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THE USE OF CONTINUOUS GLUCOSE MONITORING SYSTEM IN COMBINATION WITH INDIVIDUALIZED LIFESTYLE AND THERAPEUTIC RECOMMANDATIONS ON GLYCEMIC CONTROL OF TYPE 2 DIABETES PATIENTS

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Abstract

Background and aims. *The aim of our research was to evaluate the impact of short-time continuous glucose monitoring (CGM) on glycemic control evaluated by HbA1c and within-day glucose variability. We also assessed if the initiation of insulin therapy in conjunction with lifestyle recommendations may prevent the weight gain.* ***Materials and method***. *We included 28 patients with type 2 diabetes with 2 consecutive CGMS recordings available (baseline and follow-up) and for which were collected data on weight, body mass index (BMI), percentage (%) of body fat, visceral fat area, HbA1c and glycemic variability.* ***Results***. *The HbA1c decreased significantly from 8.8% at baseline to 7.3% at follow-up (p <0.0001) in the whole group, and from 10.5% to 7.5% in the subgroup for which the insulin therapy was initiated at baseline (p=0.011). The BMI, % body fat and visceral fat area decreased significantly from 29.2 kg/m^2 to 28.4 kg/m^2; from 32.3% to 30.4%; and from 141.6 to 129.3 (cm^2), respectively. No increase of these parameters was observed in the subgroup for which the insulin therapy was initiated at baseline.* ***Conclusion***. *The use of CGMS in combination with individualized lifestyle and therapeutic recommendations may have a beneficial effect on glycemic control and may prevent the weight gain associated with insulin initiation.*

key words: *type 2 diabetes mellitus, glycemic control, CGMS, weight gain, insulin therapy*

Introduction

Landmark diabetes trials have shown that tight blood-glucose control can delay the progression of diabetic microvascular complication, but has limited effect on macrovascular complications. Additionally, it is widely accepted that tight glucose control and especially insulin therapy is associated with weight gain [1]. A meta-analysis published by Pontiroli et al including 46 clinical trials and 14,250 participants has shown that the initiation of insulin therapy is followed by an increase in body weight during the first year, ranging from 3.1 kg for basal regimens to 6.4 kg for prandial insulin regimens [2].

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Hyperglycemia, and its surrogate marker, glycated hemoglobin (HbA1c), are used to estimate the risk of developing diabetic complications, to define the targets and measure the efficacy of diabetes treatments. The current guidelines have established targets for fasting and post-prandial glucose values and for HbA1c [3]. But fasting glucose and/or HbA1c levels cannot entirely explain the risk of complications and cardiovascular death associated with diabetes. The role of glucose variability in the development of microvascular complications was initially suggested by the analysis of the Diabetes Control and Complications Trial (DCCT) data [4]. Subsequently, it has been postulated that blood glucose instability, through oxidative stress and free radical production, activate vascular damage and may contribute, perhaps even more than HbA1c, to the development of diabetes complications [5-8]. A systematic review of clinical studies has shown that, in patients with type 2 diabetes, glucose variability, regardless of HbA1c values, may represent a predictor for diabetic retinopathy, cardiovascular events and mortality [9].

The concept of glycemic variability is heterogeneous [10]. A number of concepts have been proposed for glycemic variability: between-day fasting glycemic variability, postprandial glycemia peaks, HbA1c variability over time, hypoglycemic episodes or, the most common, within-day glucose variability, evaluated by self-monitoring or continuous glucose monitoring using a continuous glucose monitoring system (CGMS). No golden standard has been established for glycemic variability evaluation. Several tens of different indices for glycemic variability quantification have been proposed, but many of them provide similar information. Recently, Fabris et al showed that a subset of up to 10 different glucose variability indices may be sufficient to describe more than 60% of the variance originally explained by 25 indices selected for evaluation [11].

During the past years new technologies for glucose monitoring have emerged. Glucose levels from interstitial fluid can accurately be measured at every 5 minutes using a disposable glucose sensor which is approved for 3–5 days of use. CGMS provides information about the direction, magnitude, duration, frequency and causes of fluctuations in blood glucose levels [12]. The professional CGMS has some advantages: there is no feedback to the user so that no immediate regimen changes can be made and there are no alarms to warn of hyperglycemia or hypoglycemia (because for the majority of the patients these were very annoying).

The aim of the present analysis was to evaluate the impact of short-time professional CGMS on glycemic control as evaluated by HbA1c and within-day glucose variability. As a second objective, we aimed to investigate if insulin treatment initiated in conjunction with lifestyle recommendations has any impact on body weight and body fat and to assess the relationship between the changes in these later parameters and the therapeutic effect on glycemic control and glycemic variability.

