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Glucose concentrations after insulin-induced hypoglycemia and glycemic variability in healthy and diabetic cats

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Background: Little information is available about posthypoglycemic hyperglycemia (PHH) in diabetic cats, and a causal link between hypoglycemia and subsequent hyperglycemia is not clear. Fluctuations in blood glucose concentrations might only represent high glycemic variability.

Hypothesis: Insulin induces PHH in healthy cats, and PHH is associated with poorly regulated diabetes and increased glycemic variability in diabetic cats.

Animals: Six healthy cats, 133 diabetic cats.

Methods: Insulin (protamine-zinc and degludec; 0.1-0.3 IU/kg) administered to healthy cats. Blood glucose curves were generated with portable glucose meter to determine the percentage of curves with PHH. Data from insulin-treated diabetic cats with blood glucose curves showing hypoglycemia included data of cats with and without PHH. Post-hypoglycemic hyperglycemia was defined as blood glucose concentrations <4 mmol/L followed by blood glucose concentrations >15 mmol/L within 12 hours. Glycemic variability was calculated as the standard deviation of the blood glucose concentrations.

Results: In healthy cats, all insulin doses caused hypoglycemia but PHH was not observed; glycemic variability did not differ between insulin preparations. Among diabetic cats with hypoglycemia, 33 (25%) had PHH. Compared with cats without PHH, their daily insulin dose was higher (1.09 ± 0.55 versus 0.65 ± 0.56 IU/kg; $P < .001$), serum fructosamine concentration was higher (565 ± 113 versus 430 ± 112 μmol/L; $P < .001$), remission was less frequent (10% versus 56%; $P < .001$), and glycemic variability was larger (8.1 ± 2.4 mmol/L versus 2.9 ± 2.2 mmol/L; $P < .001$).

Conclusions and Clinical Importance: Insulin-induced hypoglycemia did not cause PHH in healthy cats but it occurred in 25% of diabetic cats with hypoglycemia, particularly when diabetes was poorly controlled. Glycemic variability was increased in cats with PHH.

KEYWORDS
cat, diabetes mellitus, endocrinology, pancreas

Abbreviations: DM, diabetes mellitus; ID, insulin degludec; PHH, posthypoglycemic hyperglycemia; PZI, protaminezinc insulin; SD, standard deviation.

1 | INTRODUCTION

It has been postulated that hypoglycemia induced by a slight overdose of insulin leads to counter-regulatory hormone release and subsequent hyperglycemia in humans with diabetes mellitus (DM). This phenomenon, also known as rebound hyperglycemia or the Somogyi effect, was characterized by nocturnal hypoglycemia followed by early morning fasting hyperglycemia.[1] Recent studies in human medicine have cast doubt on the existence of rebound hyperglycemia as described by Somogyi, or proposed that it is rare.[2–4] Indeed, most humans with type 1 DM had fasting hypoglycemia and not hyperglycemia after nocturnal hypoglycemia.[2,3] Furthermore, diabetic patients with the phenomenon did not have higher concentrations of counter-regulatory hormones than diabetics without it, but had a relative insulin deficiency, suggesting that increased fasting blood glucose is related to insufficient insulin treatment.[4]

In human diabetology, the concept of glycemic variability has gained particular attention in recent years.[5,6] Although currently there is no uniformly accepted definition, glycemic variability refers to intraday glycemic excursions consisting of episodes of hypoglycemia followed by hyperglycemia, or of hyperglycemia followed by hypoglycemia, with no apparent causal link.[6] Hence, the main differences between the definitions of rebound hyperglycemia and glycemic variability are timing and sequence; rebound hyperglycemia is nocturnal to early morning hypoglycemia followed by hyperglycemia, whereas glycemic variability refers to oscillations of blood glucose concentrations including episodes of hypoglycemia and hyperglycemia that occur during the day or night.

In cats, information pertaining to blood glucose concentrations after insulin-induced hypoglycemia is scarce and its clinical relevance is currently unknown.[7,8] To date, only the term rebound hyperglycemia has been used in diabetic cats,[7,8] and the event was described during the day, in contrast to the Somogyi's classical definition described in human diabetics which occurs at night. In the first description of rebound hyperglycemia in 6 diabetic cats,[7] cats were receiving a single daily insulin dose of 2–22 IU/cat at the time of rebound hyperglycemia, and in 4 of them the phenomenon did not recur after the dose of insulin was decreased or the type of insulin was changed.[7] In 2016, a second investigation based on data provided by owners in a web-based forum described rebound hyperglycemia in 14 of 55 (25.5%) insulin-treated diabetic cats.[8] Overall, however, only 45 of 10 767 (0.4%) blood glucose curves showed rebound hyperglycemia. No association was found between the episodes and the amount of insulin administered.[8] In contrast to rebound hyperglycemia, the concept of glycemic variability has not yet been investigated.

