PHARMACOLOGY

Understanding Basal Insulins: A Steady Approach to Canine Diabetes Management

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Abstract

Basal insulins are an excellent option for managing canine diabetes. Their predictable and long-lasting duration of action allows frequent dose adjustments to quickly achieve glycemic control. In many cases, dogs can be successfully managed with once-daily dosing, and insulin administration can be separated from feeding. This consistent insulin response, combined with a simpler treatment routine and reduced mealtime stress, has the potential to significantly improve quality of life for diabetic dogs and their owners.

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Take-Home Points

- Basal insulins are an excellent choice for treating diabetic dogs.
- They provide a consistent, predicable glucose-lowering effect with minimal glycemic variability within and between days.
- Many dogs achieve glycemic control with once-daily dosing, improving compliance and quality of life.
- Continuous glucose monitoring is essential for titrating basal insulin doses.
- Basal insulin administration can be uncoupled from mealtime, reducing stress and allowing more flexible feeding schedules.

Diabetes mellitus is a common endocrinopathy in dogs and cats, and, although treatable, an estimated 20% to 30% of patients are euthanized within the first year of diagnosis for many reasons related to perceptions about management (**BOX 1**).[1] Therefore, it is essential that veterinarians tailor treatment plans specifically to the individual pet and owner, based on the owner's abilities and available resources. The treatment goals for canine diabetes are to resolve clinical signs and minimize adverse effects, in contrast to human medicine, where tight glycemic control and sustained euglycemia are desired.[2]

Exogenous insulin is essential for diabetic dogs, and there is no universal "best" insulin choice. Factors to consider when choosing an insulin for an individual patient include insulin pharmacology, the owner's specific goals and financial resources, expected owner compliance, desired diet, and planned monitoring strategy. Fortunately, veterinarians today have more options than ever when choosing an exogenous insulin, including newer basal insulins that can help achieve rapid glycemic control and improve quality of life for both pets and their owners.

BOX 1
Common Reasons for Euthanasia of Diabetic Dogs[1]

- Costs associated with treatment (44%)
- Concerns for pet welfare (35%)
- Concerns for impact on owner lifestyle (32%)
- Animal age (37%)
- Concurrent diseases (45%)
- Difficulty achieving glycemic control (35%)

Physiologic Insulin Secretion

Endogenous insulin secretion follows a "basal-bolus" pattern. In the basal phase, insulin is secreted continuously at a relatively constant rate. The main function of basal insulin is to partially suppress hepatic glucose production and lipolysis during periods of fasting, preventing excessive hyperglycemia and ketogenesis while still allowing sufficient glucose output to maintain euglycemia.[2,3] In contrast, bolus insulin is secreted at mealtime in response to nutrients absorbed from the gastrointestinal tract, especially carbohydrates, fats, and proteins, as well as gastric emptying rate and the influence of intestinal hormones.[2,3] Bolus insulin primarily functions to minimize postprandial hyperglycemia. Diet composition can significantly impact the magnitude and duration of the bolus insulin phase.[4-6] In dogs, bolus insulin increases rapidly within minutes after eating, peaking within the first 30 minutes, and can remain increased for up to 6 to 9 hours depending on diet composition.[3]

CASE EXAMPLE 1
Newly Diagnosed Diabetes Mellitus in a German Shorthaired Pointer

Signalment and History
A 4-year-old female spayed German shorthaired pointer presented with a history of acute-onset polyuria and polydipsia of 2 weeks' duration, mild polyphagia, and 2 days of hyporexia and hematochezia.

