Day-to-day variability of blood glucose concentration curves generated at home in cats with diabetes mellitus

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Objective—To evaluate day-to-day variability in blood glucose curves (BGCs) generated at home and at the clinic for cats with diabetes mellitus.

Design—Prospective study.

Animals—7 cats with diabetes mellitus.

Procedures—BGCs generated at home on 2 consecutive days and within 1 week at the clinic were obtained twice. On each occasion, insulin dose, amount of food, and type of food were consistent for all 3 BGCs. Results of curves generated at home were compared with each other and with the corresponding clinic curve.

Results—Differences between blood glucose concentration determined after food was withheld (fasting), nadir concentration, time to nadir concentration, maximum concentration, and mean concentration during 12 hours had high coefficients of variation, as did the difference between fasting blood glucose and nadir concentrations and area under the curve of home curves. Differences between home curve variables were not smaller than those between home and clinic curves, indicating large day-to-day variability in both home and clinic curves. Evaluation of the paired home curves led to the same theoretical recommendation for adjustment of insulin dose on 6 of 14 occasions, and evaluation of home and clinic curves resulted in the same recommendation on 14 of 28 occasions. Four of the 6 paired home curves in cats with good glycemic control and 2 of the 8 paired home curves in cats with poor glycemic control led to the same recommendation.

Conclusions and Clinical Relevance—Considerable day-to-day variability was detected in BGCs generated at home. Cats with good glycemic control may have more reproducible curves generated during blood collection at home than cats with poorer control. (J Am Vet Med Assoc 2007;230:1011–1017)

Measurement of blood glucose concentration and generation of BGCs are commonly used during long-term management of cats with diabetes mellitus.1 Until recently, BGCs were almost always generated in a veterinary hospital because many cat owners are unable to collect blood samples by venipuncture. However, the procedure is time-consuming and relatively expensive and is therefore not performed as frequently as may be indicated. Additionally, stress or decreased food intake can substantially influence blood glucose concentrations in cats. For these reasons, home monitoring of blood glucose concentrations was introduced.2,3 Owners use an automatic lancet device to collect a drop of capillary blood from the cat’s ear, and the blood glucose concentration is determined by use of a PBGM. Values obtained from capillary blood correlate well with those of venous blood obtained from a peripheral vein.4,5 Most owners of diabetic cats are willing and able to learn the technique of home monitoring, and long-term compliance is good.5,7

Home monitoring has been used by humans with diabetes since the late 1970s. Because the long-term complications of diabetes mellitus in humans can be greatly reduced with good glycemic control,8 home monitoring has become an integral part of treatment. However, blood glucose concentration can vary markedly from day to day in humans.9-11 It is assumed that fluctuations are a result of variation in food intake, physical activity, and emotional stress10 or variable absorption of injected insulin.11 Day-to-day variation in blood glucose concentration is also thought to occur in diabetic cats.1 To the authors’ knowledge, only 1 study7 investigating the reproducibility of blood glucose curves in cats with diabetes mellitus has been reported. In that study, BGCs generated at home by owners were compared with curves performed at the clinic. Differences between the home and clinic curves were substantial, and in almost 40% of the cats, the hypothetical treatment decisions derived from the 2 BGCs did not agree.7 The goal of the present study was to investigate day-to-day variability in home-generated BGCs in cats with diabetes mellitus. We hypothesized that there would be better agreement between paired BGCs generated at home than between curves generated at home and those generated in the clinic.

Abbreviations

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<thead>
<tr>
<th>BGC</th>
<th>Blood glucose curve</th>
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<td>PBGM</td>
<td>Portable blood glucose monitor</td>
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Materials and Methods

Selection of cats—Seven cats with diabetes mellitus that ranged in age from 7 to 14 years (median, 12 years) and weighed 4.3 to 7.5 kg (9.5 to 16.5 lb; median, 6.1 kg [13.4 lb]) were included in the study. Five cats were castrated males, and 2 were spayed females; breeds included domestic shorthair (n = 3), Persian (1), Siamese (1), Burmeese (1), and Cornish (1). The diagnosis of diabetes mellitus was made on the basis of characteristic clinical signs, hyperglycemia after withholding of food (fasting), glucosuria, and high serum fructosamine concentration (> 340 µmol/L). Cats were included in the study if owners were willing to learn home monitoring, return cats to our clinic for reevaluations, and generate BGCs at home. Diabetes mellitus had been diagnosed in all cats 89 to 690 days (mean, 252 days) prior to enrollment in the study. Treatment consisted of SC injection of a porcine intermediate-acting insulin every 12 hours. The insulin dosage, time of insulin administration, and feeding regimen were constant for each cat in all 3 BGCs; however, they were not necessarily the same as in part 1. Collection of capillary blood and measurement of blood glucose concentration at home and in the clinic were performed with the same lancing device and PBGM. Blood glucose curves generated at home were referred to as home curves, and those generated in the clinic were referred to as clinic curves.