In our study, the more generic term posthypoglycemic hyperglycemia (PHH) is proposed in cats instead of rebound hyperglycemia because a causal link between low and subsequent high glucose concentrations is uncertain. Our aims were to determine whether PHH occurs after insulin-induced hypoglycemia in healthy cats and to define the frequency of PHH in diabetic cats. Moreover, signalment, insulin treatment, clinicopathologic data, metabolic control, and remission were evaluated and compared in diabetic cats with and without PHH. Glycemic variability also was explored in healthy and in diabetic cats.

2 | MATERIALS AND METHODS

2.1 | Healthy cats and insulin treatment

Six, healthy, purpose-bred, neutered male, domestic shorthair cats, with a mean age of 3.7 ± 0.1 years and a mean body weight of 5.0 ± 0.2 kg were treated with protamine zinc insulin (PZI; ProZinc, Boehringer Ingelheim, Ingelheim am Rhein, Germany) and insulin degludec (ID; Tresiba, Novo Nordisk Pharma, Bagsværd, Denmark), as previously reported.[9] The cats were housed in the animal research facility of the Vetsuisse Faculty, University of Zurich, and were fed a commercial dry food (Feline Adult Light, Hill's Pet Nutrition, Topeka, Kansas), twice daily. Cats had continuous access to water, and food intake was adjusted to maintain stable body weight. The cats were housed in individual standard hospital cages for 24 hours before and 24 hours after insulin administration. Food was withheld for 10 hours before and 24 hours after insulin administration. The 2 insulin preparations and their dosages were tested in a randomized crossover trial. Each cat received 0.1, 0.2, and 0.3 IU/kg of PZI or ID SC, 2 weeks apart. The dose was rounded up to the nearest half unit. Capillary blood for blood glucose determination using a portable blood glucose meter (AlphaTRAK2; Abbott Animal Health, Abbott Park, Illinois) was collected from the inner pinna 30 and 5 minutes before, and 30, 60, 90, 120, 180, 240, 300, and 360 minutes after insulin injection, and every 2 hours during the following 18 hours. Hypoglycemia was arbitrarily defined as blood glucose concentration <4 mmol/L and PHH as blood glucose concentration <4 mmol/L followed by an increase in blood glucose concentration >15 mmol/L within 12 hours of the administration of insulin.

When hypoglycemia caused tremors, vocalization, vomiting, or seizures, an additional meal was offered or 50% glucose solution was administered IV, and the cat was withdrawn from the study. When a decrease in physical activity was the only clinical sign observed, no attempt was made to correct the hypoglycemia. The study protocol was approved by the Cantonal Veterinary Office of Zurich (permission number: 110/2014).

2.2 | Diabetic cats and insulin-induced hypoglycemia

The medical records of the Clinic for Small Animal Medicine of the Vetsuisse Faculty, University of Zurich, were searched for diabetic cats admitted between 1997 and 2014. Cats were included in the study provided they were receiving insulin treatment and at least 1 blood glucose curve, generated at our clinic or at home by the owner, was available. It was necessary that blood glucose curves include at least 4 measurements over a 12-hours period and show hypoglycemia; cats with curves generated over a longer period were excluded. The blood glucose curves were evaluated for nadir, time to nadir, and episodes of PHH. The definitions of hypoglycemia and PHH were the same as those used in healthy cats. The signalment, including age, body weight, sex (male, female, neutered), and breed (crossbred, purebred), type of

insulin (glargine [Lantus, Sanofi Aventis, Meyrin, Switzerland] or porcine zinc [Caninsulin, MSD Animal Health, Luzern, Switzerland]), daily insulin dose, quality of metabolic control, occurrence of diabetic remission, and serum fructosamine concentration at the time of hypoglycemia were retrieved from the medical records. The quality of metabolic control was defined as good when cats on insulin treatment had no clinical signs of DM (eg, polyuria, polydipsia, polyphagia), body weight was stable, and serum fructosamine concentration was only slightly increased (350–450 μmol/L; reference interval, 200–340 μmol/L). The occurrence of diabetic remission was defined as the absence of clinical signs of DM and normal blood glucose and fructosamine concentrations for at least 4 weeks after discontinuation of insulin treatment.[10] The chance of remission is highest during the first 6 months after diagnosis of DM,[10] and thus a follow-up examination at a minimum of 6 months after the start of insulin treatment was considered necessary. Cats that required insulin treatment but had had their last follow-up examination <6 months after initial presentation were excluded for analysis of remission.

2.3 | Statistical analysis

Commercial software (GraphPad Prism version 5.0, GraphPad Software, La Jolla, California) was used for all calculations. In healthy cats, the frequencies of hypoglycemia and PHH were calculated for both insulin preparations. The percentages of blood glucose curves with at least 1 blood glucose concentration above baseline after the hypoglycemic episode were computed. For each cat, blood glucose concentrations after hypoglycemia were considered to be significantly higher than baseline when they were greater than the mean of the blood glucose concentrations recorded 30 and 5 minutes before insulin administration plus the 90% range of differences. The 90% range of differences was calculated using previously described method.[11] In brief, all blood glucose concentrations recorded at 30 and 5 minutes before insulin administration were used to calculate the critical value of the t-distribution and the residual mean square from analysis of variance; the formula of the 90% range of differences was: $(\text{critical value}) \times \sqrt{((\text{residual mean square})/2 + (\text{residual mean square}))}$.[11]

