

2018 AAHA Diabetes Management Guidelines for Dogs and Cats*

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ABSTRACT

Diabetes mellitus (DM) is a common disease encountered in canine and feline medicine. The 2018 AAHA Diabetes Management Guidelines for Dogs and Cats revise and update earlier guidelines published in 2010. The 2018 guidelines retain much of the information in the earlier guidelines that continues to be applicable in clinical practice, along with new information that represents current expert opinion on controlling DM. An essential aspect of successful DM management is to ensure that the owner of a diabetic dog or cat is capable of administering insulin, recognizing the clinical signs of inadequately managed DM, and monitoring blood glucose levels at home, although this is ideal but not mandatory; all topics that are reviewed in the guidelines. Insulin therapy is the mainstay of treatment for clinical DM. The guidelines provide recommendations for using each insulin formulation currently available for use in dogs and cats, the choice of which is generally based on efficacy and duration of effect in the respective species. Also discussed are non-insulin therapeutic medications and dietary management. These treatment modalities, along with insulin therapy, give the practitioner an assortment of options for decreasing the clinical signs of DM while avoiding hypoglycemia, the two conditions that represent the definition of a controlled diabetic. The guidelines review identifying and monitoring patients at risk for developing DM, which are important for avoiding unnecessary insulin therapy in patients with transient hyperglycemia or mildly elevated blood glucose. (*J Am Anim Hosp Assoc* 2018; 54:1–21. DOI 10.5326/JAHA-MS-6822)

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ALP (alkaline phosphatase); BG (blood glucose); BGC (blood glucose curve); BP (blood pressure); CBC (complete blood count); DM (diabetes mellitus); HAC (hyperadrenocorticism); NPH (Neutral Protamine Hagedorn); PD (polydipsia); PP (polyphagia); PU (polyuria); PZI (protamine zinc insulin); T4 (thyroxine); U (units); UG (urine glucose); UPC (urine protein:creatinine ratio)

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is intended as a guideline only, not an AAHA standard of care. These guidelines and recommendations should not be construed as dictating an exclusive protocol, course of treatment, or procedure. Variations in practice may be warranted based on the needs of the individual patient, resources, and limitations unique to each individual practice setting. Evidence-based support for specific recommendations has been cited whenever possible and appropriate. Other recommendations are based on practical clinical experience and a consensus of expert opinion. Further research is needed to document some of these recommendations. Because each case is different, veterinarians must base their decisions on the best available scientific evidence in conjunction with their own knowledge and experience.

Note: When selecting products, veterinarians have a choice among those formulated for humans and those developed and approved by veterinary use. Manufacturers of veterinary-specific products spend resources to have their products reviewed and approved by the FDA for canine or feline use. These products are specifically designed and formulated for dogs and cats and have benefits for their use; they are not human generic products. AAHA suggests that veterinary professionals make every effort to use veterinary FDA-approved products and base their inventory-purchasing decisions on what product is most beneficial to the patient.

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Introduction

Diabetes mellitus (DM) is a treatable condition that requires a committed effort by veterinarian and client. Due to many factors that affect the diabetic state, a pet's changing condition, and variable response to therapy, management of DM is often complicated. Success requires understanding of current scientific evidence and sound clinical judgment. Each patient requires an individualized treatment plan, frequent reassessment, and modification of that plan based on the patient's response. This document provides current recommendations for the diagnosis, treatment, and management of DM in dogs and cats.

Previous AAHA DM guidelines published in 2010 are still applicable and provide useful background for the 2017 guidelines.¹ Readers will note that the 2017 guidelines use the same organizing framework as the 2010 guidelines. In some cases, essential content from the earlier guidelines has been retained verbatim. Practitioners will find several items or topics in the updated DM guidelines to be particularly relevant. These include:

- Quick-reference algorithms on responding to hypoglycemia, DM monitoring, and DM troubleshooting.
- New information on commercially available insulin formulations and recommendations for their use in dogs and cats.
- Recommendations for home monitoring of DM, a disease management approach that can contribute substantially to a favorable treatment response.
- Information on non-insulin therapeutic agents and treatment modalities such as dietary management.
- The implications of identifying patients at risk for developing DM and how to monitor and treat them.

Diabetes mellitus is a syndrome associated with protracted hyperglycemia due to loss or dysfunction of insulin secretion by pancreatic beta cells, diminished insulin sensitivity in tissues, or both. In the dog, beta-cell loss tends to be rapid and progressive, and is usually due to immune-mediated destruction, vacuolar degeneration, or pancreatitis.² Intact female dogs may be transiently or permanently diabetic due to the insulin-resistant effects of the diestrus phase. In the cat, loss or dysfunction of beta cells is the result of insulin resistance, islet amyloidosis, or chronic lymphoplasmacytic pancreatitis.³ Studies have shown that diabetic cats have remission rates that have been reported to be variable (15–100%). Because remission can occur, cat owners may be advised that remission is a possibility when treated with combination of diet and insulin.^{4,5}

Risk factors for developing DM for both dogs and cats include insulin resistance caused by obesity, certain diseases (e.g., acromegaly and kidney disease in cats; hyperadrenocorticism [HAC], hypertriglyceridemia, and hypothyroidism in dogs; dental disease, systemic

infection, pancreatitis, and pregnancy/diestrus in both dogs and cats), or medications (e.g., steroids, progestins, cyclosporine). Genetics is a suspected risk factor, and certain breeds of dogs (Australian terriers, beagles, Samoyeds, keeshonden) and cats (Burmese, especially in Australia and Europe) are more susceptible.^{6,7} Researchers continue to redefine and reclassify the different etiologies responsible for the development of DM in dogs and cats.⁸ As different etiologies become better understood, treatment can be more specifically tailored to the individual patient. Treatment that is more specific to the underlying etiology will presumably lead to better control of clinical signs of DM and possibly increase remission rates.

Regardless of the underlying etiology, classic clinical signs of polyuria (PU), polydipsia (PD), polyphagia (PP), and weight loss result from protracted hyperglycemia and glucosuria. Increased fat mobilization leads to hepatic lipidosis, hepatomegaly, hypercholesterolemia, hypertriglyceridemia, and increased catabolism. Eventually, if left untreated or inadequately controlled, ketonemia, ketonuria, and ketoacidosis develop and result in progressive compromise of the patient's health.

It is important to differentiate patients with clinical DM from those with transient hyperglycemia or mildly increased blood glucose (BG). The subgroup of patients with mildly elevated BG but without concurrent clinical signs associated with higher levels of hyperglycemia may require additional diagnostic and therapeutic measures but not insulin therapy. At this time, there is not a standard definition for subclinical DM in veterinary medicine or any validated testing to determine which patients are at risk for developing DM. In lieu of "subclinical DM," the Task Force has elected to use the more descriptive terminology "patients at risk of developing DM," or simply "at-risk patients" throughout the guidelines. As potential new etiologies emerge for overt or subclinical DM, they will be discussed in future guidelines or consensus statements.

Diagnosis and Assessment

These guidelines describe different approaches to DM diagnosis and assessment depending on the level of hyperglycemia and the presence of clinical signs. For cats and dogs who present with clinical signs suggestive of DM, perform a physical exam and full laboratory evaluation (complete blood count [CBC]), chemistry with electrolytes, urine analysis with culture, urine protein:creatinine ratio (UPC), triglycerides, blood pressure (BP), and thyroxine (T4); to confirm the diagnosis as well as to rule out other diseases. Elevated BG can sometimes be identified on blood work in the absence of consistent clinical signs. In such cases, if stress hyperglycemia can be ruled out, the patient may be classified as at-risk for developing DM. Clinical signs of PU/PD do not develop until the BG concentration exceeds the renal tubular threshold for spillage of glucose into the urine.

Glucosuria will typically develop when the BG concentration exceeds approximately 200 mg/dL in dogs and 250–300 mg/dL in cats.

Clinical signs of DM will typically be present when there is persistent hyperglycemia and glucosuria. Clinical signs are usually absent with glucose levels ranging between the upper reference levels and the renal threshold values noted above. Blood glucose concentrations in these ranges may occur for a variety of reasons, including stress hyperglycemia in cats, corticosteroid administration, the presence of concurrent insulin-resistant disease (hyperadrenocorticism, obesity), or as part of the early stage of developing DM.

Dogs and cats in the early stages of nonclinical DM appear healthy, have a stable weight, and are usually identified as a result of routine laboratory evaluation. They do not have clinical signs of DM. Stress hyperglycemia needs to be ruled out, as well as correction of any insulin-resistant disorders and discontinuation of drugs associated with impaired insulin release or sensitivity. Reassessing BG or monitoring urine glucose (UG) levels once the patient is no longer stressed at home or measuring serum fructosamine concentrations may help differentiate between stress hyperglycemia and DM, and determine if further action should be taken.

Clinical DM is diagnosed on the basis of persistent glucosuria, persistent hyperglycemia, and presence of characteristic clinical signs. Documentation of an elevated serum fructosamine concentration may be necessary to confirm the diagnosis in cats.⁹ Fructosamine levels may be only mildly elevated with lower levels of persistent hyperglycemia, and should be interpreted as part of a complete evaluation.⁹

Animals with clinical DM will present with PU, PD, PP, and weight loss. Some may present with lethargy, weakness, and poor body condition. Dogs may have cataracts, and cats may present with a complaint of impaired jumping and abnormal gait. Some patients will present with systemic signs of illness due to diabetic ketosis/ketoacidosis, such as anorexia, vomiting, dehydration, and depression.

The initial evaluation of the diabetic dog and cat should:

- Assess the overall health of the pet (history including diet and concurrent medications, and a complete physical exam).
- Identify any complications that may be associated with the disease (e.g., cataracts in dogs, peripheral neuropathy in cats).
- Identify any concurrent problems often associated with the disease (e.g., urinary tract infections, pancreatitis).
- Identify any conditions that may interfere with the patient's response to treatment (e.g., hyperthyroidism, renal disease, hyperadrenocorticism).
- Evaluate for risk factors such as obesity, pancreatitis, insulin-resistant disease, diabetogenic medications, and diestrus in female dogs.

