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Diabetes Remission in Cats: Which Insulin Is Best?

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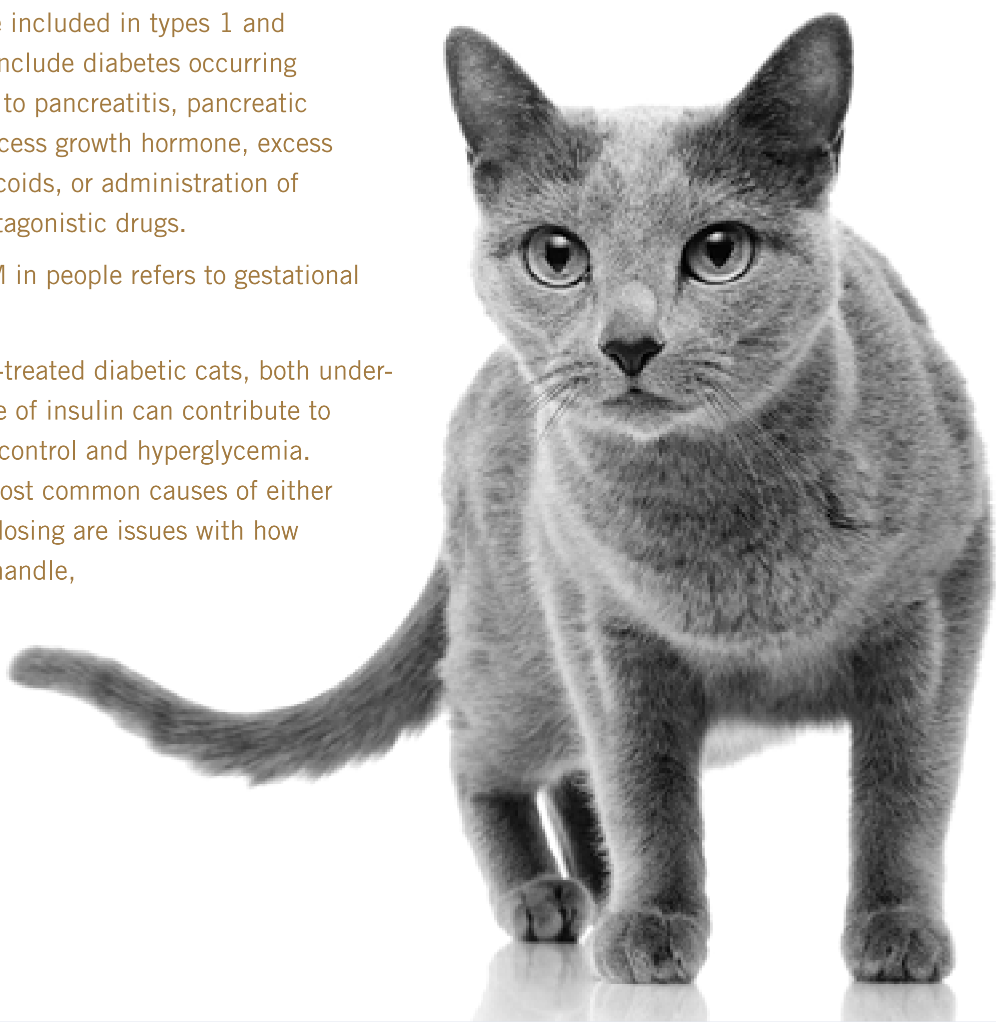
There is interest in increasing remission rates among cats diagnosed with diabetes mellitus (DM). The question is, how can diabetic cats best be treated to enhance the possibility of resolving their hyperglycemia and eliminating their need for insulin administration via injection? Several factors—including effective insulin therapy—can contribute to the potential for remission. Insulin's role involves controlling hyperglycemia to a degree that allows recoverable (viable) pancreatic β cells to produce sufficient endogenous insulin to maintain normoglycemia.

