Research Article

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Optimal time for capillary blood glucose monitoring in patients with type 2 diabetes treated with insulin: a cross-sectional observation study

Abstract

Our objective was to determine the frequency and time of day when we detect the greatest number of hyperglycaemic and hypoglycaemic episodes in patients with type 2 diabetes mellitus (DM) on insulin. We also studied whether any clinical feature could be associated with more frequent hypoglycaemia or hyperglycaemia.

We conducted an observational study of 51 patients with type 2 diabetes mellitus who were on insulin and metabolically stable. We followed the patients for 8weeks, performing two daily capillary blood glucose measurements before and 2hours after each of the three main meals in turn. A profile was also prepared from 6 capillary blood glucose measurements performed before and after meals every 4days.

The likelihood of observing hyperglycaemia increased 48% before dinner (taking pre-breakfast capillary blood glucose as a reference). The likelihood of observing hypoglycaemia was 3.4times greater in pre-lunch capillary blood glucose measurements and was more frequent in patients with lower BMI.

In patients with type 2 DM stabilised by insulin, performing pre-dinner capillary blood glucose measurements identifies hyperglycaemia more often than at other times of the day, while pre-lunch measurement identifies hypoglycaemia more often, the latter being more common in patients with lower BMI.

Keywords: type 1 diabetes mellitus, type 2 diabetes mellitus, insulin, capillary blood glucose

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Abbreviations: BMI, body mass index; DM, diabetes mellitus; SMBG, self monitoring of blood glucose; OAD, oral antidiabetic agents; JDS, japanese diabetes society; JSCC, japanese society for clinical chemistry; DCCT, diabetes control and complications trial; GLMM, generalised linear mixed models; OR, odds ratios; CI, confidence intervals

Introduction

The self monitoring of blood glucose (SMBG) provides real-time information that helps patients to manage their diabetes, especially patients on an insulin regime. The purpose of SMBG is to facilitate appropriate clinical interventions to achieve and maintain blood glucose within an acceptable range by detecting hyperglycaemia and hypoglycaemia, thus improving metabolic control and patient satisfaction.[1]

The recommendations for SMBG are not uniform but differ among countries and patients. They depend on treatment intensity and metabolic state and they are often influenced by cost. International guidelines recommend that the frequency and timing of SMBG should be determined by the needs and goals of each patient. More frequent monitoring may be appropriate for poorly controlled patients; in contrast, stable patients who do not adjust insulin doses require less testing.

Although we provide patients with instructions on the number of measurements and times of day when they should perform self-monitoring, there is no well-defined pattern in such instructions[2–4] and major discrepancies concerning the recommendations for metabolic self-monitoring are found in patients with type 2 diabetes receiving conventional insulin therapy. Usually, SMBG preprandial and postprandial are recommended but the timing and number of measurements vary highly and frequently are performed in an erratic way. Our hypothesis is that a structured SMBG program with readings at specific times may provide a thorough information of blood glucose patterns that allowed us to drive the right treatment.[5,6]

The aim of this study was to investigate the frequency and optimal time of SMBG in patients with type 2 diabetes on insulin and with stable glycaemic control. In addition, the clinical features associated with episodes of hypoglycaemia and/or hyperglycaemia was investigated.

Materials and methods

Observational study involving 51 patients (20 men and 31 women) who met the following criteria:

a) Older than 40years

b) Body mass index (BMI) <40kg/m^2

c) Type 2 diabetes mellitus (DM) of at least 1year duration

d) On insulin therapy for at least 3months before recruitment

e) Ability to perform self-monitoring and

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f) Stable metabolic situation, defined as having no need to add new treatments or make changes in insulin dose >10%.[7] Oral antidiabetic agents (OAD) used: metformin(69%), DPP-IV inhibitors(16%), sulfonylureas (10%) and glinides(5%). The patients were recruited when they came to their routine check at the University Hospital of Santiago de Compostela, Spain. The recruitment period was from July 2012 to May 2013. The clinical characteristics of the participants are described in (Table 1).

Table 1 Clinical characteristics of patients

N	51
Men	20(39%)
Women	31(61%)
Age(years)	62±7
Duration of diabetes(years)	11±7
Age range(years)	49.77
BMI(kg/m²)	31.8±3.9
Treatment	
Insulin alone	18
Insulin+oral monotherapy	21(64%)
Insulin+OAD Combination	12(36%)
Insulin**	
A	16(31%)
B	15(30%)
C	20(39%)

*Treatment with oral antidiabetic agents; **A, Basal insulin; B, Mixtures of standard insulin (30/70, 50/50); C, Basal insulin+3-rapid insulin

The initial consultation occurred after obtaining informed consent and included a complete clinical evaluation of the patient, who was instructed on SMBG using BG Star® (Sanofi-Aventis). The patients were instructed to record daily blood glucose measurements and to maintain their usual diet.