Physical exam results of the diabetic cat or dog can be relatively normal early in the course of the disease. As the disease persists

without treatment, the physical exam may reveal weight loss, dehydration, poor hair coat, abdominal pain if concurrent pancreatitis is present, or cataracts. Some cats with longstanding hyperglycemia can develop peripheral neuropathy, which manifests as a plantigrade stance. If ketosis is present, a sweet odor may be noticed on the breath of the pet.

Laboratory evaluation includes a basic minimum database (CBC, chemistry with electrolytes, urine analysis with culture, triglycerides, UPC, BP, and T4 level in cats). Typical findings include hyperglycemia, glucosuria, and stress leukogram, as well as increased cholesterol and triglycerides. Dogs frequently show increased levels of alkaline phosphatase (ALP) and alanine aminotransferase. Cats, however, show more variability in the presence of a stress leukogram and elevated ALP. Elevated liver enzymes in a cat may warrant further evaluation for concurrent liver disease.¹⁰ Pancreatitis is a common comorbidity and may need to be addressed.¹⁰

Cats and dogs with diabetic ketoacidosis may show very elevated BG concentrations, azotemia, and decreased total CO₂ secondary to metabolic acidosis, osmotic diuresis, dehydration, and, in the case of profound hyperosmolarity, coma.

Urinalysis will reveal the presence of glucose. It may also show presence of protein, ketones, bacteria, and/or casts. Because a urinary tract infection cannot be ruled out by the absence of an active urine sediment, a urine culture should always be performed in glucosuric animals, because infection is commonly present.

If thyroid disease is suspected in a dog, it is best to perform thyroid testing after DM is stabilized because of the likelihood of euthyroid sick syndrome. Cats over 7 yr of age with weight loss and PP should be tested for hyperthyroidism because DM and hyperthyroidism cause similar clinical signs and can occur concurrently.

Treatment

The mainstay of treatment for clinical DM in dogs and cats is insulin along with dietary modification. Goals include controlling BG below the renal threshold for as much of a 24 hr period as possible, which will improve clinical signs of DM, and avoiding clinically significant hypoglycemia.

Treatment for Cats

In cats, diabetic remission is a reasonable goal.⁴ Successful management of DM in cats consists of minimal or no clinical signs, owner perception of good quality of life and favorable treatment response, avoidance or improvement of DM complications, (specifically, diabetic ketoacidosis and peripheral neuropathy), and avoidance of hypoglycemia. Predictors of diabetic remission in cats include achieving excellent glycemic control within 6 mo of diagnosis, using intensive home monitoring, discontinuation of

insulin-antagonizing medications, and use of insulin glargine (Lantus) or detemir (Levemir) along with a low-carbohydrate diet.⁴ A clinically sick, diabetic, ketotic cat should be hospitalized to initiate aggressive therapy. If 24 hr care is not feasible, the patient should be referred to an emergency or specialty hospital. Adjunct therapy for diabetic cats should include environmental enrichment using creative feeding tools such as food puzzles, particularly for obese cats. Oral hypoglycemic drugs are neither recommended nor considered appropriate for long-term use. Their use is considered temporary and only if combined with dietary modification if the owner refuses insulin therapy or is considering euthanasia for the pet.

The initial approach to management of the diabetic cat is to initiate insulin therapy with glargine (Lantus) or protamine zinc insulin (PZI; Prozinc) at a starting dose of 1–2 units (U) per cat *q* 12 hr. The decision to monitor BG on the first day of insulin treatment is at the discretion of the veterinarian. The goal of first-day monitoring is solely to identify hypoglycemia. The insulin dose should **not** be increased based on first-day BG evaluation. If monitoring is elected, measure BG *q* 2–4 hr for cats on PZI and *q* 3–4 hr for those on glargine for 10–12 hr following insulin administration. Decrease the insulin dose by 50% if BG is <150 mg/dL any time during the day. Treat the diabetic cat as an outpatient after the first day of monitoring, if elected, and plan to reevaluate in 7–14 days regardless of whether BG values are monitored on the first day. Immediately re-evaluate if clinical signs suggest hypoglycemia or if lethargy, anorexia, or vomiting is noted. See Algorithm 2, “Monitoring blood glucose levels in diabetic dogs and cats” and **Table 1**, “Insulin Products” for more information on monitoring and dosing.

Treatment for Dogs

Treatment of clinical DM in the dog always requires exogenous insulin therapy. U-40 pork lente (porcine insulin zinc suspension; Vetsulin) is the Task Force’s first-choice recommendation for dogs using a starting dose of 0.25 U/kg *q* 12 hr, rounded to the nearest whole U. The duration of action is close to 12 hr in most dogs, and the amorphous component of the insulin helps to minimize postprandial hyperglycemia. As with cats, a clinically sick, diabetic, ketotic dog should be admitted for 24 hr care for aggressive therapy of the ketosis and other underlying illnesses. A critical initial goal of treatment is avoidance of symptomatic hypoglycemia, which may occur if the insulin dose is increased too aggressively. Feed equal-sized meals twice daily at the time of each insulin injection. In contrast to cats, diabetic remission occurs only rarely in dogs with naturally acquired DM. Performing an ovariohysterectomy in intact diabetic dogs will support remission, regardless of the underlying cause of the diabetes.

In dogs with subclinical DM, investigate and address causes of insulin resistance, including obesity, medications, hyperadrenocorticism and diestrus in intact females. Initiate dietary therapy to limit postprandial hyperglycemia (see “Dietary Therapy Goals and Management” for additional information.) Evaluate the dog closely for progression to clinical DM. Subclinical DM is not commonly identified in the dog. Most dogs in the early stages of naturally acquired diabetes (i.e., not induced by insulin resistance) quickly progress to clinical DM and should be managed using insulin.

Veterinarians use a variety of insulin products, but only two are presently approved by the FDA for use in dogs and cats. One of these is a porcine lente product (**porcine insulin zinc suspension, Vetsulin**) that is approved for both species. The other FDA-approved insulin, human recombinant **protamine zinc insulin or PZI (Prozinc) insulin**, is labeled as having an appropriate duration in cats, the only species for which it is approved. It is considered by clinicians as a long-acting insulin. Because of limited controlled comparative studies, most expert recommendations are based on a combination of clinical and anecdotal experience. The guidelines Task Force strives to make evidence-based recommendations when data are available. However, the ability to make specific recommendations based on differences and preferences between veterinary insulin products is limited. Members of the Task Force most commonly use porcine lente insulin (Vetsulin) in dogs and glargine (Lantus) in cats, recognizing that other acceptable options used by many clinicians include Neutral Protamine Hagedorn (NPH; Humulin N, Novulin N) in dogs and PZI (Prozinc) in cats.

Although compounded insulin is available, its use is not recommended because of concerns about production methods, diluents, sterility, and insulin concentration consistency between lots. A study comparing commercially available insulin with its compounded counterparts showed that the manufactured insulin met all US Pharmacopeia requirements and only 1 of 12 compounders met US Pharmacopeia specifications at all time points. The variability between compounded insulins was also significant enough to have clinical consequences.¹¹ It is also not recommended to dilute insulin because dilution can produce unpredictable results, alter insulin efficacy, and result in bacterial contamination.^{5,12}

Insulin Products (see Table 1)

1. **Lente** (U-40 porcine insulin zinc suspension; Vetsulin, Merck Animal Health) is an intermediate-acting insulin commonly used by the Task Force in dogs. It is FDA approved for use in dogs and cats. It has a close to 12 hr duration of action in most dogs and is useful for minimizing postprandial hyperglycemia.
2. **Glargine** (U-100 human recombinant; Lantus, Sanofi) is a longer-acting insulin commonly used by the Task Force in

TABLE 1

Insulin Products Commonly Used in Dogs and Cats

Insulin Products	Product Description	Brand Name (Manufacturer)	Veterinary FDA Approval Status	Peak Action (Nadir) and Duration of Effect	Starting Dose	Concentration	Comments
Lente (intermediate-acting)	Porcine insulin zinc suspension	Vetsulin (Merck Animal Health)	Dogs, cats	Cats Nadir 2–8 hr. Duration 8–14 hr. ¹⁹ Dogs Nadir 1–10 hr. ²⁰ Duration 10–24 hr. ²⁰	Cats 0.25–0.5 U/kg <i>q</i> 12 hr (not to exceed 3 U per cat). ⁵ Dogs 0.25–0.5 U/kg <i>q</i> 12 hr.	U-40	Commonly used in dogs; injection pens (in either 0.5 U or 1 U increments) available for dogs and cats. Shaking insulin bottle is required. NOTE: In dogs, the manufacturer recommends a starting dose of 0.5 U/kg <i>q</i> 24 hr.
Glargine (long-acting)	Recombinant DNA origin human insulin	Lantus (Sanofi)	Not approved	Cats Nadir 12–14 hr. Duration 12–24 hr. Dogs Nadir 6–10 hr. ²¹ Duration 12–20 hr.	Cats 0.5 U/kg <i>q</i> 12 hr if BG > 360 mg/dL and 0.25 U/kg <i>q</i> 12 hr if BG < 360 mg/dL. Dogs 0.3 U/kg <i>q</i> 12 hr.	U-100, U-300	Commonly used in cats; use only U-100 (U-300 available); potential option in dogs
PZI (long-acting)	Recombinant DNA origin human insulin	Prozinc (Boehringer Ingelheim Animal Health)	Cats	Cats Nadir 5–7 hr. Duration 8–24 hr. ¹⁴ Dogs Nadir 8–12 hr. ²²	Cats 1–2 U per cat <i>q</i> 12 hr. Dogs 0.25–0.5 U/kg <i>q</i> 12 hr. ²²	U-40	Commonly used in cats; not commonly used in dogs. Some clinicians believe that for dogs, a starting dose of 0.25 U/kg is appropriate and 0.5 U/kg should be reserved for potentially challenging diabetics.
NPH (intermediate-acting)	Recombinant human insulin	Novolin (Novo Nordisk) Humulin (Lilly)	Not approved	Dogs Nadir 0.5–8.5 hr. ¹⁵ Duration 4–10 hr.	Dogs 0.25–0.5 U/kg <i>q</i> 12 hr. ¹⁵	U-100	Option for dogs; rarely recommended for cats due to short duration of effect. Consider using the lower end of the starting dose for a large dog and higher end for a small dog.
Detemir (long-acting)	Recombinant DNA origin human insulin	Levemir (Novo Nordisk)	Not approved	Cats Nadir 12–14 hr. Duration 12–24 hr. ^{16,17}	Cats 0.5 U/kg <i>q</i> 12 hr if BG > 360 mg/dL, and 0.25 U/kg <i>q</i> 12 hr if BG < 360 mg/dL. ¹⁷ Dogs 0.10 U/kg <i>q</i> 12 hr. ¹⁸	U-100	Very potent in dogs (caution required); used in dogs and cats; suitable for dogs in which NPH and lente have short duration of activity.

