Common Complications of Insulin Therapy in Diabetic Cats

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INTRODUCTION

Establishing an effective treatment regimen for diabetes mellitus is often challenging in cats. Variables such as severity of pancreatic beta cell loss, responsiveness of tissues to insulin, presence or absence of glucose toxicity, problems with absorption and duration of effect of exogenously-administered insulin, asymptomatic hypoglycemia and induction of glucose counterregulation, and presence and reversibility of concurrent disease affect the success of treatment, lead to confusion and frustration for the veterinarian and owner, and create the perception that feline diabetes mellitus is a difficult disease to treat. The purpose of this article is to briefly discuss several of the commonly encountered problems that impact the success of treatment—problems which should be considered whenever control of glycemia becomes difficult in the diabetic cat.

FLUCTUATING INSULIN DEPENDENCY

Insulin dependency is unpredictable in diabetic cats. Some diabetic cats always require insulin, some cats rarely require insulin, and some cats oscillate between needing and not needing insulin to control the diabetic state. The severity of destruction of pancreatic beta cells and the presence, severity, and reversibility of concurrent disorders that negatively affect insulin sensitivity are perhaps the two most important factors dictating insulin dependency in diabetic cats. Destruction of pancreatic beta cells can be rapid and complete and insulin-dependent diabetes mellitus (IDDM) may exist at the time diabetes is diagnosed. Alternatively, cats may gradually lose the ability to secrete insulin if beta cells are destroyed slowly. These cats may have an initial period when hyperglycemia and clinical signs of diabetes can be controlled with treatments other than insulin (ie, non-insulin-dependent diabetes mellitus [NIDDM]). However, if the underlying pathologic process causing destruction of beta cells is progressive, eventually the ability to secrete insulin is lost and IDDM develops. The progression from NIDDM to IDDM is unpredictable and dependent, in part, on the type and progression of islet pathology and the reversibility of concurrent insulin resistant disease.

The presence and severity of insulin resistance is an important variable that influences the clinical picture in cats with partial destruction of pancreatic beta cells. Insulin resistance increases the demand for insulin secretion by beta cells; a demand which may not be met in some cats with partial loss of beta cells. The more severe the insulin resistance and the more severe the loss of beta cells, the more likely hyperglycemia will develop. Persistent hyperglycemia can, in turn, suppress function of remaining beta cells, causing hypoinsulinemia and worsening hyperglycemia; a syndrome referred to as glucose toxicity.[1] Examples of concurrent insulin-resistant disorders include obesity, chronic pancreatitis and other chronic inflammatory diseases, infection, and insulin-resistant disease like hyperthyroidism, hyperadrenocorticism and acromegaly ***(Table)***. Identification and correction of concurrent problems that

Table. *Recognized causes of insulin resistance in diabetic cats*

Disorders Typically Causing Severe Insulin Resistance	Disorders Typically Causing Mild or Fluctuating Insulin Resistance
Hyperadrenocorticism	Obesity
Acromegaly	Chronic Pancreatitis
Progesterone excess	Disease of the oral cavity
Diabetogenic drugs (most notably glucocorticoids)	Chronic inflammation Renal insufficiency Liver insufficiency Hyperthyroidism Infections Pancreatic exocrine insufficiency Hyperlipidemia Neoplasia

affect insulin sensitivity is critical to the successful treatment of diabetes in cats, regardless of the health of the beta cells.

In cats with partial loss of beta cells, improvement in insulin sensitivity may cause reversion from an insulin-dependent to a noninsulin dependent or subclinical diabetic state.[1] Obesity-induced carbohydrate intolerance is the classic insulin-resistant disorder affiliated with development of NIDDM in humans and has been identified as a potential causative factor in the development of diabetes in cats as well.[2,3] Obesity causes a reversible insulin resistance that is a result of down-regulation of insulin receptors, impaired receptor binding affinity for insulin, and postreceptor defects in insulin action.[4] The abnormalities responsible for insulin resistance are reversible with correction of obesity, which is why correction and prevention of obesity is always an important component of the treatment regimen for diabetes.[5-6] With weight loss, insulin resistance improves, exogenous insulin becomes more effective in controlling glycemia, and insulin administration can be discontinued in some diabetic cats.