Important Considerations in Feline Diabetes

- No single insulin type is more likely to induce remission of DM; rather, control of hyperglycemia enhances the possibility of achieving remission. Remission of DM in cats is associated as much, or more, with the introduction of a low-carbohydrate, high-protein diet than with a particular type of insulin.
- No test can differentiate between type 1 and type 2 DM in cats. “Type” of diabetes in cats is derived from people and applied similarly to cats.
  - **TYPE 1** DM in people is defined as an absolute insulin deficiency that is permanent (lifelong) and requires insulin administration for long-term survival. Remission is extremely rare.
  - **TYPE 2** DM in people is defined as a relative insulin deficiency, typically associated with both insulin resistance and an inability to synthesize and secrete sufficient insulin to maintain glycemic control. Insulin resistance is most commonly associated with obesity, lack of exercise, and consumption of a diet too high in carbohydrates and too low in fiber. Remission of this type of DM is not only possible but is relatively common.
  - **TYPE 3** DM in people refers to an association with diseases or factors other than those included in types 1 and 2. These include diabetes occurring secondary to pancreatitis, pancreatic cancer, excess growth hormone, excess glucocorticoids, or administration of insulin antagonistic drugs.
  - **TYPE 4** DM in people refers to gestational diabetes.
- Among insulin-treated diabetic cats, both under- and overdosage of insulin can contribute to poor glycemic control and hyperglycemia. Some of the most common causes of either under- or overdosing are issues with how owners store, handle, or administer insulin.



OVERVIEW OF HUMAN AND FELINE DIABETES

Background

Based on histologic evidence of islet amyloidosis and β cell loss, as well as data from clinical trials, as many as 60% to 80% of cats with DM appear to have a condition similar to type 2 diabetes in humans.[1–4] The clinical similarities between people and cats with DM include a higher incidence of type 2 versus type 1 diabetes in both species; onset in middle age; an association with obesity, inactivity, and improper diet; related complications such as neuropathy; and the potential for not needing exogenous insulin therapy through the use of proper treatment strategies.[3] As in people, some diabetic cats have been shown to develop "insulin resistance," defined as a reduced capacity of tissues to respond to insulin.

Cats with intrinsically low insulin sensitivity are at increased risk of developing glucose intolerance with weight gain. Male cats develop DM more commonly than female cats, perhaps partly because males have lower insulin sensitivity.[5] This gender predisposition is one area in which there is an obvious difference between diabetic people and diabetic cats.

Obesity is the most common cause of insulin resistance in people and is considered a likely cause for resistance with a similar physiologic background in cats. The increase in obesity is paralleled with an increase in the incidence of type 2 diabetes. Adipose tissue (particularly central visceral stores) is an active endocrine organ and part of the innate immune system. Adipose tissue in lean people secretes relatively high levels of the adipocytokine adiponectin, which has antiinflammatory action and is associated with increased insulin sensitivity and, therefore, a favorable metabolic status. With obesity, adiponectin secretion decreases and large amounts of nonesterified fatty acids, leptin, and proinflammatory cytokines are secreted by adipocytes and/or activated macrophages within the adipose tissue. These secretions impair insulin signaling and induce or worsen insulin resistance.[6]

It is relevant to point out that not all obese cats become diabetic and that not all diabetic cats are obese. In one report, it was estimated that at the time of diagnosis, about 50% to 60% of diabetic cats are obese, 30% to 40% have a normal weight, and 5% to 10% are underweight.[7] Insulin resistance is also commonly associated with infection or inflammatory conditions. Dysfunction of β cells is also crucial in the development of type 2 DM because not all obese individuals (people or cats) develop diabetes.

The exact nature of the underlying mechanisms leading to β cell dysfunction is unclear. Islet cell mass in individuals with type 2 DM is reduced by 40% to 60% as a result of apoptosis (a form of cell death). Apoptosis is likely triggered by a combination of genetic and acquired factors. Acquired factors include glucose toxicity, lipotoxicity, and increased deposition of amyloid in islets.[7]