Material and methods

Study design and study patients

In this retrospective observational study performed in an outpatient clinic form Cluj-Napoca, Romania, we enrolled patients with type 2 diabetes who had 2 consecutive CGMS recordings available. As this was not an interventional study, the time period between the 2 CGMS testing was not pre-set and the time period was decided by the doctor together with the patient, ranging from 3 to 6 months. The CGMS recordings were downloaded from our clinic´s database stored on iPRO (Medtronic)

Carelink site and the patients´ data were collected from their medical charts. All patients received at baseline lifestyle recommendations according to the anthropometric evaluation and medical status of the patient.

Evaluated parameters

The following data, recorded on the day of each sensor insertion, were collected from the charts: age, sex, weight, height, body mass index (BMI), diabetes treatment, percentage (%) of body fat, visceral fat area, and HbA1c. As per institutions` laboratory procedures, HbA1c levels were measured by high-performance liquid chromatography at the first and the second CGMS recording, and one year after first recording. Additionally, during the first and the second CGMS recording, patients were asked to fill-in a qualitative food diary.

The CGMS recordings were performed using the iPRO^{TM} device (*Medtronic*, Northridge, CA) over a 3-5 day interval, in a blinded manner. The iPRO was placed on and removed from the patient by a trained member of the medical staff, in abdominal area, left or right part, depending on patient preferences, in recumbent position, at distance from the sites used for insulin injection (although recent data support the idea that insulin infusion near sensor insertion do not influence glycemic values [13]). The CGMS recordings were downloaded and were delivered to the treating physician within the day of removal of the device. Between the 2 CGMS recordings, patients were managed by their doctors according to the individual preferences, which typically involved office follow-ups at 1-3 months intervals.

The parameters of glycemic variability were calculated with Glyculator, using glycemic values recorded by the iPRO device during the first 24 hours of full recording (288 glucose values – between 00:00 and 23:59 of the day following the day of the device insertion) [14]. We did not use the values recorded immediately after the insertion because current sensors are generally less accurate during this time period due to local tissue inflammation following tissue trauma associated with sensor insertion [15].

The glycemic variability indices assessed on CGM readings were [14]:

Mean level of 24h interstitial glucose value (MG) and standard deviation (SD) - an index of the dispersion of data around mean blood glucose.

Percentage coefficient of variation (%CV) is the ratio of SD of the glucose values to mean of the glucose values. This parameter describes the magnitude sample values and the variation within them.

M100-weighted average of glucose values; provides a measure of stability of glycemia in comparison with an arbitrary assigned glucose value, initially set to 100 mg/dl.

Mean amplitude of glycemic excursion (MAGE) - calculated based on mean of differences between consecutive glucose values picks and nadirs, only for differences greater than SD. The small variations are excluded. MAGE provides a measure of intra-day, high amplitude, glucose variability.

Fractal Dimension (FD) - an experimental method based on the works of Higuchi and adapted by the authors of Glyculator [14] that describes glucose variability of high frequency and small amplitude.

Continuous overall net glycemic action (CONGA) at 1, 2, 4 and 6 hours (CONGA -1, -2, -4, -6) - shows glycemic variability within a predetermined time window. It is an indicator of within-day glucose variability.

Percent of body fat and visceral fat area were measured by bioelectric impedance, using InBody (720) (Biospace, Korea). This is a multifrequency impedance plethysmograph body

composition analyzer, which takes readings from the body using an eight-point tactile electrode method, measuring resistance at five specific frequencies (1 kHz, 50 kHz, 250 kHz, 500 kHz, and 1 MHz) and reactance at three specific frequencies (5 kHz, 50 kHz, and 250 kHz) which were pre-set by the manufacturer to assess extracellular fluid and total body water and introduced into the body in ascending order of frequency. VFA are automatically determined when the patient stands on the electrodes embedded within the scale platform of each octapolar analyzer. The % body fat is computed through the proprietary algorithms, displayed on the analyzer's control panel, and recorded.

Statistical analysis

Statistical analysis was carried out using SPSS-PC 15.0 software (SPSS Inc., Chicago, IL, USA). Distribution of variables was tested with Kolmogorov-Smirnov test. Statistical data is presented as mean ± standard deviation (SD) for normally-distributed variables, median (1st quartile; 3rd quartile) for variables with abnormal distribution and percentage for categorical variables. Student t-test was used to compare variables with normal distribution, and Mann-Whitney U test for variables with abnormal distribution. The correlation between HbA1c, parameters evaluating glycemic variability, % body fat and visceral fat area was assessed by Spearman correlation coefficient. The level of significance was set at 0.05.

