflict of interest.

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