- In contrast to acute hyperglycemia, which stimulates insulin secretion and glucose utilization, chronic hyperglycemia (glucose toxicity) impairs insulin secretion and contributes to insulin resistance. Interestingly, one of the first experiments on glucose toxicity was performed in cats: In 1948, researchers administered large doses of glucose to normal cats and induced permanent hyperglycemia, degeneration of islets, and ketonuria.[8] In more recent studies, chronic hyperglycemia in previously normal cats resulted in insulin concentrations consistent with type 1 DM within 5 days.[9]
- Lipotoxicity refers to the deleterious effects fatty acids can have on β cells, a condition that likely requires hyperglycemia to be fully manifested.[10]
- Islet amyloid is derived from amylin, a protein co-secreted with insulin from the pancreas. In a state of chronic increases in insulin secretion, as occurs with resistance, secretion of amylin also increases. This, in turn, can lead to increased islet deposition of amyloid that contributes to β cell apoptosis. Amyloid deposition is found in 65% to 90% of cats with DM but is also common in nondiabetic older cats. Therefore, amyloid is likely to be a contributing but not the primary cause of β cell failure.[11,12]

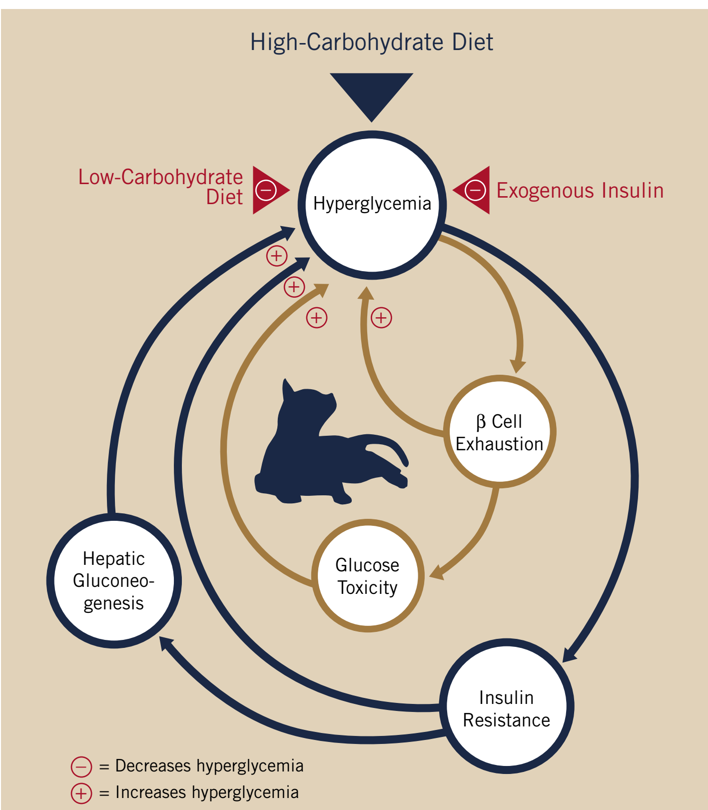
Thus, the pathogenesis of DM in insulin-resistant cats is believed to involve a cycle that includes insulin resistance in tissues (i.e., insulin receptors that are less responsive than normal), increased insulin secretion, hyperglycemia, and, ultimately, β cell loss with reduced concentrations of insulin secretion (Figure 1). Remission is believed possible through reduction and stabilization of blood glucose concentrations in cats that have recoverable β cell function.[13,14] One must remember, however, that good diabetic control is often difficult to achieve. Treatment of diabetes always involves an attempt to avoid significant under- or overdosing of insulin, as either can result in hyperglycemia, apparent resistance, and further β cell damage.

Remission of the Diabetic State

Factors that positively influence the likelihood of remission include the following:

