

GLUCOSE VARIABILITY IN PERSONS WITH DIABETES EVALUATED BY CONTINUOUS GLUCOSE MONITORING

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Abstract

Blood glucose level is the main indicator of diabetes control. It is related to diabetes evolution and appearance of chronic complications. Daily and/or postprandial glucose fluctuations induce oxidative stress and endothelial dysfunction in a higher extent than sustained hyperglycemia. Glucose excursions can be expressed by glucose variability and by mean amplitude of glucose excursions (MAGE), parameters which are determined by continuous glucose monitoring (CGM). In our study glucose variability and MAGE were significantly higher in persons with type 1 diabetes, in women and in insulin treated persons. They were correlated with haemoglobin A1c values. They did not vary significantly after 3 months since the first CGM.

key words: *type 1 and type 2 diabetes, glucose variability, mean amplitude of glucose excursions, continuous glucose monitoring.*

Background

Nowadays, the importance of glucose control in diabetes is well established. A large body of clinical evidence shows the reduction of microvascular and macrovascular complications of diabetes following tight glucose control. DCCT (Diabetes Control and Complications Trial), SDIS (Stockholm Diabetes Intervention Study), DCCT-EDIC (DCCT - Epidemiology of Diabetes Interventions and Complications Study), SDIS in type 1 diabetes and UKPDS (United Kingdom Prospective Diabetes Study),

Kumamoto Study, VACSDM (Veterans Affairs Cooperative Study in Type 2 Diabetes Mellitus), VADT (Veterans Affairs Diabetes Trial), STENO-2 in type 2 diabetes are studies which support these findings.

Glycated haemoglobin A1c (A_{1C}) indicates long-term glucose status and is used as marker of glucose control as well as therapeutic goal in large epidemiologic studies [1-4]. A_{1C} represents the standard of evaluation, glucose control defining element and inclusion criteria for continuous glucose

monitoring studies in persons with diabetes [5-17].

Acute hyperglycemia and glucose variability seem to play an important role in increasing oxidative stress and further comorbidities, with more deleterious effects than stable hyperglycemia. Increased apoptosis, enhanced protein kinase C activity, nitrotyrosine formation and generation of adhesion molecules in endothelial cells are possible mechanisms by which acute hyperglycemia and glucose variability could determine their pathological effects [18]. Acute hyperglycemia, which increases glucose variability, manifests during postprandial periods for most of the time, but also includes random hyperglycemic spikes or even Dawn phenomenon.

Postprandial hyperglycemia is an independent risk factor for macrovascular disease, it is associated with increased risk for diabetic retinopathy, the increase of carotid intima-media thickness, the appearance of oxidative stress, inflammation and endothelial dysfunction. It also decreases myocardial blood volume and flow, enhances risk of cancer and impairs cognitive function in elderly type 2 diabetics. Evidence shows that treating postprandial hyperglycemia leads to reduction of cardiovascular events, and in the same time contributes to obtaining and maintaining optimal glucose status along with fasting plasma glucose control. Actual guidelines recommend a postprandial glycemic goal of 140 mg/dl on the condition of avoiding hypoglycemia.

Self-monitoring blood glucose is a practical method for postprandial glucose monitoring, which should be used with a proper frequency for guiding therapy in

achieving postprandial goal [18]. Clinical studies proved that intermittent glucose monitoring does not reflect real glucose fluctuations which are better detected by continuous glucose monitoring (CGM) [19].

Monnier L. et al. (2007) emphasized the importance of CGM for determining mean amplitude of glucose excursions (MAGE), an important index of glucose variability [19, 20]. Monnier L. et al. (2006) have shown a close direct relation between glucose variability quantified by MAGE and oxidative stress estimated by 24 hour urinary excretion of free 8 iso-prostaglandin F_{2α}, which approximates free radicals production. The authors suggested that MAGE is a more precise indicator of glucose excursions than incremental postprandial glucose area under the curve [21, 22]. Brownlee M. and Hirsch IB. (2006) stated that the study of Monnier et al. may explain the reduction of risk for diabetic retinopathy in type 1 diabetic persons from DCCT from intensive treatment arm, compared with persons who had the same A1C from the conventional treatment arm [23]. Data regarding oxidative stress induced by glucose variability are also presented in the study of Quagliaro L et al. (2003) [24]. There are studies that do not support the hypothesis of oxidative stress being related to glucose variability [25]. Bolli G. (2006) sustains the importance of reducing glucose variability in persons with T1D in order to decrease the number and severity of symptomatic or asymptomatic hypoglycemic episodes, which is important especially when A1C goal is less than 7% [15].