During a period of 8weeks, the patients underwent structured pre- and post-prandial blood glucose monitoring at the three main meals, alternating throughout the week following the scheme in (Table 2) (Day 1: pre-breakfast and 2hours post-breakfast, Day 2: pre-lunch and 2hours post-lunch, Day 3: pre-dinner and 2hours post-dinner and Day 4: pre- and post-prandial 6-point profile). Plasma HbA1c was determined at the end of week 8.

The HbA1c was determined by high-performance liquid chromatography in a Menarini Diagnostics HA-8140 analyser. All HbA1c values were converted from the Japanese Diabetes Society (JDS)/Japanese Society for Clinical Chemistry (JSCC)-referenced values to Diabetes Control and Complications Trial (DCCT)-aligned units using the following equation: A1CNGSP=0.985 A1CJDS/JSCC+0.46%, where NGSP is the National Glycohaemoglobin Standardisation Program.[8]

Hyperglycaemia was defined as pre-prandial capillary blood glucose >7.22mmol/l and post-prandial capillary blood glucose >10mmol/l.[9] Hypoglycaemia was defined as capillary blood glucose values <3.89mmol/l. Out of range readings were defined as preprandial or postprandial glucose values beyond these limits.

Statistical analyses

Descriptive statistical analyses were used to analyse and describe the clinical characteristics and patient demographics. The means±SD are reported for continuous variables.

Generalised Linear Mixed Models (GLMM), with the patient and timing as random effects, were used to investigate the clinical characteristics associated with episodes of hypoglycaemia or hyperglycaemia. In both models the variables age, gender, BMI, time from diagnosis, timing, type of treatment and HbA1c levels were included as fixed effects. A binomial distribution and its canonical link function (log it) were implemented to model the presence/absence of these episodes (hypoglycaemia/hyperglycaemia), which allowed us to express the results in terms of odds ratios (OR) and their 95% confidence intervals (CI). The effect is statistically significant at the 5% level if the CI does not include 1. Statistical analyses were performed using the lme4 R package.[10]

Table 2 Capillary blood glucose schedule

Day	Pre-breakfast	Post-breakfast	Pre-lunch	Post-lunch	Pre-dinner	Post-dinner
1	X	X				
2			X	X		
3					X	X
4	X	X	X	X	X	X
5	X	X				
6			X	X		
7					X	X

Results

Of the 65 patients recruited for the study, 51 completed all 8weeks of recording capillary blood glucose measurements; 5 did not they complete the study; and 9 were excluded for not meeting the inclusion criteria. Of the 144 capillary blood glucose measurements scheduled for every patient within the 8weeks, 93% of them were performed.

(Figure 1) shows the capillary blood glucose measurements of all participants according to the time of measurement and HbA1c levels.

A direct relationship can be observed between the capillary blood glucose and HbA1c levels (Figure 1). The HbA1c levels at baseline and at the end of the study were 60±10mmol/mol (7.6±1.3%) and 59±10mmol/mol (7.5±1.3%), respectively.
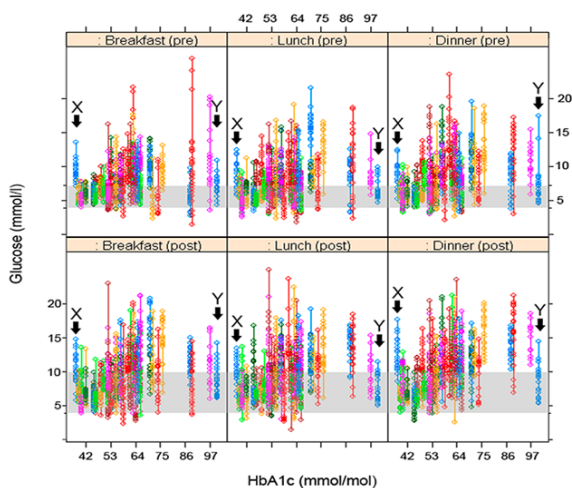
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Figure 1 Capillary blood glucose pre and post prandial Vs HbA1c values during the 8-weeks period. Each line corresponds to a patient and his capillary blood glucose values. X and Y are patients with similar capillary blood glucose and very different HbA1c values.

(Table 3) lists the mean pre- and post-prandial capillary blood glucose measurements along with the hypoglycaemias and hyperglycaemias and their percentage. The lowest blood glucose levels appear before meals and are highest after meals, with increases over the day.

Hyperglycaemia

All patients had at least one episode of pre-prandial hyperglycaemia and most (92%) also had at least 1 episode of post-prandial hyperglycaemia. (Table 4) shows the results of multivariate analysis. Of the clinical variables analysed (age, sex, BMI, HbA1c, time from diagnosis and type of treatment), only elevated HbA1c levels were significantly associated with the occurrence of episodes of hyperglycaemia (p<0.001).

