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Glucose variability and glycated hemoglobin HbA_{1c} in type 1 and type 2 diabetes

ABSTRACT

Introduction. The ultimate goal of diabetes therapy is to prevent chronic complications of the disease. HbA_{1c} level is closely related to the risk of development of micro- and macrovascular complications, however blood glucose variability (BGV) has emerged recently as yet another possible risk factor for vascular, particularly endothelial damage in diabetes. Continuous glucose monitoring systems (CGMS) are currently used for the BGV assessment, however due to their costs they are rarely utilised in daily clinical practice. The aim of the study was to assess BGV and its relationship with HbA_{1c} in patients with well (HbA_{1c} ~7%) and poorly (HbA_{1c} ~10%) controlled type 1 and type 2 diabetes.

Material and methods. 131 patients subdivided in 4 groups according to diabetes type and level of metabolic control were enrolled into the study. All patients underwent continuous glucose monitoring with the use of iPRO2 system (Medtronic).

Results. BGV was lower in type 2 than in type 1 diabetes patients. There was no statistically significant relationship between BGV and HbA_{1c} in well or poorly controlled patients with type 1 or type 2 diabetes. However, well controlled type 1 diabetes patients presented with greater degree of BGV than poorly controlled type 1 diabetes subjects.

Conclusions. HbA_{1c} does not reflect blood glucose variability as assessed with CGMS in type 1 or type 2 diabetes subjects. BGV is significantly greater in type 1 diabetes than in type 2 diabetes, therefore the use CGMS might be of particular benefit for the former group of patients, especially those with good glycemic control. (Clin Diabetol 2017; 6, 2: 48–56)

Key words: glycaemic variability, continuous glucose monitoring system, glycated haemoglobin HbA_{1c}

Introduction

In recent years, high blood glucose variability (BGV) has been documented to damage endothelial cells [1–6]. Glucose enters endothelial cells through the facilitated diffusion, proportionally to the plasma concentration. It is assumed that large fluctuations in plasma glucose and subsequently in availability of glucose as an energy substrate have a substantial effect on the intracellular energy metabolism. By affecting oxygen chain large plasma glucose sways may lead to the increased production of radical oxygen species. The first reports that glycaemic variability may affect

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Table 1. Patients characteristics

	DM 1 ~7%	DM 1 ~10%	DM 2 ~7%	DM 2 ~10%
Age (years)	40.1 ± 8.2	43.9 ± 9.1	62.4 ± 7.4	64.2 ± 6.8
Diabetes duration (years)	15.1 ± 10.7	13.1 ± 7.2	11.5 ± 5.8	17.0 ± 7.7
Body mass index [kg/m^2]	23.3 ± 3.3	26.2 ± 3.9	30.7 ± 5.2	33.0 ± 4.9
HbA_{1c} (%)	7.12 ± 0.56	10.0 ± 0.92	7.16 ± 0.54	10.3 ± 0.81

Data were provided as means ± standard deviations

the processes leading to the development of vascular complications were published in 2006. Monnier et al. have demonstrated that fluctuations in blood glucose cause the aggravation of oxidative stress in patients with type 2 diabetes [1]. The importance of glycaemic variability for the development of diabetic micro- and macro-angiopathy in different groups of patients has not been clearly established, yet there is an ongoing debate over the role of glycaemic fluctuations in chronic vascular damage in diabetes [3–6]. The assumption of influence of glycaemic variability on vascular complications risk is based on the fact that some patients with well-controlled diabetes still do develop chronic complications. High fluctuations of BGV are assumed to have been the damaging factor of the vasculature system in this group of patients. As a result, new antidiabetic agents are also assessed in regard to their effect on BGV [7].

In clinical practice glycated haemoglobin HbA_{1c} has been used for decades as an indicator of metabolic control in diabetes. BGV in daily practice is very difficult to assess as it should require the use of continuous glucose monitoring systems (CGMS). Moreover, it still is unclear how to interpret CGMS data in clinical care. We conducted a study aiming at assessing BGV in well and poorly controlled type 1 and type 2 diabetes, including the analysis of the relationship between BGV and HbA_{1c} as we hypothesized that HbA_{1c} may also carry the information on glycemic variability.

