PREVALENCE AND EXTENT OF GLYCEMIC EXCURSIONS IN WELL-CONTROLLED PATIENTS WITH TYPE 2 DIABETES MELLITUS USING CONTINUOUS GLUCOSE-MONITORING SYSTEM

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ABSTRACT

BACKGROUND: *Continuous glucose-monitoring system (CGMS) is a tool for assessment of glycemic excursions. Glucose variability is a risk factor independent of glycosylated hemoglobin (HbA1c) for diabetic complications; hence CGMS may be a better method for management of diabetes.* ***AIM:*** *To evaluate the extent of glycemic excursions in well-controlled type 2 diabetic patients.* ***SETTING AND DESIGN:*** *The study was carried out in 21 diabetic patients on oral agents.* ***MATERIALS AND METHODS:*** *Patients underwent continuous glucose-monitoring by CGMS for 3 days. Number and duration of glycemic excursions, correlation coefficient (%) between CGMS and self-monitoring blood glucose (SMBG), mean absolute difference (%MAD) and complications of CGMS were analyzed.* ***STATISTICAL ANALYSES:*** *The statistical analyses were performed with the use of mean ± SD, t-test and Mann-Whitney test.* ***RESULTS:*** *The mean age of patients was 51.9 ± 9.7 years. The mean HbA1c was 6.7 ± 0.38%. The mean number of glycemic readings was 753.6 ± 203.5 times. The correlation coefficient was 0.83 and the MAD was 11.7 ± 8.0%, which were considerable. Three (14.2%) patients experienced, altogether, 9 hypoglycemic events with an average duration of 162 minutes. Twenty (94.7%) patients had hyperglycemic events. The mean duration of hyperglycemia was 19.4 ± 12.8 hours. All events were asymptomatic. Disconnection of device was the most common complication (3 patients).* ***CONCLUSION:*** *This study demonstrated that well-controlled type 2 diabetic patients have a considerable number of hypoglycemia and hyperglycemia events that may be missed by SMBG.*

Key words: *Continuous glucose-monitoring system, hyperglycemia, hypoglycemia, self-monitoring blood glucose, type 2 diabetes*

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INTRODUCTION

The benefits of intensive management of diabetes in prevention of chronic complications have been established.[1] Frequent self-monitoring of blood glucose (SMBG) and glycosylated hemoglobin (HbA1c) offered the possibility of control of glycemia, but HbA1c is a measure for prediction of average glycemia; and despite an ideal HbA1c, several events of glycemia may occur.[2,3] SMBG is a partial and incomplete picture of blood glucose excursions.[4,5] Hypoglycemia, especially

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nocturnal hypoglycemia, is the most prevalent complication in the tight control of diabetes that is usually not detected by SMBG.[6] In addition, postprandial hyperglycemia may occur even in well-controlled type 2 diabetic patients.[7] The role of postprandial hyperglycemia in the pathogenesis of diabetic complications has been confirmed,[8,9] which is usually neglected in patients who are managed by SMBG. The continuous glucose-monitoring system (CGMS) allows identification of glucose excursions. The aim of this study was to determine the prevalence and extent of unrecognized hypoglycemia and hyperglycemia in well-controlled diabetic patients.

MATERIALS AND METHODS

The CGMS system

The sensor of CGMS is inserted subcutaneously into the tissue of anterior abdomen wall in all patients.[10] All sensors are inserted by one person. The difference in plasma and interstitial fluid glucose was estimated to be <6%.[11] This system helps to identify periods of significant glycemic excursions and allows physicians to suggest specific changes in the timing and dosage of drugs or changes in timing and frequency of blood glucose measurement or in dietary regimes of patients.[12] The accuracy of CGMS sensor was based on its correlation with SMBG by Pearson correlation during hypoglycemia and hyperglycemic events, with significant *P* values <0.05.

Patient selection

Twenty-four type 2 diabetic patients were recruited from among the outpatients. We had a limitation on the sample size because the sensor of CGMS was very expensive; hence we selected a convenient sample size. Patients were eligible for enrollment in the study if they met the following inclusion criteria: diagnosis of type 2 diabetes, oral agent treatment for control of diabetes, an HbA1C less than 7% and fasting blood sugar less than 130 mg/dL. It seems that diabetes was well controlled in these patients. The patients were maintained on the diet prescribed by the dietitian, which included isocaloric or hypocaloric diet depending on whether the body mass index (BMI) was <25 or >25 kg/m^2. This diet contained 45% to 50% of carbohydrates, 30% to 35% of fats and 15% to 20% of proteins. The main exclusion criteria included the following: patients with history of insulin treatment, renal failure, liver dysfunction; and those using concomitant drugs that cause hyperglycemia or hypoglycemia. The patients were divided into 2 groups: one group comprising of patients on sulfonylurea or glinids treatment; and the other group comprising of patients on metformin therapy only.