Physical Examination and Key Diagnostic Findings
On physical examination, the patient weighed 38 kg (84 lb) with a body condition score of 8/9. She was anxious and displayed signs of mild cranial abdominal pain. Hematochezia was demonstrated on rectal examination. Diagnostic testing revealed the following results consistent with uncomplicated diabetes mellitus and mild pancreatitis:

TABLE A Daily Interstitial Glucose (IG) Values and Dose Adjustments

DAY OF TREATMENT	DAILY MEAN IG (MG/DL)	DAILY IG NADIR (MG/DL)	ACTION	NOTES
1	401	≥350	Start 19 U SC q24h	0.5 U/kg once daily
2	401	≥350	Increase to 23 U	20% dose increase
3	401	≥350	Increase to 27 U	20% dose increase
4	400	≥350	Increase to 32 U	Primarily eating new diet; 20% dose increase
5	400	400	No change	
6	373	340	Increase to 35 U	10% dose increase
7	359	250	Increase to 38 U	10% dose increase

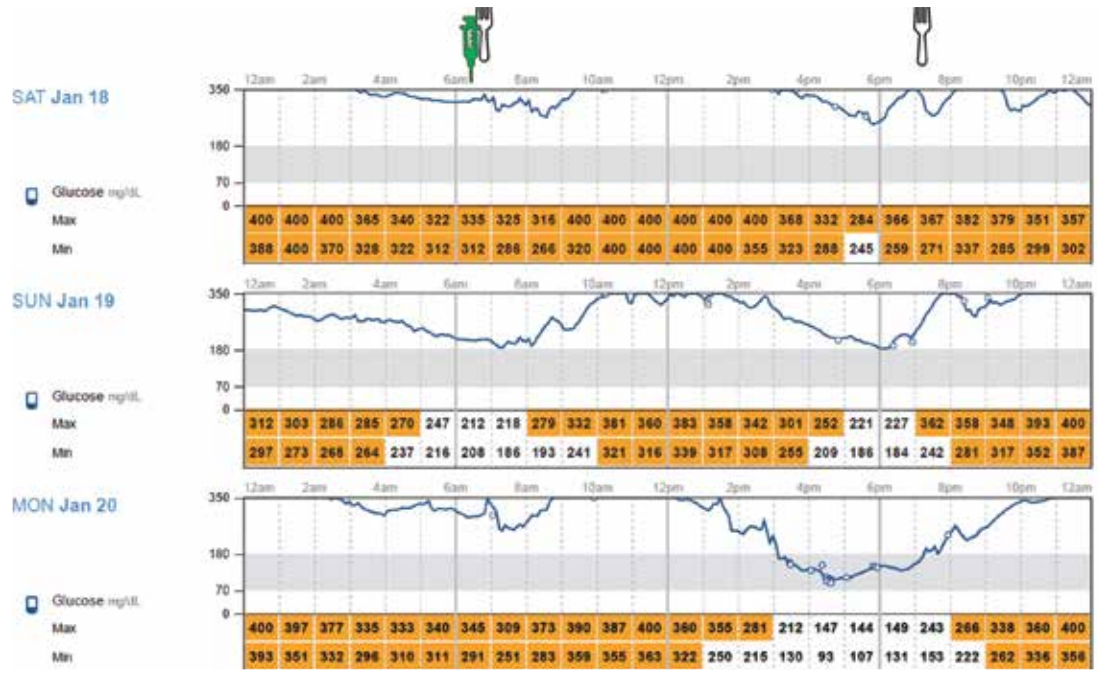

FIGURE A. Interstitial glucose monitor curves on days 10 through 12 of once-daily insulin degludec therapy at a dose of 38 U q24h (1 U/kg/d) **(green syringe)** and twice-daily meals **(forks)**.

- Glucose 361 mg/dL (reference range, 82–132 mg/dL) with glucosuria
- No ketonuria
- Pancreatic lipase immunoreactivity 554 µg/L
- No ova or parasites seen on fecal examination

Case Concerns and Treatment Goal

This dog was at risk for elective euthanasia due to both owner and patient factors:

- **Owner factors:** Elderly with limited mobility; experiencing significant anxiety and overwhelm following the diabetes mellitus diagnosis, particularly regarding insulin administration and glucose monitoring.
- **Patient factors:** Highly energetic and reactive; attempted to bite experienced veterinary staff during insulin injections in the hospital

Therefore, the treatment goal for this owner and patient was to rapidly achieve glycemic control using the simplest possible regimen while minimizing the risk of complications.