Patients

131 patients with type 1 or type 2 diabetes were enrolled into the study. They were subdivided in 4 groups according to the HbA_{1c} level assessed within 1 week before the study. The first group consisted of 30 patients with well controlled type 1 diabetes (HbA_{1c} ~7%; (6.0–8.0%; 16 women, 14 men), the second group comprised 32 patients with poorly cotrolled type 1 diabetes (HbA_{1c} ~10%; 9.0–11.0%; 18 women, 14 men), the third group consisted of 29 patients with well controlled type 2 diabetes (HbA_{1c} ~7%; 6.0–8.0%, 15 women, 14 men) and the fourth group were poorly controlled type 2 diabetes patients (HbA_{1c} ~10%; 9.0–11.0%, 20 women, 20 men). The mean age of the groups with one type of diabetes was similar. All patients with type 1 diabetes were treated with intensive insulin therapy, whilst the type 2 diabetes patients received oral medications or insulin (1–4 injections per day). Patient characteristics is presented in Table 1. All patients gave their written informed consent; the study protocol was approved of the Bioethics Committee of the Medical University of Lodz.

Methods

After giving written informed consent, all patients underwent full physical examination including detailed diabetes history and anthropometric measurements (height, weight for BMI calcuation). 2 mL of whole blood using a vacuum system (Becton Dickinson Vacutainer) to for HbA1c measurement (HPLC method, G-8, Horiba Medical) was drawn no sooner than one week before inclusion into the study.

All patients underwent continuous glucose monitoring with the use of Medtronic iPRO2 system. All the activities including CGMS application, patient education regarding its use, handling, and calibration were performed by one person (AB). All patients were given detailed instruction how to protect CGMS during daily activities (personal hygiene regimen, refraining from excessively intensive physical exercise).

The iPRO2 system was applied in the abdominal area for up to 5 days. Patients were instructed to record daily events the diary.

During the study all patients measured capillary glucose with a glucose meter at least 4 times a day — fasting, before each meal and before bedtime. The results were recorded in the diary. The participants also recorded the hours of meals, the duration of any exercise, any incidents affecting the fluctuations of glucose levels, e.g. emotional distress. Oral antidiabetic medication and insulin doses were also noted.

Upon completion of glucose monitoring the data were analysed with the use of Medtronic CareLink iPro software. In order to assess the clinical significance of differences between the glucose meter readings and iPro2 readings the Clarke error grid was applied.

For each of the patients, eight periods during each day were identified: sleep time, before and after breakfast, before and after lunch, before and after dinner and before bedtime. The amount of time spent by each patient during the operation of the CGMS during hyperglycaemia (when the glucose level was > 140 mg/dL), hypoglycaemia (< 70 mg/dL) and normoglycaemia (70–140 mg/dL) was also calculated. The average glucose levels of each period and the duration of hyper-, hypo and normoglycaemia were analysed in order to assess their variability and relationship to the level of HbA_{1c}. For each patient and each above mentioned period of the day the coefficient of BGV (CV, coefficient of variability, expressed in %) was calculated as the quotient of standard deviation (SD) and mean glucose.

The results were statistically analysed using the Statistica 9.1 software. Normality of the distribution was evaluated with Shapiro-Wilk's test. If it was confirmed, the student's T-test for independent samples was used to assess the differences between mean values. In other case the non-parametric U Mann-Whitney test was applied. The relationship between the continuous data was assessed with the Pearson correlation analysis. In order to identify HbA_{1c} determinants factors multiple regression model was used with HbA_{1c} as a dependent variable (HbA_{1c}) and mean blood glucose values of the day periods as independent variables. The assumed level of significance was $p < 0.05$.

Results

In all patients CGMS was used for mean (± SD) 5.1 ± 0.7 days, with mean number of glucose measurements 688 ± 206. The course of monitoring was uneventful, no side effects occurred during testing.

Table 2 shows minimum, maximum and mean blood glucose from previously defined day periods as well as throughout the whole day (24 hours), including the percentage time which patients spent in hyper-, normo- and hypoglycaemia. Table 3 and Figure 1 present mean CVs for day periods in each group of patients. Table 4 shows the results of the analysis of the correlation between the mean blood glucose and HbA_{1c}.