BG, blood glucose; NPH, Neutral Protamine Hagedorn; PZI, protamine zinc insulin; U, units.

cats because it has an adequate duration of action in most diabetic cats. Several studies have demonstrated that glargine is effective for controlling blood sugar levels in diabetic cats and achieving high remission rates.¹² Glargine can also be used in dogs. It is a human analog insulin with modifications that provide variable solubility at different pHs. Glargine is soluble at a pH of 4.0, the pH at which it is supplied and stored, but in the neutral pH of the body's blood or subcutaneous tissues it forms microprecipitates, facilitating slow absorption after injection. This results in rapid onset and long duration of action. Glargine is sometimes described as a "peakless" insulin, although peakless does not mean an absence of a nadir in cats but rather refers to glucose utilization rates.⁴ In dogs, a flat blood glucose curve (BGC) may be seen, so glargine can be referred to as a peakless insulin in that species.¹³

3. **PZI** (U-40 human recombinant protamine zinc insulin; Pro-Zinc, Boehringer Ingelheim Animal Health) is considered by clinicians as a long-acting insulin, and is FDA approved for use in cats. In field studies in cats, mean time of the BG nadir was between 5 and 7 hr and the duration of action was 8–24 hr, which was deemed an appropriate duration of action by the FDA.¹⁴ The results suggested that Prozinc should be administered twice daily in most diabetic cats to maintain control of glycemia.¹⁴ This insulin is used in both cats and dogs, although it is less commonly used in dogs. Protamine zinc insulin can have a prolonged duration of action in dogs and may be tried on once-daily dosing schedule to minimize the chances of clinically significant hypoglycemia and/or the Somogyi phenomenon.
4. **NPH** (U-100 human recombinant; Neutral Protamine Hagedorn, Humulin N, Lilly or Novulin N, Novo Nordisk) is an intermediate-acting insulin that is used in dogs. The Task Force does not recommend use of this insulin in cats due to its short duration of action. The duration of action of NPH in dogs is often <12 hr. Some dogs can have postprandial hyperglycemia when treated with this insulin.¹⁵ A combination form of NPH plus regular insulin (70 NPH/30 Regular) is available that may be suitable if the dog has an appropriate duration of action (8–12 hr) with an early nadir or postprandial BG spike. Some clinicians use this product in dogs who develop postprandial hyperglycemia when being treated with NPH.
5. **Detemir** (U-100 human recombinant; Levemir, Novo Nordisk) is a long-acting insulin that can be used in both dogs and cats. Detemir is a human analog insulin engineered with modifications that allow it to bind albumin with high affinity in the subcutaneous and intravascular spaces, prolonging the

insulin's absorption.^{4,16} This prolonged absorption gives detemir a long and steady duration of action and less variability in biological activity.⁴ Detemir has a very similar profile to glargine (Lantus) in cats in terms of BG control and remission rates.¹² However, cats receiving detemir require a lower median maximal dose than cats receiving glargine (1.75 U per cat for detemir versus 2.5 U per cat of glargine).¹⁷ Dogs are very sensitive to the higher potency of this insulin and require lower starting doses (0.1 U/kg).¹⁸ Particular caution must be used in small dogs because they are more likely to have more frequent hypoglycemic excursions.¹⁸

Insulin dosages should be based on the patient's estimated ideal body weight. Judicious initial dosing is recommended because dietary change may alter food intake and affect the therapeutic response to insulin. Insulin dosages should not be increased more often than *q* 1–2 wk. The Task Force recognizes that clients are often cost-constrained. However, choosing a less efficacious insulin can result in higher total costs and careful monitoring. In addition, comparing per-U costs of insulin is more useful than comparing cost per vial. The cost per U of insulin gives a more accurate assessment of the overall cost of using the insulin versus cost per vial.

In the majority of feline diabetes cases, the Task Force recommends a starting dose of glargine (Lantus), *q* 12 hr based on the estimated ideal body weight of the cat and BG levels (0.5 U/kg *q* 12 hr if BG > 360 mg/dL and 0.25 U/kg *q* 12 hr if BG < 360 mg/dL). This equates to 1 U *q* 12 hr in the average cat. Even in a very large cat, the starting dose of insulin should not exceed 2 U per cat *q* 12 hr. Most cats are well regulated on insulin at an average dose of 0.5 U/kg *q* 12 hr, with a range of 0.2–0.8 U/kg. With PZI (Prozinc), a typical starting dose is 1–2 U per cat.

In diabetic dogs, the Task Force recommends a starting dose of 0.25 U/kg of lente (Vetsulin) *q* 12 hr, rounded to the nearest whole U. Most dogs are well controlled on insulin at an average dose of 0.5 U/kg *q* 12 hr with a range of 0.2–1.0 U/kg.

See Table 1 for more detailed information on alternative dosing and insulin selections for both dogs and cats.

It should be noted that product pharmacokinetics vary depending on insulin type, product formulation, and the individual patient's response. One should employ reasonable dosing flexibility based on individual patient response and the owner's compliance limitations. For example, a 12 ± 2-hour window on each side of the dosing interval and occasional missed doses are considered acceptable by most practitioners. Other insulin types and other therapeutics can be used in dogs and cats based on the patient's response to first-line insulin therapy and associated recommendations, as discussed in the "Monitoring" section of the guidelines.

Although none of the insulin products available for use in dogs and cats have canine- or feline-specific amino acid sequences, anti-insulin antibodies do not appear to cause a significant clinical problem.

Insulin manufacturers generally recommend discarding opened and used bottles of insulin after 4–6 wk or until the date of expiration listed by the manufacturer. However, if handled carefully and stored in the refrigerator, the Task Force is comfortable using insulins beyond the date of expiration (up to 3–6 mo) as long as they are not discolored, flocculent, or have any change in consistency. Insulin must be discarded if these changes occur. If a lack of BG regulation is noted 3–6 mo after using a specific bottle of insulin, it may be prudent to replace the bottle prior to increasing insulin dose.

Non-Insulin Therapeutic Agents (see Table 2)

1. **Sulfonylureas** such as glipizide promote insulin secretion from the pancreas and can be used in cats. Oral glipizide has been used successfully in cats with DM, with benefits being reported in approximately 40% of cats. Transdermal application is unreliable.²³ Adverse effects following oral administration include cholestasis, hypoglycemia, and vomiting. There is concern that glipizide may contribute to progression of DM and pancreatic amyloidosis.²³ The Task Force only recommends glipizide for use in cats with owners who refuse insulin therapy, and only with concurrent dietary therapy. The initial dose is 2.5 mg/cat orally *q* 12 hr. The dose can be increased to 5 mg/cat *q* 12 hr if an inadequate response is seen after 2 wk. If no response is seen after 4–6 weeks, insulin therapy should be instituted.²³ If the cat appears to be clinically responsive, the trial can continue for 12 wk to assess response to therapy. Obtaining BGCs is important to confirm therapeutic response. To screen for

liver toxicity, regular liver monitoring should be performed. Glipizide should not be used in dogs because they do not have any functional pancreatic beta cells due to the pathogenesis of canine DM.

2. **α -glucosidase inhibitors** such as acarbose are used to inhibit intestinal glucose absorption and reduce postprandial hyperglycemia. Acarbose has been used in cats along with insulin and a low-carbohydrate diet.²³ Acarbose can be used in dogs along with insulin therapy to help improve glycemic control and may decrease the dose of exogenous insulin administration. As a sole agent, acarbose is seldom if ever sufficient, especially in dogs. Advise owners that diarrhea is a possible side effect.²⁴
3. **Incretins** such as GLP-1 (glucagon-like peptide 1) are metabolic or gastrointestinal hormones that can be used in dogs and cats. They can be used along with glargine (Lantus) insulin therapy and diet in cats to help achieve remission.²⁵ Incretins can help improve diabetic control in cats and dogs. In healthy animals and potentially diabetic cats, GLP-1 increases insulin secretion (in cats it also protects beta cells from oxidative and toxic injury and promotes expansion of the β -cell population) and functions to help delay gastric emptying and increase satiety. In dogs and cats, improved diabetic control is presumed to be via glucagon suppression.²⁶ Currently, although more research is needed, the most promising results have been reported in cats treated with exenatide ER (Bydureon) and in dogs with liraglutide (Victoza).^{26,27}

Dietary Therapy Goals and Management

The goals of dietary therapy are to optimize body weight with appropriate protein and carbohydrate levels, fat restriction, and caloric

TABLE 2

Non-Insulin Therapeutic Agents Used to Treat Canine and Feline Diabetes Mellitus

Therapeutic Class	Examples	Mode of Action	Used with Insulin Cotherapy	Comments
Sulfonylureas	Glipizide	Stimulates insulin secretion from the pancreas.	No	Only recommended for owners who refuse to use insulin in cats. Not for use in dogs.
α-glucosidase inhibitors	Acarbose	Inhibits intestinal glucose absorption and reduces postprandial hyperglycemia.	Yes	Can be used in dogs and cats. Useful when peak activity of insulin occurs too soon (2 hr after administration).
Incretins	Glucagon-like peptide-1; Exenatide (Byetta); Exenatide ER (Bydureon); Liraglutide (Victoza)	Stimulates insulin secretion from pancreas, delays gastric emptying, increases satiety, protects beta cells, promotes expansion of beta cell population, suppresses glucagon.	Yes	Promising results with exenatide ER in cats and liraglutide in dogs. ^{24,25} The mode of action is seen most commonly in healthy animals and possibly, diabetic cats, but not in dogs with classic diabetes.