Considering pre-breakfast capillary blood glucose levels as the reference, the likelihood of hyperglycaemia increases by 48% in pre-dinner blood glucose measurements (p<0.001) and decreases in the post-breakfast (p<0.001) and post-lunch (p<0.001) measurements. At other times of the day, no statistical significance was obtained. By measuring the pre-dinner blood glucose, we captured 20.6% of the hyperglycaemic episodes.

Table 3 Mean glucose levels and proportion of hypoglycemic, hyperglycemic and out-of-range readings captured at different testing times

	Valid Reading (%)	Mean±SD (mmol/l)	Hypoglycemic readings (%)	Hyperglycemic readings (%)	Out-of-range readings (%)
Total	6648(93.2)	8.8±3.3	135(100)	3209(100)	3344(100)
Pre-breakfast	1168(95.4)	7.7±2.5	26(19.2)	600(18.7)	626(18.7)
Post-breakfast	1135(92.7)	9.2±3.5	20(14.8)	383(11.9)	403(12.0)
Pre-lunch	1154(94.3)	7.8±2.9	43(31.9)	573(17.8)	616(18.4)
Post-lunch	1128(92.1)	9.5±3.3	19(14.1)	430(13.4)	449(13.4)
Pre-dinner	1146(93.6)	8.4±3.2	20(14.8)	662(20.6)	682(20.4)
Post-dinner	1117(91.2)	10.4±3.6	7(5.2)	561(17.5)	568(17.0)

Table 4 Timings and clinical variables associated with hyperglycemia and hypoglycemia

	Hyperglycemia		Hypoglycemia	
	OR(95% CI)	p-value	OR(95% CI)	p-value
Age(years)	1.02(0.97, 1.08)	0.403	0.93(0.85, 1.02)	0.143
Sex(male/female)	1.09(0.39, 1.65)	0.54	0.67(0.20, 2.21)	0.511
BMI(kg/m^2)	0.99(0.91, 1.09)	0.91	0.77(0.66, 0.90)	0.001
Time of diagnosis	1.01(0.96, 1.06)	0.733	1.02(0.94, 1.11)	0.563
Treatment				
A(basal)	**Ref**		**Ref**	
B(basal + rapid)	2.30(0.90, 5.90)	0.083	0.97(0.26, 3.63)	0.967
C(basal + 3 rapid)	1.10(0.50, 2.41)	0.813	1.03(0.28, 3.88)	0.958
HbA1c, %	1.82(1.37, 2.41)	0	1.03(0.63, 1.69)	0.902
Capillary glycemia				
Time	**Ref**		**Ref**	
Pre-breakfast	0.38(0.31, 0.47)	0	0.44(0.16, 1.17)	0.101
Post-breakfast	0.91(0.75, 1.10)	0.338	3.40(1.28, 9.00)	0.013

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Table Continued....

	Hyperglycemia		Hypoglycemia	
	OR(95% CI)	p-value	OR(95% CI)	p-value
Pre-lunch	0.52(0.43, 0.63)	0	1.39(0.48, 4.05)	0.54
Post-lunch	1.48(1.22, 1.80)	0	1.20(0.44, 3.32)	0.722
Pre-dinner	1.03(0.84, 1.25)	0.803	0.26(0.06, 1.11)	0.07
Post-dinner				

OR, odd ratio; 95% CI, 95% confidence interval; BMI, body mass index; HbA1c, glycated hemoglobin; treatment A; Ref, reference category

Hypoglycaemia

There were 135 hypoglycaemic values, representing 1.97% of the capillary blood glucose measurements performed. Thirty-seven per cent (19 patients) had at least one hypoglycaemic episode. In the univariable analysis, episodes of hipoglucemia were more frequent in patients treated with basal insulin (34.6%) and in patients treated with mixtures of standard insulin (34.6%) than in patients treated with basal insulin added to 3 rapid insulin (30.8%), but these differences did not reach statistical significance. However after adjusting for HbA1c, BMI, age, sex and time from diagnosis, insulin treatment was not associated with hypoglycaemia events. Adding oral antidiabetic drugs was not associated with hypoglycaemia events.

Regarding the clinical variables studied, only BMI was significantly associated with hypoglycaemia (p<0.001), with a higher frequency of episodes in individuals with lower BMI. Considering the pre-breakfast capillary blood glucose levels as reference, the likelihood of hypoglycaemia is 3.4times greater in the pre-lunch capillary blood glucose measurements (p<0.001). By measuring pre-lunch blood glucose, we captured 31.9% of the hypoglycaemic episodes.

