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Glycemic Variability and Vascular Complications in Patients with Type 2 Diabetes Mellitus

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Background: Presence of macro- and microvascular complications in patients with diabetes mellitus (DM) is not only related to chronic hyperglycemia represented by glycated hemoglobin (HbA1c) but also to acute glycemic fluctuations (glycemic variability, GV). The association between GV and DM complications is not completely clear. Aim of our study was to evaluate GV by MAGE index in patients with type 2 DM and to verify association of MAGE index with presence of macro- and microvascular DM complications.

Methods: 99 patients with type 2 DM were included in the study. Every patient had done big glycemic profile, from which MAGE index was calculated. Anthropometric measurements, evaluation of HbA1c and fasting plasma glucose (FPG) and assessment for macrovascular (coronary artery disease – CAD; peripheral artery disease – PAD; cerebral stroke – CS) and microvascular (diabetic retinopathy – DR; nephropathy – DN; peripheral neuropathy – DPPN) DM complications were done.

Results: Average MAGE index value was 5.15 ± 2.88 mmol/l. We found no significant differences in MAGE index values in subgroups according to presence of neither CAD, CS, PAD nor DR, DN, DPPN. MAGE index value significantly positively correlated with FPG ($p < 0.01$) and HbA1c ($p < 0.001$) and negatively with weight ($p < 0.05$).

Conclusion: In our study we failed to show association of MAGE index with presence of macrovascular and microvascular complications in patients with type 2 DM. However, this negative result does not necessarily disprove importance of glycemic variability in pathogenesis of diabetic complications.

BACKGROUND

Diabetes mellitus (DM) is a metabolic disease accompanied by development of specific micro- and macrovascular complications. Presence of both complications depends mostly on disorder of glucose levels, which has two main components: long-term chronic hyperglycemia (both fasting and postprandial) and acute glycemic fluctuations between high and low values (glycemic variability).¹ All those components lead to diabetic complications through two main mechanisms: increased glycation of proteins and activation of oxidative stress. Glycated hemoglobin (HbA1c) is the main marker of fasting and postprandial hyperglycemia and its level posi-

tively correlates with presence of both macro- and microvascular diabetic complications.^{2,3} On the other hand, many authors suggested, that glycemic variability could be also an independent risk factor for development of diabetic complications.^{4,5,6,7}

Measurement of glycemic variability can be realized by various calculations. The most simple is standard deviation (SD) calculated of all measured glucose levels. Another method is called MAGE index (Mean Amplitude of Glycemic excursions), calculated as arithmetic mean of differences between those glucose measurements, which are higher than 1 SD.⁸ Other methods of glycemic variability calculations are shown in review articles by Hill.⁹

and Martinka.¹⁰

Good reproducibility of glycemic variability measurement requires standardization of both calculation of glycemic variability and glucose level measurements. Glucose levels can be measured repeatedly during one day (within-day glucose variability) or during more days (between-day glucose variability).¹¹ Other method is continual measurement of glucose levels by Continual Glucose Monitoring System (CGMS).¹²

The rationale for glycemic variability measurement was studied by many authors.^{4,5,6,7} Glucose levels fluctuations had negative impact on function of pancreatic beta-cells, renal mesangial and tubulointerstitial cells and endothelial cells.¹³ Increased value of glycemic variability evaluated by MAGE index correlated with increased excretion of 8-oxo-prostaglandine F2-alpha, which is considered a marker of oxidative stress in patients with DM.^{14,15,16} but other study did not support this findings.¹⁷ Importance of glycemic variability monitoring was ambiguous in clinical studies and was different in patients with type 1 and type 2 DM.⁶ Data analysis from Diabetes Control and Complications Trial (DCCT), which included 7 measurements of glucose level during one day, did not show relationship of glycemic variability evaluated by SD or MAGE index to presence of microvascular complications¹⁸, neither peripheral nor autonomic neuropathy.¹⁹ However, in type 2 DM patients, increased values of MAGE index were associated with presence of coronary artery disease.²⁰ Increased glycemic variability was associated with total and cardiovascular mortality in patients older than 75 years.^{21,22} These results in type 2 DM patients were confirmed by another study.²³ Glycemic variability was also responsible for development of diabetic retinopathy^{24,25}, but this was not confirmed by another study.²⁶ However, possible explanation for presented differences between the studies could be different methods of glycemic variability evaluation.

AIM OF THE STUDY

Primary aim of the presented study was to analyze glycemic variability by MAGE index in hospitalized patients with type 2 diabetes mellitus, who underwent complex examination by diabetologist and evaluate the association of glycemic variability to presence of diabetic macro- and microvascular complications. Secondary goal was to evaluate impact of DM treatment on glycemic variability.