- **Early diagnosis:** Cats in the early stages of DM are more likely to have recoverable β cells compared with cats that have more chronic disease; therefore, earlier diagnosis gives cats a better chance of achieving remission.[15]
- **Extent of β cell damage:** Some cats are unable to achieve remission even with early treatment because either their β cells lack the capacity to recover and produce insulin or they have persistent insulin resistance due to consumption of a less-than-ideal diet, obesity, inactivity, chronic inflammation, chronic infection, or any of a wide variety of other conditions. Inability to achieve diabetes remission could also be the result of irreversible β cell damage, whether simply from chronic type 2 diabetes or from destruction of cells by other causes, such as pancreatic cancer (type 3 DM). Further, some cats appear to progress from type 2 to type 1 DM regardless of the level of care provided,[14,16] perhaps as a result of ongoing immune-mediated destruction of pancreatic β cells.
- **Effective insulin treatment:** The goal of insulin treatment is to maintain blood glucose concentrations between 120 and 300 mg/dl (some researchers suggest attempting to maintain blood glucose concentrations between 90 and 270 mg/dl).[5] Maintaining blood glucose concentrations within the standard laboratory reference range (~75 to 110 mg/dl) is not recommended in people or cats because attempts to maintain normoglycemia are often associated with overdosage, which can lead to severe life-threatening hypoglycemia and/or severe hyperglycemia. However, underdosage results in continuing significant hyperglycemia and must also be avoided.
- **Diet:** Change of diet alone, particularly to one that is low in carbohydrates and high in protein, may allow remission in about one-third of cats on insulin therapy according to some authors,[17–19] whereas others claim remission rates in excess of 50%.[5] A diet that is also high in fiber would likely be beneficial.
- **Monitoring:** Low-stress or at-home blood glucose monitoring is preferred as an aid in achieving glycemic control.[15,20] The answer to the question of how often diabetic cats should be monitored remains elusive, but an appropriate monitoring schedule likely depends at least in part on individual cats and their owners.
- **Duration of therapy:** Although many cats that enter remission do so within 16 weeks of initiating insulin treatment, remission has been reported to occur as long as 30 months after diagnosis and initiation of exogenous insulin therapy.[17–19]

Figure 1. The vicious cycle of diabetes mellitus in cats.



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Remission may last for years, but diabetic cats that no longer require exogenous insulin are not generally considered "cured." Many cats that go into remission are likely to have ongoing subclinical pathology and the potential for recurrence.[14] The exception would be cats that are misdiagnosed with DM when they actually have temporary stress-induced hyperglycemia. Remission in feline diabetes is comparable to the postpartum status of women with gestational diabetes (type 4 DM). Such women develop insulin resistance because of insulin antagonism associated with the progesterone concentrations necessary to maintain pregnancy. Ultimately, progesterone-induced antagonism can lead to hyperglycemia during pregnancy, but there is the potential for return to euglycemia once progesterone decreases after pregnancy.
Studies have shown that

women with a history of gestational diabetes may be 70% more likely to develop clinical diabetes later in life than women with no such history.[21,22]

Feline DM is a disease that requires lifelong care and monitoring, even during phases of remission. The onset of clinical disease in cats can be associated with events that increase insulin resistance, most notably indoor confinement and physical inactivity; obesity; and feeding a high-carbohydrate, low-protein diet. The second tier of contributors to chronic insulin resistance includes chronic infection (especially periodontal disease, skin disease, or urinary tract infection) and chronic inflammatory conditions (especially periodontal disease and pancreatitis). Certain medications (e.g., glucocorticoids) are known to cause insulin resistance. Many other chronic illnesses (e.g., kidney disease, heart failure) can lead to insulin resistance as well. Much less common but still important causes of insulin resistance include diseases associated with excess production of insulin antagonistic hormones, such as acromegaly (growth hormone) and hyperadrenocorticism (glucocorticoids).[3,23–25]

Because DM in some cats is similar to type 2 diabetes in humans, management of the disease should also be similar. The cornerstones of type 2 diabetes management in people include weight loss, switching to a diet lower in carbohydrates and higher in fiber, and exercise. Prevention and/or treatment of concurrent diseases (especially those associated with infection and/or inflammation) can assist in stabilizing blood glucose concentrations and reducing the need for insulin.[17–19,26,27]

Because cats are generally diagnosed after chronic hyperglycemia develops, stabilization of blood glucose with insulin may be a core therapeutic strategy along with changing the diet. Veterinary practitioners must decide which insulin to use based on available published data.