In diabetic cats, the frequency of PHH was calculated only for those with documented hypoglycemia. Differences between cats with and without PHH with respect to sex, breed, insulin type, location where the blood glucose curve was generated, rate of good metabolic control, and remission were analyzed using a chi-square test, and differences with respect to age, body weight, daily insulin dose, serum fructosamine concentrations, nadir, and time to nadir of blood glucose curves with hypoglycemia were analyzed using a *t*-test. Data were tested for normal distribution using the Shapiro-Wilk test, and non-normal data were log-transformed and then analyzed using parametric tests. The Bonferroni correction was applied to account for multiple comparisons and adjusted *P*-values were calculated. Data were reported as means ± standard deviations (SD) or as percentages.

The SD describes the dispersion of data on both sides of the mean and is considered the simplest approach for the evaluation of glucose variability in human diabetics.[12] Hence, the SD was calculated from blood glucose concentrations from the blood glucose curve in each diabetic cat with and without PHH, and in each healthy cat. In human medicine, glycemic variability is considered acceptable when the SD of the blood glucose curve does not exceed mean/2 for patients with type 1 DM and mean/3 for patients with type 2 DM.[12] The percentages of cats with acceptable glycemic variability based on these 2 formulas were calculated. The difference between the SDs of all cats with PHH and of all cats without PHH was analyzed using a *t*-test with Levene's test to assess equality of variances. This analysis was performed to verify whether cases with PHH had greater glycemic variability than those without PHH. Fisher's exact test was used for comparison of the percentages of cats with and without PHH with acceptable glycemic variability. In cats with PHH having a second blood glucose curve available, comparison of paired SDs and of percentages of acceptable glycemic variability between curves were carried out using the Wilcoxon paired test and Fisher's exact test, respectively. Differences between SDs of healthy cats treated with PZI and those treated with ID were examined for each dosage (0.1, 0.2, and 0.3 IU/kg) using the Wilcoxon paired test. Differences were considered significant at $P < .05$.

3 | RESULTS

3.1 | Healthy cats and insulin treatment

In healthy cats, hypoglycemia was observed after all 36 (100%) insulin administrations, regardless of the type of insulin used (Figure 1). At the highest dosage (0.3 IU/kg), PZI and ID caused hypoglycemia (1.2 and 1.8 mmol/L, respectively), which was associated with an episode of vomiting in 3 cats (2 with PZI, 1 with ID). Each of the 3 cats was offered a meal, which resulted in prompt correction of the hypoglycemia. The blood glucose curves of these 3 cats were excluded from all analyses. In all other cases, administration of PZI and ID led to a decrease in physical activity, which was associated with hypoglycemia and resolved without treatment within 1–3 hours after insulin administration.

None of the hypoglycemic episodes induced PHH. However, in 4 of 33 (12.1%) available blood glucose curves, blood glucose concentrations after hypoglycemia slightly exceeded baseline; 3 cats had received PZI at dosages of 0.1, 0.2, and 0.3 IU/kg, respectively, and 1 had received ID at a dosage of 0.2 IU/kg. The glucose values and differences above baseline were 5.7 and +0.3 mmol/L, 4.9 and +0.3 mmol/L, and 5.8 and +0.1 mmol/L in cats given PZI and 5.6 and +0.3 mmol/L in the cat that received ID.

Results of glycemic variability in healthy cats treated with PZI and ID are shown in Table 1. The SDs did not differ between PZI and ID at any of the 3 dosages administered.

3.2 | Diabetic cats and insulin-induced hypoglycemia

The medical records of 300 diabetic cats with DM were retrieved and yielded a total of 2106 blood glucose curves for evaluation. Blood glucose curves with hypoglycemia were documented in 133 of the 300