ER, extended release.

and portion control. Weight loss in obese patients and stopping DM-associated weight loss are treatment goals for diabetic canine and feline patients. The following approach is recommended for dietary management of DM:

- The cat or dog's daily caloric requirements, based on lean body mass, should be calculated.
- Body weight (using the same scale) and BCS should be obtained at least once or twice monthly and adjustments made in dietary intake to maintain optimal weight.
- A weight loss goal in obese cats is 0.5–2% reduction per wk and in dogs is 1–2% reduction per wk.
- Managing protein and carbohydrate intake is recommended to minimize postprandial hyperglycemia.

Diabetic cats should be fed a high-protein diet (defined as $\geq 40\%$ protein metabolizable energy) to maximize metabolic rate, limit the risk of hepatic lipidosis during weight loss, improve satiety, and prevent lean muscle-mass loss.²⁸ This dietary regimen is necessary to prevent protein malnutrition and loss of lean body mass. High-protein diets typically provide the lowest amount of carbohydrates without impacting palatability. The following dietary principles for diabetic cats should also be considered:

- Protein normalizes fat metabolism and provides a consistent energy source.
- Arginine stimulates insulin secretion.
- Carbohydrate intake should be limited because carbohydrates may contribute to hyperglycemia and glucose toxicity. The Task Force recommends a diet of approximately 12% ME, recognizing that there are a variety of expert opinions on this topic.^{23,28}
- Diabetic cats have reported remission rates between 15 and 100% when given a combination of a high-protein/low-carbohydrate diet and insulin.^{4,5} The highest remission rates occur when glargine (Lantus) and detemir (Levemir) insulin are used in newly diagnosed (glargine) diabetics or those within 6 mo of diagnosis (both insulin forms).¹²
- High-fiber diets are not typically recommended for cats with DM.

Feeding portioned meals has several advantages for dietary management of diabetic cats:

- It is easier to monitor intake and appetite.
- Portion control is facilitated.
- Free-choice feeding is acceptable if a cat's eating habits cannot be changed (the Task Force recommends that the daily ration be divided into multiple meals. The use of timed feeders may be helpful in this scenario).²⁸
- Canned foods are preferred over dry foods. Canned foods provide:
 - Lower carbohydrate levels.
 - Ease of portion control.

- Lower caloric density; cats can eat a higher volume of canned food and obtain the same caloric intake as smaller volumes of dry food.
- Additional water intake.

Dietary recommendations for both dogs and cats should be adjusted if concurrent diseases are present (e.g., chronic kidney disease, pancreatitis, intestinal disease). For dogs, a diet that will correct obesity, optimize body weight, and minimize postprandial hyperglycemia is recommended. Unlike cats, dogs are not at appreciable risk for the clinical complications of hepatic lipidosis. Dogs with DM can do well with any diet that is complete and balanced, is fed at consistent times in consistent amounts, and is palatable in order to achieve predictable and consistent intake.

For dogs, diets that contain increased quantities of soluble and insoluble fiber or that are designed for weight maintenance in diabetics or for weight loss in obese diabetics can:

- Improve glycemic control by reducing postprandial hyperglycemia.
- Restrict caloric intake in obese dogs undergoing weight reduction.

Some clinicians recommend that owners supplement with canned pumpkin, green beans, or commercial fiber supplements containing psyllium or wheat dextrin. Additionally, regular and appropriate exercise should be considered an adjunct of any diet-based weight-loss program.

In underweight dogs, the principal goal of dietary therapy is to normalize body weight, increase muscle mass, and stabilize metabolism and insulin requirements. Underweight dogs should be fed a high-quality maintenance diet or a diabetic diet that has both soluble and insoluble fiber and is not designed for weight loss. The diet should be palatable in order to provide predictable caloric intake when fed at consistent times and in consistent amounts. Owners should include treats when calculating daily caloric intake.

Monitoring

The overarching goal of monitoring diabetic cats and dogs is to control clinical signs of DM while avoiding hypoglycemia. ***Stated another way, the definition of a controlled diabetic is absence of clinical signs and hypoglycemia.*** Blood glucose levels do fluctuate and short periods of mild hyperglycemia are acceptable. The goal is not necessarily to normalize BG, but to keep the BG below the renal threshold (200 mg/dL in dogs and 250–300 mg/dL in cats) and to avoid hypoglycemia. When BG is above the renal threshold, glucosuria occurs, resulting in PU/PD. None of the monitoring modalities are perfect, and they each have strengths and weaknesses. Although normalizing clinical signs (such as resolution of PU/PD/PP and achieving ideal body weight) supersedes all other monitoring

MONITORING BLOOD GLUCOSE LEVELS IN DIABETIC DOGS AND CATS

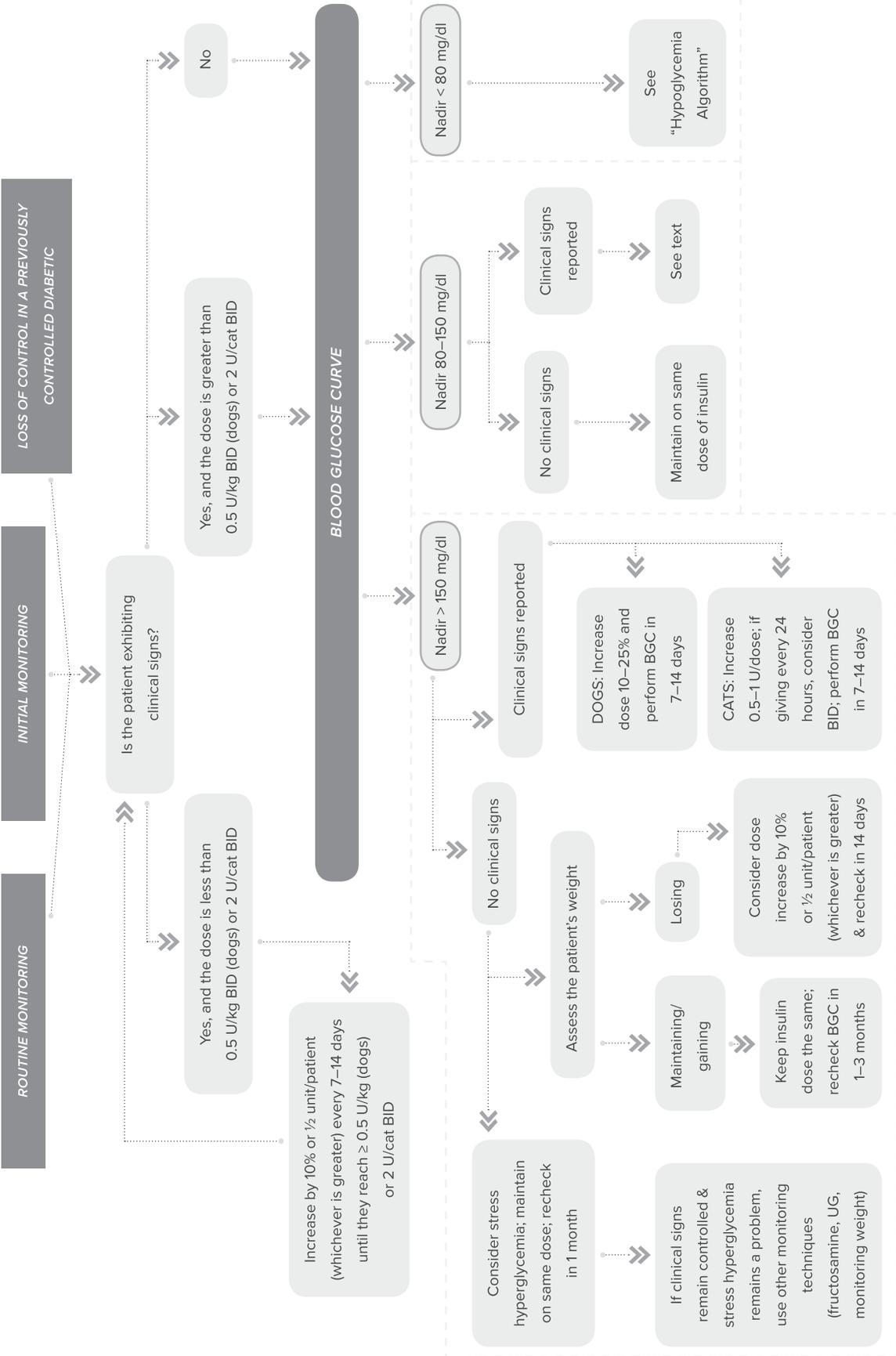


FIGURE 1 Monitoring blood glucose levels in diabetic dogs and cats.

indicators, every attempt should be made to also monitor BG in the diabetic patient. To illustrate, if a patient is consistently negative for glucosuria, without measuring BG it is impossible to determine if the individual is a “perfectly regulated” diabetic or hypoglycemic.