Results

Baseline characteristics of the patients included in the analysis

We included in our analysis 28 patients with type 2 diabetes who had 2 consecutive CGMS recordings available. Patients' characteristics at baseline (first evaluation) are displayed in Table 1. At the initial CGMS evaluation 11 (39.3%) patients were treated with insulin, 8 (28.6%) with metformin as monotherapy or in combination with other oral anti-diabetic drugs, 1 (3.6%) with a GLP-1 analogue, and 8 (28.6%) were on diet alone. After the evaluation, the insulin therapy was stopped in 2 patients and was initiated in 6 patients receiving other types of hypoglycemiant treatment. At the date of the second CGMS recording 15 (53.6%) patients were treated with insulin, 9 (32.2%) with metformin as monotherapy or in combination with other oral anti-diabetic drugs, 3 (10.8%) with a GLP-1 analogue, and 1 (3.6%) was on diet alone.

Table 1. The baseline characteristics of patients included in the analysis.

Parameter	CGMS group N=28
Age, years	55.7±5.8
Women, n (%)	12 (42.9)
BMI, kg/m^2	29.2±5.8
Diabetes therapy	
Diet, n (%)	8 (28.6)
Oral hypoglycemiants, n (%)	8 (28.6)
GLP-1 agonists, n (%)	1 (3.6)
Insulin, n (%)	11 (39.3)

BMI, body mass index; GLP-1, glucagon like peptide-1 analogues; N/n,number; %, percentage

Glycemic control and glycemic variability

In the CGMS group included in the analysis, HbA1c had a statistically significant decrease from 9.8% before the initial CGMS to 7.3% after the second CGMS ($p<0.0001$).

At both timepoints and for each patient we analyzed 288 glycemic values recorded during the CGMS. The mean glucose values and the SD decreased significantly from 183.9±36.3 mg/dl at baseline to 132.1±24.5 mg/dl at the time of the second CGMS evaluation (follow-up). A similar significant decrease was observed for MAGE, M100, CONGA-1, CONGA-2, CONGA-4 and CONGA-6 (Table 2). The parameters evaluating the small amplitude glycemic excursions (%CV and FD) were not significantly changed during the observation period ($p >0.05$) for both.

Table 2. Glycemic control and glycemic variability parameters.

Parameter	Total		
	Baseline CGMS N=2	Follow-up (2nd CGMS) N=28	p-value
HbA1c (%)	9.8±2.1	7.3±1.1	<0.0001
Mean glucose values (mg/dl)	183.9 (136.4; 238.9)	132.1 (115.5; 175.3)	0.007
SD (mg/dl)	36.3 (25.6; 52.2)	24.5 (20.1; 35.8)	0.001
%CV	21.8 (15.5; 28.8)	18.4 (14.9; 21.1)	0.104
M100	25.2 (7.1; 62.6)	3.7 (1.9; 21.1)	0.005
FD	1.1 (1.0; 1.1)	1.1 (1.0; 1.1)	0.417
MAGE	107.7 (78.4; 148.7)	79.9 (59.0; 103.3)	0.002
CONGA-1	27.7 (19.3; 36.8)	23.7 (20.0; 27.1)	0.014
CONGA-2	41.3 (27.6; 57.8)	32.6 (27.7; 39.1)	0.007
CONGA-4	43.0 (33.3; 69.9)	39.1 (31.9; 48.6)	0.010
CONGA-6	44.4 (33.2; 72.3)	35.9 (27.4; 48.7)	0.016

CGMS - continuous glucose monitoring system; HbA1c - glycated hemoglobin; SD - standard deviation; %CV - percentage coefficient of variation; M100 - weighted average of glucose values; FD - fractal dimension; MAGE -mean amplitude of glucose excursions; CONGA-1, -2, -4,-6 - continuous overall net glycemic action at 1, 2, 4 and 6 hours.

Table 3. Correlations between HbA1c and mean glucose values recorded during the CGMS.

