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Evaluation of the Glycemic Fluctuation as Defined as the Mean Amplitude of Glycemic Excursion in Hospitalized Patients with Type 2 Diabetes

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BACKGROUND
In addition to hemoglobin AIc (HbAIc), fasting plasma glucose (FPG), and postprandial glucose (PPG) levels, it is recommended to take glycemic variability into consideration for an assessment of the glycemic control of patients with type 2 diabetes. The mean amplitude of glycemic excursion (MAGE) is proposed to be a more sensitive method than HbAIc in evaluation of the glycemic variability. The objective of this study was to determine the MAGE levels of patients with type 2 diabetes who were hospitalized for poor glycemic control and to investigate whether these levels showed differences according to the diabetes duration and treatment characteristics.

MATERIAL and METHODS
This study included a total of 50 patients with type 2 diabetes (39 female, 11 male; mean age: 59.54±11.96; mean diabetes duration: 12.1 years) who were hospitalized at İstanbul Medeniyet University Department of Internal Medicine for glycemic control. Capillary venous blood samples were collected from the patients 10 times a day for 2 days and the MAGE levels were determined.

RESULTS
The MAGE, HbAIc, fasting plasma glucose, and postprandial glucose levels of the patients were 85.18±21.64 mg/dL, 10.71±2.40%, 196.70±61.25 mg/dL, and 240.02±79.51 mg/dL, respectively. MAGE levels were found to be 93.93±19.85 mg/dL in patients who use insulin, 82.94±21.41 mg/dL in those who use oral antidiabetics (OAD), and 74.37±19.75 mg/dL in patients who use both insulin and OAD. MAGE levels were higher in the insulin-using patients compared to those using insulin and OAD together (p=0.002).

CONCLUSION
It was observed in the present study that MAGE levels were higher in type 2 diabetic patients with impaired glycemic control.

Keywords: Type 2 diabetes, glycemic control, MAGE levels, treatment characteristic

INTRODUCTION

Glycemic variability is the variation of blood glucose between hypoglycemia and hyperglycemia during the day. A high variability leads to oxidative stress, which plays a role in the pathogenesis of vascular complications, ultimately resulting in endothelial damage (1, 2). Glycemic control of patients with type 2 diabetes (T2DM) is often assessed with hemoglobin AIc (HbAIc), fasting plasma glucose, and postprandial glucose. However, these three parameters do not always provide sufficient information about the glycemic variability (3-5). The mean amplitude of glycemic excursion (MAGE), glycoalbumin, and 1.5-anhydroglucitol measurements are usually used in evaluation of the glycemic variability (6-8). The MAGE level is calculated as the arithmetic mean of the elevations and reductions in blood glucose levels (9-11) and is reported to be a more sensitive method than HbAIc in evaluation of the glycemic variability (6, 12, 13).

The objective of this study was to determine the MAGE levels of patients with T2DM who were hospitalized for glycemic control and to investigate whether these levels showed differences regarding the diabetes duration and treatment characteristics and to evaluate their relationship with the clinical features.

MATERIALS and METHODS

Patients with T2DM who were hospitalized at İstanbul Medeniyet University Department of Internal Medicine were recruited. The exclusion criteria were: presence of severe renal, cardiac, and hepatic dysfunction; intensive care unit requirement (e.g., acute coronary syndrome, severe sepsis); diabetic decompensation (diabetic ketoacidosis, hyperglycemic hyperosmolar coma, lactic acidosis); and malignancy. The study was approved by the ethics committee of İstanbul Medeniyet University

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(blinded for peer review) (Date: 07/18/2014, No: 2014/0088) and written consents were received from the patients. The principles of the Helsinki Declaration were followed during the study.

Study Design: A detailed history was received from each of the patients, whereby age, gender, history, diabetes duration, treatment characteristics, smoking, alcohol consumption, and use of drugs were questioned. A physical examination was performed on patients who met the inclusion criteria and who agreed to participate in the study. In the physical examination, blood pressure, height, body weight, and waist circumference were measured by the same person using standard measuring instruments. Waist circumference was measured with the patients in a standing-up position with mild expiration, from the narrowest part of the waist at the plane that crosses between the spina iliaca anterior superior and arcus costa. Body mass index (BMI) was calculated by dividing the body weight in kilograms by the square of the height in meters (kg/m^2). Capillary venous blood samples were collected from the patients 10 times a day for 2 days and the MAGE levels were determined. The calculated MAGE levels were compared according to diabetes duration and the treatment characteristics [insulin, oral antidiabetic (OAD), insulin+OAD].