Besides generating BGCs, clinical reevaluations included a detailed and updated history; physical examination; and measurement of Hct and serum concentrations of fructosamine, albumin, and total protein. Serum fructosamine analyses were performed by use of an automated analyzers and commercial reagents supplied by the manufacturer. Cats were allocated to 2 groups on the basis of glycemic control. Group A consisted of cats that were considered to have good glycemic control; there was resolution or marked improvement in clinical signs, and serum fructosamine concentration was ≤ 500 µmol/L. Group B consisted of cats that were considered to have moderate to poor glycemic control; there was persistence or little improvement in clinical signs, and serum fructosamine concentration was > 500 µmol/L.

Statistical analysis—For each BGC, 7 variables were determined: blood glucose concentration determined after fasting, nadir glucose concentration, time to nadir concentration, maximum blood glucose concentration, mean blood glucose concentration during 12 hours, difference between fasting blood glucose concentration and nadir concentration (fasting-nadir), and area under the blood glucose curve. For parts 1 and 2, differences between the 7 variables were calculated for the following 3 pairs of curves: the 2 home curves, first home curve and clinic curve, and second home curve and clinic curve. For each of the 6 pairs of curves, the mean, SD, and coefficient of variation were calculated for the requirements of this study. A normality test performed by use of statistical software revealed no significant difference between the values and a normal distribution; therefore, parametric tests were used. A paired t test and 1-way ANOVA were used to analyze differences between values obtained in parts 1 and 2, between values of pairs of home curves, and between values of pairs of a home curve and clinic curve. To identify significant sources of variation in the paired curves, a factorial ANOVA was performed, followed by a Bonferroni-Dunn post hoc test. Differences were considered significant at values of P ≤ 0.05. Scatterplots were used for graphical presentation of the data, with a horizontal line indicating the mean. To examine possible clinical implications of day-to-day variations, a theoretical recommendation was made for adjustment of the insulin dose, which was based on the results of each BGC. The recommendation was to increase or decrease the insulin dosage or to leave it unchanged when the nadir was ≥ 9.0 mmol/L, < 5.0 mmol/L, or 5.0 to 8.9 mmol/L, respectively.

To determine possible causes of variability in the BGCs, the mean and nadir blood glucose concentration of each home curve were compared with the corresponding clinic curve in each cat. Thus, on the basis of the mean and nadir concentrations, values on the clinic curve could be higher or lower than one or both of the home curves. The same criteria were used to compare the home curves.
Values for fasting blood glucose concentration, maximum blood glucose concentration, mean blood glucose concentration, and area under the blood glucose curve were significantly lower in the first home curve than in the second home curve (Figure 2). The fasting blood glucose and maximum blood glucose concentrations of the first home curve were significantly lower than those of the clinic curve. Values for nadir concentration, fasting-nadir concentration, and time from insulin injection to nadir concentration did not differ significantly between the first and second home curve. The nadir concentration, fasting-nadir concentration, time from insulin injection to nadir concentration, mean blood glucose concentration, and area under the curve did not differ significantly between the first home curve and clinic curve. There were no significant differences between the second home curve and clinic curve with respect to any of the 7 variables.

Theoretical recommendations for adjustment of insulin dose—Fourteen sets of paired home curves (7 from part 1 and 7 from part 2) were compared to determine a theoretical recommendation for adjustment of the insulin dose. For 6 of the 14 paired curves, the same recommendations for adjustment of insulin dose resulted, whereas theoretical recommendations were different for 8 of the 14 paired curves. In 6 of the latter 8 paired curves, there would have been no dose adjustment on the basis of results of one of the home curves, and there would have been an increase or decrease in the insulin dose on the basis of results of the other home curve. In the remaining 2 paired curves, an opposite theoretical recommendation for insulin dose adjustment resulted; assessment of the results of one of the home curves led to a theoretical recommendation for a reduction in the insulin dose, whereas results of the other home curve led to a recommendation for an increase in the dose. Twenty-eight curve comparisons were made between the second home curve and clinic curve with respect to any of the 7 variables.