MATERIAL AND METHODS

Patients included in the study were hospitalized at 2nd Department of Internal Medicine, University Hospital Bratislava between January 2012 and October 2013 and during hospitalization sent to complex examination by diabetologist. Every included patient underwent within-day glucose measurement ("glycemic profile"), which consisted of 7 values of glucose measured from capillary blood by local biochemistry lab. Glucose levels were measured 10 minutes before and 90 minutes after main meals (breakfast, lunch and dinner) and at 3:00am in the night. Glycemic variability was calculated by MAGE index according to equation by Service et al.⁸

Every patient underwent basic anthropometric measurements (height, weight and waist circumference), from which body mass index (BMI) was calculated. Pathologic values for BMI were 25-30 kg/m² (overweight patients) and >30 kg/m² (obese patients)²⁷; pathologic values for waist circumference were chosen according to International Diabetes Federation: men > 94cm, women > 80cm.²⁸ Patients had also measured fasting plasma glucose from venous blood (FPG) and glycated hemoglobin (HbA1c) by method according to International Federation of Clinical Chemistry (IFCC). In those patients, who had HbA1c measured by Diabetes Control and Complications Trial (DCCT) method, we used transformation equation.²⁹ results are presented by both methods. Good metabolic compensation was in patients with HbA1c < 53 mmol/mol (IFCC) or < 7.0% (DCCT) respectively.³⁰ Treatment of diabetes mellitus in study patients was also evaluated (diet alone, oral antidiabetic drugs – OAD, insulin).

Presence of macrovascular complications – coronary artery disease (CAD), myocardial infarction (MI), cerebral stroke (CS) and peripheral artery disease (PAD) was evaluated by history taking and confirmed by patients' documentation. Presence of PAD was also evaluated by measurement of ankle-brachial pressure index (ABI); diagnostic criterion for PAD was ABI < 0.90.³¹

Of microvascular complications we evaluated retinopathy, nephropathy and peripheral neuropathy. Presence of diabetic retinopathy was evaluated by funduscopy by ophthalmologist or by history taking. Diabetic nephropathy (chronic kidney disease, CKD) was evaluated by presence of decrease estimated glomerular filtration rate (eGFR) calculated by Modification of Diet in Renal Disease study (MDRD) equation < 60 ml/min/1.73m².³² and/or excretion ratio of albumin and creatinine (ACR)

> 3 mg/dl.³³ Peripheral sensory diabetic neuropathy was assessed by evaluation of peripheral sensitivity: light touch, pinprick and warm-cold difference sensation, examination with Semmes-Weinstein 10g monofilament, vibratory sense by biothesiometer and patellar and Achilles tendon reflexes³⁴; of those measurements, Neuropathy Symptoms Score (NSS) and Neuropathy Disability Score (NDS) were calculated after Young.³⁵

Acquired data were entered into Microsoft Excel database and statistical analysis was performed by IBM SPSS for Windows. Numeric data with normal distribution were described by arithmetic mean and standard deviation (SD). To analyze statistical relationship between categorical variables we used chi-square test, to compare continuous data

between two groups we used unpaired Student's t-test, comparison between more than 2 groups was done by analysis of variance (ANOVA) test. Strength of association between 2 parametric variables was evaluated by Pearson's correlation analysis. Significance level for all statistical tests was set below 0.05.

RESULTS

Basic information about the patients is shown in **Table 1**. There were 99 patients (46 men, 53 women) included in the study, aged 32-91 years (mean age 69.59 ± 12.29 years). Duration of diabetes mellitus was 0-50 years (mean duration 15.76 ± 11.83 years). Mean fasting plasma glucose was 11.60 ± 5.51 mmol/l, mean level of glycated hemoglobin