The Importance of Diet

Diet is one of the understated factors in reported remission rates among cats with DM. This becomes obvious when reviewing studies reported to date. Switching diabetic cats that are already being treated with insulin to a low-carbohydrate, high-protein diet can have a significant influence on the likelihood of remission. This is true in as many as 50% of afflicted cats.[5] The bottom line is that cats are metabolically adapted to consume primarily protein and fat, and diets high in carbohydrates appear to be unfavorable. It has been shown that feeding a low-carbohydrate, high-protein diet results in better clinical control and increased rates of diabetic remission. According to data from the University of Zurich, Switzerland, remission rates are 15% to 25% when diets with variable compositions are fed and exceed 50% when high-protein, low-carbohydrate diets are fed. The positive effect of diet change is often evident before any apparent loss of body weight can be documented.[5]

THE RESEARCH: INSULIN THERAPY AND REMISSION IN CATS

There has been discussion regarding the use of porcine, bovine, and human insulins and the importance of their differing amino acid sequences as compared with natural cat insulin. Dog and porcine insulins are similar, as are cat and bovine insulins. Experience suggests that amino acid differences are not critical in determining the insulin type used in managing DM. Rather, it is the dose and frequency of insulin administration, diet, and many other factors that determine success or failure in therapy or the achievement of remission. Also, because any cat may respond better to one insulin than to another, having several choices is always an advantage.

> When combined with other key factors in diabetes management, any insulin that helps achieve proper glycemic control can enhance the chances for remission.

Porcine Insulin Zinc Suspension without Dietary Restrictions

Several studies have evaluated the use of porcine insulin zinc suspension (Vetsulin® [United States] and Caninsulin® [outside the US], Intervet/Schering-Plough Animal Health) in the management of diabetic cats. Porcine insulin zinc suspension is classified as an intermediate-acting Lente insulin. Most studies include both cats with newly diagnosed DM and those with previously diagnosed and treated DM. Further, cats were not required to be on a specific diet to be entered into some studies. This information is useful, especially considering the potential variation among cats with diabetes and the variability of success in controlling their diet.

The largest studies of insulin therapy without dietary modification carried out in the United States are the field trials whose data supported the addition of the feline claim to the Vetsulin label. Reported remission rates in two field trials were 33% (4 of 12) and 13% (8 of 61) of the cats studied, respectively.[28] The generally tighter serum glucose control, based on fructosamine and mean glucose concentrations, achieved in the first trial may have been responsible for the higher percentage of remissions. These remission rates were achieved without changes in diet. Remission rates might have been higher if low-carbohydrate diets (with or without increased fiber) had been required in all cats.

Other studies that grouped new and previously treated diabetic cats and that had no dietary requirements identified similar numbers of cats going into remission with porcine insulin zinc suspension treatment. These prospective clinical studies reported 41% (13 of 32 cats) in remission within 16 weeks of beginning porcine insulin zinc suspension treatment, 28% (7 of 25 cats) in remission within 12 months, and 17% (8 of 46 cats) reaching remission within about 16 weeks.[29–31]

Porcine Insulin Zinc Suspension in Cats with Diabetes Mellitus and Severe Ketoacidosis

Porcine insulin zinc suspension is the only available insulin for which diabetes remission was documented in cats that previously had severe diabetic ketoacidosis (DKA). Sieber-Ruckstuhl and associates conducted a retrospective study of cats presented to the veterinary teaching hospital at the University of Zurich, Switzerland, from 2003 to 2007.[32] Cats newly diagnosed with documented diabetes and ketoacidosis were studied. Once DKA resolved via treatment with a standardized protocol that included the use of short-acting insulin, insulin therapy was changed to porcine insulin zinc suspension (Vetsulin). This insulin was given at a starting dose of 0.25 to 0.5 U/kg q12h. The cats were also fed a commercial low-carbohydrate, high-protein diet. Seven of 12 (58%) cats that were initially ketoacidotic achieved remissions lasting as long as 3 years. These cats had more pancreatic disease, bacterial urinary tract infections, and cardiomyopathy than cats at the same hospital with newly diagnosed uncomplicated DM achieving remission. Thus, DKA, once thought to occur only in cats with type 1 DM, has been documented in cats with type 2 disease as well. These data demonstrate that cats with DKA can eventually achieve remission from diabetes through appropriate insulin and dietary therapy.