CGM is a complex method for glucose status evaluation with certain advantages in detection of asymptomatic hypoglycemia,

proper evaluation of glucose excursions and specific changes in antidiabetic therapy in order to obtain tight glucose control.

The aim of this study was to evaluate the relation between glucose variability, MAGE, and sex, diabetes type, diabetes treatment, currently and prospectively in subjects with diabetes, evaluated by CGM.

Material and method

Study group. A group of 55 individuals with type 1 and type 2 diabetes was evaluated by CGM for 3 days. 13 patients with type 1 diabetes (T1D) and 8 patients with type 2 diabetes (T2D), all on insulin therapy, performed a second CGM procedure after 3 months.

Baseline parameters assessed were as following:

- gender - 29 women, 26 men,
- age (mean (minim-maxim)) - 47 (11-80) years,
- diabetes type - 24 persons – T1D and 31 persons – T2D,
- diabetes duration (mean (minim-maxim))– 9.86 (0-31) years,
- diabetes treatment - 39 persons insulin-treated (24 - T1D, 15-T2D), 16 subjects on oral therapy (T2D),
- A1C assessment. We divided the group according to A1C domains (<6.0%, 6.0-6.9%, 7.0-7.9%, ≥8.0%).

Continuous glucose monitoring. We determined interstitial glucose levels in the abdominal subcutaneous tissue by continuous glucose monitoring system – CGMS (Medtronic MiniMed). The system records almost continuously (every 5 minutes) interstitial glucose values for 72 hours using a

subcutaneous catheter based on glucose oxidase reaction.

We also calculated GV and MAGE based on continuous monitoring data. We evaluated the same parameters during the second monitoring. Individual variation of interstitial glucose values (GV) was defined as standard deviation of all glucose determinations from one CGM evaluation of a subject [5]. MAGE was calculated using the method of Monnier et al. (2006): the mean of all differences between maximal and minimal interstitial glucose levels (peaks and nadirs), for the differences, that are higher than standard deviation of all glucose values from CGM [21].

Statistical analysis was performed with SPSS 13.0 program. The assessment of relation between diabetes type, diabetes treatment, gender distribution and GV or MAGE was performed with Mann-Whitney test for two independent samples. The relation of GV and MAGE with A1C was tested with Spearman correlation test for ordinal data. The variation of GV and MAGE with A1C category was evaluated by Kruskal-Wallis test for multiple independent samples. Prospective analysis of A1C, GV and MAGE was performed with Wilcoxon test for paired samples. Statistical significance level was reached for $p < 0.05$.

Results

In the study group, A1C was significantly higher in women than in men with diabetes ($p = 0.027$), but did not vary significantly with diabetes type or treatment at initial visit. (Mann-Whitney test) (Table 1).

GV and MAGE were significantly higher in type 1 diabetes persons at both initial and

final visits ($p < 0.001$, Mann-Whitney test) (Figure 1).

GV and MAGE were significantly higher in insulin treated persons at first visit ($p < 0.01$,

Mann-Whitney test) (Figure 2). The relation with diabetes treatment could not be tested at final visit because all subjects were insulin treated.

Table 1. A1C assessment in the study group

A1C (%) mean \pm SD	Gender		Diabetes type		Diabetes treatment	
	Women	Men	Type 1	Type 2	Insulin	Oral therapy
	8.81 \pm 1.71	7.81 \pm 1.68	8.80 \pm 1.84	8.10 \pm 1.65	8.62 \pm 1.67	7.63 \pm 1.81
	p=0.027		p=0.293		p=0.051	