Table 1. Basic history, biochemical and anthropometric parameters

Parameter	All patients (n=99)	Men (n=46)	Women (n=53)	Significance men vs. women
Age [years]	69.59 ± 12.29	67.09 ± 12.37	71.75 ± 11.92	NS
Duration of DM [years]	15.76 ± 11.83	15.40 ± 12.98	16.06 ± 10.89	NS
FPG [mmol/l]	11.60 ± 5.51	11.65 ± 5.16	11.55 ± 5.90	NS
HbA1c (IFCC) [mmol/mol]	75.40 ± 27.71	74.06 ± 26.33	76.56 ± 29.05	NS
HbA1c (DCCT) [%]	9.05 ± 2.54	8.93 ± 2.41	9.15 ± 2.66	
HbA1c (IFCC) < 53 mmol/mol [%]	22.7 %	24.4 %	21.2 %	NS
MAGE index [mmol/l]	5.15 ± 2.88	4.81 ± 2.33	5.45 ± 3.28	NS
BMI [kg/m ²]	31.38 ± 6.56	30.08 ± 6.89	32.40 ± 6.19	NS
BMI 18 – 25 kg/m ²	18.3 %	19.4 %	17.5 %	p<0.05
BMI 25 – 30 kg/m ²	29.6 %	45.2 %	17.5 %	
BMI > 30 kg/m ²	52.1 %	35.5 %	65.0 %	
WC [cm]	109.75 ± 13.35	107.35 ± 13.77	111.26 ± 13.11	NS
WC > 80 cm (women)	93.2 %	88.2 %	96.3 %	NS
WC > 94 cm (men)				

Table 2. Basic information about treatment of diabetes mellitus

Parameter	All patients (n=99)	Men (n=46)	Women (n=53)	Significance men vs. women
Diet only	8.1 %	4.3 %	11.3 %	NS
Oral antidiabetic drugs	25.3 %	32.6 %	18.9 %	
Insulin	39.4 %	41.3 %	37.7 %	
Oral antidiabetic drugs + insulin	27.3 %	21.7 %	32.1 %	

according to IFCC was 75.40 ± 27.71 mmol/mol (according to DCCT $9.05 \% \pm 2.54 \%$). Mean BMI value was 31.38 ± 6.56 kg/m²; in men was lower prevalence of obesity (BMI > 30 kg/m²) compared to women (35.5 % vs. 65.0 %; $p < 0.05$). Mean waist circumference was 107.35 ± 13.77 cm in men and 111.26 ± 13.11 cm in women; 93.2 % of subjects had higher waist circumference than recommended values by IDF.²⁸

Table 2 describes the treatment of diabetes mellitus in study patients. There were 8 patients treated by diet alone (8.1 %), 25 patients treated by OAD (25.3 %), 39 patients treated by insulin (39.4 %) and 27 patients treated by combination of OAD and insulin (27.3%).

Prevalence of macrovascular and microvascular

diabetic complications is shown in **Table 3**. History of CAD was present in 59.8 % patients and 18.8 % was after myocardial infarction. Prevalence of cerebral stroke was 27.1 % and peripheral artery disease 27.8 %. Most common microvascular complication was peripheral diabetic polyneuropathy in 87.9 % of patients and nephropathy in 67.1 % of patients.

Fig. 1 and **Fig. 2** show mean values of MAGE index according to presence or absence of macro- and microvascular diabetic complications. There were no significant differences in glycemic variability represented by MAGE index between presented subgroups.

Correlation analysis was performed between MAGE index and patients' age, duration of DM,

Table 3. Prevalence of macrovascular and microvascular diabetic complications

Parameter	All patients (n=99)	Men (n=46)	Women (n=53)	Significance men vs. women
Coronary artery disease	58.8 %	48.9 %	67.3 %	NS
Myocardial infarction	18.8 %	15.6 %	21.6 %	NS
Cerebral stroke	27.1 %	35.6 %	19.6 %	NS
Peripheral artery disease	26.3 %	35.6 %	18.0 %	NS
Diabetic retinopathy	38.2 %	32.4 %	44.1 %	NS
Diabetic nephropathy	67.1 %	57.1 %	77.1 %	NS
Diabetic peripheral polyneuropathy	87.9 %	91.3 %	84.9 %	NS

Table 4. Correlation analysis between MAGE index and patients' age, duration of diabetes mellitus, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c)

	Age	Duration of DM	FPG	HbA1c
MAGE index	$r = + 0.116$ NS	$r = + 0.139$ NS	$r = + 0.359$ $p < 0.01$	$r = + 0.339$ $p < 0.001$

Figure 1. Mean values of MAGE index according to presence or absence of macrovascular diabetic complications. CAD – coronary artery disease, MI – myocardial infarction, CS – cerebral stroke, PAD – peripheral artery disease.

Figure 2. Mean values of MAGE index according to presence or absence of microvascular diabetic complications. DR – diabetic retinopathy, DN – diabetic nephropathy, DPPN – diabetic peripheral polyneuropathy.