Multivariate analysis revealed no statistically significant relationship between the assessed glycemic parameters and HbA_{1c} in any group of patients.

The results may be summarised as follows:

1. BGV was lower in type 2 than in type 1 diabetes patients.
2. BGV was higher in the afternoon than in the morning in all studied groups.
3. No statistically significant differences in BGV between well or poorly controlled patients with both type 1 or type 2 diabetes was noted.
4. There was a trend towards higher BGV in the group of well controlled patients with type 1 diabetes (DM1 ~7%) than in the group with poorly controlled type 1 diabetes patients (DM ~10%), particularly before noon.
5. Except for patients with poorly controlled type 2 diabetes (HbA_{1c} ~10%) maximum blood glucose levels correlated with HbA_{1c} level in all other groups, especially before and after dinner.
6. In well controlled patients with type 1 and 2 diabetes (HbA_{1c} ~7%) the duration of hyperglycaemia showed positive correlation with HbA_{1c}, while the duration of normal blood glucose levels — a negative correlation. There was no relationship between the duration of hypoglycaemia and the level of HbA_{1c}.

The main result of the study is that the HbA_{1c} values in the diverse population of diabetes patients cannot be used to reliably assess BGV, even though some BGV parameters showed some relationship to HbA_{1c} level.

Table 2. The minimum, maximum and mean (± SD) blood glucose levels (mg/ml) in eight periods of the day, throughout the whole day and the duration (% of CGMS use time) hyperglycaemia, normo- or hypoglycaemia in the studied groups

		DM1 ~7%	DM1 ~10%	DM2 ~7%	DM2 ~10%
Before breakfast [mg/dL]	Minimum	99 ± 49	112 ± 59	102 ± 27	129 ± 53
	Maximum	199 ± 64	232 ± 82	148 ± 23	220 ± 64
	Mean	145 ± 51	171 ± 63	126 ± 21	177 ± 55
After breakfast [mg/dL]	Minimum	84 ± 31	132 ± 66	122 ± 31	160 ± 42
	Maximum	249 ± 59	282 ± 82	224 ± 46	296 ± 63
	Mean	137 ± 36	207 ± 68	173 ± 31	232 ± 50
Before lunch [mg/dL]	Minimum	83 ± 30	128 ± 49	113 ± 38	138 ± 47
	Maximum	209 ± 64	256 ± 74	200 ± 57	256 ± 73
	Mean	137 ± 36	192 ± 64	150 ± 39	191 ± 47
After lunch [mg/dL]	Minimum	80 ± 28	116 ± 51	107 ± 31	132 ± 48
	Maximum	228 ± 45	269 ± 76	204 ± 47	287 ± 66
	Mean	144 ± 26	193 ± 62	153 ± 35	206 ± 45
Before dinner [mg/dL]	Minimum	89 ± 40	126 ± 59	115 ± 32	132 ± 48
	Maximum	221 ± 65	255 ± 86	179 ± 51	261 ± 74
	Mean	151 ± 40	187 ± 62	145 ± 38	194 ± 48
After dinner [mg/dL]	Minimum	79 ± 32	126 ± 63	113 ± 33	135 ± 40
	Maximum	225 ± 59	261 ± 82	201 ± 60	272 ± 67
	Mean	142 ± 34	189 ± 64	154 ± 42	202 ± 46
Before bedtime [mg/dL]	Minimum	69 ± 25	92 ± 41	85 ± 29	110 ± 46
	Maximum	256 ± 61	274 ± 75	190 ± 44	259 ± 73
	Mean	146 ± 32	175 ± 52	130 ± 32	177 ± 58
During the night [mg/dL]	Minimum	74 ± 30	87 ± 34	87 ± 30	103 ± 46
	Maximum	220 ± 66	261 ± 81	161 ± 42	234 ± 73
	Mean	137 ± 37	166 ± 49	118 ± 25	164 ± 58
24-hour [mg/dL]	Minimum	56 ± 18	69 ± 23	73 ± 21	84 ± 35
	Maximum	297 ± 58	334 ± 64	244 ± 50	329 ± 54
	Mean	145 ± 25	181 ± 41	138 ± 24	187 ± 43
Duration of hyperglycaemia (%)		48 ± 18	66 ± 20	44 ± 21	77 ± 17
Duration of normoglycaemia (%)		45 ± 17	30 ± 18	53 ± 19	21 ± 15
Duration of hypoglycaemia (%)		6 ± 7	4 ± 8	3 ± 4	2 ± 4