Criteria of the American Diabetes Association were used for type 2 diabetes diagnosis (3). Glucose, total cholesterol, HDL-cholesterol, LDL-cholesterol, and triglyceride values were measured using the COBAS 8000 (Roche Diagnostics, Risch-Rotkreuz, Switzerland) auto-analyzer with the enzymatic method, while the HbAIc measure was carried out using the Primus Ultra 2 (Trinity Biotech, Jamestown, New York, USA) device with the boronate affinity HPLC method.

Mean Amplitude of Glycemic Excursion Measurements: Capillary venous blood samples were collected from the patients 10 times a day (at: 06.00, 08.00, 10.00, 12.00, 14.00 17.00, 19.00, 22.00, 24.00, and 03.00 hours) for 2 days. Blood glucose was measured using the Code free blood glucose measurement device (measures with electrochemical method used the Wide Gold Electrode technique). Standard deviation values were calculated using all the measurements for each patient. Each measurement value was subtracted from the previous one to calculate the difference (delta value). After absolute values of the delta were obtained, delta values smaller than the standard deviation were eliminated. The MAGE values were calculated by using the mean delta values that were greater than the standard deviation values (9).

Statistical Analysis: Number cruncher statistical system (NCSS) 2007 (NCSS, LCC, Kaysville, Utah, USA) and Power analysis and sample size (PASS) 2008 statistical software (NCSS, LCC, Utah, USA) were used for the statistical analysis. In addition to the descriptive statistical methods (the mean, standard deviation, median, frequency, percentage, minimum, and maximum), for comparison of the quantitative data, the Student t-test was used for comparisons between two groups of the variables with a normal distribution and the Mann–Whitney U test for comparisons between two groups of the variables with a non-normal comparison. The Kruskal–Wallis test was used for comparison between three or more groups with a non-normal distribution and the Mann–Whitney U test in the determination of the group causing the difference. Pearson correlation and Spearman correlation coefficients were used to evaluate the relationships between the variables. The significance level was set at $p<0.01$ and $p<0.05$ values.

TABLE 1. Treatment characteristics of the patients

			Total patients (n=50)
Oral antidiabetics (n, %)			25 (50.0)
Insulin (n, %)	Basal insulin	Glargine	33 (66.0)
		Detemir	10 (20.0)
	Bolus insulin	Aspart	30 (60.0)
		Lispro	2 (4.0)
		Glulisine	4 (8.0)
Oral antidiabetic+Insulin (n, %)			19 (38.0)
Antihypertensive (n, %)			33 (66.0)
Others (n, %)			38 (76.0)

TABLE 2. Demographic, anthropometric, and biochemical characteristic of the patients

	Total (n=50)	Female (n=39)	Male (n=11)	p
Age (year)	59.54±11.96	58.90±11.92	61.82±12.38	0.432
Smoking (n, %)	11 (22.0)	8 (20.5)	3 (27.2)	0.118
Alcohol (n, %)	2 (4.0)	0 (0.0)	2 (18.2)	0.008
Body mass index (kg/m2)	30.82±6.00	31.73±6.05	27.59±4.75	0.038
Waist circumference (cm)	105.56±15.86	107.05±16.20	100.27±14.02	0.271
Systolic blood pressure (mmHg)	131.82±16.95	133.10±16.00	127.27±20.17	0.397
Diastolic blood pressure (mmHg)	74.62±8.16	74.90±7.94	73.64±9.24	0.609
Fasting plasma glucose (mg/dL)	196.70±61.25	200.51±65.14	183.18±44.76	0.380
Postprandial plasma glucose (mg/dL)	240.02±79.51	242.44±76.48	231.45±93.02	0.779
HbAIc (%)	10.71±2.40	10.42±2.41	11.74±2.18	0.146
Total cholesterol (mg/dL)	222.86±96.08	224.13±101.51	218.36±77.81	0.972
HDL-cholesterol (mg/dL)	39.78±17.71	39.97±17.73	39.09±18.45	0.935
LDL-cholesterol (mg/dL)	121.05±40.27	120.52±39.58	122.80±44.66	0.863
Triglyceride (mg/dL)	274.76±239.20	269.33±183.29	294.00±390.09	0.287
ALT (IU/L)	28.96±32.66	26.54±33.24	37.55±30.43	0.108
Creatinine (mg/dL)	0.96±0.31	0.95±0.30	0.97±0.35	0.897
GFR (mL/dk)	91.87±38.42	88.76±35.47	102.90±47.7	0.433
MAGE (mg/dL)	85.18±21.64	83.38±20.75	91.56±24.48	0.297