Lente Insulin versus Insulin Glargine in Cats Fed a Low-Carbohydrate, High-Protein Diet

A randomized, open study by Weaver and colleagues investigated human recombinant Lente insulin (0.5 U/kg q12h; $n = 7$) versus insulin glargine (0.5 U/kg q24h; $n = 6$). There were three newly diagnosed cats in the Lente-treated group and five in the insulin glargine–treated group; the other five cats had been previously treated, but glycemic control was poor. All the cats were fed low-carbohydrate, high-protein diets and were monitored for 12 weeks. Three of the Lente-treated cats (43%) and one of the insulin glargine–treated cats (17%) went into remission.[33]

Reports of diabetic cats fed a low-carbohydrate, high-protein diet include a study by Boari et al that investigated five newly diagnosed and previously treated diabetic cats administered insulin glargine at an initial dose of 0.25 to 0.5 U/kg twice daily. They reported that two of five cats (40%) went into remission within 12 weeks.[34] Roomp and Rand looked primarily at previously treated cats (50 of 55 cats) and began treatment with insulin glargine twice a day (dose not specified) with the addition of home monitoring via glucose curves (another glycemic control factor); 64% (35 of 55) of the cats achieved remission.[15]

A study by Hall and colleagues suggested that diet did not have the intended effect on feline metabolism. Their study was designed to differentiate between the effects of a maintenance diet (six cats) and a low-carbohydrate, high-protein diet (six cats) in diabetic cats. The authors noted that their maintenance diet may have been too low in carbohydrates to serve as a control. Also, obese cats did not lose weight and cats that were not overweight at the beginning of the study became overweight during the study. Half the cats were newly diagnosed with DM, and all received insulin glargine at an initial dose of 0.25 U/kg twice daily. Two cats (17%)—one from each diet group—went into remission within 10 weeks.[35]

Lente Insulin, Protamine Zinc Insulin, or Insulin Glargine in Newly Diagnosed Cats on a Low-Carbohydrate, High-Protein Diet

In 2005, Marshall and Rand reported a prospective clinical study limited to newly diagnosed diabetic cats fed a low-carbohydrate, high-protein diet. Although this study is commonly cited, only an abstract—not the complete study—has been published.[36] Inclusion criteria and randomization techniques used were not reported, and this study should remain outside of decision processes until it has been appropriately reviewed and published. Cats were treated with Lente insulin, protamine zinc insulin, or insulin glargine at an initial dose of 0.25 to 0.5 U/kg twice daily. In this study, 25% (two of eight) of Lente-treated cats, 38% (three of eight) of protamine zinc insulin–treated cats, and 100% (eight of eight) of insulin glargine–treated cats went into remission within 16 weeks. The high level of remission observed in the

> Additional research will likely continue to support the evidence that in newly diagnosed cats on a total diabetes management program, including dietary control, remission rates with Vetsulin treatment will be comparable to those achieved with other insulin types.

insulin glargine–treated cats has not been replicated in other studies.

Porcine Insulin Zinc Suspension versus Insulin Glargine

No statistical difference in remission rates can be shown between Lente insulin (Vetsulin) and insulin glargine when diet is controlled.[37] A meta-analysis of the available data regarding cats fed a low-carbohydrate, high-protein diet demonstrates no statistically significant difference ($P = .196$) in remission rates among diabetic cats treated with Lente insulin (44.4%) and those treated with insulin glargine (58.8 %) (Table 1). The achievement of good glycemic control in any diabetic cat, regardless of insulin type used, improves the chances for achieving remission when used in combination with other factors known to contribute to DM remission in cats.