Treatment Plan

- A low-fat diet was recommended. A kibble diet was selected due to cost considerations.
- A continuous glucose monitor was placed.
- Insulin degludec was prescribed with a starting dose of 0.5 U/kg q24h.
- A probiotic, an analgesic, and an appetite stimulant were prescribed as supportive care.

Monitoring and Outcome

The patient's daily mean interstitial glucose (IG) and daily IG nadir for the first 7 days of treatment, along with corresponding actions taken, are shown in **TABLE A**. **FIGURE A** shows the glucose monitor curves on days 10 through 12 after a dose of 38 U q24h was reached. The dog's clinical signs resolved. Considering the owner's low-risk tolerance and unwillingness to continue glucose monitoring, further dose adjustment was not elected.

Traditionally Available Insulins for Dogs

Prior to the availability of basal insulins for the veterinary market, common at-home insulin choices for dogs included those listed in **BOX 2**. Most dogs require twice-daily administration of these insulin types to achieve glycemic control. However, approximately 33% of dogs can be managed with once-daily Vetsulin (Merck) and 57% with once-daily ProZinc (Boehringer Ingelheim).[7,8]

In general, with intermediate-acting insulins, the glucose nadir (i.e., lowest blood glucose concentration) correlates with the peak insulin action. Therefore, the standard of care is a recommendation for these insulins to be administered immediately following a meal. Feeding the dog before administering insulin is important because if the dog eats less than expected, the insulin dose should be reduced to lower the risk of hypoglycemia. However, coordinating food intake with insulin injections can increase caregiver stress, as it requires careful scheduling and ensuring that the dog consumes adequate calories.

All of the traditional insulins, except insulin glargine U-100, are suspensions that must be resuspended prior to each dose (e.g., rolling, shaking). Multiple factors affect absorption, including the degree of precipitation in the vial, appropriate resuspension before injection, and rate of crystal dissolution in the subcutaneous tissue.[2,9] Insulin crystals in the subcutaneous depot vary in size and shape, which leads to inconsistent breakdown, or variable deprecipitation, at the injection site. Therefore, the action of insulin suspensions is

BOX 2

Traditional Insulins for Management of Canine Diabetes

- Porcine lente insulin (e.g., Vetsulin [Merck Animal Heath])
- Protamine zinc recombinant human insulin (e.g., ProZinc [Boehringer Ingelheim Animal Health])
- Neutral protamine Hagedorn insulin (e.g., Humulin N, Novolin N)
- Insulin glargine U-100 (e.g., Lantus, Basaglar, Semglee) for difficult cases

inherently unpredictable and can lead to significant daily glycemic variability (**FIGURE 1**).[10] Glycemic variability refers to fluctuations in blood glucose concentrations within a day and between days. In humans, glycemic variability reflects overall glycemic control and is considered a risk factor for diabetic complications.[11] Traditional insulins are often adequate to meet the clinical goals of canine diabetic management, but they do not mirror physiologic insulin secretion. Their onset of action is too slow and their duration too prolonged to replicate the bolus phase; simultaneously, their action profiles are too peaked and their duration too short to effectively mimic the basal phase.[2]

Basal Insulins in Dogs

Until recently, basal insulin formulations were prohibitively expensive and, therefore, impractical for use in veterinary patients. However, with the introduction of an unbranded biologic (insulin degludec in 2023) and changes in market pricing, some