Comparison of differences between home and clinic curves—Differences among the 7 variables from BGCs obtained on 3 days (2 home curves and 1 clinic curve) would be small if there was minimal day-to-day variability of the BGCs. However, differences between the variables were large for all pairs of BGCs. This was reflected by SDs of the differences that were nearly as large as the means and by large coefficients of variation that ranged from 69% to 101% (Table 1). To test our hypothesis that there would be better agreement between paired BGCs generated at home than between curves generated at home and those generated in the clinic, differences between variables of the home curves were compared with differences between variables of the home and clinic curves. There were no significant differences, indicating that agreement between the home curves was not better than between the home and clinic curves and that the hypothesis was to be rejected. Comparison of the differences between the paired home curves generated in parts 1 and 2 of the study revealed that the difference between the maximum blood glucose concentration in part 2 was significantly (P = 0.045) higher than that in part 1; no other significant differences were detected (Figure 1). There were also no significant differences between parts 1 and 2 in comparison to the home and clinic curves or fructosamine concentrations.

Comparison of home and clinic curves—For these comparisons, absolute values of the BGC variables were used. The results of parts 1 and 2 were considered together because corresponding BGCs of the 2 parts (eg, first home curve of part 1 and first home curve of part 2) did not differ with respect to any of the 7 variables. Values for fasting blood glucose concentration, maximum blood glucose concentration, and area under the curve did not differ significantly between the first home curve and clinic curve. There were no significant differences between the second home curve and clinic curve. There were no significant differences between the second home curve and clinic curve with respect to any of the 7 variables.
home and clinic curves. Evaluation of results of the home and clinic curves led to the same recommendations for adjustment of insulin dose in 14 instances. In the other 14 instances, recommendations differed: in 7 instances, results of the home curves indicated no adjustment and an increase or decrease in the insulin dose would have been recommended on the basis of results of the clinic curves. In 1 instance, no adjustment of the insulin dose was made on the basis of the clinic curve, whereas a reduction in the insulin dose was recommended on the basis of the home curve. Evaluation of 6 paired curves led to opposite recommendations; in 3 instances, an increase in insulin dose was recommended on the basis of the clinic curve and a decrease in insulin dose was recommended on the basis of the home curve. In the other 3 instances, a decrease in the insulin dose was recommended on the basis of the clinic curve and an increase was recommended on the basis of the home curve.

Quality of glycemic control—Two cats in parts 1 and 2, 1 cat in part 1, and 1 cat in part 2 (different cats) were considered to have good glycemic control. Thus, when the home curves of parts 1 and 2 were considered together, there were 6 home curve pairs from cats with good glycemic control (group A) and 8 from cats with moderate to poor glycemic control (group B). In group A, 4 of the 6 home curve pairs led to the same theoretical recommendations for insulin dose adjustment and the remaining 2 home curve pairs led to different recommendations. In group B, the same recommendation for insulin dose adjustment was made in only 2 of 8 home curve pairs; a different recommendation was made in the other 6 instances. Of the 28 home curve and clinic curve pairs, 12 were from cats of group A and 16 were from cats of group B. In group A, 8 of the 12 home and clinic curve pairs and in group B, 6 of the 16 home and clinic curve pairs led to identical recommendations for insulin dose adjustment. There were no significant differences between the 7 variables obtained from the home curves in groups A and B; however, differences between all of the variables in group A tended to be smaller than those in group B (Figure 3).

Comparison of individual blood glucose curves—Regarding comparison of home and clinic curves, the clinic curves in 2 cats were higher than the home curves in both parts of the study. In 1 other cat, the clinic curve was considerably higher than the first home curve but corresponded to the second home curve. The mean and nadir concentrations of the clinic curves were considerably lower than those of the home curves in both parts of the study in 1 cat and in 1 part of the study in another cat. In the remaining 2 cats, the clinic curves corresponded to those home curves with the lower mean and nadir concentration in both parts of the study.
Regarding comparison of the home curves, the second home curve in 3 cats was much higher than the first; the difference was even more pronounced in part 2 of the study. In 1 cat, the second home curve was slightly higher than the first. In 2 cats, the home curves were the same in both study parts. In the remaining cat, the first home curve was slightly higher than the second curve in the first part of the study and the second home curve was slightly higher than the first curve in the second part.