Monitoring diabetic pets can be challenging. The algorithm in **Figure 1** provides a quick reference for three types of DM patients—newly diagnosed, previously diagnosed, and previously diagnosed but currently unregulated. Monitoring options include performance of BGCs, monitoring UG, measuring fructosamine, and assessment of clinical signs and weight. Results from different monitoring approaches may conflict. In a review of 53 cases of canine DM, BG measurements and fructosamine concentrations were consistent with good glycemic control in only 60% of dogs judged to have good clinical control. Furthermore, although all monitoring parameters were significantly improved in dogs with good clinical control, considerable overlap existed between dogs with good and poor clinical responses.²⁹ In cats, no single monitoring parameter best correlates with the level of clinical control identified.³⁰

In-Hospital Blood Glucose Curves

Blood glucose curves serve two very useful purposes that other monitoring parameters do not. They identify clinically undetectable hypoglycemia so that the insulin dose can be decreased before clinical signs of hypoglycemia develop. Thus, a periodic BGC is recommended for seemingly well-controlled patients. More importantly, although other techniques and clinical signs may suggest control is lacking, multiple reasons for poor control exist, including too low and too high an insulin dose. The only way to know how to appropriately change an insulin dose is to perform a BGC.

There are several situations when a BGC should be performed: (1) after the first dose of a new kind of insulin; (2) at 7–14 days after an insulin dose change; (3) at least *q* 3 mo even in well-controlled diabetics; (4) any time clinical signs recur in a controlled patient; and (5) when hypoglycemia is suspected.

To construct a BGC, BG is generally measured *q* 2 hr for one interval between injections (i.e., for 12 hr if insulin is administered twice daily and for 24 hr if insulin is given once daily). When using glargine (Lantus) in cats, BG should be monitored every 3–4 hr. However, when BG is <150 mg/dL in both cats and dogs during any curve, BG should be measured hourly.

The AlphaTrak 2 may be the most accurate BG meter (glucometer) for veterinary patients because it has been calibrated in dogs and cats.^{31,32,33} Although human glucometers are readily accessible to pet owners, the Task Force does not recommend their use due to inaccuracies when reading canine and feline blood.

A normal insulin treatment and feeding schedule *must* be maintained as much as possible during the BGC. Unless patients eat their normal amount of the normal food at the normal time, a BGC should probably not be obtained. When first regulating a diabetic patient, assessment of owner technique is crucial. Therefore, it is ideal if the feeding and insulin injection are done in the hospital so the injection can be observed. Obtaining a fasting blood sample for BG measurement prior to insulin injection can also aid in appraisal of glycemic control. However, this may not be possible if normal feeding time occurs before a hospital opens or if a dog or cat will not eat in the hospital. If an owner’s technique is suspect, the injection time can be changed to occur in front of the veterinarian. Clearly, cooperation between client and veterinarian is necessary to optimize the information obtained with minimal disturbance to routine.

A BGC should establish duration of treatment effect and the lowest BG (i.e., the nadir). The ideal nadir is a BG of 80–150 mg/dL. The highest BG should be close to 200 mg/dL in dogs and 300 mg/dL in cats. In assessing a BGC, whether it is the first curve performed on a patient or the most recent of many, two basic questions need to be asked. First, has the insulin succeeded in lowering BG? And second, how long has the BG been controlled? By answering these questions, logical changes in dosing regimen can be made.

The first aim in regulating a diabetic is to achieve an acceptable nadir. If an acceptable nadir is not achieved, the insulin dosage should be adjusted (see below). An acceptable nadir with good clinical control may not be obtained if the insulin used has a short duration of activity. Hypoglycemia must always be avoided. No matter what other BG concentrations are during the day, if BG is ever <80 mg/dL, the insulin dose must be reduced.

Once an acceptable nadir is achieved, duration of action, roughly defined as the amount of time BG is controlled, can be determined. Duration cannot be evaluated until the nadir is optimized. The BG should be controlled for as close to 24 hr per day as possible.

The Somogyi or overswing phenomenon, also called hypoglycemia-induced hyperglycemia, refers to hypoglycemia followed by marked hyperglycemia. It results from a physiological response when an insulin dose causes BG to be <60 mg/dL or when BG concentration decreases quickly. In either case, counter-regulatory hormones, which act to increase BG (e.g., cortisol, epinephrine, and glucagon), are released. Hyperglycemia usually occurs rapidly and can be followed by a period of insulin resistance. In cats, however, hypoglycemia does not always trigger a Somogyi phenomenon and resistance may not occur.³⁴ The same is likely true for dogs. If a Somogyi phenomenon is observed, insulin dosage must be decreased. Once the nadir is >80 mg/dL,

counter-regulatory hormones will no longer interfere and the true duration of effect will become apparent.

Glucose curves are not perfect and must always be interpreted in light of clinical signs. Blood glucose curves vary from day to day and can be affected by deviation from the patient's normal routine.^{35,36} Stress hyperglycemia falsely elevates results. See the Online Resource Center at aaha.org/diabetes for examples of interpreting various glucose curves.

At-Home Blood Glucose Curves

Obtaining a BGC at home is strongly recommended both for dog and cat owners, but even more so in the case of feline patients due to the chance of stress hyperglycemia in a hospital setting. For home BGC, capillary blood is suitable.³⁷ Commonly used sites of blood collection are the ear, gums, non-weight bearing or accessory foot pads, or elbow callus. If using devices designed for pricking human fingertips, one with a variable needle depth should be chosen. A hypodermic needle can also be used, especially if the marginal ear vein is the site of blood collection.³⁸

Not all owners are suited to the task of obtaining a home BGC, something that takes time and patience to master. The most frequent problems encountered by owners are the need for more than one puncture to obtain a blood drop, obtaining a sufficient volume of blood, the need for assistance in restraining a pet, and the pet's

resistance to obtaining a blood sample.³⁸ Curves can vary from day to day even when done at home and must always be interpreted in light of clinical signs.³⁹ Practice team members can refer to the Diabetes Management Guidelines Online Resource Center at aaha.org/diabetes for more detailed information and resources for pet owners on at-home monitoring utilizing BGCs.

Urine Glucose Measurements

Urine glucose measurements can be helpful, but it should be remembered that dipsticks have a relatively low accuracy in dogs, often underestimating UG.⁴⁰ Also, UG concentration is only a reflection of the average BG over the time interval the bladder was filling. Relying solely on UG measurements is not recommended.

Regardless, UG concentration can aid in assessment of a patient when other data conflict. Also, regular determination of UG concentration (at least weekly) can help in assessment of ongoing DM control (see **Table 3**). Consistently negative UG readings may indicate that insulin dosages are excessive. However, a negative UG reading only means that BG was below the renal threshold (i.e., BG could have been 150 mg/dL or 40 mg/dL). The only way to know is to measure BG.⁴¹ Lastly, especially for cats for whom stress hyperglycemia prevents obtaining an accurate BGC, UG measurements can be used to adjust the insulin dose. However, such an approach is a last resort because of the potential for causing hypoglycemia. Although far from ideal, there

TABLE 3

Interpreting Urine Glucose Measurements

UG Result	Remarks	Suggested Action
No color change - Negative for glucose	There should be concern that the insulin dose is too high.	If the reading stays negative, reduce dose of insulin and recheck in 2–3 days. NOTE: Negative UG in the absence of BGC results could potentially become a dangerous hypoglycemic condition and should be monitored accordingly.
First level color change - 100 mg/dL	Ideally, the UG would stay between negative and 100 mg/dL.	No change in insulin dose, but need to monitor weekly for any changes.
Second and third level color change - 250 and 500 mg/dL	In the Task Force's opinion, this is the hardest level to evaluate without a corresponding BG test.	Consider any dietary changes or deviations ("cheats"). If none are noted, and the cat is not exhibiting clinical signs, recheck daily for 2–3 days. If the owner is willing, obtaining additional BG data at this time would be ideal depending on the presence or absence of clinical signs. However, if the owner refuses to perform blood work, consider increasing the insulin dosage by half a unit <i>q</i> 12 hr at this time.
Third, fourth, and fifth level change - 1,000–2,000+ mg/dL	Cat should have clinical signs at this point.	Increase insulin by 1 unit <i>q</i> 12 hr and recheck in 5–7 days. NOTE: Continuing to increase the insulin dose more than two or three times is not recommended due to the possible presence of Somogyi or insulin resistance.

Abbreviations: BG, blood glucose; BGC, blood glucose curve; UG, urine glucose.

are scenarios where this is the most practical monitoring scheme. Table 3 lists the suggested protocol for using UG test strip readings in cats is based on the Task Force's clinical experience.

Glycosylated Proteins

The glycosylated proteins include fructosamine and glycosylated hemoglobin (A1C). Fructosamine, the glycosylated protein used in veterinary medicine, is formed by nonenzymatic, irreversible binding of glucose to serum proteins, mainly albumin.⁴² Rate of formation is proportional to the average BG level, so the higher the mean BG concentration is over time, the greater the fructosamine concentration should be. Because fructosamine concentration is also affected by the half-life of albumin, it reflects glycemic control over the previous 1–2 wk. Unfortunately, well-controlled diabetics can have elevated fructosamine concentrations. Conversely, uncontrolled diabetic pets can have normal levels.⁴³ Fructosamine may be elevated in sick, hyperglycemic, but nondiabetic cats.⁴³ For these reasons, fructosamine trends are more useful than isolated values. Because fructosamine is typically not affected by stress, it can help to differentiate stress hyperglycemia from diabetes.