Discussion

Hyperglycaemia is a primary factor that leads to vascular damage in diabetes. The existence of a close relationship between hyperglycaemia and vascular and peripheral nerve damage has been the subject of numerous studies and is well known [8, 9]. It has been repeatedly indicated that the improvement of the metabolic control of diabetes results in the reduction of a vascular risk [10]. There has been suggested that excessive blood glucose fluctuations may cause damage to blood vessels, particularly endothelium. An excess amounts of glucose entering endothelial cells cannot be metabolized in an adequately short time through glycolysis, hence additional metabolic pathways are stimulated which results in excessive free oxygen radicals production. When plasma glucose decreases

Table 3. CV of glycemia (%) in eight periods of the day and throughout the whole day in the four groups

	DM1 ~7%	DM1 ~10%	DM2 ~7%	DM2 ~10%
Before breakfast	21	24	13	17
After breakfast	29	24	17	16
Before dinner	29	20	17	18
After lunch	27	26	17	24
Before dinner	25	28	14	27
After dinner	29	27	16	20
Before bedtime	33	30	23	26
During the night	31	31	20	24
24-hour	31	26	19	24

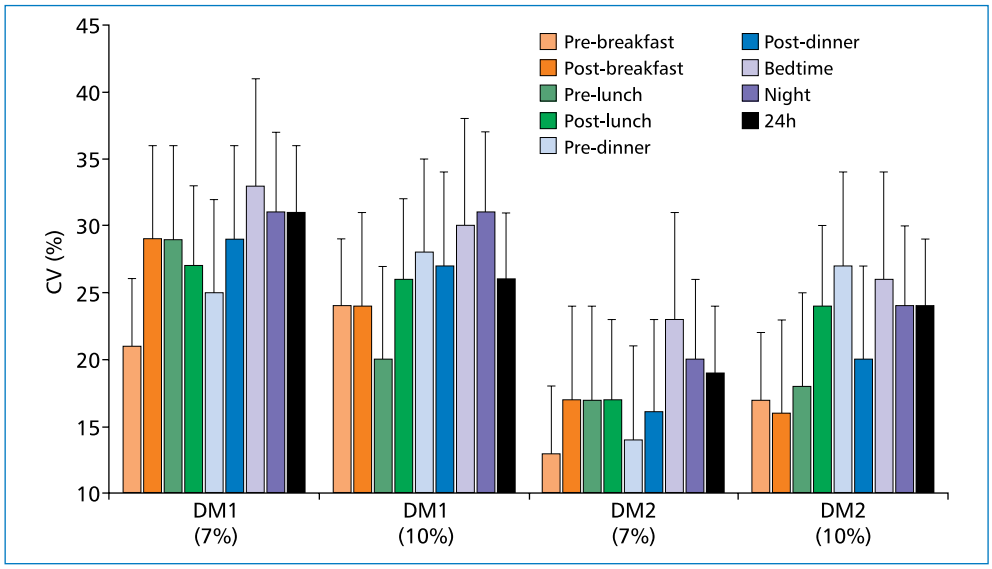

Figure 1. CV of glycemia in eight periods of the day and throughout the whole day in the four examined groups

abruptly, this decrease in energy supply may fully disrupt cell metabolism and lead to cell degeneration and death [11, 12].

So far no clear relationship between glycemic variability and vascular damage have been identified [1, 2, 13]. Excessive plasma glucose fluctuations have been shown to be realted to macrovascular [14] and microvascular [5] risk as well as no relationship has been found [2].

The development of vascular complications in patients with well controlled diabetes leads to further search for vascular risk factors. The detailed assessment of BGV is currently not a part of everyday clinical practice. Therefore our study aimed at establishing whether any evaluation of BGV can be done upon HbA_{1c} value. If this was the case (e.g. if a high level of HbA_{1c} was associated with high [or low?] BGV, and a low level of HbA_{1c} meant low [or high?] BGV), the evaluation of diabetes metabolic control through the determination of the HbA_{1c} level would be more comprehensive.