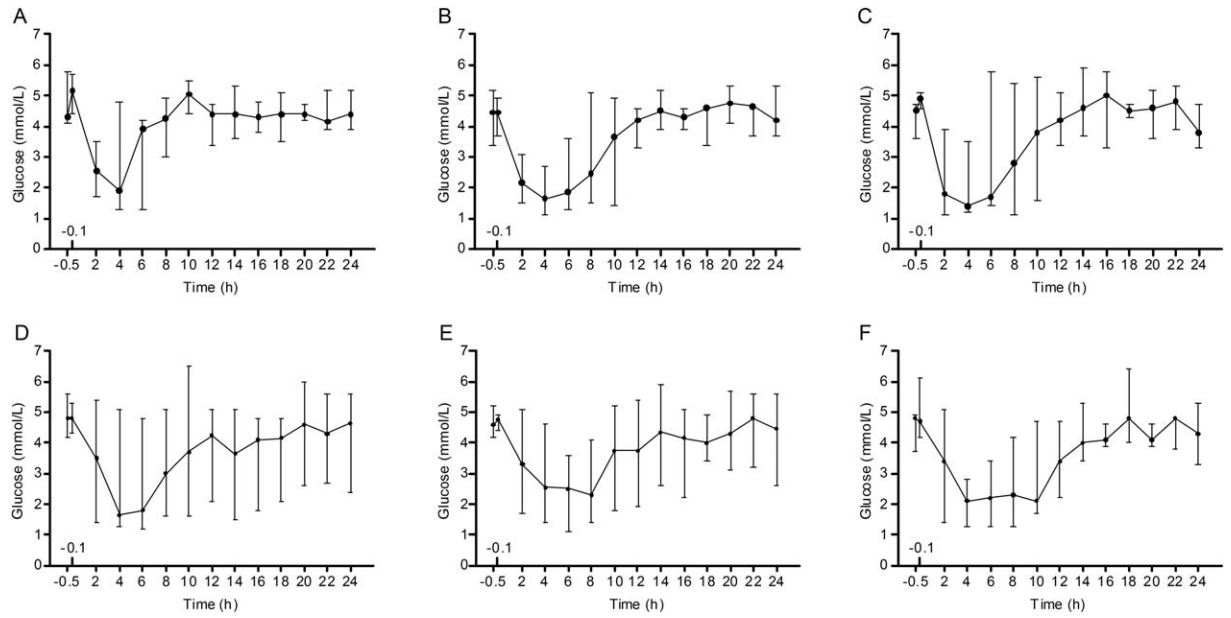

FIGURE 1 Blood glucose curves showing hypoglycemia in healthy cats (2 cats treated with PZI and 1 treated with ID were excluded because received a meal to correct hypoglycemia) treated with PZI at 0.1 (A), 0.2 (B), and 0.3 IU/kg (C) or ID at 0.1 (D), 0.2 (E), and 0.3 IU/kg (F). Median and range are shown for each time point

(44.3%) diabetic cats. Of those 133 diabetic cats, 33 (24.8%) had PHH and 100 (75.2%) did not (Figure 2). Posthypoglycemic hyperglycemia was identified in 11% of all diabetic cats and in 1.7% of all glucose curves. With regard to blood glucose curves of the 133 diabetic cats, the mean number of glucose measurements in each curve was 6 ± 1 and the mean duration of each curve was 9 ± 2 hours.

In the group of 33 cats with PHH, the mean age was 10.3 ± 3.4 years and the mean body weight was 5.5 ± 1.5 kg. Twenty-one cats (63.6%) were neutered males and 12 (36.4%) were spayed females. Twenty-four were domestic shorthair or longhair (72.7%) and 9 were purebred (27.3%) cats. In the group of 100 cats without PHH, the mean age was 11.3 ± 3.2 years and the mean body weight was 5.4 ± 1.4 kg; age was unknown in 1 cat. Seventy-four cats (74%) were male, including 72 neutered and 2 intact, and 26 (26%) were female, including 25 spayed and 1 intact cat. Seventy-six were domestic shorthair or longhair (76%) and 24 were purebred (24%) cats. Cats with and without PHH did not differ in age, body weight, sex, or breed distribution.

TABLE 1 Assessment of glycemic variability based on calculation of the SD of the blood glucose curve in healthy cats treated with PZI versus ID at each dosage (0.1, 0.2, and 0.3 IU/kg)

Insulin (type and dosage)	Glycemic variability[a] (mean ± SD; mmol/L)	*P* value
PZI 0.1 IU/kg	1.0 ± 0.4	.589
ID 0.1 IU/kg	1.1 ± 0.5	
PZI 0.2 IU/kg	1.2 ± 0.2	.589
ID 0.2 IU/kg	1.1 ± 0.5	
PZI 0.3 IU/kg	1.2 ± 0.2	.905
ID 0.3 IU/kg	1.2 ± 0.2	
PZI total	1.1 ± 0.3	.986
ID total	1.1 ± 0.4	

Abbreviation: SD, standard deviation.
Note that SD refers only to the SD of the mean of the SDs of the glucose curves (ie, those used to assess glycemic variability).
[a]Two cats treated with PZI and 1 treated with ID were excluded because received a meal to correct hypoglycemia.

The proportions of cats treated with insulin glargine and porcine-zinc insulin did not differ between groups ($P = .205$) and comprised 42.4% and 57.6% of the group with PHH and 64% and 36% of the group without PHH, respectively. The daily amount of insulin administered per kg in cats with PHH was significantly higher than in cats without PHH (1.09 ± 0.55 versus 0.65 ± 0.56 IU/kg; $P < .001$; Figure 3). Serum fructosamine concentrations were available for 15 cats with PHH and 85 without PHH; serum fructosamine concentration was significantly higher in the group with PHH (565 ± 113 versus 430 ± 112 μmol/L; $P < .001$; Figure 4). Good metabolic control was documented in 1 of 15 (6.7%) cats with PHH and in 58 of 85 (69.4%) in the group without PHH; the prevalence of good metabolic control was significantly lower in cats with PHH ($P < .001$). Glucose nadir (2.7 ± 0.8 versus 2.8 ± 0.7 mmol/L; $P = 1.000$) and time to nadir (4.0 ± 1.6 versus 4.9 ± 2.5 hours; $P = .530$) did not differ in diabetic cats with and without PHH. Finally, the frequency of blood glucose curves generated at home and at the hospital was 48.5% and 51.5% in cats with PHH versus 13% and 87% in cats without PHH; blood glucose curves generated at home were significantly more common in the PHH group ($P < .001$).