HbAIc: hemoglobin AIc; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ALT: alanine aminotransferase; GFR: glomerular filtration rate; MAGE: mean amplitude of glycemic excursion

RESULTS

A total of 50 patients (39 female, 11 male; mean age: 59.54±11.96; min–max: 44–86) were included in the study. The mean diabetes duration was 12.1 years. Table 1 shows the treatment modalities of the patients.

The demographic, anthropometric, and biochemical characteristics of the patients are given in Table 2. The BMI score was

TABLE 3. Comparison of the MAGE levels according to the treatment characteristics of the patients

		MAGE (mg/dL)	HbAlc (%)	FPG (mg/dL)	PPG (mg/dL)
[1]Insulin		93.93±19.85	11.10±2.52	199.76±72.06	261.44±76.47
[2]OAD		82.94±21.41	9.12±2.94	177.83±54.02	195.67±56.68
[3]Insulin+OAD		74.37±19.75	10.69±1.93	198.63±48.40	225.84±83.77
	p	0.008	0.295	0.614	0.097
[a]Post-hoc	[1-2]p	0.291	-	-	0.067
	[1-3]p	0.002			0.115
	[2-3]p	0.514			0.437

MAGE: mean amplitude of glycemic excursion; HbAlc: hemoglobin Alc; OAD: oral antidiabetic; FPG: fasting plasma glucose; PPG: postprandial glucose

TABLE 4. Comparison of the MAGE levels according to the basal insulin types

	MAGE (mg/dL)
Glargine (n=33)	84.09±22.72
Detemir (n=10)	89.68±20.64
p	0.386

MAGE: mean amplitude of glycemic excursion

TABLE 5. Comparison of the MAGE levels according to the HbAlc values

	MAGE (mg/dL)	p
HbAlc: ≤8% (n=8)	75.49±26.25	
HbAlc: 8.1–10% (n=7)	82.98±18.00	0.432
HbAlc: ≥10% (n=35)	87.83±21.10	
HbAlc: <8% (n=8)	75.49±26.25	0.278
HbAlc: ≥8% (n=42)	87.03±20.49	

MAGE: mean amplitude of glycemic excursion; HbAlc: hemoglobin Alc

TABLE 6. Comparison of the MAGE levels according to diabetes duration of the patients

Diabetes duration (years)	n	MAGE (mg/dL)	p
0–5	12	86.83±14.93	0.775
6–10	11	75.96±20.19	
11–15	7	84.56±17.84	
16–20	9	95.24±27.70	
>20	11	84.76±25.45	

MAGE: mean amplitude of glycemic excursion

higher (p=0.038) and alcohol consumption was lower (p=0.008) in females than in males. MAGE values differed between 31.6 and 139.88 mg/dL with an average of 85.18±21.64 mg/dL. No statistically significant difference was found between the genders in terms of MAGE values (p>0.05). The overall average blood glucose level was found to be 211.88 mg/dL, with a standard deviation of 67.57 mg/dL.

Comparison of the MAGE, HbAlc, fasting blood glucose, and postprandial blood glucose values are given in Table 3. MAGE values were found to be higher in insulin users than in insulin+OAD users (93.93±19.85 mg/dL vs 74.37±19.75 mg/dL, p=0.002). No significant difference was found between insulin, OAD, or insulin+OAD users in terms of HbAlc, fasting plasma glucose, or postprandial plasma glucose. Although not statistically significant, HbAlc, fasting blood glucose, and postprandial blood glucose values were found to be higher in OAD users compared to insulin or insulin+OAD users.

The mean MAGE levels according to the basal insulin types used by patients are given in Table 4. The mean MAGE levels did not show a significant difference between insulin glargine and detemir users (84.09±22.72 mg/dL vs 89.68±20.64 mg/dL, p>0.05).