Study protocol: The study was a pilot, descriptive, open-label, non-interventional study. All patients gave informed voluntary consent, and the protocol was approved by the local ethics committee in accordance with the ethical standards of Helsinki Declaration. Patients that satisfied inclusion criteria received intensive training for duration of approximately 1 hour in the use of CGMS. A sensor was then inserted into the abdomen in the subcutaneous tissue. Each patient was asked to record 4 capillary glucose measurements, which were taken each day by using an AcuuCheck glucometer that was provided by us, and then capillary values were entered into the monitor

for calibration. Also, it was mandatory for all patients to record their dietary programs, the time of all meals, the quality and quantity of meals and the time and duration of any exercise. The timings of meals and drug usage and exercise were entered into the device by the patients. Each patient was asked to refer back to us in 72 hours for disconnection of sensor and download of the data using the Medtronic MiniMed software. We defined a biochemical hypoglycemic event as a glucose value less than 50 mg/dL with or without symptoms. Postprandial hyperglycemia was defined as a value more than 140 mg/dL, 2 hours after the start of meal. We counted the number of glucose periods with a glucose value less than 50 mg/dL and their duration, as well as prolonged periods with a glucose value more than 140 mg/dL postprandial. The correlation coefficient and mean absolute difference (MAD) were calculated by Medtronic software and defined as >0.79 and <28%, respectively, optimal. The MAD was determined by the average value of differences between sensor glucose values and blood glucose values in percentage.

Statistical analyses

All statistical analyses were performed using the SPSS (statistical package for the social sciences, version 14, SPSS Inc., Chicago, USA) software. Normally distributed quantitative variables were demonstrated as mean ± standard deviation; and for values which were not normally distributed, median and the interquartile range were used. For comparison of quantitative variables, the independent *t* test and Mann-Whitney test were utilized. Pearson correlation was used to compare sensor readings with SMBG results.

RESULTS

Twenty-four patients with type 2 diabetes mellitus participated in this study. In 3 patients, CGMS was disconnected and they were excluded from the study. The baseline characteristics of 21 patients are shown in Table 1. The mean number of glucose readings by CGMS during the 72 hours was 753.6 ± 203.5 in each patient. This number (86.7%) was in the normal range (normal, greater than 80%). The correlation coefficient between SMBG and CGMS was 0.83 (normal, greater than 0.79). The mean value of MAD was 11.7 ± 8.0% (normal, less than 28%). The mean glucose values were as follows: 125.6 ± 20.5 mg/dL in fasting state; 156.6 ± 54.1 mg/dL, 2 hours post-breakfast; 141.8 ± 24.6 mg/dL, 2 hours post-lunch; 135.0 ± 25.9 mg/dL, 2 hours post-dinner. During the study, 3 (14.2%) patients experienced a total of 9 hypoglycemic events with average duration of 162 minutes (range, 45-378 min). Seven (77.8%) of the hypoglycemic events occurred between 10 pm and 4 am. All the events were asymptomatic. We divided the patients into 2 groups: group I, comprising of patients whose treatment regimens included only metformin; and group II, comprising of patients who

Table 1: Clinical and biochemical data of the study population

Age (years)	51.04±9.7
12(57.1%) male, 9(42.9%) female	Sex (number, %)
Duration of diabetes (month)	24.0(24-60)*
Body mass index (kg/m2)	26.9±2.7
Systolic blood pressure(mm Hg)	123.5±14.3
Diastolic blood pressure(mm Hg)	77.1±8.7
HbA1C (%)	6.7±0.38
Fasting blood sugar(mg/dl)	115.6±10.5
Ischemic heart disease (number, %)	9 (19%)
Retinopathy (number, %)	1(4.8%)
Albuminuria (number, %)	2(9.5%)

*Median with (interquartile)

received sulfonylurea or meglitinids in their treatment regimen. No significant difference was found between the 2 groups in duration (P = 0.08, df = 19) and the number of hypoglycemia events (P = 0.11, df = 19). Another important observation in this study was the detection of postprandial hyperglycemia. Twenty (94.7%) patients had hyperglycemic events. Mostly, these events occurred after breakfast. The mean number of hyperglycemic events was 8.8 ± 4.5 times in each patient with a mean duration of 19.4 ± 12.8 hours (minimum, 35 minutes; and maximum, 303 minutes). No significant difference was found in frequency (P = 0.92 with df = 19, mean difference = 0.24, 95%CI = -4.9 to 5.4) and duration of hyperglycemia (P = .83 with df = 19, mean difference = -1.2, 95% CI = -13.8 to 11.3) between the 2 groups. The characteristics of patients according to groups are shown in Table 2. A typical 24-hour sensor tracing of a patient with metformin treatment and a tracing of a patient on glibenclamide therapy are shown in Figures 1, 2, respectively. We analyzed all complications during sensor implantation (bleeding, pain) and during the exam (local infection, disconnection [technical problem]). Disconnection was the most common complication in 3 (12.5%) of the patients. No trauma, local infection, allergy, bleeding or other complications were observed in our patients. All patients (with the exclusion of the patients in whom the device got disconnected) completed the CGMS integrity.