With regard to glycemic variability, the SDs were significantly higher in cats with PHH than in cats without PHH (8.1 ± 2.4 mmol/L versus 2.9 ± 2.2 mmol/L; $P < .001$). Using the formulas for evaluation of the rate of acceptable glycemic variability in humans with type 1 and 2 DM,[11] 3 (9.1%) and 0 (0%) cats with PHH and 63 (63%) and 40 (40%) cats without PHH had acceptable glycemic variability. Based on the

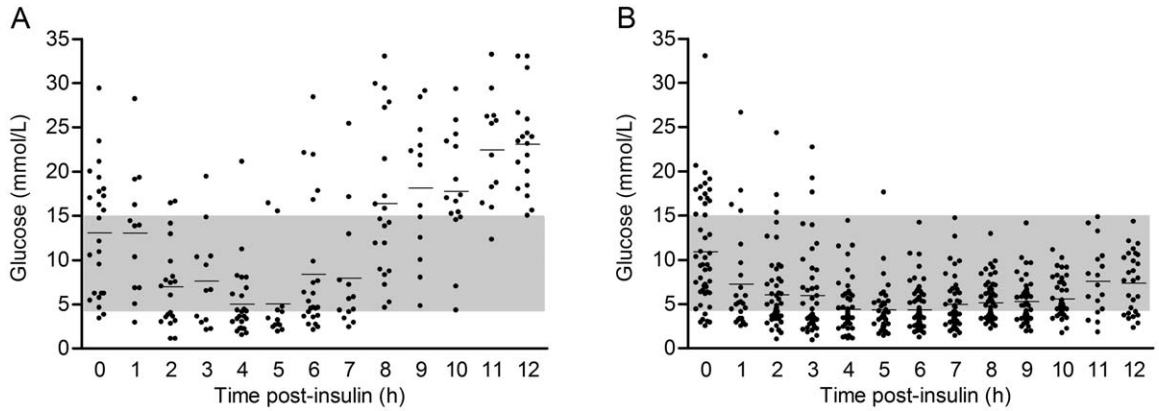

FIGURE 2 Scatter plots of blood glucose curves in diabetic cats with posthypoglycemic hyperglycemia (A) and without PHH (B). The gray box depicts the glucose concentrations between 4 and 15 mmol/L. Means are shown as horizontal bars in each scatter plot

values for both criteria, cats with PHH were significantly less likely to have acceptable glycemic variability than those without PHH ($P < .001$ for each comparison).

3.3 | Follow-up of diabetic cats

Overall, 47 cats (43.1%) had remission from DM and 62 (56.9%) did not. Twenty-four cats that required insulin treatment, consisting of 3 in the group with PHH and 21 in the group without PHH, had their final follow-up examination <6 months after initial presentation and were excluded from analysis. Remission was achieved in 3 of the 30 cats (10%) with PHH and in 44 of the 79 cats (55.7%) without PPH; the rate of remission was significantly lower in cats with PHH ($P < .001$).

Of the 33 cats with PHH, 31 (93.4%) had a blood glucose curve repeated an average of 14 ± 15 days after the curve showing PHH. A second episode of PHH occurred in 2 of the 31 (6.5%) cats and in both cases the dose of insulin had not been decreased after the first episode of PHH. A second episode of PHH was not documented in the remaining 29 cats; the dose of insulin had been decreased by an average of 37 ± 18% in 12, not been changed in 11 (37.9%), and increased in the remaining 6 (20.7%). The complete clinical and clinicopathologic data used by the attending veterinarian to increase or maintain the amount of insulin prescribed were not available from the medical records.

Regarding glycemic variability of the 31 blood glucose curves, their SDs were 4.8 ± 3.1 mmol/L. Compared with initial curves with PHH, the SD calculated in a repeated blood glucose curve was significantly lower ($P < .001$); SD decreased in 26 of 31 (83.9%) curves. Using the formulas for humans with type 1 and 2 DM,[12] 24 (77.4%) and 19 (61.3%) of 31 blood glucose curves had acceptable glycemic variability. Compared with initial curves with PHH, the frequency of acceptable glycemic variability was significantly increased using either formula ($P < .001$, for each).