One of the best uses of fructosamine is to evaluate trends in glycemic control if measured at each recheck. Declining fructosamine values indicate a lowering in BG overall, whereas increasing values indicate the opposite. A fructosamine concentration below the reference range is highly suggestive of chronic hypoglycemia, in which case a BGC should be performed. Additionally, this scenario may be an indicator that a feline patient may be nearing diabetic remission. Cats with hyperthyroidism or conditions that cause hypoalbuminemia, increased protein turnover rates, or hypoglobulinemia may have decreased fructosamine concentrations. Corrections can be performed by the laboratory performing the analysis.

Commercial testing of canine and feline A1C is available. This glycosylated hemoglobin is commonly used to monitor diabetes in humans. More studies are needed to assess clinical use in pets.

Home Monitoring

Observation of clinical signs is crucial to effective monitoring of DM. Owners should be encouraged to keep a daily log of appetite, observation of thirst (i.e., increased or normal), and insulin dose administered. Where DM monitoring is concerned, clinical signs supersede all else. When the patient has no clinical signs and the body weight is steady or increasing, DM is likely well controlled. In cats, one of the parameters considered to be the most useful and practical indicator of clinical DM control is the amount of water consumed over 24 hr.³⁰ Cat owners are often happy with the level of clinical DM control, despite not having laboratory

evidence of tight glycemic control, emphasizing that the long-term goal of DM treatment is to normalize clinical signs.³⁰ However, because a placebo effect can occur, judging the adequacy of DM control should not rely solely on owner observations.

Monitoring on the Initial Day of Treatment

- Initiate insulin therapy.
- Measure fructosamine.
- Perform a BGC to ensure that hypoglycemia does not occur.
- If BG is <150 mg/dL at any time:
 - Decrease dose by 10–50% in dogs.
 - Decrease dose by 0.5 U in cats.
 - In both species, re-curve the next day and daily thereafter until a nadir >150 mg/dL is reached.
- If BG is >150 mg/dL, discharge the patient and re-evaluate in 7–14 days (sooner if concerns for hypoglycemia arise). The insulin dose should not be increased on day 1 no matter how high BG may be.

Monitoring Until Control Is Attained

- In a new diabetic, have owner administer insulin in hospital to observe technique.
- BGC will need to be performed *q* 7–14 days until acceptable dose is found.
- Review owner log.
- Perform a physical examination, including measurement of body weight.
- Perform a BGC and measure fructosamine.

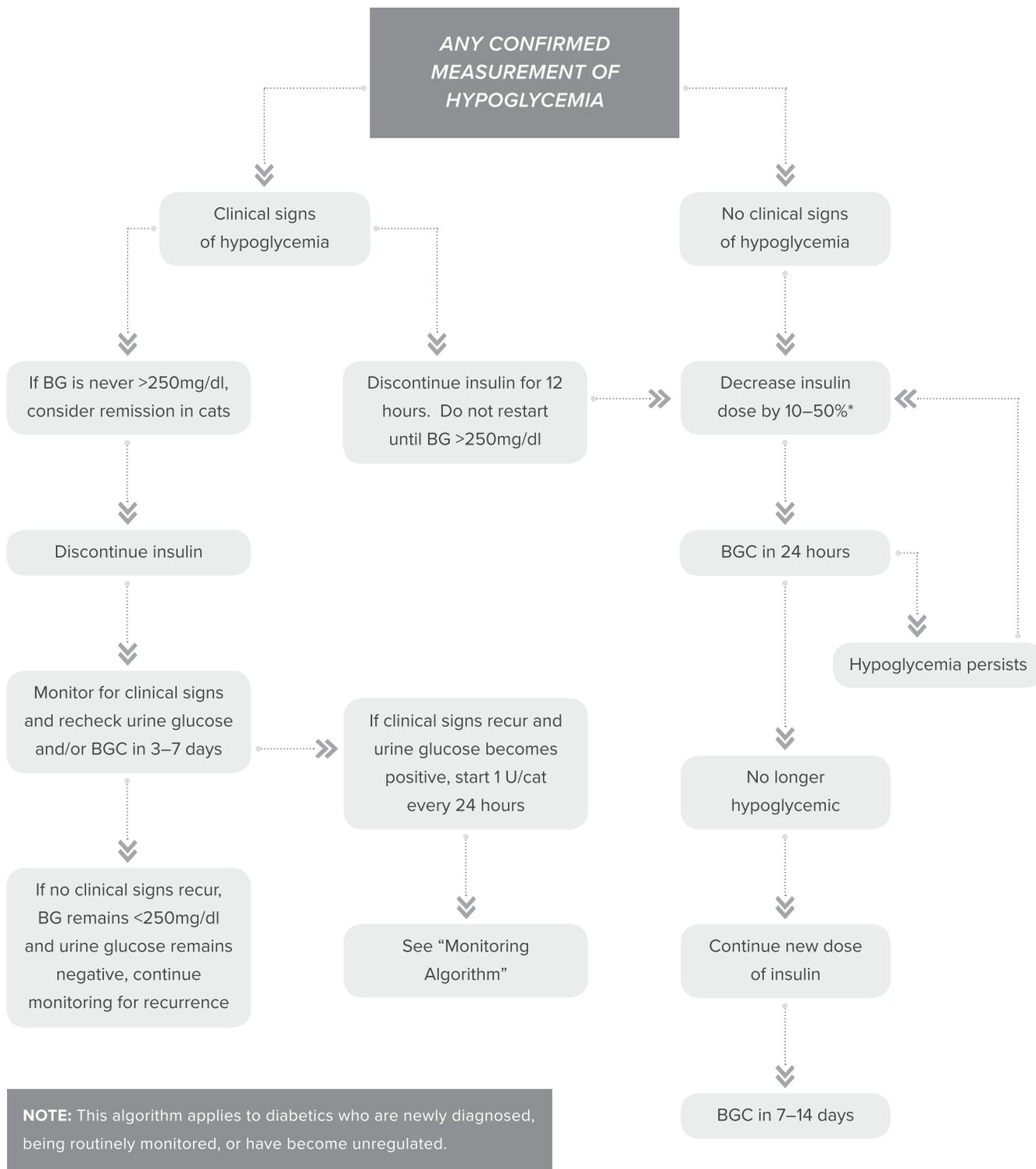
Ongoing Monitoring

- Review owner log.
- Perform a physical examination, including measurement of bodyweight.
- Perform a BGC and measure fructosamine.
- Semiannually, perform full laboratory work including urinalysis, urine culture, triglycerides, thyroid levels (cats), and BP.
- Any time an insulin dose is changed, a BGC should be performed in 7–14 days.
- Utilizing “spot checks” or isolated BG values by themselves is not recommended as a sole reason to increase an insulin dose, but can sometimes be used to decrease the dose (if verified).

Insulin Adjustments if the Nadir Is <80 mg/dL (see Figure 2)

- If clinical signs of hypoglycemia are present, treat as necessary.
- Once the BG becomes >250 mg/dL, reinstate therapy.
 - Decrease the dose 10–25% in dogs depending on the BG level and if there are no clinical signs of hypoglycemia.

MANAGING HYPOGLYCEMIA IN DIABETIC DOGS AND CATS



*See text for explanation of range of dosage

FIGURE 2 Managing hypoglycemia in diabetic dogs and cats.

- Decrease the dose 50% in dogs if there are clinical signs of hypoglycemia.
- Decrease the dose 0.5–1 U in cats depending on BG and if there are clinical signs of hypoglycemia.
- A BGC should be obtained after the next dose to ensure hypoglycemia does not recur. If hypoglycemia recurs with the lower dose, continue to decrease dose and obtain a BGC until hypoglycemia is not seen. Obtain a BGC in 7–14 days.
- If BG never returns to >250 mg/dL, consider remission, especially in cats. Monitor for hyperglycemia recurrence, in which case reinitiate insulin therapy as for new patient.

Insulin Adjustments if the Nadir Is >150 mg/dL

- If clinical signs are present:
 - Increase the dose 10–25% in dogs depending on the size of the patient and the degree of hyperglycemia.
 - Increase the dose 0.5–1 U in cats depending on the size of the patient and the degree of hyperglycemia.
 - If giving insulin once daily, consider *q* 12 hr therapy.
- If clinical signs are not reported:
 - Consider stress hyperglycemia OR placebo effect.
 - If weight is stable, leave dose unchanged and recheck in 1–3 mo.
 - If weight is decreasing, consider dose increase and recheck in 14 days.
- Consider the presence of insulin resistance if:
 - In dogs, insulin dose >1 U/kg/dose with no response or >1.5 U/kg fails to bring BG below 300 mg/dL.
 - In cats, insulin dose >5 U/dose.

Insulin Adjustments if the Nadir Is 80–150 mg/dL

- If clinical signs are controlled, no adjustment needed.
- If clinical signs are not controlled, do not adjust the insulin dose. Consider the following possibilities:
 - BGC is not reflective of overall control; BGC varies day to day.
 - There is inappropriate insulin duration of action. If giving insulin once a day, consider *q* 12 hr therapy. If giving *q* 12 hr, may need to consider changing insulin.
 - There is overlap of insulin action. If BG is still decreasing at end of day, the subsequent dose may cause hypoglycemia. May need to give a lower dose in the evening.
 - Presence of another disease is causing the clinical signs.

Ongoing Home Monitoring

- Log food and water intake and appetite daily.
- Log insulin doses daily.

- Note any signs suggestive of hypoglycemia; contact veterinarian if persistent.
- Periodically test urine; record glucose level and ketones. If ketones are present, contact veterinarian.

Key Points about Monitoring

- The hallmark of an appropriate DM-monitoring approach is to interpret all monitoring modalities in light of clinical signs.
- In cats and dogs, DM is probably well controlled if the pet is not showing signs of PU, PD, or PP and weight is stable.
- Senior cats and dogs of advanced age need to be closely monitored.
- Performing spot checks for BG is not a reliable monitoring modality; obtaining BGCs is a reliable monitoring strategy.
- Obtaining BGCs at home is preferred to doing so in the clinic.
- It is important not to place undue importance on isolated hyperglycemic values without considering clinical signs and stress-related BG increases.
- Monitoring BG is the only way to identify hypoglycemia.
- If hypoglycemia exists in an insulin-treated patient, the insulin dose must be decreased, even in cases where one low value is obtained on an otherwise normal BGC.
- In veterinary medicine, stringent BG control is not as critical as in human medicine, although senior cats and dogs should be monitored more closely than younger animals.