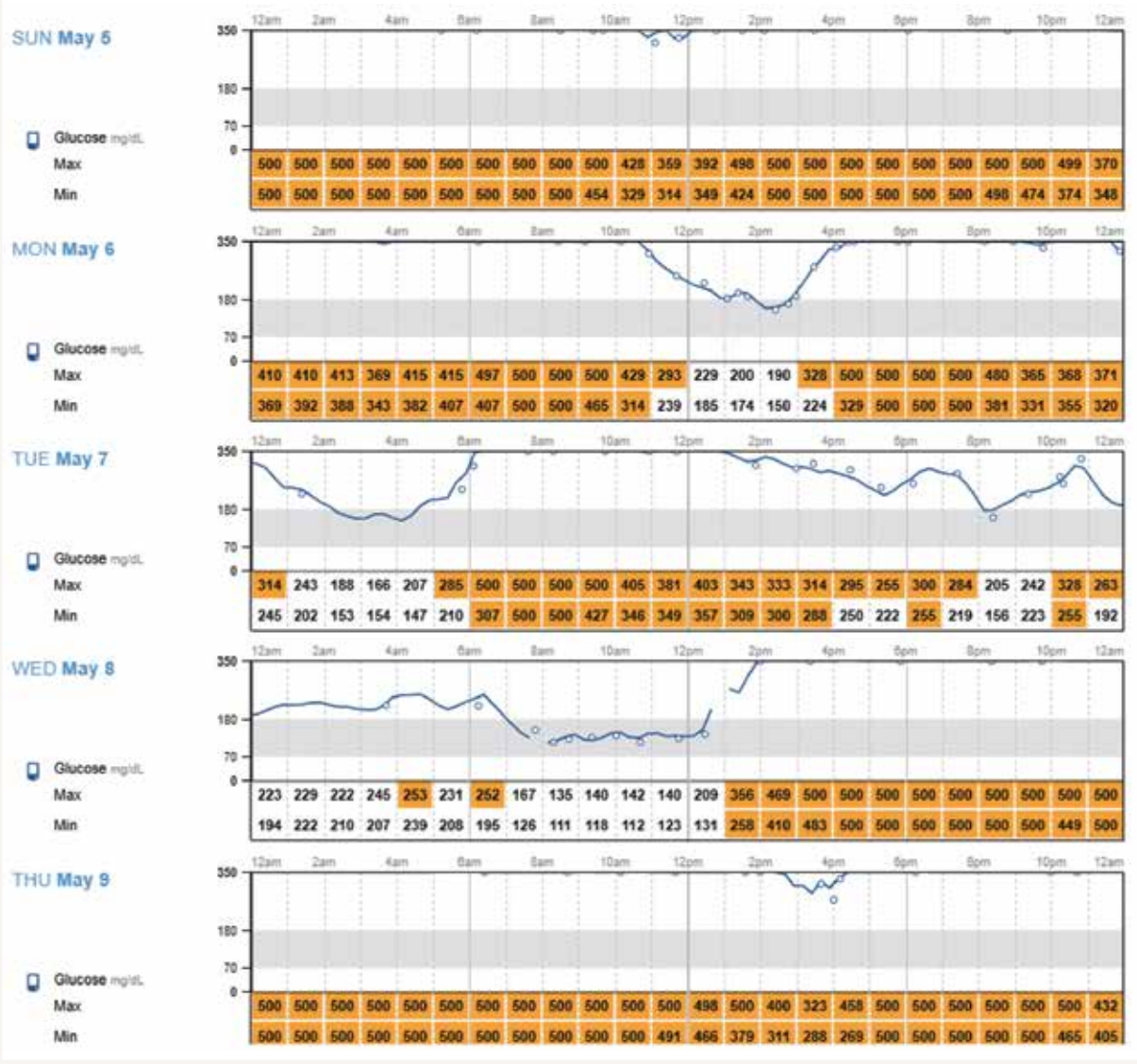

FIGURE 1. Continuous glucose monitoring over 5 days in a dog treated with porcine lente insulin (0.6 U/kg SC q12h). These curves demonstrate an example of the wide glycemic variability that can be observed with insulin suspensions. Glucose values >350 mg/dL are at the upper limit of the daily rectangle, with the gray-shaded rectangles indicating a range of 70 to 180 mg/dL.

basal insulins have become highly accessible and are now among the least expensive insulins on a per-unit basis in the U.S. market.[12]