A sustained demand for insulin secretion in response to insulin resistance can also lead to worsening islet pathology, a further reduction in the population of beta cells, and ultimately IDDM. Islet amyloidosis is a classic example of this concept. Amyloid is a common pathologic finding in the pancreatic islets of diabetic cats ***(Figure 1)***. Amylin is the principle constituent of islet amyloid, is located within beta cell secretory granules, and is co-secreted with insulin by the beta cell.[7,8] Stimulants of insulin secretion also stimulate the secretion of amylin. Amylin acts as a neuroendocrine hormone with several glucoregulatory effects that collectively complement the actions of insulin in postprandial

Figure 1. *Pancreatic islets from one healthy cat and three cats with diabetes mellitus. Pancreatic islets have been stained for insulin and illustrate differences in loss of beta cells between diabetic cats. Insulin-containing beta cells stain orange in color. (Note that in the photos shown here, the insulin-containing beta cells appear dark pink.)*

A. *Normal population of beta cells in a healthy cat.*

B. *Mild loss of beta cells and minimal pathologic changes in the islet in a cat with noninsulin-dependent diabetes mellitus treated with diet and glipizide*

C. *Islet amyloidosis and moderate to severe loss of beta cells in a cat with initial noninsulin-dependent diabetes mellitus that progressed to insulin-dependent diabetes mellitus. Pancreatic biopsy was obtained during insulin-dependent diabetic state.*

D. *Severe islet amyloidosis and absence of beta cells in a diabetic cat with insulin-dependency beginning at the time diabetes was diagnosed. (Immunoperoxidase stain, x100)*

glucose control.[9,10] Chronic increased secretion of insulin and amylin, as occurs with obesity and other insulin resistant states, results in aggregation and deposition of amylin in the islets as amyloid ***(Figure 2)***. Amylin-derived amyloid fibrils are cytotoxic and associated with apoptotic cell death of islet cells.[11,12] If deposition of amyloid is progressive, as occurs with persistent insulin resistant states such as obesity, islet cell destruction progresses and the cat will progress from a subclinical diabetic state to NIDDM and ultimately to IDDM.

Our current understanding of the etiopathogenesis of diabetes in the cat suggests that the difference between IDDM and NIDDM is primarily a difference in severity of loss of beta cells and severity and reversibility of concurrent insulin resistance. Most cats with IDDM and NIDDM have islet amyloidosis, vacuolar degeneration of beta cells, or islet hypoplasia.[1,13] The more severe the islet pathology, the more likely the cat will have IDDM, regardless of concurrent insulin resistance ***(Figure 1)***. The less severe the islet pathology, the greater the role of concurrent insulin resistance in dictating whether the cat has IDDM or NIDDM. The more severe and the less reversible the cause of the insulin resistance, the more likely the cat with mild islet pathology will be insulin-dependent, and vice versa. Fluctuations in severity of insulin resistance, as occurs with chronic pancreatitis, can cause a cat with mild islet pathology to oscillate between IDDM and NIDDM as the severity of pancreatic inflammation and insulin resistance waxes and wanes. Persistent insulin resistance may cause progressive loss of beta cells, worsening insulin deficiency, and eventually IDDM.[1,14]

Figure 2. *Schematic of the interplay between insulin resistance, amylin secretion, and amyloid deposition in the pancreatic islets. Insulin secretion increases to compensate for insulin resistance induced by environmental factors, insulin-antagonistic drugs, and concurrent illness. Because amylin and insulin are co-secreted, amylin secretion also increases in insulin-resistant states. If sustained, increased amylin secretion can lead to amylin aggregation and the formation of amyloid in the islets. (From Feldman EC, Nelson RW. Canine and Feline Endocrinology and Reproduction, 3rd ed. Philadelphia, WB Saunders Co, 2004; in press.)*