**Discussion**

Results indicate that there is considerable day-to-day variability in BGCs in diabetic cats, even when factors such as insulin dose and meal size remain constant and the cat is at home in a stress-free environment. There was a large difference between the values of home curves obtained on 2 consecutive days. In particular, the maximum blood glucose concentration, time from insulin injection to nadir concentration, and fasting blood glucose concentration differed considerably between the 2 home curves. Contrary to our hypothesis, there was no greater agreement between the home curves than between the home and clinic curves. In humans with insulin-dependent diabetes mellitus, variations in blood glucose concentrations occur within a 24-hour period as well as from day to day and are associated primarily with activity level, meal composition and size, stress, and intake of certain medications. However, studies have revealed that even when these factors remain constant, day-to-day variability in glucose concentration persists. Causes include variable rate of insulin absorption when different injection sites are used, variation in the length of insulin activity, variation in insulin sensitivity among individuals, and variation in residual beta-cell function.

In humans with diabetes, consistent SC insulin injection in the abdominal region results in faster absorption and smaller day-to-day fluctuations in blood glucose concentrations than when the injection site is rotated. In the present study, owners varied the SC injection site regularly, which may have resulted in variable rates of insulin absorption. This aspect of administration has not been investigated in diabetic cats, to the authors' knowledge. The duration of action of the insulin used is approximately 12 hours, but may be shorter in some cats. The duration of insulin action was < 12 hours in all 3 BGCs generated during part 1 of the present study in 1 cat. Moreover, the blood glucose concentration returned to baseline after 8 to 10 hours, resulting in a marked difference in the morning fasting blood glucose concentration.

Because most cats have type 2 diabetes mellitus, the insulin dose depends on the severity of insulin resistance and the amount of residual beta-cell function. The degree of insulin sensitivity varies diurnally and also varies from day to day in humans with diabetes. Healthy cats also have substantial day-to-day variability in insulin sensitivity, and the same may also be true in diabetic cats, although, to the authors' knowledge, this has not been investigated.

In addition to internal factors, reproducibility of the BGCs may have also been affected by external factors. The activity level of the cats was difficult to control, and it may have differed on the consecutive days of blood glucose measurement at home. Although the insulin dose remained constant, there may have been slight errors in the amount of insulin as drawn up by the owners.

In the individual comparison of home and clinic curves, different patterns were observed: in the 3 cats in which the nadir and mean blood glucose concentrations in the clinic curves were higher than those in 1 or both home curves, stress-induced hyperglycemia caused by hospitalization was suspected. In 2 cats, the mean and nadir concentrations in the clinic curves were lower than both home curves. In the remaining 2 cats, the clinic curves corresponded to the home curves with the lower mean and nadir. Three of those 4 cats did not eat or ate later in the day while they were hospitalized for generation of the clinic curves. It is possible that the lower blood glucose concentrations were attributable to reduced food intake while cats were in the clinic. In an earlier study, some variables of BGCs generated in the clinic in diabetic cats were significantly lower than those variables in curves generated at home, a finding that was thought to be a result of decreased food intake in the clinic.

Two of the 3 cats in which the second home curve was much higher than the first in both study parts also
had noticeably high blood glucose concentrations in the clinic in 1 or both parts of the study, which was thought to be stress induced. It is plausible that in these cats, frequent pricking of the ear was stressful, even at home. These cats had been subjected to home monitoring for several months, but had not undergone 2 consecutive days of blood collection prior to the study. Information on whether the cats were cooperative during blood collection was not available. However, fractiousness is not the only indicator of stress; some cats can be anxious and stressed while remaining cooperative and quiet. The fact that 3 of 7 cats had higher values in the second home curve than in the first led to significant differences in the statistical analysis: fasting blood glucose concentration, maximum blood glucose concentration, mean blood glucose concentration, and area under the curve were significantly higher on the second day of home testing than on the first, further supporting the likelihood of stress-induced hyperglycemia on the second day of home testing.