To be considered a basal insulin, an insulin must have stable and reliable absorption and achieve a long duration of action with minimal intraday and interday variability. This means that the insulin effects are relatively constant at every hour of the day (i.e., peakless profile) and similar from a single day to the next. Basal insulins have more predictable absorption kinetics because they are formulated as solutions rather than suspensions, and the use of insulin pens ensures consistent and accurate delivery. The high predictability of insulin action allows veterinarians to quickly dose-titrate these insulins. Continuous glucose monitoring (CGM) is essential to guide decisions regarding basal insulin dose and frequency and whether a bolus insulin should be added. By using CGM to guide dose change recommendations, glycemic control is rapidly achieved in a median of 14 to 16 days (range, 3 to 99 days).[12,13] Once the ideal dosing and frequency of the basal insulin is determined, less intensive monitoring is needed (**CASE EXAMPLE 1**).[13]

The predictable basal insulin effect also helps minimize the risk of hypoglycemic events.[10,12,14] Unlike intermediate-acting insulins, basal insulins provide a consistent effect throughout the day. This means that the glucose nadir does not necessarily correspond to peak insulin action but instead reflects periods of lowest carbohydrate intake. As a result, the risk of hypoglycemia is low if a meal is skipped (e.g., refused, vomited, deliberately withheld). Additionally, this represents a major shift in the management of canine diabetes, as insulin injections no longer need to be timed with meals, allowing owners greater flexibility in feeding schedules and dietary selection.[12,13,15]

TABLE 1 Guidelines for Dosing Basal Insulins Based on Continuous Glucose Monitoring[12,13]

SCENARIO	GUIDELINE	
Newly diagnosed patient		
Initial dose	0.5 U/kg SC q24h	
Dose adjustments based on IG nadir	**Dogs >8 kg (18 lb)**	**Dogs ≤8 kg (18 lb)**
If nadir is >350 mg/dL	Increase dose by 10%–30% every 1–3 days	Increase dose by 1 U/day every 1–3 days
If nadir is ≤350 mg/dL	Monitor for 2–5 days or until a consistent daily pattern emerges, then adjust dose as below	
If nadir is 150–350 mg/dL	Increase dose by 10%–30% every 1–3 days	Increase dose by 1 U/day every 1–3 days
If nadir is 80–150 mg/dL and all IG concentrations are <180 mg/dL	No change	
If nadir is <150 mg/dL and IG concentration is >300 mg/dL for longer than 12 hours during a 24-hour period	Change to q12h dosing with 30% dose reduction per injection ▪ Administer the new dose 12 hours after the last 24-hour injection ▪ Reevaluate over the following 2–5 days	
If nadir is <80 mg/dL and mean IG concentration is <120 mg/dL	Decrease dose by 10%–30% q24h	Decrease dose by 1 U/day q24h
Transition from a different insulin type		
From intermediate-acting to basal insulin	Start with same dose (previous q12h dose = q24h dose; e.g., 5 U q12h intermediate-acting insulin → 5 U q24h basal insulin) ▪ Administer first dose of basal insulin 12 hours after the last dose of previous insulin. ▪ Adjust subsequent doses as described above (for q24h administration). ▪ Most dogs will need at least 30% per dose increase with q24h dose schedule of basal insulin, but some dogs will need less.	
From one type of basal insulin to another	Use same dose	

IG = interstitial glucose

CASE EXAMPLE 2
Use of Basal Insulin in a Chihuahua With Diabetes Mellitus and Comorbidities

Signalment, History, and Physical Examination
A 9-year-old male neutered Chihuahua presented for a routine 3-month recheck. He had a history of diabetes mellitus, pituitary-dependent Cushing's syndrome, stage B1 degenerative mitral valvular disease, and glomerular proteinuria. He was on an established treatment plan (**BOX A**) and was clinically normal. On physical examination, weight was stable (4.9 kg [10.8 lb] with a body condition score of 5/9). Immature cataracts were noted in both eyes, and a grade 2/6 left apical systolic heart murmur was detected.

Monitoring
FIGURE A shows interstitial glucose monitor curves over 3.5 days of monitoring in this patient. This case illustrates the flat-action profile characteristic of basal insulins and highlights their consistency and predictable day-to-day performance. Good to excellent glycemic control is frequently achieved with once-daily insulin administration, even in dogs with comorbidities.