DISCUSSION

The main finding was the high frequency of postprandial hyperglycemia in well-controlled

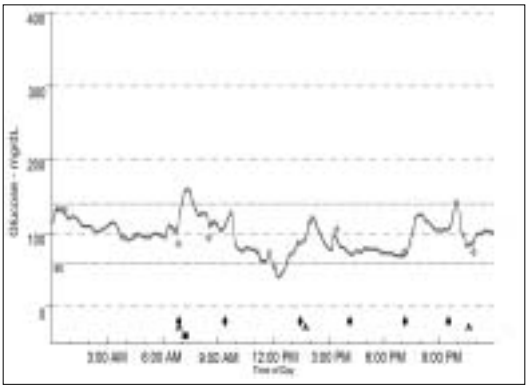

Figure 1: Twenty-four glucose profiles from a patient on metformin therapy demonstrating hypoglycemic and hyperglycemic events

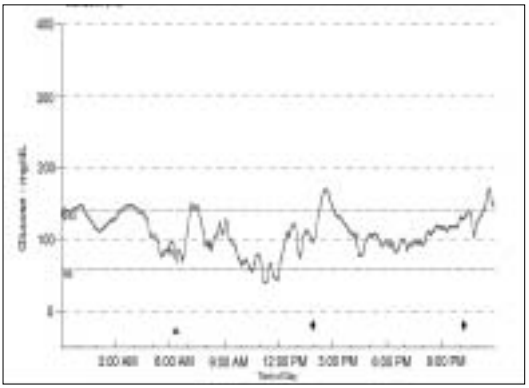

Figure 2: Twenty-four glucose profiles from a patient on glibenclamide demonstrating hypoglycemic and hyperglycemic events

Table 2: Characteristics of the study population according to type of treatment

	Only metformin	*Metformin+ sulfonylurea or only sulfonylurea*	*P*
Number of patients	12(57.1%)	9(42.8%)	
Number of hyperglycemic event	8.9±5.4	9.1±4.1	0.92
Duration of hyperglycemia (hour)	19.1±10.7	17.9±13.6	0.83
Number of hypoglycemic event	0.1±0.3	1.2±2.5	0.11
Duration of hypoglycemia (hour)	0.04±0.1	2.2±3.4	0.08

patients. Postprandial hyperglycemia has been shown to be closely related with cardiovascular disease,[13] aggravation of oxidative stress and endothelial dysfunction.[14,15] The high frequency of hyperglycemic events in our study is consistent with other studies[7,9,16] and indicates that relying on only HbA1c in the management of diabetes (as is being advised presently) is inadequate for reducing the rate of cardiovascular complications. Another primary outcome of our study was to detect hypoglycemia in well-controlled patients. Nocturnal hypoglycemia is a problem specific to tightly controlled diabetic patients, which can lead to delays in correction of the hypoglycemia. In ADVANCE study, severe hypoglycemia occurred in more patients in the intensively treated arm (2.7% versus 1.5%). In one study by Hay HC *et al.* on old patients with well-controlled type 2 diabetes, it was shown that 80% of patients experienced hypoglycemia.[7] We found that 14.2% of our patients had hypoglycemic events. The frequency is less than that in previous studies. We think this is due to the age group of our patients being different when compared to previous studies. In our results, no significant difference was found in hypoglycemic and hyperglycemic events between patients with only metformin usage and those on other treatments. Iatrogenic hypoglycemia with metformin was less frequent than with sulfonylurea, but it has been reported in other studies.[17,18] These results may be related to the small sample size in the 2 groups of patients. Analyses of initial multicenter evaluation of CGMS revealed a median correlation between sensor and SMBG readings 0.92.[19] Despite the difficulty of wearing CGMS for 72 hours, it was well tolerated by most patients. The most common complication was disconnection of device, which is similar to other studies.[4,20] Other complications were not registered in our study and in other studies. This study is the first report on utility of CGMS and evaluation of glycemic excursions in well-controlled type 2 diabetes patients in Iran. The most important limiting factor in the interpretation of our results was the small sample size. A recent meta-analysis for investigation of potential effects of CGMS in type 1 diabetes found that CGMS is not better than SMBG in improving metabolic control,[21] but all trials in type 2 diabetes are small. Therefore, our results cannot be generalized to all type 2 diabetic patients. More well-conducted clinical studies with larger number of participants are needed.

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