The nadir concentration, time to nadir concentration, and difference between fasting blood glucose concentration and nadir concentration are critical for evaluation of insulin doses. The theoretical recommendation for insulin dose adjustment in the present study was similar to that used in a recent review on cats with diabetes mellitus. Comparison of the home curves led to the same recommendation on only 6 of 14 occasions, and comparison of home and clinic curves resulted in the same recommendation on only 14 of 28 occasions. In an earlier study, the reproducibility of BGCs in 10 diabetic dogs was investigated by comparing 3 pairs of BGCs generated on 2 consecutive days in the clinic. In that study, the theoretical recommendation for insulin dose adjustment was the same on 17 of 30 occasions. In addition, 20 sets of paired curves from dogs with good glycemic control (nadir concentration < 10 mmol/L) were compared, and the theoretical recommendation was the same in only 7 of those curves. This led to the conclusion that BGCs vary greatly from day to day, particularly in dogs with good glycemic control. In contrast to the results of that study, there was better agreement between the BGCs of cats with good glycemic control in the present study: 6 of 14 pairs of home curves led to the same theoretical adjustment of insulin dose, and 4 of those were curves from cats with better glycemic control. In cats with moderate to poor glycemic control, comparison of the home curves led to the same recommendation in only 2 of 8 paired curves. This suggests that there is less day-to-day variability in blood glucose concentrations in cats with good glycemic control. There was a nonsignificant finding that the differences between variables of the home curve pairs were smaller in cats with good glycemic control. A larger number of diabetic cats or paired BGCs may have yielded more explicit results. These results, however, are comparable to those found in humans; in a 1972 study, day-to-day variability in blood glucose concentration curves differed among healthy subjects and those who had good and poor glycemic control. Healthy humans had considerably less day-to-day variability in blood glucose concentrations than humans with diabetes mellitus, and human diabetics with poor glycemic control had significantly more variability than those with good glycemic control.

Overall day-to-day variability in blood glucose concentration curves was substantial in the cats with diabetes mellitus in the present study. This finding is in agreement with those in dogs and humans with the disease. Stress associated with hospitalization was thought to be a cause of the high blood glucose concentrations in some cats, although blood glucose concentrations in the clinic may also have been lower than those at home because of low food intake. The day-to-day variability between the home and clinic curves was not larger than that between paired home curves. The reproducibility of home curves in diabetic cats with good glycemic control was somewhat better than that of cats with moderate to poor control. We therefore assume that BGCs generated at home in cats with good glycemic control are more reliable than those in cats with poorer glycemic control. Results also indicate that serial blood collection on 2 consecutive days may result in stress-related hyperglycemia in diabetic cats.

References


Selected abstract for JAVMA readers from the American Journal of Veterinary Research

Changes in the myocardial performance index during dobutamine administration in anesthetized cats
Yasutomo Hori et al

Objective—To investigate the relationship between myocardial performance index (MPI, also known as the Tei index) and cardiac function in anesthetized cats administered dobutamine.

Animals—6 adult cats.

Procedures—Cats were anesthetized by administration of propofol (6 mg/kg, IV), and anesthesia was maintained by administration of isoflurane. Heart rate and systolic arterial pressure (SAP) were monitored. Stroke volume, cardiac output, and arterial blood flow (ABF) were measured by use of transesophageal ultrasonography. Left ventricular fractional shortening (LVFS), mitral E-wave velocity-to-A-wave velocity (E:A) ratio, and ejection time were measured by use of transthoracic echocardiography. Dobutamine was administered via a cephalic vein at rates of 2.5, 5.0, and 10 µg/kg/min.

Results—Heart rate, SAP, cardiac output, and ABF increased with dobutamine administration, whereas stroke volume significantly decreased. The LVFS significantly increased, and the E:A ratio significantly decreased. Total isovolumic time and the MPI significantly decreased. The MPI was negatively correlated ($r = -0.63$) with LVFS. Conversely, the MPI was positively correlated with the E:A ratio ($r = 0.47$), stroke volume ($r = 0.66$), and total isovolumic time ($r = 0.95$). However, the MPI was not significantly correlated with heart rate, SAP, cardiac output, or ABF.

Conclusion and Clinical Relevance—Analysis suggested that the MPI provides a sensitive clinical assessment of cardiac response to medication in cats, which may be similar to the reported usefulness of the MPI in humans. (Am J Vet Res 2007;68:385–388)