Discussion
Interstitial glucose monitoring supports excellent control of diabetes mellitus. The lack of clinical signs in this patient supports good control of Cushing's syndrome, which could be further assessed by evaluating biochemistry panel findings (e.g., platelet count, alkaline phosphatase activity, lipid profile) with or without an adrenocorticotropic hormone stimulation test. Indirect blood pressure and urinalysis, specifically urine specific gravity, proteinuria (with urine protein:creatinine ratio), and sediment, inform management of glomerular proteinuria.

BOX A
Ongoing Treatment Plan

- Insulin degludec 8 U once daily (1.6 U/kg/d)
- Trilostane 5 mg twice daily (1 mg/kg q12h)
- Telmisartan 5 mg twice daily (1 mg/kg q12h)
- Diet: Commercial prescription diabetic formulation, canned

Two insulin formulations have a long enough duration of action (>20 hours) to act as a basal insulin in dogs: insulin degludec (Tresiba) and insulin glargine U-300 (Toujeo).[16] Dosing recommendations are provided in **TABLE 1**. Of note, the only insulin that acts as a basal insulin for cats is insulin glargine U-300.

Insulin Degludec

Insulin degludec 100 U/mL (pen, vial) is bioequivalent to insulin degludec 200 U/mL (pen). This means that although insulin degludec 100 U/mL and 200 U/mL differ in concentration, they have equivalent biological activity on a unit-for-unit basis; however, they are not automatically interchangeable.

Insulin degludec is a recombinant human insulin analogue formed by replacing the amino acid at the B30 position with fatty acid (hexadecanedioic acid).[12] Following injection, it forms large multihexamers in the subcutaneous tissue, and the slow diffusion of zinc out of these hexamers results in a gradual and consistent release of monomers into circulation.[10,12,17] These insulin monomers reversibly bind to albumin and slowly dissociate before interacting with insulin receptors.[12] Insulin degludec has an extremely long