4 | DISCUSSION

Administration of PZI and ID at all dosages in healthy cats resulted in hypoglycemia but was not associated with PHH. It appears that even after episodes of severe hypoglycemia, healthy cats are able to fine-tune glycemia so that the secretion of counter-regulatory hormones, released in response to hypoglycemia, is transient and quickly offset once normoglycemia is restored. Hence, PHH did not occur in this population of healthy cats. Epinephrine and corticosteroids are

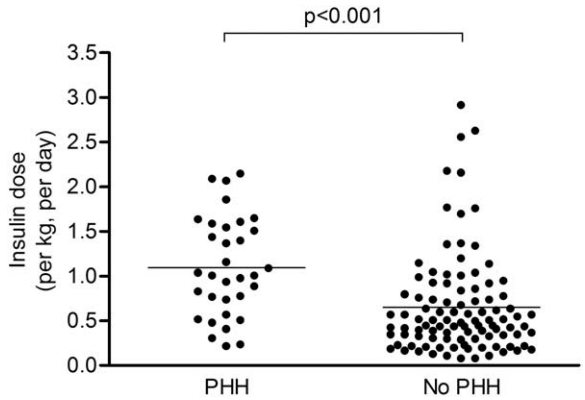

FIGURE 3 Scatter plots of daily insulin dose in diabetic cats with PHH and without PHH. Means are shown as horizontal bars in each scatter plot

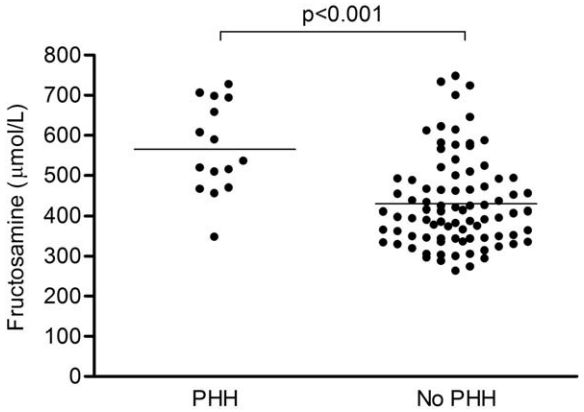

FIGURE 4 Scatter plots of serum fructosamine concentrations in diabetic cats with PHH and without PHH. Means are shown as horizontal bars in each scatter plot

counter-regulatory hormones that have been shown to play an important role in glycemic control in cats with hypoglycemia. In 1 study healthy cats that received 10 IU/kg of insulin had a 10-fold increase in circulating epinephrine with the highest concentration recorded during the glucose nadir; epinephrine secretion ceased with IV administration of a glucose solution.[13] In another study, healthy cats that received 4 IU/kg of insulin had a 6-fold increase in circulating corticosteroids within 1 hour of administration.[14] However, neither of the studies reported whether hyperglycemia occurred after insulin-induced hypoglycemia. Only 12% of the blood glucose curves of healthy cats had measurements slightly above baseline after insulin-induced hypoglycemia (ranging from +0.1 to +0.3 mmol/L), which probably reflected normal physiological variability. Therefore, insulin administration in healthy cats causes hypoglycemia, but compensatory mechanisms appear to prevent blood glucose concentrations from exceeding baseline and resulting in hyperglycemia. The dosage of insulin administered to healthy cats in our study was much lower than that used in previous studies,[13,14] and it is not known whether higher doses of insulin would have caused more marked hypoglycemia followed by a more pronounced increase in blood glucose concentration. Furthermore, lack of counter-regulatory hormone measurement also precludes further conclusions with respect to our findings.

Assessment of glycemic variability showed no differences between healthy cats treated with PZI and those treated with ID, at any of the 3 dosages. Therefore, the 2 insulin preparations seem to cause similar fluctuations in blood glucose concentrations when administered to healthy cats. Further studies are needed to clarify the usefulness of SD for assessment of glycemic variability in experiments using different insulin preparations in healthy cats.

Of the 300 diabetic cats with complete medical records, almost half had a blood glucose curve showing hypoglycemia, and 25% of these had PHH. Of all diabetic cats, approximately 10% had PHH, which shows that this phenomenon is common and in agreement with a recent investigation describing PHH in 25% of diabetic cats.[8] Although PHH occurred in a considerable number of diabetic cats, the proportion of blood glucose curves with PHH was low at ~1 in 50 in our investigation and 1 in 200 in a previous study.[8] Therefore, although some diabetic cats may have blood glucose curves with PHH, this phenomenon may be observed only once. In our study, only 6.5% of diabetic cats with PHH had a second episode of PHH, whereas most did not. A continuous glucose monitoring system rather than a portable blood glucose meter may have been a better tool to evaluate the occurrence of PHH.