Table 5. Correlation analysis between weight, body mass index (BMI), waist circumference (WC) and MAGE index, fasting plasma glucose (FPG), glycated hemoglobin (HbA1c)

	Weight	BMI	WC
MAGE index	r = - 0.246 p < 0.05	r = - 0.184 NS (p = 0.12)	r = - 0.243 NS (p = 0.11)
FPG	r = + 0.275 p < 0.05	r = + 0.233 NS (p = 0.09)	r = + 0.134 NS
HbA1c	r = + 0.288 p < 0.05	r = + 0.324 p < 0.01	r = + 0.117 NS

Table 6. Mean values of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), diabetes compensation and MAGE index according to diabetes therapy subgroups

Therapy of DM	Diet only (n = 8)	OAD only (n = 25)	Insulin only (n = 39)	OAD + in- sulin (n = 27)	Signifi- cance
FPG [mmol/l]	15.35 ± 5.90	9.23 ± 4.11	11.94 ± 5.61	11.44 ± 5.69	NS
HbA1c (IFCC) [mmol/mol]	103.64 ± 38.43	69.31 ± 24.32	71.41 ± 27.63	78.40 ± 22.60	p < 0.05
HbA1c (DCCT) [%]	11.63 ± 3.52	8.49 ± 2.23	8.86 ± 2.53	9.32 ± 2.07	
HbA1c (IFCC) < 53 mmol/mol [%]	0.0 %	36.0 %	28.9 %	7.7 %	p < 0.05
MAGE index [mmol/l]	5.38 ± 4.02	5.18 ± 2.26	5.17 ± 3.12	5.03 ± 2.83	NS

weight, BMI, waist circumference, fasting plasma glucose and glycated hemoglobin. We found significant moderate positive correlations between MAGE index and FPG ($r = + 0.359$; $p < 0.01$), MAGE index and HbA1c ($r = + 0.339$; $p < 0.001$) and weak but significant negative correlation between MAGE index and weight ($r = - 0.246$; $p < 0.05$). No significant correlation was found between MAGE index and BMI, age and duration of DM (**Tables 4, 5**). There was also significant positive correlation between FPG and HbA1c and weight and BMI (**Table 5**).

Mean values of MAGE index, fasting plasma glucose, glycated hemoglobin and percentage of well compensated diabetics in patients' subgroups according to therapy of diabetes mellitus are shown in **Table 6**. We found no significant association between MAGE index and type of therapy. There was significant difference in mean HbA1c values between therapy groups ($p < 0.05$), mostly due to higher HbA1c values in patients treated by diet only. Similar differences were observed for percentages of good compensation of DM ($p < 0.05$), but not for mean FPG values.

DISCUSSION

Chronic metabolic compensation of plasma glucose represented by glycated hemoglobin does not reflect daily glycemic variations, which increase oxidative stress in diabetic patients and contribute to formation of diabetic complications. Patients with similar values of glycated hemoglobin can have markedly different glycemic values during the day. Monitoring of glycemic profile or continual monitoring of glycemia gives about changes of plasma glucose during the day and adds more information about glycemic dysbalance together with HbA1c. This is also supported by presence of significant correlation of HbA1c with glycemic variability represented by MAGE index ($r = + 0.339$; $p < 0.001$); this was also observed by other authors.^{36,37,38}

Average value of MAGE index in presented study was 5.15 ± 2.88 mmol/l; this is markedly more, than 2.8 mmol/l, the highest recommended value in healthy subjects by.⁹ Value below 2.8 mmol/l was achieved in our study only by 23.3% of patients. However, other authors recommend different upper limit values for MAGE index: Monnier et al recommended even lower normal value 40 mg/dl,

which corresponds approximately to 2.22 mmol/l.¹ On the other hand, newer study of Chinese authors Su, Mi, Tao et al suggested MAGE index > 3.4 mmol/l as independent predictor for incidence of coronary heart disease.²⁰ The same group of authors used discrimination value of 3.9 mmol/l to compare incidence of cardiovascular events in patients after acute myocardial infarction.³⁹

Values of MAGE index were not significantly different between subgroups of patients according to treatment; there was a minor trend to higher values of MAGE index in patients without any treatment, which could be attributed to presence of newly diagnosed diabetic patients who were present in the study (this could also explain higher levels of HbA1c and glycemia in this subgroup). Other authors found decreased glycemic variability in patients treated by oral antidiabetic drugs.^{38,40} HEART2D study, which compared effects of basal and prandial insulin treatment on incidence of cardiovascular events, found lower glycemic variability in patients with prandial insulin treatment, however, this was not reflected in decrease of cardiovascular events.⁴¹ Some authors showed positive effect of DPP-4 inhibitors (gliptins), especially vildagliptin, on lowering glycemic variability.^{42,43,44}; in our study we could not evaluate effect of gliptins on MAGE index, because only 6 patients were treated by gliptins: 3 patients were treated by sitagliptin and 3 patients by vildagliptin.