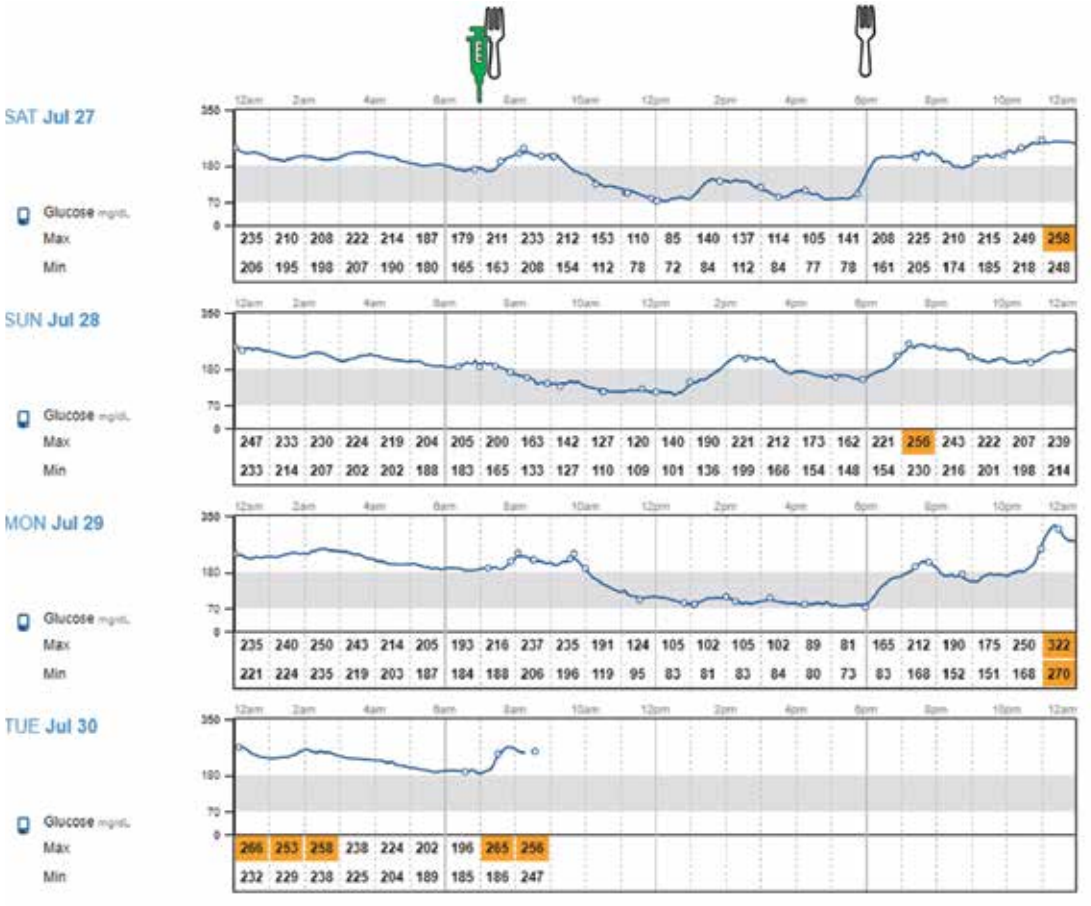

FIGURE A. Interstitial glucose monitor curves in a dog treated with once-daily insulin degludec administration **(green syringe)** and twice-daily meals **(forks)**.

half-life in humans (> 40 hours); in healthy dogs, the duration of action is more than 20 hours.[16,18] This is especially promising for canine diabetic management as a long duration of insulin action can allow for less frequent insulin administration and increase compliance, quality of life, and owner satisfaction.

In a recent study of 33 dogs, including newly diagnosed and previously insulin-treated dogs, 84% of dogs achieved glycemic control with once-daily administration of insulin degludec.[12] Encouragingly, these once-daily responders included dogs with comorbidities (**CASE EXAMPLE 2**). All dogs achieved rapid glycemic control within the first month (median, 14 days; range, 3 to 32 days), guided by CGM.[12] The incidence of clinical hypoglycemia was low in dogs treated with insulin degludec (n = 1 dog, 3%), and only 1 dog required the addition of a mealtime bolus insulin (neutral protamine Hagedorn [NPH]).[12] All dogs were considered to have good to excellent diabetic control.[12]

Insulin Glargine U-300

Insulin glargine is a recombinant human insulin analogue in which 2 arginine residues are added to position B30.[17] Insulin glargine remains in solution at a

pH of 4 (as supplied) but forms stable microprecipitates in neutral pH when injected into the subcutaneous space.[2,17] Both insulin glargine U-100 and insulin glargine U-300 have the same amino acid modifications; however, insulin glargine U-300 is 3 times more concentrated, resulting in a smaller subcutaneous depot and slower rate of absorption.[13,17] Toujeo is available in a 300-U/mL pen only.

In a recent study of 95 diabetic dogs, including newly diagnosed and previously insulin-treated dogs, insulin glargine U-300 resulted in good or excellent glycemic control and there was a low incidence of clinical hypoglycemia.[13] Glycemic control was achieved with once-daily dosing in 72% of dogs without concurrent diseases, whereas only 50% of dogs with concurrent disease (e.g., hyperadrenocorticism, chronic gastroenteropathy, acute or chronic pancreatitis) were controlled with once-daily administration.[13] In other words, 28% of dogs without concurrent disease and 50% of dogs with concurrent disease required twice-daily administration of insulin glargine U-300.[13] Within the first month of treatment with insulin glargine U-300, 72% of dogs achieved glycemic control (median time, 16 days; range, 3 to 99 days).[13] Similar to the study using insulin degludec, clinical hypoglycemia was infrequent in dogs treated with insulin glargine U-300 (6% of dogs), and a small number of dogs (5%) required a mealtime bolus injection (70/30 NPH/regular insulin or porcine lente insulin).[13]

Postprandial Hyperglycemia

A minority of dogs treated with a basal insulin formulation have postprandial hyperglycemia significant enough to cause clinical signs.[12,13] As reviewed earlier, the primary function of basal insulins is not to curb postprandial hyperglycemia; rather, bolus insulin secretion reduces postprandial hyperglycemia and, in dogs, can last for several hours (6 to 9 hours in normal dogs versus 6 to ≥12 hours in cats and 2 to 4 hours in humans), depending on factors such as dietary composition.[3] If interstitial glucose is more than 300 mg/dL consistently for 4 to 12 hours after 1 or more meals during each 24-hour period and clinical signs of hyperglycemia are observed, then treatment is warranted.