Conclusion

Based on data from available studies, porcine insulin zinc suspension (Vetsulin) is effective in achieving remission in diabetic cats that are not on a controlled diet (13% to 41%).[28] These results are similar to those achieved with the use of other insulin types under comparable conditions.[16,17,33] In addition, porcine insulin zinc suspension is effective in achieving remission in cats that have had severe DKA (58%).[32] No statistical difference in remission rates can be shown between Lente insulin (including Vetsulin) and insulin glargine when diet is controlled.[37]

Because nearly all of the studies reporting remissions with insulin types other than porcine insulin zinc suspension (Vetsulin) also included other diabetes management strategies (e.g., dietary control) in their design, simple comparison of remissions achieved without considering these factors can be misleading. For example, with the exception of one study, the data available for insulin glargine–treated cats are from studies performed in cats fed a low-carbohydrate, high-protein diet (Table 1). Switching to this type of diet led to remission in three of nine cats that were already being treated and stabilized with insulin.[18] Such a switch also increased the number of remissions in a study by Bennett and associates in which diabetic cats were being treated with various insulins; 68% of cats on a low-carbohydrate, high-protein diet achieved remission compared with 41% of cats on a moderate-carbohydrate, high-fiber diet.[17] The wide range of remission rates reported in the literature with insulin glargine treatment reinforces the influence of multiple factors in achieving remission.

In the often-cited Marshall and Rand study,[36] of eight newly diagnosed cats on a low-carbohydrate, high-protein diet treated with Lente insulin, the percentage of cats achieving remission (25%) is similar to that reported in several other studies without such dietary requirements (13% to 41%).[28–31] Based on the evidence that dietary control in conjunction with Vetsulin treatment promotes remission and that remission is more likely in newly diagnosed cats, it is reasonable to expect that remission rates may exceed 50%, as reported by Sieber-Ruckstuhl et al,[32] when Vetsulin treatment is combined with other management factors, including early diagnosis, good glycemic control, diet, and frequent at-home testing.[15,17,18] This is evident from the summary of studies (Table 1) in which remission rates reached 44.4% when only one management factor (i.e., dietary control) was added to insulin therapy. Additional research will likely continue to add supporting evidence that newly diagnosed cats on a total diabetes management program, including dietary control, can achieve remission rates with porcine insulin zinc suspension treatment that are comparable to rates associated with other insulin types.

Table 1. Meta-Analysis of Lente Insulin* vs. Insulin Glargine When Cats Are Fed a Low-Carbohydrate, High-Protein Diet†

	No. (%) of Cats Achieving Remission	
Study	***Lente Insulin***	***Insulin Glargine***
Sieber-Ruckstuhl et al[32]	7/12 (58.3%)‡	—
Weaver et al[33]	3/7 (42.9%)‡	—
Marshall and Rand[36]	2/8 (25.0%)‡	8/8 (100.0%)§
Roomp and Rand[15]	—	35/55 (63.6%)§
Boari et al[34]	—	2/5 (40.0%)§
Hall et al[35]	—	2/12 (16.7%)§
Remission Rate	**12/27 (44.4%)‡**	**47/80 (58.8%)§**

*Vetsulin/Caninsulin is classified as a Lente insulin and was the specific Lente insulin used in the studies by Sieber-Ruckstuhl et al and Marshall and Rand.

†Combining the Lente insulin and insulin glargine studies, the remission rate is 44.4% (12 of 27) for Lente insulin compared with 58.8% (47 of 80) for insulin glargine. The null hypothesis of equal remission rates was tested with a two-tailed chi-square test, yielding a P value of .196. Therefore, the conclusion can be made that there is insufficient evidence in the available data to declare a statistically significant difference between remission rates for Vetsulin and insulin glargine.

‡If the cats in studies that used recommended dietary controls (similar to the Marshall and Rand study) are considered, a high percentage of cats treated with Vetsulin or Lente insulin (44%) achieved remission.

§If the cats in studies that used recommended dietary controls (similar to the Marshall and Rand study) are considered, the percentage of cats achieving remission when treated with insulin glargine (59%) is similar to that for cats treated with Vetsulin or Lente insulin.

SUMMARY

In the context of remission, the goal of insulin therapy is to lower blood glucose concentrations long enough to allow glucose toxicity to resolve. If adequate numbers of viable β cells remain, diabetic cats may be able to produce sufficient endogenous insulin to maintain glycemic control. Control of hyperglycemia in cats using one of several available various insulin types, as presented in this article, can enhance the possibility of remission when used in conjunction with early diagnosis, good glycemic management, and proper diet. Porcine insulin zinc suspension (Vetsulin) and insulin glargine can be expected to achieve similar remission rates under these same conditions.

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