Although episodes of PHH were seen only once in the majority of diabetic cats, there were several intriguing features associated with this phenomenon. For example, diabetic cats with PHH received almost twice as much daily insulin per kg as did diabetic cats without PHH and had 25% higher serum fructosamine concentrations. Furthermore, good metabolic control was seen in 70% of cats without PHH, but in only 6.7% of cats with PHH. At first glance, these results may merely suggest that DM is more difficult to treat in cats with PHH than in cats without PHH. Alternatively, the data would support the hypothesis that an excessively high dosage of insulin leads to PHH, which in turn renders the management of DM more difficult in cats, as originally assumed in diabetic humans presented with rebound hyperglycemia or the Somogyi effect.[1] However, the existence of this phenomenon has been questioned, and in the majority of human diabetics the episodes were shown to be attributable to short duration of insulin action rather than rebound hyperglycemia.[2–4] Unfortunately, it was not possible to assess the duration of insulin action from the blood glucose curves and therefore determine whether the effect of insulin was shorter in cats with PHH. Blood glucose curves spanning >12 hours would have been necessary to make this determination. Time to nadir did not differ between cats with and without PHH,[15] but this parameter does not necessarily mirror the duration of insulin action. In addition, no differences were observed between the nadir, which suggests that hypoglycemia was not more severe in cats with PHH, although they had received more insulin than did diabetic cats without PHH. Epinephrine secretion is a variable that appears to reflect the degree of hypoglycemia in cats,[14] and thus it is possible that PHH occurs when there is marked hypoglycemia. Why PHH occurs in some diabetic cats but not in others, despite a similar degree of hypoglycemia, remains unclear.

By calculating the SD of glucose concentrations in blood glucose curves, cats with PHH had higher glycemic variability than did those without PHH. The importance of decreasing large excursions in glucose concentrations to improve glycemic variability recently was highlighted in human medicine, and is considered by some authors to be as crucial as decreasing glycated hemoglobin.[16] The rationale behind calculation of glycemic variability is that optimal values of glycated hemoglobin in some diabetic patients do not rule out the presence of relevant fluctuations in blood glucose concentrations, such as phases of marked hypoglycemia and hyperglycemia, which necessitate prompt treatment.[16] In addition, glycemic variability was shown to be associated with the development of diabetic retinopathy in humans with type 1 and 2 DM, and higher glycemic variability was observed in patients with this ocular complication, regardless of glycated hemoglobin results.[17] Based on our experience, fluctuations are frequently observed in blood glucose curves in cats with DM. Therefore, the concept of glycemic variability relative to PHH was investigated in this species using the SD, which is the simplest formula available in human medicine.[12] Further studies are needed to determine whether higher glycemic variability plays a role in the occurrence of diabetic complications, such as polyneuropathy and ketoacidosis, or in remission and survival. Of note, glycemic variability was less likely to be acceptable in cats with PHH (~10%) than in cats without PHH (~50%). Although these results may not look promising, it is worth noting that the initial application of glycemic variability, which has so far not been optimized for cats, proved useful and showed clear differences in a population of diabetic cats with hypoglycemia. Actually, it is possible that selection bias was introduced by including only diabetic cats with episodes of hypoglycemia. The general population of diabetic cats, including those with and without hypoglycemia, might have a higher rate of acceptable glycemic variability than this group.

Follow-up examinations in diabetic cats showed that remission occurred in only 10% of those with PHH compared with almost 66% of those without PHH. Our finding suggests that when a blood glucose

curve shows PHH, every effort should be made to improve the chance of remission. Although our results showed that PHH was seen only once in most cats with DM, it is probable that metabolic control in diabetic cats remains inadequate over time and eventually decreases the viability of pancreatic β-cells, making remission unlikely. It is unclear if glycemic variability decreases the chances of remission in cats. Our investigation showed that cats with PHH had follow-up blood glucose curves with improved SD and rate of acceptable glycemic variability. Therefore, glycemic variability may play only a limited role in remission. However, to elucidate the relevance of glycemic variability longitudinal studies with several blood glucose curves are definitely required.

Of note, after the episode of PHH, the attending veterinarian in approximately half of the cases did not decrease the dose of insulin. Despite this, PHH was not demonstrated in the subsequent blood glucose curves in most of these cats. This surprising finding might be explained by the fact that some inconsistency of blood glucose curves has been demonstrated in diabetic cats, in particular if DM is poorly controlled, even if curves are repeated on the subsequent day and insulin dose, amount of food, and type of food are left unchanged.[18] Information regarding diets was not available. Therefore, it is possible that dietary changes also contributed to blood glucose concentrations in the follow-up curves.

Finally, blood glucose curves more often were generated at home than in the hospital in cats with PHH compared to cats without PHH. The hospital setting is expected to be associated with more stress, which would decrease the overall chance of hypoglycemia and, presumably, of PHH. Furthermore, cats with an episode of hypoglycemia in the hospital may be unwilling to eat because of environmental stress, thus preventing subsequent hyperglycemia. However, owners at home may easily increase blood glucose concentrations of their cats by offering an additional meal in case of hypoglycemia, favoring PHH. Because of the retrospective nature of our study, information regarding feeding was insufficient both for cats with hospital and home-based glucose curves to make any assumption on the role of diet on PHH.

Using the results of blood glucose curves generated with portable glucose meters rather than with continuous glucose monitoring systems represents a potential limitation of our study. True nadirs and fluctuations in glucose concentrations of short duration can be missed when using portable blood glucose meters.[19] However, the potential bias caused by the use of portable glucose meters instead of continuous glucose monitoring systems was likely minor because portable glucose meters were used consistently in all of the cats. Furthermore, it is worth reiterating that the results of our study on diabetic cats come from a selected population of cases with hypoglycemia, and interpretation of data cannot be extended to the general population of diabetic cats.