CGMS used in our study provides real-time glucose information through an electrochemical sensor

Table 4. Peason's coefficients between the maximum, minimum and mean blood glucose level, standard deviations of eight periods of the day, the duration of the hypoglycaemia, normo- or hyperglycaemia and HbA_{1c} level (statistically significant values marked in blue)

	DM1 7%	DM1 10%	DM2 7%	DM2 10%
Max. night	0.289779	0.411121	0.179016	0.239693
Max. before breakfast	0.265040	0.341790	0.267722	0.381177
Max. after breakfast	0.426080	0.329377	0.576561	0.272319
Max. before dinner	0.503000	0.561172	0.415126	0.118849
Max. after dinner	0.523838	0.370132	0.576649	–0.064071
Max. before supper	0.664822	0.360107	0.406620	0.156309
Max. after supper	0.422393	0.321253	0.499125	0.146374
Max. in the evening	0.301555	0.389863	0.322734	0.223538
Max. throughout the day	0.489122	0.462486	0.583488	0.086022
Min. night	0.056198	0.000889	0.238346	0.149493
Min. before breakfast	–0.049268	0.114721	0.254343	0.159676
Min. after breakfast	0.234859	0.165506	0.210364	0.138744
Min. before dinner	–0.002266	0.122599	0.092143	–0.120860
Min. after dinner	0.042091	0.294163	0.239383	–0.163170
Min. before supper	0.241083	0.124866	0.358387	–0.101845
Min. after supper	0.139712	0.125558	0.458660	0.082796
Min. in the evening	–0.127738	–0.075414	0.280448	0.229571
Min. throughout the day	0.087387	0.083812	0.133426	–0.020878
Avg. night	0.176385	0.409693	0.300551	0.244778
Avg. before breakfast	0.115925	0.368281	0.283042	0.337931
Avg. after breakfast	0.443558	0.286315	0.565651	0.293687
Avg. before dinner	0.434198	0.493254	0.293817	–0.008329
Avg. after dinner	0.567594	0.303749	0.457121	–0.149288
Avg. before supper	0.573716	0.307156	0.443711	0.059497
Avg. after supper	0.424509	0.337328	0.530325	0.173345
Avg. in the evening	0.225862	0.251279	0.341069	0.229275
Avg. throughout the day	0.451622	0.447336	0.508667	0.221875
SD night	0.238113	0.444849	0.011607	0.174327
SD before breakfast	0.262267	0.295751	–0.208800	0.299224
SD after breakfast	0.059678	0.209738	0.401105	0.270071
SD before dinner	0.479295	0.505465	0.373528	0.213319
SD after dinner	0.387226	0.257489	0.523784	0.116428
SD before supper	0.460057	0.285718	0.302557	0.177100
SD after supper	0.294833	0.164137	0.432855	0.098053
SD in the evening	0.298187	0.489170	0.096209	0.153714
SD throughout the day	0.389665	0.521016	0.440249	0.072343
The period of hiperglycaemia	0.589653	0.325036	0.476320	0.103344
The period of normoglycaemia	–0.648145	–0.395023	–0.462259	–0.070436
The period of hiperglycaemia	0.067420	0.171857	–0.214076	–0.169451

inserted in the subcutaneous tissue. The oxidation of glucose occurs in the presence of glucose oxidase; as a result, free electrons are produced. The sensor determines the parameters of their current, which are proportional to the concentration of blood glucose at the time of the measurement. The signal from the sensor is transmitted to the receiver every 5 minutes, thus 288 measurements a day are made. The sensor requires calibration, which involves the entering capillary glucose values as measured with the use of a glucose meter to be entered to CGMS at regular intervals (usually four times daily) [15].

Szymborska-Kajanek et al. studied the relationship between standard parameters of diabetes metabolic control and CGMS results and the clinical significance of the device itself. 17 patients with type 2 diabetes (10 women and 7 men, mean age of 62.9 ± 9.4 years, duration of insulin therapy 13.5 ± 6.0 years) were asked to use CGMS for 24 hours and a 4–5 point blood glucose profile was taken. The results showed a significant relationship between the standard parameters and the levels of blood glucose given by the CGMS system, confirming that CGMS may be useful in metabolic control evaluation [16].