VARIABLE EFFECTIVENESS OF INSULIN PREPARATIONS

Diabetic cats are notoriously unpredictable in their response to exogenous insulin. There is no single type of insulin which is routinely effective in maintaining control of glycemia, even with twice-a-day administration. Ultralente insulin is the longest-acting but least potent of the commonly-used commercial insulins. Although considered a long-acting insulin, ultralente insulin has to be administered twice a day in most diabetic cats and absorption of ultralente insulin is inadequate for controlling glycemia in approximately 25% of cats. Lente and NPH insulin are more potent insulin preparations that are more consistently and rapidly absorbed following subcutaneous administration than ultralente insulin. Unfortunately, the duration of effect of lente and especially NPH insulin can be considerably shorter than 12 hours in some diabetic cats, resulting in inadequate control of glycemia despite twice-a-day administration.

Protamine-zinc insulin (PZI) is a longer acting insulin that is more consistently absorbed than ultralente insulin and has a more acceptable duration of effect than NPH insulin. However, the timing of the glucose nadir is quite variable and occurs within 9 hours of PZI administration in greater than 80% of treated diabetic cats.[15] We routinely administer PZI insulin twice a day. In a recent study, PZI was very effective in significantly improving control of glycemia in newly diagnosed diabetic cats and poorly-controlled diabetic cats previously treated with ultralente or NPH insulin.[15] Comparison of efficacy between PZI and lente insulin has not been reported.

Insulin glargine is a long-acting insulin analog that forms microprecipitates at the site of injection from which small amounts of insulin glargine are slowly released. In humans, the slow sustained release of insulin glargine from these microprecipitates results in a relatively constant concentration/time profile over a 24 hour period with no pronounced peak in serum insulin. Insulin glargine is currently recommended as a basal insulin (ie, sustained long-acting insulin to inhibit hepatic glucose production) administered once a day at bedtime in human diabetics.[16-17]

In a preliminary study involving healthy cats, most of the pharmacokinetic pharmacodynamic properties (ie, onset of action, glucose nadir, time for blood glucose concentration to return to baseline, mean daily blood glucose concentration, and area under the 24-hour blood glucose curve) were similar for insulin glargine and PZI. Similar studies in diabetic cats have yet to be reported. In our experience, insulin glargine has a duration of effect ranging from 10 to 16 hours in most diabetic cats. We have not yet encountered prob-

lems with inadequate absorption of insulin glargine, as described with ultralente insulin, although it seems likely that this problem will be encountered as we gain more experience with this insulin analog. Currently, we consider using insulin glargine in diabetic cats with problems of short duration of effect of NPH, lente, and PZI insulin.

It is not possible to predict which type of insulin will work best in individual diabetic cats. The initial insulin of choice ultimately is based on personal preference and experiences. Currently, we recommend either lente or PZI insulin at a dosage of 1 to 2 U per cat administered twice daily. Dietary therapy is initiated concurrently. Because greater than 80 to 90% of diabetic cats require insulin twice a day, we prefer to start with twice-a-day insulin therapy. Establishing control of glycemia is easier and problems with hypoglycemia and glucose counterregulation are less likely when twice daily insulin therapy is initiated while the insulin dose is low; ie, at the time insulin treatment is initiated.