	Baseline CGMS		Follow-up (2nd CGMS)	
	ρ	p	ρ	p
Mean glucose values (mg/dl)	0.894	<0.001	0.242	0.223
SD (mg/dl)	0.540	0.003	0.557	0.003
%CV	-0.143	0.467	0.417	0.030
M100	0.891	<0.001	0.521	0.005
FD	-0.149	0.451	-0.277	0.162
MAGE	0.506	0.006	0.554	0.003
CONGA1h	0.437	0.020	0.330	0.093
CONGA2h	0.464	0.013	0.343	0.006
CONGA4h	0.461	0.013	0.484	0.011
CONGA6h	0.447	0.017	0.636	<0.001

CGMS - continuous glucose monitoring system; HbA1c - glycated hemoglobin; SD - standard deviation; %CV - percentage coefficient of variation; M100 - weighted average of glucose values; FD - fractal dimension; MAGE - mean amplitude of glucose excursions; CONGA-1, -2, -4,-6 - continuous overall net glycemic action at 1, 2, 4 and 6 hours; ρ – Spearman's coefficient of correlation

The most impressive decrease in HbA1c was observed in patients from CGMS group for whom insulin therapy was initiated after the baseline evaluation: from 10.4% at baseline to 7.7% at follow-up (p=0.009). In this subgroup, the following parameters related to glycemic variability decreased significantly at follow-up compared to baseline: mean level of 24 h interstitial glucose value 126.2 mg/dl vs. 268.5 mg/dl (p = 0.021); and M100 5.4 vs. 86.1 (p = 0.026). The values of the other parameters were not statistically different at follow-up compared with baseline: SD 27.2 mg/dl vs. 46.3 mg/dl; MAGE 82.9 mg/dl vs. 127.8 mg/dl; CONGA-1 23.1 vs. 28.3; CONGA-2 31.6 vs. 41. 6; COGA-4 41.5 vs. 50.3; CONGA-6 41.6 vs. 54.9; %CV 19.2 vs. 16.9; FD 1.05 vs. 1.04 (p >0.05 for all).

Correlations between HbA1c and mean glucose values recorded during the CGMS are depicted in Table 3. The HbA1c values at baseline were significantly correlated with the mean glucose values, SD, M100, MAGE and CONGA calculated for the first CGMS. HbA1C recorded at the second time point did not correlate with mean glucose values, but correlated with SD, %CV, M100, MAGE and CONGA calculated for the second CGMS.

Body weight, percent body fat and visceral fat area changes

The body weight, BMI, % body fat and visceral fat area decreased significantly during the follow-up ($p<0.05$ for all parameters) as shown in Table 4. Because the initiation of insulin treatment is usually associated with weight gain, we analyzed the parameters related to body composition separately for the subgroup of 6 patients with insulin therapy initiated at baseline. For this subgroup no significant changes were observed in the BMI between the 2 timepoints. The % body fat and visceral fat area decreased also non-significantly from 31.3 to 29.6% and from 111.4 to 104.1 cm^2, respectively.

Table 4. Body weight, percent body fat and visceral fat area at baseline and follow-up.

Parameter	Baseline	Follow-up	p-value
Whole CGMS group			
Weight (kg)	85.1±20.5	82.6±19.5	0.008
BMI (kg/m^2)	29.2±5.8	28.4±5.7	0.005
Percentage of body fat (%)	32.3±9.1	30.4±9.1	0.024
Visceral fat area (cm^2)	141.6±50.1	129.3±44.5	0.006
Subgroup with insulin treatment initiated at baseline			
Weight (kg)	73.3±9.8	72.8±11.1	0.003
BMI (kg/m^2)	26.4±1.1	26.2±3.2	0.739
Percentage of body fat (%)	31.3±9.6	29.6±7.1	0.316
Visceral fat area (cm^2)	111.4±27.3	104.1±21.2	0.361

CGMS - continuous glucose monitoring system; BMI - body mass index; % percentage

We did not observe any correlations between the parameters describing the glycemic control at follow-up and the% body fat, visceral fat area or the changes of these 2 parameters in the whole group or in the sub-group with insulin therapy initiated at baseline ($p >0.005$ for all correlations; data not shown).

Discussions

The role of using professional CGMS in the clinical setting of an office practice in order to influence the value of HbA1c is controversial. In our analysis we have shown that the CGMS monitoring used in conjunction with lifestyle recommendations was associated with improved glycemic control (as evaluated by HbA1c and mean glucose values) and glycemic variability. Except for the parameters evaluating the small amplitude glycemic excursions (%CV and FD), all other parameters were improved after the first CGMS insertion, probably due to the life style optimization and the adequate pharmacological recommendation.