Ryan et al. analyzed the use of CGMS in preventing severe hypoglycaemia in 16 patients with type 1 diabetes (mean age 52.0 ± 2.3 years, diabetes duration 29.4 ± 2.8 years, HbA_{1c} 8.4 ± 0.3%). The patients used the CGMS for 2 months and afterwards they were followed for for 3 months. The number of hypoglycaemia episodes (defined as blood glucose < 3.0 mmol/L) during CGMS use was significantly lower than during follw up period. The patients were also less afraid of hypoglycaemia as they were aware of the alarm function of the CGMS. 13 out of 16 patients decided to resume the use of CGMS after the study [17].

Guillod et al. analyzed the relationship between nocturnal hypoglycaemia and morning plasma glucose in 88 type 1 diabetes patients who used CGMS for 6–9 months. Nocturnal hypoglycaemia episodes were found in 67% patients, and half of these episodes went unnoticed by the patients. These incidents were not related — as previously thought — to the hyperglycaemia in the morning, but to morning hypoglycemia [18].

Nor suprisingly, in our study BGV was less pronounced in patients with type 2 diabetes than in patients with type 1diabetes. In type 1 diabetes, due to an absolute deficiency of insulin, patients take insulin several times a day, its absorption is affected by many factors and thus insulin action is of fluctuating character. In type 2 diabetes insulin secretion is long preserved, which makes the glycaemic profile much more stable.

Absence of statistically significant differences in BGV between the patients with the well and poorly controlled type 1 as well as type 2 diabetes was a more intriguing finding. Apparently, in general HbA_{1c} level is not related to the fluctuations of glycaemia. Similarly, Kohnert et al. demonstrated no relationship between the fluctuations of glycaemia and the level of HbA_{1c} in patients with the well-controlled diabetes [19].

We noted, however, a tendency for highest BGV in patients with the well-controlled type 1 diabetes (Fig. 1). This finding may at least partly explain the presence of vascular complications in subjects with well controlled diabetes. Therefore, the use of CGMS may be of particular clinical value in this group of patients.

In all groups a greater degree of BGV was observed in the evening than in the morning hours, and it is likely to a physiological phenomenon. Afternoon and evening hours is a period of greater variability of physical activity as well as eating habits. If, however, therapy of diabetes should aim at the reduction of BGV, this observation may be relevant to the time of drug administration etc. [20].

Additionally, we confirmed that HbA_{1c} level reflects rather higher than lower levels of glycaemia [21]. Maximum values of glycaemia, standard deviations as well as the duration of hyperglycaemia correlated best with HbA_{1c}, and lower HbA_{1c} levels were related to the longer duration of normoglycaemia. However, no relationship between HbA_{1c} and the duration of hypoglycaemia was found, but very short total duration of hypoglycemic episodes (2–6% of CGMS use time) in the studied patients is a likely explanation.

No significant relationship between the CGMS parameters and HbA_{1c} was found in poorly controlled type 2 diabetes. However, this group was heterogeneic

in terms of diabetes therapy, also in subjects with long standing diabetes glucose control is affected by many unaccounted for elements.

The study results however should be interpreted with caution as it has its limitations. The examined groups were small, HbA_{1c} levels taken for satisfactory and unsatisfactory metabolic control were adopted arbitrarily, and the BGV data were obtained from a single CGMS use lasting several days. The studies enrolling larger groups of patients as well as of longer duration of CGMS use would help determine the relationship between blood glucose variability and HbA_{1c} level more precisely.

In summary, the results of the study may lead to the following conclusions:

1. HbA_{1c} level does not reflect and is not related to the BGV in patients with well or poorly controlled type 1 or type 2 diabetes.
2. BGV is significantly greater in type 1 than in type 2 diabetes, therefore the use of CGMS might be of particular benefit for the former ones, especially those with good glycaemic control (see 3 below).
3. Patients with well controlled type 1 diabetes presented the highest BGV, which at least partly may explain the risk of developing vascular complications in this group of patients.
4. BGV is greater in the evening than in the morning in type 1 and type 2 diabetes.
5. HbA_{1c} value positively correlates with the duration of hyperglycaemia while inversely with the duration of normoglycaemia in type 1 and well controlled type 2 diabetes.

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