Troubleshooting

The uncontrolled diabetic is one with poor control of clinical signs. This may include hypo- and hyperglycemic pets, those with insulin resistance (decreased responsiveness to the insulin, defined by >1.5 U/kg per dose in dogs or >5U/dose in cats), or those with frequent increases or decreases in insulin doses. Any dog or cat with persistent clinical signs (PU/PD/PP) and unintended weight loss should be re-evaluated using the following protocol (see algorithm in **Figure 3**):

1. Rule out client and insulin-handling issues first. A common misconception is that a patient who does not respond to insulin has insulin resistance, but this is not necessarily true; other insulin-related factors should be considered.
 - a. Observe client's administration and handling of insulin, including type of syringes used. Assess insulin product and replace if out of date or if the appearance of the insulin changes (i.e., becomes flocculent, discolored, or, in the case of glargine [Lantus] or detemir [Levemir], cloudy).
2. Review diet and weight-loss plan.
3. Rule out concurrent medications that could cause insulin resistance, such as glucocorticoids, cyclosporine, and progestins.

Specifically ask owners about steroid-containing eye and ear drops and progestins that might be transferred from an owner via medicated cream used as hormone-replacement therapy in women.

- a. If the concurrent medication can be discontinued, the patient should be reassessed 2 wk later. For example, if the patient is placed on a short course of steroid eye drops before or after cataract surgery, the insulin dose does not usually need to be changed despite a short period of increased clinical signs.
- b. If the comedication cannot be discontinued within 2 wk, the insulin dose may need to be increased. Consultation with or referral to a specialist may be helpful in these situations, particularly if the diabetic patient has a concurrent immune-mediated disease that is being managed with glucocorticoids.
4. If not already done, obtain a BGC to rule out hypoglycemia. At-home monitoring is preferred. If hypoglycemia is detected, the insulin dose needs to be decreased.
5. Rule out concurrent disease.
 - a. Repeat a physical exam. Specifically, evaluate the teeth and gums for dental disease. Ovariohysterectomies must be performed in intact, diabetic female dogs and cats. Note that anesthesia is not contraindicated in otherwise healthy, stable, nonketoacidotic diabetic patients. See aaha.org/diabetes for sample protocols for managing diabetic patients under anesthesia.
 - b. Perform baseline laboratory testing (CBC, serum biochemistry with electrolytes, and urinalysis with culture both in dogs and cats; BP, UPC, and total T4 in cats), if not already completed recently.
 - c. Consider second-level diagnostics, such as abdominal and thoracic radiographs, abdominal ultrasound, species-specific pancreatic lipase immunoreactivity (specPLI), trypsin-like immunoreactivity (TLI), B12/folate, and symmetric dimethylarginine (SDMA) for International Renal Interest Society (IRIS) staging. These diagnostic tests, in conjunction with baseline diagnostics, will help identify many causes of insulin resistance, including renal disease, pancreatitis, urinary tract infection, and neoplasia. Acute and chronic pancreatitis can both destabilize a previously controlled patient and make it difficult to regulate a pet initially. Diagnosis is sometimes challenging, and requires a multifaceted approach because not all abnormalities will be present in a given patient. Evaluation of clinical signs in conjunction with clinicopathologic abnormalities, species-specific PLI, and abdominal ultrasound is critical. Pets with

chronic pancreatitis may have variable insulin requirements that increase when the patient has a flare-up, and decrease with improvement. If insulin doses are increased, hypoglycemia can occur when insulin resistance resolves with improvement of the pancreatitis. Thus, conservative dose adjustments should be made, and home monitoring for hypoglycemia is ideal.⁴⁴

- d. Consider specific diagnostics for (HAC), acromegaly, and thyroid disease. Hyperadrenocorticism can cause insulin resistance in dogs and cats, and cause persistent PU/PD in diabetic dogs who otherwise appear to be well regulated. Both species may have alopecia and dermatologic disease, and fragile skin is a hallmark feature of HAC in cats. Note that ALP is often increased in diabetic dogs, so increased ALP alone does not suggest HAC. Generally, endocrine testing for HAC should not be performed before diabetic regulation has been attempted for approximately 1 mo, because unregulated diabetes can lead to false-positive results in dogs who do not have HAC. ACTH stimulation tests and low-dose dexamethasone suppression tests can be used for diagnosis in dogs. The ACTH stimulation test is more specific (fewer false positives) but less sensitive (more false negatives) than the low-dose dexamethasone suppression test.⁴⁵ The low-dose dexamethasone suppression test is preferred in cats, but requires a higher dose of dexamethasone than that used in dogs (0.1 mg/kg).⁴⁶ Acromegaly is more common in diabetic cats than once believed, and may occur in up to 32% of diabetic cats.^{47,48} Acromegalic cats are sometimes on high insulin doses, reported to be as high as 35 U q 12 hr.⁴⁷ They may lose weight initially, but gain weight (or maintain weight) later in the course of the disease despite inadequate regulation and severe PU/PD/PP. Owners may report recent onset of snoring. Physical examination may reveal a large head with prognathia inferior, cranial organomegaly, or stertorous respiration. Insulin-like growth factor 1 (IGF-1) concentration is most often used for acromegaly screening in the United States. Consider testing once a cat has had approximately 6 wk of exogenous insulin. Hyperthyroidism and hypothyroidism can both cause significant insulin resistance. Diagnosis of hyperthyroidism in cats is often possible with a total T4 at initial diagnosis of diabetes, but diagnosis of hypothyroidism in diabetic dogs can be challenging. Many euthyroid diabetic dogs will have a decreased total T4 concentration due to euthyroid sick syndrome, so a decreased total T4 alone cannot confirm hypothyroidism. In most cases, testing for hypothyroidism should be delayed for a

TROUBLESHOOTING DIABETIC DOGS AND CATS RECEIVING THE “UPPER RANGE”¹ OF INSULIN DOSES

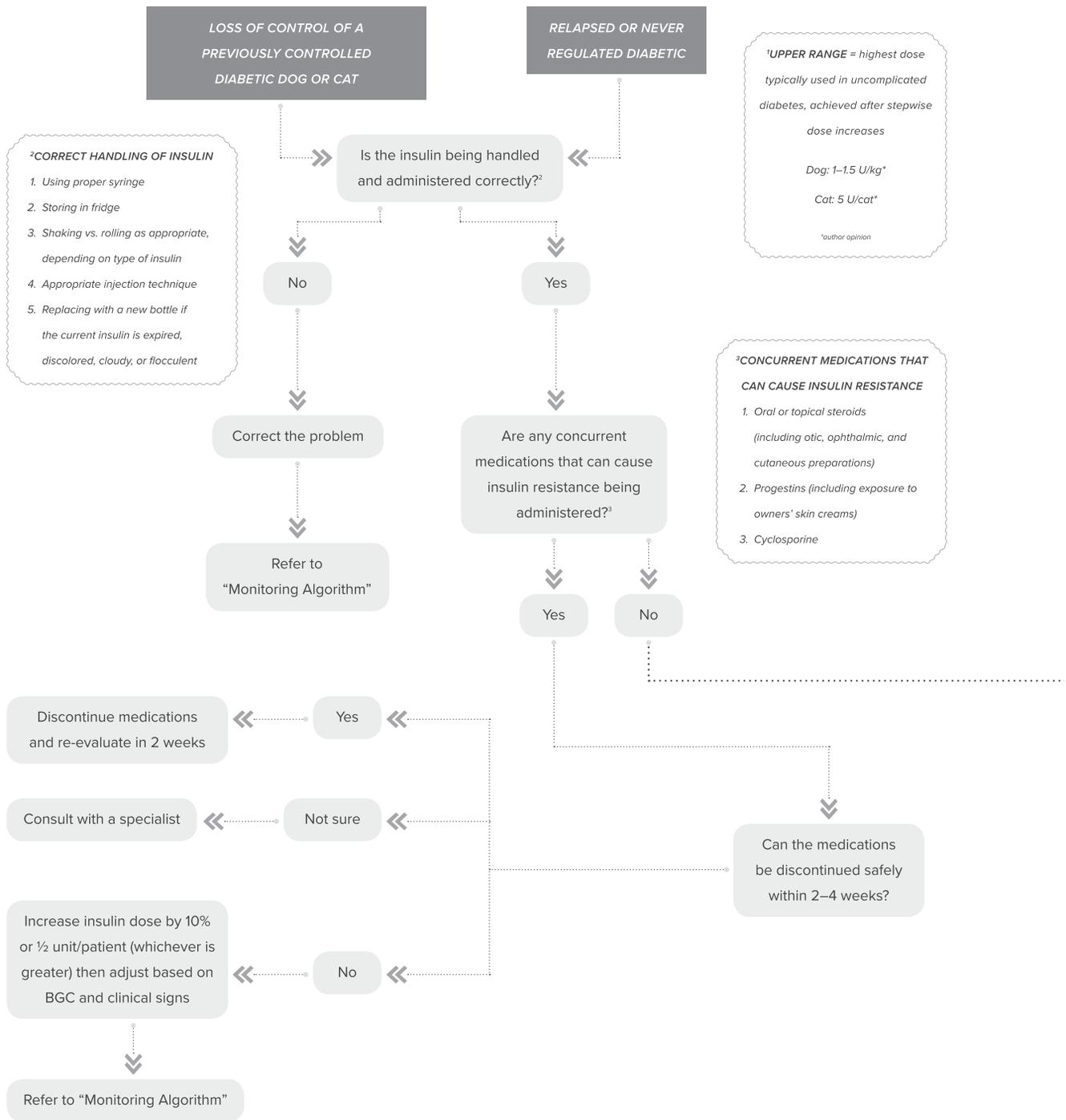


FIGURE 3 Troubleshooting diabetic dogs and cats receiving the “upper range”¹ of insulin doses.