The role of CGMS in improving the glycemic control of patients with type 1 and type 2 diabetes is controversial. A meta-analysis including 5 trials and 131 type 1 diabetic patients showed that CGMS use did not reduce significantly HbA1c levels as compared with self-monitoring of blood-glucose and increased the number of changes of insulin doses changes per patient [16]. Another meta-analysis of 7 randomized controlled trials comparing CGMS and SBGM in patients with type 1 diabetes showed that when compared with self-blood finger-stick glucose monitoring, CGMS was associated with a non-significant reduction in HBA1c (0.22%; 95% CI: -0.439%; 0.004%, p=0.055) [17]. In a study enrolling 102 consecutive patients with type 1 or type 2 diabetes showed no improvement of HbA1c at 7 months after the CGMS procedure (7.7 ± 1.0% vs 7.8±1.1%) [18]. However, more recent randomized controlled trials demonstrated that real time-CGM use lowered HbA1c levels and time spent with blood sugar levels in the

hypoglycemia range in adults and children with good baseline blood sugar control and was associated with reduced rates of hypoglycemia in both adults and children [18-20]. In a case-control study with 52 participants with type 2 diabetes (non-insulin requiring, sedentary lifestyle), the use of CGMS to clearly depict glucose reductions in response to physical activity was accompanied by a significant increase in physical activity and a significant decrease of HbA1c and BMI after 8 months [19]. We think that the reduction of HbA1c observed in our study was due to the fact that the CGMS findings helped the physician to choose the most appropriate pharmacological antidiabetic agent for either postprandial picks or "a plateau" hyperglycemia. Additionally, the use of a food diary during the CGMS recording enabled both physicians and patients to identify foods and drinks which increased glycemic values and to adapt the treatment and lifestyle recommendations.

Previously it has been shown that HbA1c values correlate with mean glucose values recorded during the CGMS. Thus, in a 12-weeks longitudinal study by Nathan et al. enrolling 22 patients with type 1, type 2 diabetes and 3 non-diabetic participants, mean HbA1c levels at weeks 8 and 12 correlated strongly with the CGMS results [21]. A multicenter Chinese study enrolling 742 participants (with no diabetes, prediabetes or newly diagnosed type 2 diabetes) showed a strong correlation between the level of HbA1c and the mean blood glucose values registered by CGMS [22]. In our study, we observed a correlation between the HbA1c values and the mean glycemic values recorded by CGMS only at baseline. A possible explanation for these results may a "Big Brother" phenomenon that occurred during the second CGMS recording: the patient already knew that all glycemic values were recorded and his adherence to lifestyle recommendations were increased during the follow-up CGMS.

The individualized lifestyle recommendations probably can explain the significant decrease in weight, BMI, % body fat and visceral fat area observed in our study. The lack of association between the HbA1c, the parameters describing the glucose variability and the changes of the body weight and body composition support the hypothesis that the improvement in glycemic control in our study was independent of the changes in the body weight and body composition, and was mainly linked to the changes in the diabetes treatment and lifestyle recommendations. The most important finding in our study was the decrease in the body weight in patients for which the insulin was initiated after the baseline CGMS. It is widely accepted that the initiation of insulin therapy is associated with weight gain and this weight gain in already obese patients may represent a barrier for insulin initiation and may be associated with an adverse effect on the cardiovascular risk profile [23]. In the UKPDS, weight gain was significantly higher in patients assigned to insulin therapy than in those assigned to other therapies (4.0 kg vs. 1.7-2.6) [24]. Several mechanisms have been proposed to explain this change in the body weight: the anabolic effects of insulin, decreased glycosuria linked to improved glycemic control, decreased metabolic rate, aggressive treatment of hypoglycemia and eating to prevent hypoglycemia [25-27]. Our results showed that with the appropriate lifestyle recommendations the weight gain after the insulin initiation can be avoided in patients well motivated. It should be noted that our patients were followed for a maximum of 12 months. Previous studies have shown that the weight gain occurs during the first 3 years following the insulin initiation. Therefore, due to the limited follow-up of our

patients, we cannot conclude on the possibility to avoid the weight gain on a long term basis.

Our study has some limitations resulting mainly from its retrospective design. The main limitation is the lack of control group evaluated by intermittent self-blood finger-stick glucose monitoring. The presence of this group would have allowed the evaluation of the CGMS effect on the reduction of HbA1c.

Conclusion

In conclusion, the use of short-term CGMS in clinical practice and the individualized lifestyle and therapeutic recommendations based on these recordings have a beneficial effect on glycemic control and body weight of diabetic patients. Furthermore, they may prevent the weight gain associated with insulin initiation.

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