ASYMPTOMATIC HYPOGLYCEMIA AND GLUCOSE COUNTERREGULATION

Asymptomatic hypoglycemia is a common complication of insulin therapy in diabetic cats. In a recent study evaluating the efficacy of PZI insulin in 67 diabetic cats, asymptomatic hypoglycemia (defined as a blood glucose concentration less than 80 mg/dl) was identified in 24 (9%) of 268 9-hour blood glucose curves and in 21 (31%) of 67 cats.[15] The median daily insulin dosage at the time asymptomatic hypoglycemia developed was 0.8 U/kg, with a range of 0.4 to 1.4 U/kg. When hypoglycemia develops or when the blood glucose concentration decreases rapidly regardless of the glucose nadir, direct hypoglycemia-induced stimulation of hepatic glycogenolysis and secretion of diabetogenic hormones, most notably epinephrine and glucagon, increase the blood glucose concentration, minimize signs of hypoglycemia, and cause marked hyperglycemia within 12 hours of glucose counterregulation. The marked hyperglycemia that occurs after hypoglycemia is due, in part, to an inability of the diabetic cat to secrete sufficient endogenous insulin to dampen the rising blood glucose concentration. Secretion of diabetogenic hormones during the hypoglycemic episode may induce insulin resistance, which can last 24 to 72 hours after the hypoglycemic episode.

Clinical signs of hypoglycemia are typically mild or not recognized by the owner; clinical signs caused by hyperglycemia tend to dominate the clinical picture. The insulin dose that induces hypoglycemia is variable and unpredictable, can be induced with insulin dosages less than 0.4 U/kg per injection, and can result in cats receiving 10 to 15 units of insulin per injection as veterinarians react to the persistence of clinical signs and high blood glucose and serum fructosamine concentrations by increasing the insulin dose and perpetuating the problem. If a serial blood glucose curve is obtained on the day glucose counterregulation occurs, hypoglycemia will be identified and the diagnosis established. However, if the serial blood glucose curve is obtained on a day when insulin resistance predominates, hypoglycemia will not be identified and the insulin dose may be incorrectly increased in response to the high blood glucose values. A cyclic history of one or two days of good glycemic control (ie, minimal clinical signs) followed by several days of poor control should raise suspicion for insulin resistance caused by glucose counterregulation. Serum fructosamine concentrations are unpredictable but are usually increased (>500 µmol/l); such results confirm poor glycemic control but do not identify the underlying cause.

Insulin-induced hypoglycemia and rebound hyperglycemia induced by glucose counterregulation was originally described in diabetic humans by Dr. Somogyi in the 1930's and subsequently became known as the Somogyi phenomenon.[19] Asymptomatic hypoglycemia and its physiologic consequences is one of the most common causes of poor control of glycemia in insulin-treated diabetic cats and should always be considered, regardless of the insulin dose being administered. Treatment involves arbitrarily reducing the insulin dose 1 to 2 units per injection and evaluating the cat's clinical response over the ensuing 2 to 5 days, or starting glycemic regulation over using an insulin dose of 1 unit per injection twice a day.

FLUCTUATING INSULIN REQUIREMENTS

One of the most frustrating problems encountered with insulin treatment is the sudden inability to maintain control of glycemia in a previously well-controlled diabetic cat. Typically, the diabetic cat has been well-controlled with a consistent dose of insulin for weeks to months and then suddenly becomes symptomatic (eg, lethargy, weakness, polyuria polydipsia, weight loss). Concurrent problems are not readily apparent and an increase in the insulin dose may improve clinical signs for a short period of time (days to weeks), only to have clinical signs recur and often improve with a further increase in the insulin dose. If this routine continues, the insulin dose may eventually exceed 1.5 to 2.0 U/kg/injection with variable but inconsistent improvement in clinical signs.

Control of glycemia often remains erratic and unpredictable and the insulin dose is changed frequently in an attempt to reestablish consistent control of glycemia. Hypoglycemia may suddenly be identified despite weeks to months of poor control and consistently high blood glucose concentrations. In many cats, the increased frequency of visits to the veterinary hospital and blood glucose measurements ultimately leads to stress-induced hyperglycemia and the frustration of the veterinarian and owner intensifies.