Discussion

The level of compliance with the performance of capillary blood glucose measurements in our group (93%) was similar to other studies.[11] Despite the large number of glucose measurements performed during these 8weeks, the mean HbA1c levels decreased slightly from 60mmol/mol(7.6%) to 59mmol/mol(7.5%), indicating that the patients were in a stable metabolic state. It is also expected that patients with approximately normal HbA1c values would not present great changes in their SMBG values.[6,12–14]

The most important result of this study in patients with stable insulin-treated type 2 diabetes mellitus is that the times of day when hyperglycaemia or hypoglycaemia occurs more frequently can be identified and associated with the clinical characteristics of the patients. Specifically, in this group of patients, hyperglycaemia is more frequent in subjects with elevated HbA1c levels and in pre-dinner capillary measurements, while hypoglycaemia is more common in subjects with lower BMI and pre-lunch measurements. The highest proportion of hyperglycemic readings was found at predinner and the highest proportion of hypoglycemic readings happened prelunch. Others authors[7] concluded also that testing at prelunch/predinner times yielded the highest proportion of hypoglycemic and hyperglycemic events, respectively. The limitations of this study are that the patients included were only males and postprandial glucose measurements were not done.

Our results are more generalizables because we included female and our patients also performed postprandial glucose measurements giving a more complete glucose daily profile. Many studies have shown that HbA1c is an indicator of mean blood glucose levels. Therefore, it is expected that patients with higher HbA1c levels would have higher blood glucose levels and that hyperglycaemia would be associated with higher HbA1c levels. HbA1c is an indicator of overall glycaemic control, but it does not report glycaemic fluctuations and does not provide information about hypoglycemic episodes. Capillary blood glucose allows us to evaluate glycaemic variability apart from identifying hyperglycaemia and hypoglycaemia SMBG enables us a day to day better management of hypoglycemic and hyperglycemic events.

Hypoglycaemia and the fear of hypoglycaemia has been a limiting factor for many patients when attempting to achieve blood glucose levels within the normal range. Other authors found in a study design similar to ours[7] that 2% of patients experienced hypoglycaemic episodes. In this study, the largest proportion of hypoglycaemic episodes occurred before lunch. There are a number of possible causes of hypoglycaemia, but the most common are related to diabetes medication, the amount of food eaten, or the level of exercise performed by the patient. Low BMI was also identified as a predictor of hypoglycaemia. Other studies found that low BMI was associated with hypoglycaemia in patients with type 2 diabetes on insulin.[7,15,16] This result can be explained by the fact that patients with lower average BMI may show increased sensitivity to insulin, which thus represents a greater risk for them. Neither the type of treatment (insulin alone, insulin added to oral agents, insulin mixtures or prandial insulin added to basal insulin) age, sex or duration of diabetes were associated with more frequency of hyperglycemic or hypoglycemic readings.

SMBG is a widely accepted method for improving glycaemic control in patients with type 2 diabetes on insulin.[1,2,6,7,12–14,17–19] The improvements in glycaemic control with SMBG have also demonstrated profitability, producing long-term incremental cost-effectiveness ratios.[12,17,20] Choosing an effective strategy for capillary blood glucose monitoring also depends on the capture of out-of-range readings. Our findings suggest that strategies including predinner and prelunch readings can capture a significative proportion of out of range glucose values**.**

Observational studies of SMBG are susceptible to biases that have already been well described. The causal interpretation of these results is limited by the lack of randomisation. However, randomised controlled trials also have limitations for the study of SMBG. SMBG blind studies are not possible and the current SMBG practice guidelines make it unethical to include a group without exposure. Similarly, in our study, we did not evaluate whether the subjects with hypoglycaemic measurements were symptomatic.

This study was conducted within a well-defined framework of patients; all subjects were patients with stable insulin-treated type 2 diabetes mellitus. On the other hand, lifestyles (dietary habits,

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exercise) and patterns of insulin therapy can vary substantially among countries. Therefore, these results cannot be generalised to other patient groups or other situations.

Conclusion

In patients with stable insulin-treated type 2 diabetes mellitus, the times of day at which the occurrence of hyperglycaemia or hypoglycaemia is more frequent can be identified. The onset of hyperglycaemia is more frequent in subjects with elevated HbA1c levels and in pre-dinner measurements. The occurrence of hypoglycaemia is more common in subjects with lower BMI and in pre-lunch measurements.

Acknowledgements

Novelty statement

The self monitoring of capillary blood glucose plays an important role in the control of diabetes mellitus. The ideal number of measurements to be performed and time of day have not been well established. Our study shows that predinner and prelunch capillary blood glucose captures a higher proportion of hyperglycemia and hypoglycemia, respectively. Patients with lower body mass index (BMI) have a higher frequency of hypoglycemic episodes.

This information can help to optimise the use of capillary blood glucose measurements in the management of patients with type 2diabetes mellitus stabilised by insulin.

Conflict of interest

Author declares that there is no conflict of interest.

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