SD – standard deviation

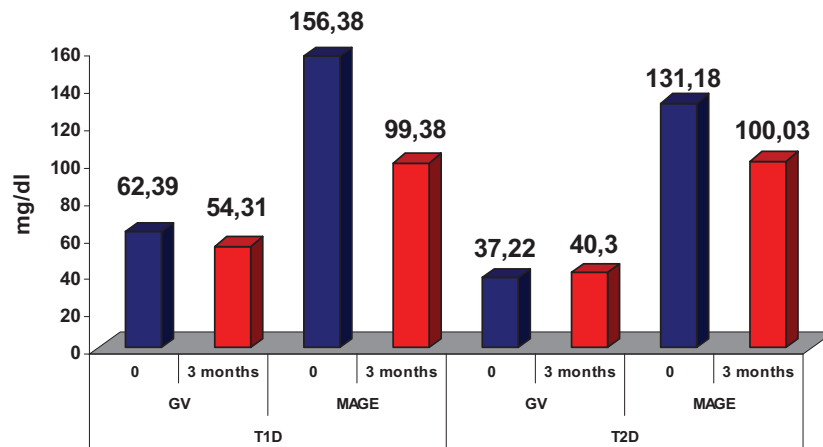


Figure 1. GV and MAGE in relation with diabetes type, prospective approach.

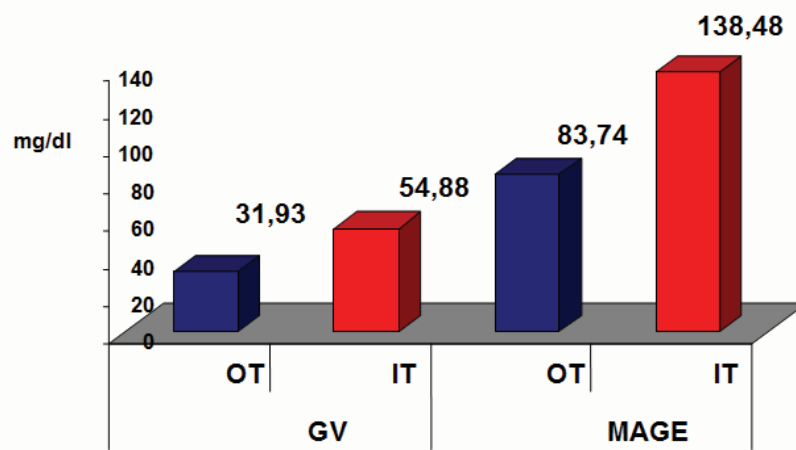


Figure 2. GV and MAGE in relation with diabetes treatment type. OT= oral therapy; IT= insulin therapy

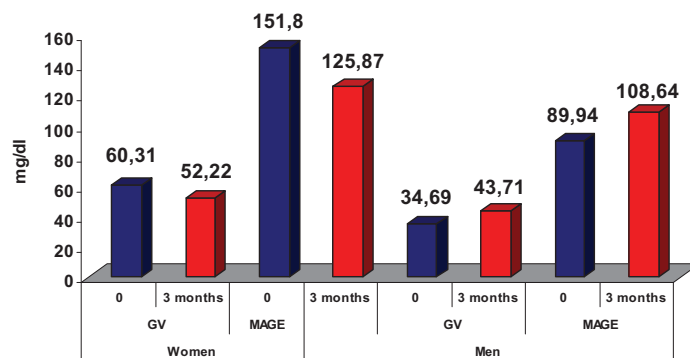


Figure 3. GV and MAGE in relation with gender, prospective approach.

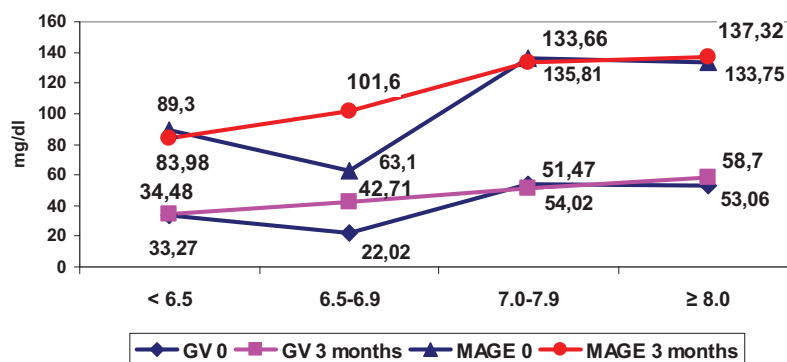


Figure 4. GV and MAGE in relation with A1C domains, prospective approach.

GV and MAGE were significantly higher in women with diabetes than in men with diabetes at first visit ($p < 0.01$, Mann-Whitney test). The differences were not significant at second visit ($p = 0.277$, $p = 0.247$, respectively) (Figure 3).

GV and MAGE were higher for A1C over 7.0% at both visits. The variation of GV and MAGE according to A1C categories was statistically significant at first visit ($p = 0.002$, $p = 0.005$, respectively) (Kruskall-Wallis test). The differences did not remain significant at second visit. ($p = 0.098$, $p = 0.199$, respectively) (Figure 4).