In our experience, the most common explanation for sudden loss of glycemic control in a previously stable diabetic cat is development of a concurrent disorder causing insulin resistance. The insulin resistance is usually mild and either spontaneously reversible or oscillates in severity over time ***(Table)***. Inflammatory disorders such as mild chronic

pancreatitis that typically go unrecognized by the owner and veterinarian are the most common culprits. In a diabetic cat receiving a fixed dose of insulin, the development of insulin resistance results in hyperglycemia and recurrence of clinical signs. An increase in the insulin dose will improve control of glycemia because the insulin resistance is relatively mild. If the insulin resistance worsens, further increases in the insulin dose will be required to maintain control of glycemia. However, if and when insulin resistance improves or resolves, the cat is suddenly at risk for developing hypoglycemia, glucose counterregulation, and persistent poor control of the diabetic state. In essence, what started out as an insulin resistance problem causing loss of glycemic control evolves into poor glycemic control because of the Somogyi phenomenon; the latter developing from an insulin overdosage created when the inflammatory process subsides and insulin resistance improves ***(Figure 3)***. A thorough history, physical examination, evaluation of a serial blood glucose curve, and if indicated, diagnostic evaluation for disorders known to cause insulin resistance in the diabetic cat should be undertaken whenever a previously well-controlled diabetic cat suddenly becomes symptomatic for the disease. Hypoglycemia inducing glucose counterregulation should always be considered if a reason for the sudden deterioration in glycemic control is not evident after a thorough evaluation of the cat, especially if the insulin dose has been arbitrarily increased prior to the evaluation.

OCCULT STRESS-INDUCED HYPERGLYCEMIA

Hyperglycemia induced by stress, aggression or excitement is the single biggest problem affecting accuracy of blood glucose measurements in cats. Stress can override the glucose-lowering effect of the insulin injection, cause high blood glucose concentrations, and if unrecognized lead to a spiraling path of insulin overdosage, hypoglycemia, glucose counterregulation, and poor control of glycemia. The biggest factors inducing stress hyperglycemia are hospitalization and multiple venipunctures Most diabetic cats do not tolerate frequent venipunctures and eventually develop a change in temperament, typically towards aggression, and stress hyperglycemia. Induction of stress hyperglycemia is variable but usually starts during a venipuncture procedure and begins earlier and earlier on subsequent visits to the veterinarian, until eventually stress hyperglycemia is induced by hospitalization and ultimately by the car ride to the veterinary hospital.

Blood glucose concentrations can remain greater than 400 mg/dl throughout the day when stress hyperglycemia develops prior to the first venipuncture of the day, despite administration of insulin ***(Figure 4)***. Failure to recognize the effect of stress on blood glucose results may lead to the erroneous perception that the diabetic cat is poorly-controlled. Insulin therapy is invariably adjusted, often by increasing the insulin dosage, and another blood glucose curve recommended 1 to 2 weeks later. A vicious cycle ensues, which eventually culminates in hypoglycemia, glucose counterregulation, and referral for evaluation of insulin resistance. Failure to identify the presence of stress hyperglycemia and its impact on interpretation of blood glucose measurements is one of the most important reasons for misinterpreting the status of glycemic control in diabetic cats.

Veterinarians must remain wary of stress hyperglycemia in diabetic cats and should take steps to avoid its development. Micro-managing diabetic cats should be avoided and serial blood glucose curves should only be done when there is a perceived need to change insulin therapy. The determination of good versus poor control of glycemia should be based on the owner's subjective opinion of presence and severity of clinical signs and overall health of their pet, ability of the cat to jump, its level of activity and grooming behavior, findings on physical examination, and stability of body weight. Serial blood glucose measurements are indicated if poor control of glycemia is suspected. The purpose of serial blood glucose measurements is to obtain a glimpse at the actions of insulin in that diabetic cat and hopefully identify a reason (eg, short duration of insulin effect) that could explain why the diabetic cat is poorly controlled.