In conclusion, insulin-induced hypoglycemia did not cause PHH in our population of healthy cats, although posthypoglycemia blood glucose concentrations slightly exceeded baseline in some cats. Furthermore, glycemic variability was similar in cats treated with PZI and ID. Posthypoglycemic hyperglycemia occurred in approximately 25% of diabetic cats with hypoglycemia and was associated with higher insulin doses, higher serum fructosamine concentrations, worse metabolic control, lower risk of remission, and increased glycemic variability compared with diabetic cats without PHH. The reason why PHH is only seen in certain diabetic cats and not others currently is unclear.

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CONFLICT OF INTEREST DECLARATION

Eric Zini serves as Associate Editor for the Journal of Veterinary Internal Medicine. He was not involved in review of this manuscript.

OFF-LABEL ANTIMICROBIAL DECLARATION

Authors declare no off-label use of antimicrobials.

INSTITUTIONAL ANIMAL CARE AND USE COMMITTEE (IACUC) OR OTHER APPROVAL DECLARATION

Part of the study was prospective. The study protocol was approved by the Cantonal Veterinary Office of Zurich (permission number: 110/2014).

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REFERENCES

[1] Somogyi M. Exacerbation of diabetes by excess insulin action. *Am J Med*. 1959;26:169–191.

[2] Hoi-Hansen T, Pedersen-Bjergaard U, Thorsteinsson B. The Somogyi phenomenon revisited using continuous glucose monitoring in daily life. *Diabetologia*. 2005;48:2437–2438.

[3] Choudhary P, Davies C, Emery CJ. Do high fasting glucose levels suggest nocturnal hypoglycemia? The Somogyi effect-more fiction than fact? *Diabet Med*. 2013;30:914–917.

[4] Gale EA, Kurtz AB, Tattersall RB. In search of the Somogyi effect. *Lancet*. 1980;2:279–282.

[5] Service FJ. Glucose variability. *Diabetes*. 2013;62:1398–1404.

[6] Suh S, Kim JH. Glycemic variability: how do we measure it and why is it important? *Diabetes Metab J*. 2015;39:273–382.

[7] McMillan FD, Feldman EC. Rebound hyperglycemia following overdosing of insulin in cats with diabetes mellitus. *J Am Vet Med Assoc*. 1986;188:1426–1431.

[8] Roomp K, Rand J. Rebound hyperglycemia in diabetic cats. *J Feline Med Surg*. 2016;18:587–596.

[9] Salesov E, Zini E, Riederer A, Lutz TA, Reusch CE. Comparison of the pharmacodynamics of protamine zinc insulin and insulin degludec and validation of the continuous glucose monitoring system iPro2 in healthy cats. *Res Vet Sci*. 2018;118:79–85.

[10] Zini E, Hafner M, Osto M, et al. Predictors of clinical remission in cats with diabetes mellitus. *J Vet Intern Med*. 2010;24:1314–1321.

[11] Marshall RD, Rand JS, Morton JM. Glargine and protamine zinc insulin have a longer duration of action and result in lower mean

daily glucose concentrations than lente insulin in healthy cats. *J Vet Pharmacol Ther*. 2008;31:205–212.

[12] Frontoni S, Di Bartolo P, Avogaro A, Bosi E, Paolisso G, Ceriello A. Glucose variability: an emerging target for the treatment of diabetes mellitus. *Diabetes Res Clin Pract*. 2013;102:86–95.

[13] Duner H. The effect of insulin hypoglycemia on the secretion of adrenaline and noradrenaline from the suprarenal of cat. *Acta Physiol Scand*. 1954;32:63–68.

[14] Lloréns I, Borrell J, Borrell S. Effects of insulin, glucagon and adrenocorticotrophin on the levels of corticosteroids, noradrenaline, adrenaline and ascorbic acid in the adrenal glands of cats. *Horm Res*. 1973;4:321–330.

[15] Gilor C, Ridge TK, Attermeier KJ, Graves TK. Pharmacodynamics of insulin detemir and insulin glargine assessed by an isoglycemic clamp method in healthy cats. *J Vet Intern Med*. 2010;24:870–874.

[16] Rodbard D. Glycemic variability: measurement and utility in clinical medicine and research-one viewpoint. *Diabetes Technol Ther*. 2011; 13:1077–1080.

[17] Sartore G, Chilelli NC, Burlina S, Lapolla A. Association between glucose variability as assessed by continuous glucose monitoring (CGM) and diabetic retinopathy in type 1 and type 2 diabetes. *Acta Diabetol*. 2013;50:437–442.

[18] Alt N, Kley S, Haessig M, Reusch CE. Day-to-day variability of blood glucose concentration curves generated at home in cats with diabetes mellitus. *J Am Vet Med Assoc*. 2007;230:1011–1017.

[19] Moretti S, Tschuor F, Osto M, et al. Evaluation of a novel real-time continuous glucose-monitoring system for use in cats. *J Vet Intern Med*. 2010;24:120–126.

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