Several strategies can help reduce postprandial glucose spikes. The first is to lower dietary carbohydrates and modify dietary fiber content. In general, a diet with less than 4 g/100 kcal is considered a relatively low-carbohydrate diet. In general, canned diets contain fewer carbohydrates than kibble, although not all canned diets are low in carbohydrates.[15] A simple first step is to ensure the diabetic dog is eating canned food instead of kibble.[15] Modifying the dietary fiber content can also be helpful. Certain types of fiber can delay carbohydrate digestion and absorption, thereby reducing postprandial hyperglycemia.[15] Clinicians should, however, be mindful of the caloric density of some "high-fiber" diets, which may be low in calories and could contribute to undesirable weight loss in thin dogs.[15] The optimal feeding approach for dogs experiencing significant postprandial hyperglycemia while receiving a basal insulin has not been studied. Dividing calories into smaller, more frequent meals is a second potential mitigation strategy; however, further investigation is needed.

The addition of an intermediate-acting insulin along with a basal insulin (i.e., basal-bolus strategy) is a third strategy for management of clinical postprandial hyperglycemia. The so-called bolus insulin may be needed once or twice a day. Common insulin choices are NPH insulin (either NPH or 70/30 NPH/regular insulin) or porcine lente insulin with starting doses of 0.25 U/kg (based on ideal body weight rounded down to whole number) at the time of feeding. Adding a second type of insulin, which increases treatment complexity, should be carefully weighed against the owner's abilities, resources, and likelihood of compliance. Fortunately, based on the current literature, only a small percentage of dogs require a basal-bolus strategy.[12,13] It is important to note that, unlike in humans where tight glycemic control is the goal, postprandial hyperglycemia in dogs treated with basal insulin might not necessitate specific intervention.

Summary

Although diabetes mellitus is a treatable disease, 20% to 30% of dogs are euthanized within the first year after diagnosis, often due to perceived management challenges.[1] Treatment should be individualized to the patient and the owner, with the primary goal being control of clinical signs rather than strict glycemic regulation. Traditional insulins can be effective but are associated with variable absorption and glycemic variability. Newer long-acting basal insulins, such as

insulin degludec and insulin glargine U-300, offer more predictable, peakless glucose control; reduced hypoglycemia risk; and greater flexibility in feeding and dosing, potentially improving quality of life in dogs. TVP

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CE Quiz Questions

1. **Which of the following statements is true of basal insulins?**
   a. Their action is roughly the same at every hour of every day.
   b. They result in significant glycemic variability from day to day.
   c. The glucose nadir correlates to the peak insulin action.
   d. Insulin injections must be timed with a meal.

2. **What percentage of dogs can achieve glycemic control with once-daily insulin degludec?**
   a. 50%
   b. 70%
   c. 84%
   d. 98%

3. **Which of the following insulin(s) can act as a basal insulin for dogs?**
   a. Insulin degludec only
   b. Insulin degludec and insulin glargine U-300
   c. Insulin degludec and insulin glargine U-100
   d. Insulin glargine U-300 only

4. **How frequently can the dose of basal insulin be increased if the nadir remains >350 mg/dL?**
   a. every 1–3 days
   b. every 3–5 days
   c. every 5–7 days
   d. every 14 days

5. **Which of the following is/are strategy(ies) to manage significant postprandial hyperglycemia in a diabetic dog receiving a basal insulin?**
   a. Lower-carbohydrate diet
   b. Smaller, more frequent meals
   c. Basal-bolus insulin dosing
   d. All of the above