Figure 3. *Schematic of the interplay between insulin resistance, hypoglycemia and glucose counterregulation, and stability of glycemic control. Development of insulin resistance has a deleterious impact on control of glycemia, which is often corrected by increasing the dosage of insulin. Worsening insulin resistance leads to additional increases in the insulin dosage to maintain control of glycemia. Spontaneous improvement in insulin resistance without a corresponding decrease in the insulin dosage may result in asymptomatic hypoglycemia, glucose counterregulation, and a transition from erratic glycemic control caused by insulin resistance to erratic glycemic control caused by the Somogyi phenomenon.*

Stress hyperglycemia should be suspected if the cat is visibly upset, aggressive or struggles during restraint and the venipuncture process. But stress hyperglycemia can also be present in diabetic cats that are easily removed from the cage and do not resist the blood sampling procedure. These cats are scared but rather than become aggressive, they remain crouched in the back of the cage, often have dilated pupils, and do not resist handling. Stress hyperglycemia should also be suspected when there is disparity between assessment of glycemic control based on results of the history, physical examination and stability of body weight, and assessment of glycemic control based on results of blood glucose measurements, or when the initial blood glucose concentration measured in the morning is in an acceptable range (ie, 150 to 250 mg/dl) but subsequent blood glucose concentrations increase steadily throughout the day ***(Figure 4)***. Once stress hyperglycemia develops it is a perpetual problem and blood glucose measurements can no longer be considered accurate. If stress hyperglycemia is suspected, a switch from reliance on serial blood glucose curves generated in the veterinary hospital to reliance on blood glucose results generated by the owner in the less stressful home environment (ie, marginal ear vein prick technique)[20] or evaluation of serum fructosamine concentrations obtained prior to and 2–3 weeks after adjusting the insulin treatment regimen should be done, in addition to the history and physical examination findings.

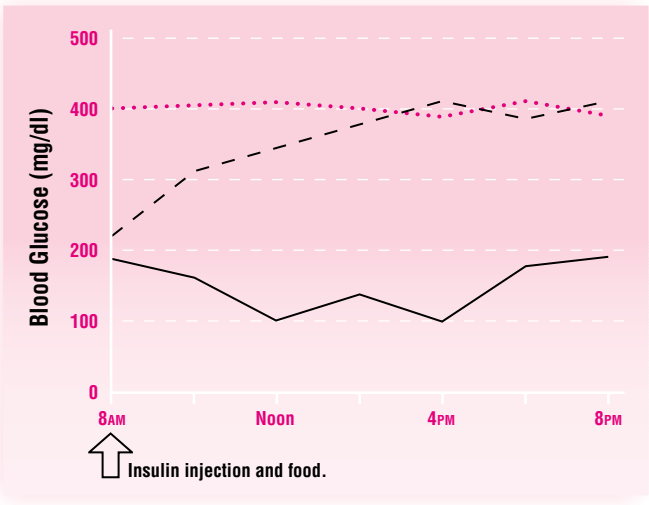

Figure 4. *Blood glucose curves in a 5.3 kg male cat receiving 2 U recombinant human Ultralente insulin (solid black line) 2 weeks after initiating insulin therapy, 2 U recombinant human Ultralente insulin (dashed black line) 2 months later, and 6 U recombinant human Ultralente insulin (dotted pink line) 4 months later. The insulin dosage had been gradually increased based on results of blood glucose curves. The owner reported minimal clinical signs regardless of the insulin dosage and the cat had maintained its body weight. The cat became progressively more fractious during each hospitalization, supporting stress-induced hyperglycemia as the reason for the discrepancy between blood glucose values and other parameters used to evaluate glycemic control. (From Feldman EC, Nelson RW.* Canine and Feline Endocrinology and Reproduction, *2nd ed. Philadelphia, WB Saunders Co, 1996; 373.)*