A1C decreased significantly from 8.56 ± 1.27 % to 7.4 ± 1.09 % (mean \pm SD) ($p = 0.003$, Wilcoxon test) after 3 months in the prospective study group (21 persons with diabetes) (Figure 5). GV and MAGE

decreased but not significantly at the second visit. GV decreased from 52.82 ± 14.37 mg/dl to 48.97 ± 17.91 mg/dl (mean \pm SD) ($p = 0.244$). MAGE decreased from 134.67 ± 40.08 mg/dl to 119.31 ± 49.79 mg/dl (mean \pm SD) ($p = 0.106$) (Figures 6, 7).

In T1D subgroup, A1C decreased significantly from 8.26 ± 1.31 % to 7.35 ± 1.05 % (mean \pm SD) ($p = 0.031$) after 3 months in the prospective study group. GV and MAGE decreased but not significantly at the second visit. GV decreased from 58.48 ± 12.51 mg/dl to 54.31 ± 17.40 mg/dl (mean \pm SD) ($p = 0.311$). MAGE decreased from 148.29 ± 36.75 mg/dl to 131.18 ± 48.39 mg/dl (mean \pm SD) ($p = 0.152$).

In T2D subgroup, A1C decreased significantly from 9.04 ± 1.10 % to 7.49 ± 1.23 % (mean \pm SD) ($p = 0.036$) after 3 months in the prospective study group. GV and MAGE

decreased but not significantly at the second visit. GV decreased from 43.61 ± 12.85 mg/dl to 40.30 ± 16.08 mg/dl (mean \pm SD) ($p=0.575$).

MAGE decreased from 112.55 ± 37.03 mg/dl to 100.03 ± 48.81 mg/dl (mean \pm SD) ($p=0.484$).

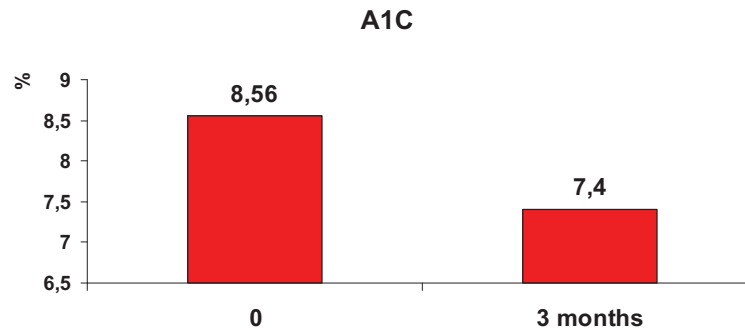


Figure 5. The prospective assessment of A1C in CGM study.

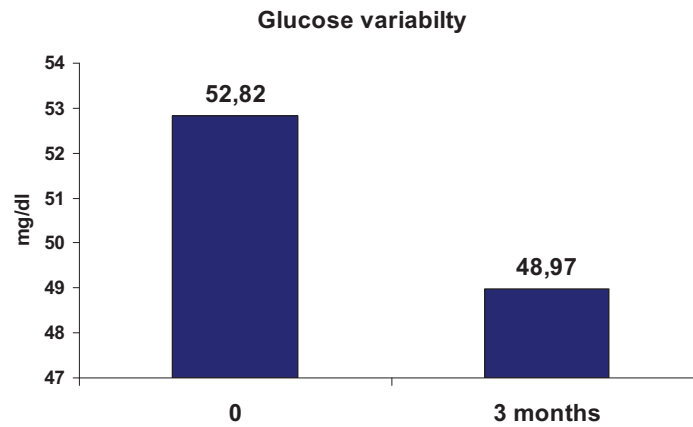


Figure 6. The prospective assessment of GV in CGM study.