Correlation analysis of MAGE index with anthropometric parameters showed significant negative correlation of MAGE index and body weight, while BMI and waist circumference showed only a trend to negative correlation with MAGE index. This finding was also present in study of Romanian authors Gribovschi et al.³⁸ On the contrary, fasting plasma glucose and HbA1c positively correlated with weight and BMI, which underlines importance of obesity in long-term compensation of diabetes mellitus. We haven't found significant correlation neither between MAGE index and age nor duration of diabetes mellitus, which was described in study by Gribovschi et al.³⁸

Analysis of MAGE index values according to presence or absence of macrovascular (**Fig. 1**) or microvascular (**Fig. 2**) complications of diabetes mellitus has not found any significant differences between subgroups. As it was stated above, some of the published studies did confirm relationship of glycemic variability in patients with type 2 diabetes mellitus to presence of macrovascular.^{20-23,39} and

microvascular complications of diabetes mellitus.^{24,25} However, majority of those studies were using continuous glucose monitoring system (CGMS) to calculate glycemic variability, while in our study we employed standard method common in our practice – measurement of within-day glycemic profile consisting of 7 values. Similar method was also used in analysis of glycemic variability in DCCT study in type 1 diabetes mellitus patients, which did not confirm association of MAGE index with presence of diabetic complications.^{18,19} Hirsch and Brownlee wrote, that evaluation of glycemic variability can be significantly underrated without continual glucose monitoring;⁴⁵ however, in our study majority of patients had higher MAGE index value than recommended 2.8 mmol/l by Hill et al.⁹ If CGMS in future becomes widely available in diagnostics and monitoring of treatment of patients with diabetes mellitus, such as 24-hour blood pressure and ECG monitoring, more precise analysis of glycemic variability can become an important tool to assess risk of diabetic complications.¹²

CONCLUSION

In our study we failed to show association of glycemic variability assessed by MAGE index calculated from within-day seven values of plasma glucose with presence of macrovascular and microvascular complications in hospitalized patients with type 2 DM. However, this negative result does not necessarily disprove importance of glycemic variability in pathogenesis of diabetic complications. Further studies with better analysis of glycemic variability, such as continuous glucose monitoring system, are needed in future.

LIMITATIONS

The method we used to measure within-day glycemic profile consisted of 7 samples over the course of a day might explain the negative results they obtain compared to other studies that used continuous glucose monitoring. In addition, the sample size of 99 patients might also contribute that hardly any statistical significant correlations were found.

CONFLICT OF INTEREST

Authors declare no conflict of interest.

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Вариабельность уровня глюкозы и микрососудистые осложнения у пациентов с сахарным диабетом 2-ого типа

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Введение: Наличие макро- и микрососудистых осложнений у пациентов с сахарным диабетом (СД) не только связывается с хронической гипергликемией, представленной гликированным гемоглобином (HbA1c), но также и с резкими гликемическими колебаниями (гликемической вариабельностью, ГВ). Взаимосвязь между ГВ и осложнениями СД полностью не выявлена. Целью нашего исследования является измерение индекса MAGE ГВ у пациентов с СД 2-ого типа и подтверждение взаимосвязи индекса MAGE с наличием макро- микрососудистых осложнений СД.

Методы: 99 пациентов с СД 2-ого типа приняли участие в исследовании. Каждому пациенту был составлен подробный гликемический профиль, на основе которого был установлен индекс MAGE. Были проведены антропометрические измерения, оценка HbA1c и уровня глюкозы в плазме крови натощак (УГПKN), оценка макрососудистых (ишемическая болезнь сердца – ИБС; заболевание периферических артерий – ЗПА; мозговой инсульт – МИ) и микрососудистых (диабетическая ретинопатия – ДР; нефропатия – ДН; периферическая нейропатия – ДПН) осложнений СД.

Результаты: Средний показатель индекса MAGE составил 5.15 ± 2.88 ммол/л., не установлены значительные различия показателей индекса MAGE в подгруппах в отношении наличия ИБС, МИ, ЗПА или ДР, ДН, ДПН. Показатель индекса MAGE в значительной степени коррелирует положительно с FPG ($p < 0.01$) и HbA1c ($p < 0.001$) и отрицательно с весом ($p < 0.05$).

Заключение: В нашем исследовании не установлена взаимосвязь между индексом MAGE и наличием микрососудистых и макрососудистых осложнений у пациентов с СД 2-ого типа. Независимо от этого, данный отрицательный результат не отвергает категорически значение гликемической вариабельности в патогенезе диабетических осложнений.