REFERENCES

1. Nelson RW, Feldman EC, Ford SL, Griffey SM. Transient clinical diabetes mellitus in cats: 10 cases (1989-1991). *J Vet Intern Med* 1998; 13:28-35.
2. Panciera DL, Thomas CB, Eicker SW, Atkins CE. Epizootiologic patterns of diabetes mellitus in cats: 333 cases (1980–1986). *J Am Vet Med Assoc* 1990; 197:1504-1508.
3. Scarlett JM, Donoghue S. Associations between body condition and disease in cats. *J Am Vet Med Assoc* 1998; 212:1725-1731.
4. Truglia JA, Livingston JN, Lockwood DH. Insulin resistance: Receptor and post-binding defects in human obesity and non-insulin-dependent diabetes mellitus. *Am J Med* 1985; 979(Suppl 2B):13-22.
5. Biourge V, Nelson RW, Feldman EC, Willitis NH, Morris JG, Rogers QR. Effect of weight gain and subsequent weight loss on glucose tolerance and insulin response in healthy cats. *J Vet Intern Med* 1997; 11:86-91.
6. Fettman MJ, Stanton CA, Banks LL, Johnson DE, Hegstad RL, Johnston S. Effects of weight gain and loss on metabolic rate, glucose tolerance, and serum lipids in domestic cats. *Res Vet Sci* 1998; 64:11-16.
7. Johnson KH, O'Brien TD, Betsholtz C, Westermark P. Islet amyloid, islet amyloid polypeptide and diabetes mellitus. *N Engl J Med* 1989; 321:513-518.
8. Lutz TA, Rand JS. Plasma amylin and insulin concentrations in normoglycemic hyperglycemic cats. *Can Vet J* 1996; 37:27-34.
9. Young AA, Gedulin BR, Rink TJ. Dose-responses for the slowing of gastric emptying in a rodent model by glucagon like peptide (7-36)NH2, amylin, cholecystokinin, and other possible regulators of nutrient uptake. *Metabolism* 1996; 45:1-3.
10. Gedulin BR, Rink TJ, Young AA. Dose-response for glucagonostatic effect of amylin in rats. *Metabolism* 1997; 46:67-70.
11. Lorenzo A, Razzaboni B, Weir GC, Yanker BA. Pancreatic islet cell toxicity of amylin associated with type-2 diabetes mellitus. *Nature* 1994; 368:756-760.
12. Hiddinga HJ, Eberhardt NL. Intracellular amyloidogenesis by human islet amyloid polypeptide induces apoptosis in COS-1 cells. *Am J Pathol* 1999; 54:1077-1088.
13. Goossens MMC, Nelson RW, Feldman EC, Griffey SM. Response to insulin treatment and survival in 104 cats with diabetes mellitus (1985-1995). *J Vet Intern Med* 1998; 12:1-6.
14. Hoenig M, Hall G, Ferguson D, Jordan K, Henson M, Johnson K, O'Brien T. A feline model of experimentally induced islet amyloidosis. *Am J Pathol* 2000; 157:2143-2150.
15. Nelson RW, Lynn RC, Wagner-Mann CC, Michels GM. Efficacy of protamine zinc insulin for treatment of diabetes mellitus in cats. *J Am Vet Med Assoc* 2001; 218:38-42.
16. Rosenstock J, Park G, Zimmerman J, US Insulin Glargine (HOE 901) Type 1 Diabetes Investigation Group. Basal insulin glargine (HOE901) versus NPH insulin in patients with type 1 diabetes on multiple daily insulin regimens. *Diabetes Care* 2000; 23:1137-1142.
17. Rosenstock J, Schwartz SL, Clark CM Jr, Park GD, Donley DW, Edwards MB. Basal insulin therapy in type 2 diabetes: 28-week comparison of insulin glargine (HOE901) and NPH insulin. *Diabetes Care* 2001; 24:631-636.
18. Marshall RD, Rand JS. Comparison of the pharmacokinetics and pharmacodynamics of glargine, protamine zinc and porcine lente insulins in normal cats. *J Vet Intern Med* 2002; 16:358 (abstr).
19. McMillan FD, Feldman EC. Rebound hyperglycemia following overdosing of insulin in cats with diabetes mellitus. *J Am Vet Med Assoc* 1986; 188:1426-1431.
20. Thompson MD, Taylor SM, Adams VJ, Waldner CJ, Feldman EC. Comparison of glucose concentrations in blood samples obtained with a marginal ear vein nick technique versus from a peripheral vein in healthy cats and cats with diabetes mellitus. *J Am Vet Med Assoc* 2002; 221:389-392.