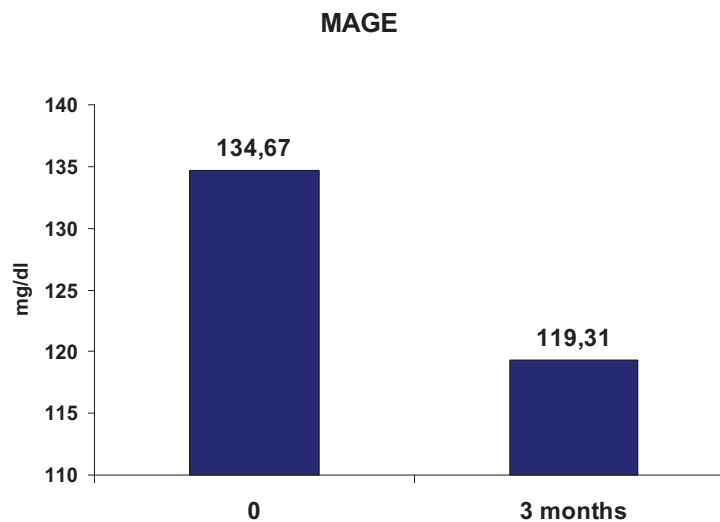


Figure 7. The prospective assessment of MAGE in CGM study.

A_{1c} was directly and significantly correlated with GV and MAGE both initially and after 3 months (Table 2).

Table 2. Correlation between A1C with GV and MAGE at initial and final CGM.

Correlation (Spearman test)	Visit 1 (initially)	Visit 2 (after 3 months)
GV - A1C	R= 0.433, p=0.011	R= 0.697, p=0.001
MAGE - A1C	R= 0.297, p=0.043	R= 0.579, p=0.012

Discussions

GV and MAGE, but not A1C, were significantly higher in T1D persons than in T2D persons before first CGM. The differences diminished and became nonsignificant after 3 months at second CGM. In accordance with our results, Bode et al. (2005) observed a higher glucose variability in persons with T1D, than in persons with T2D [5].

These results could be explained by identifying lack of proper treatment and applying precise therapeutic intervention after first CGM. Perhaps the visualization of continuous glucose profiles was one of the factors that generated therapeutic benefit by increasing patients' motivation toward adherence to therapy and more frequent use of selfmonitoring of blood glucose.

A1C, GV and MAGE were significantly higher in women at first CGM. The differences were not significant after 3 months, at second CGM. In T1D persons, A1C, GV and MAGE did not vary with gender, while in T2D persons GV and MAGE were significantly higher in women at first CGM.

GV and MAGE, but not A1C were significantly higher in insulin treated persons before first CGM. We could not verify the differences regarding these parameters after 3 months because all patients tested with the second CGM were insulin treated.

In our study we used A1C as indicator of long-term glucose control and an independent marker of glucose status for the 3 months prior to CGM. A1C decreased after 3 months from the first CGM for the whole group, but also for T1D and T2D subgroups. Many prior studies have showed similar results [6, 8-10, 12, 13, 17, 26-31].

GV and MAGE decreased nonsignificantly after 3 months from the first intervention. Weinzimer et al. (2008) obtained concordant and significant results for A1C and MAGE [32]. These preliminary data suggests the superiority of CGM systems in detecting and reducing glucose variability in persons with diabetes.

Many studies in the field showed results regarding the correlation between A1C and the mean glucose value of the interstitial glucose values recorded through CGM systems [33-35]. One of the hypotheses of our study was testing the relation between GV, MAGE and A1C, which were directly correlated. The greater was the disequilibrium in term of GV, the higher was A1c (hyperglycemia). These results need further larger and more powered studies for confirmation. A1C was correlated with chronic hyperglycemia, but not with GV and MAGE in the study of Kohnert et al. (2007) [36].

The principal limitation of the prospective study was the small number of persons that performed second CGM, which becomes even smaller when divided according to diabetes

type for specific subgroup analysis. Another limitation of the study was having no control group.

CGM detected and recorded real glucose excursions, confirmed by the patients' actions or unexplained. Based on glucose variations, we applied specific therapeutic changes and lifestyle reevaluation. An important improvement came from targeting the intervention on asymptomatic or so called "unexplained" glucose variations. Even if CGM cannot be yet largely used in clinical settings, it is an exceptional tool in research and could bring useful information in diabetes related diseases such sleep apnea, infections and also during exercise or in stressful situations. Its extended role could be as diabetes „Holter" monitor for glucose level, food intake, insulin doses and activities such as exercise.

Conclusions

Glucose variability could be evaluated more precisely by CGM, showing differences according to diabetes type, diabetes treatment and gender. Glucose fluctuations were directly related to long-term glucose status (A1C).

CGM showed more complete data regarding glucose status and determined patients' higher treatment adherence and implication in self-management. A1C, GV and MAGE decreased after three months, due to specific treatment adjustments based on CGM.

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