The mean MAGE levels of the patients according to the HbAlc values are given in Table 5. Although it did not reach statistical significance, the mean MAGE values were higher in patients with HbAlc ≥%8 compared to those with HbAlc <%8.

The mean MAGE levels according to diabetes duration are given in Table 6. No significant difference was found between the groups.

DISCUSSION

In the present study, MAGE levels were found to be higher in the group of patients hospitalized for glycemic control. MAGE levels were higher in insulin users than in insulin+OAD users but these levels did not show significant differences in terms of diabetes duration and basal insulin use.

HblAc reflects the average glycaemia in diabetic patients; however, it is insufficient to show the glycemic variability (10, 11). Therefore, today, various methods showing glycemic variability are used for the follow-up of diabetes control and in order to predict possible complications. Increased glycemic fluctuations have been demonstrated to cause more severe endothelial damage and oxidative stress, resulting in serious cardiovascular complications, compared to constantly high blood glucose levels (12, 14-16). Today, the methods used in evaluation of the glycemic variability are MAGE, 1.5- anhydroglucitol and fructosamine (7, 17-19). MAGE, which is based on close monitoring of the blood glucose variabilities, is an important parameter in providing glycemic control and for the prediction of possible complications (9, 20). However, the reference values to be used for MAGE represent a controversial issue. In a study by Zhou et al. (21), conducted in order to define reference values of MAGE, continuous glucose monitoring measures were carried out in 434 non-diabetic healthy persons for 72 h. The upper limit of MAGE was found as 70.2 mg/dL with a standard deviation (ss) of 25.2 mg/dL for healthy persons. In a study by Hill et al. (13) with different ethnic groups, MAGE values were calculated with continuous glucose monitoring of 70 non-diabetic persons for 72 h and the normal range was found as 0.0–50.4 mg/dL. Whereas in our study, the MAGE values of our patients differed between 31.6 and 139.88 mg/dL and the average value was found to be 85.18 mg/dL with a SD of 21.64 mg/dL, thus the average MAGE value calculated in our study is higher than the reference values calculated in other studies. This finding supports that MAGE may be higher in pa-

tients with type 2 diabetes with impaired glycemic control. Also, in our study MAGE levels increased as HbIAc values increased, suggesting that MAGE can be a reliable indicator for poor glycemic control.

It is known that diabetes treatments have different effects on MAGE. In a study evaluating the glycemic variability and relationship of this variability with cardio metabolic parameters and antidiabetic treatments in type 2 diabetics, MAGE values were found to be significantly higher in insulin users compared to in patients who used oral diabetics or who received diet therapy alone (4). In a study by Shimoda et al. (22), the MAGE values of 40 diabetic patients who used multiple doses of insulin therapy were evaluated with 1-day SMBG measures carried out 6 times a day, and a significant reduction was observed in MAGE values that were evaluated 12 weeks after sitagliptin was added to the treatment. In a study by Su et al. (23), acarbose was added for 2 weeks to the treatment in 45 of 86 type 2 diabetic patients who used mix analog insulin and who had a MAGE value ≥61.2 mg/dL, while the remaining 41 patients continued to use a mixed analog insulin therapy. In that study, a significant reduction by 40% was observed in the MAGE values of the group with acarbose compared to the values measured 2 weeks previously. Whereas in the present study, the MAGE values of the patients who used insulin alone were found to be significantly higher compared to the patients who used insulin and OAD in combination. This finding might have resulted due to the fact that the insulin group consisted of patients who already had poor glucose control.

There are studies investigating the effect of different insulin treatments on MAGE. In a study by Service et al. (9) investigating whether moderate acting insulin therapy and short-acting insulin therapy have any difference in the glycemic variability, no difference between the regimens was found, although the incidence of hypoglycemia was higher with the short-acting insulin.

Limitations: The most important limitation of this study is the lack of blood glucose measurements with continuous glucose monitoring to determine the MAGE values. Furthermore, it may be considered an imperfection that the 1.5-anhydroglucitol and fructosamine values were not studied.

CONCLUSION

High MAGE levels observed in poor controlled type 2 diabetic patients hospitalized for glycemic control support that MAGE may be a good marker for the evaluation and follow-up of glycemic control.

Ethics Committee Approval: Ethics committee approval was received for this study from the ethics committee of İstanbul Medeniyet University (Date: 07/18/2014, No: 2014/0088).

Informed Consent: Written informed consent was obtained from patient who participated in this study.

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