TROUBLESHOOTING DIABETIC DOGS AND CATS RECEIVING THE “UPPER RANGE”¹ OF INSULIN DOSES

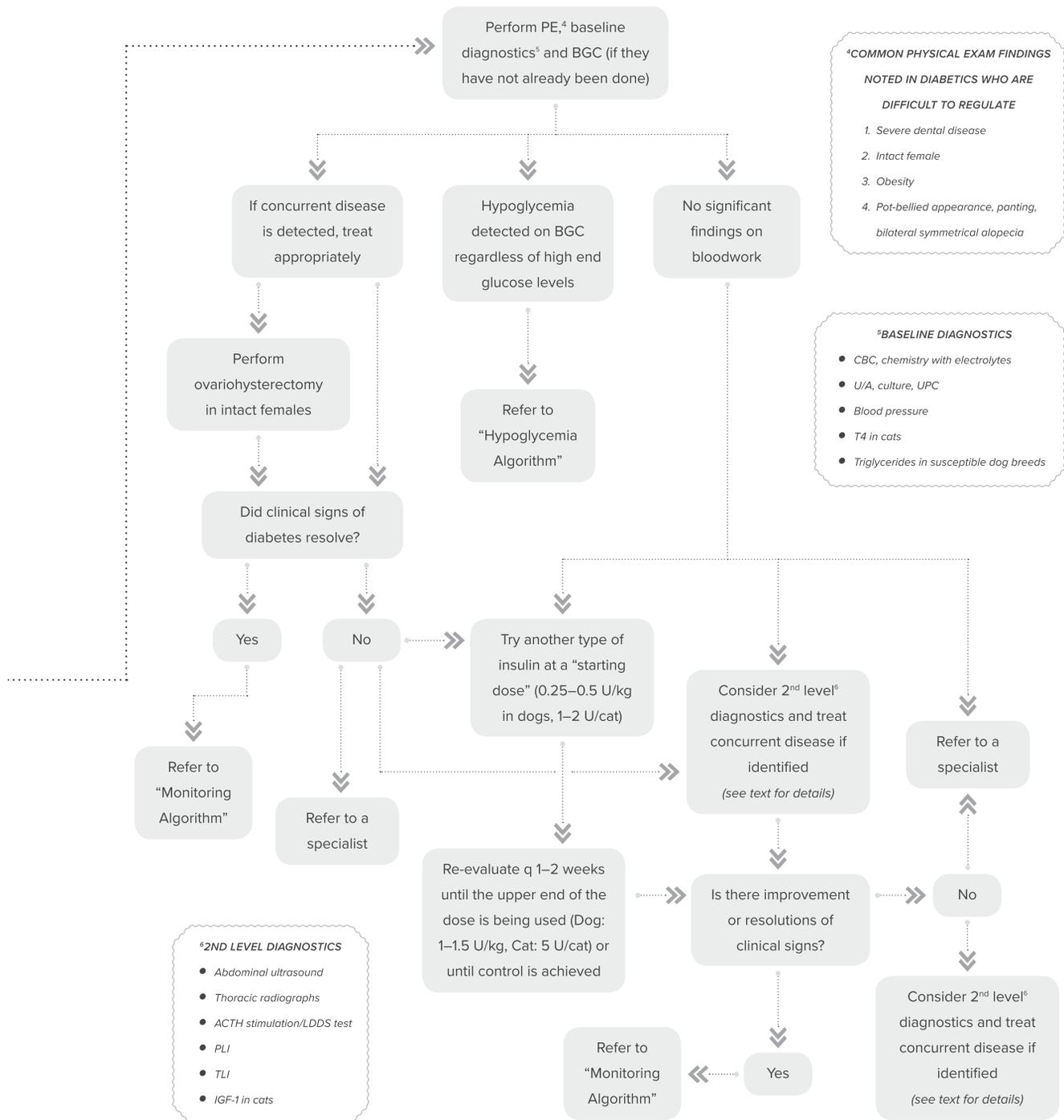


FIGURE 3 Continued

few weeks after the diagnosis of diabetes to decrease the effects of euthyroid sick syndrome. If there is clinical suspicion of hypothyroidism in a diabetic patient, a total T4, free T4 by equilibrium dialysis, and TSH (thyroid-stimulating hormone) should be evaluated concurrently.⁴⁹

- e. If the cause of insulin resistance is identified, the clinician should focus on resolving and treating that cause, then return to regulating the DM.

Common Concurrent Diseases Implicated in Insulin Resistance

- Obesity (dogs, cats)
- Hypothyroidism (dogs)
- Hyperthyroidism (cats)
- Dental disease (dogs, cats)
- Infection; for example, urinary tract infection (dogs, cats)
- Hypertriglyceridemia (dogs, especially schnauzers)
- Hyperadrenocorticism (dogs > cats)
- Kidney disease (cats > dogs)
- Acromegaly (cats)
- Pancreatitis (dogs > cats)
- Pregnancy/diestrus (dogs, cats)

6. If the patient has never been regulated and has only been administered one type of insulin thus far, consider switching insulin type. This may be attempted prior to item 5c, based on clinician preference.
7. Finally, consult with a specialist if the patient cannot be regulated.

Recognizing and Managing the Patient at Risk for Diabetes Mellitus

Patients with clinical DM must be differentiated from those with mild-to-moderate increased BG without glucosuria or clinical signs. Although the latter group may be at risk for developing clinical DM and may require additional diagnostic and therapeutic measures, they do not require insulin therapy. One well-recognized example is transient stress hyperglycemia in the cat. Stress hyperglycemia should be ruled out in patients presenting with mild hyperglycemia by rechecking BG, potentially in the home environment, or by measuring fructosamine concentration.

When evaluating patients at risk for DM, clinicians should obtain a thorough history to ensure that the patient is not receiving any medications such as glucocorticoids that can cause insulin

resistance. At-risk patients should be carefully evaluated for any concurrent diseases or conditions that may result in insulin resistance, like obesity.^{50,51} These include diestrus in intact female dogs as well as HAC. Chronic pancreatitis has also been implicated as a risk factor for DM in cats.^{8,44}

For patients at risk for developing DM, steps should be taken to prevent the patient from becoming overtly diabetic. Avoid administering medications such as corticosteroids, cyclosporine, or progestins. Patients should be treated for concurrent disease such as obesity, HAC, and chronic pancreatitis. For dogs and cats, the next step is often dietary modification. The goals of dietary therapy include optimizing body weight, minimizing postprandial hyperglycemia, and exercising control of calorie, protein, carbohydrate, and fat intake. The section on “Dietary Therapy Goals and Management” that appears earlier in these guidelines provides detailed recommendations for maintaining optimum bodyweight in at-risk dogs and cats and those with clinical DM.

Patients identified as having chronically mild-to-moderately increased BG without clinical DM should be monitored regularly. Ongoing monitoring of BG and urinalysis should be tailored to the needs of the patient. If overweight, this monitoring will determine if the hyperglycemia corrects as weight reduction is achieved. This is also essential to identify patients that do not respond to conservative therapy or who develop overt DM. Unfortunately, for patients at risk for DM who do not have a treatable underlying condition such as obesity or corticosteroid administration, there is not currently a known way to prevent DM.

Client Education

The goal of client education is to give the pet owner a realistic idea of the commitment involved in managing their pet’s DM, along with positive encouragement that successful disease management is possible but can take time to achieve. Owners need adequate access to trained veterinary support staff to answer questions and troubleshoot common problems. Client education should provide owners with written information on commonly asked questions, what to watch for at home, and how to respond to changes in the patient’s condition. Veterinarians should direct owners to helpful web links, including aaha.org/diabetes. Veterinarians should stress the importance of appropriate nutrition and weight management.

Key Points of Client Education

Insulin Mechanism, Administration, Handling, and Storage

- Explain how insulin works and its effects on BG.
- Instruct owners in the proper handling for the specific type of prescribed insulin.

- When using Vetsulin, the vial should be shaken until a homogeneous, uniformly milky suspension is obtained (noted in the Vetsulin package insert).
- When using other insulins (glargine [Lantus], PZI [Prozinc], NPH [Novolin, Humulin]), roll but do not shake vial.
- Wipe vial stopper with alcohol prior to inserting syringe needle.
- Do not freeze insulin preparations.
- Do not expose insulin to heat; avoid leaving in parked car or prolonged exposure to direct sunlight.
- Recommend storage in refrigerator for consistency in environment.
- If stored carefully, the Task Force is comfortable using insulins beyond the date of expiration as long as they are not discolored, flocculent, or have any changes of consistency. However, the Task Force also recommends referral to package insert for instructions about shelf life after opening and discarding insulin if it becomes out of date.
- Recommend new vial if insulin changes in appearance.
- For human diabetic patients, manufacturer recommendations are to maintain glargine for only 28 days and store at room temperature.
- Discuss what to do if the patient does not eat a full meal or vomits before or after insulin administration.

Types of Syringes

- Always use a U-40 insulin syringe with U-40 insulin and a U-100 insulin syringe with U-100 insulin.
- 0.3 and 0.5 mL insulin syringes or insulin pens are best to facilitate accurate dosing, especially in cats and dogs getting <5 U per dose.⁵² Clinicians should evaluate if the needles in the pens are long enough for their specific patients.
- Syringes are for single use.
- Do not use “short” needles. A standard 29 g, half-inch length needle is recommended.

Troubleshooting and Follow-up Action

- If the pet does not eat, contact the veterinarian. Ideally, instruct owners to measure BG at home. Consider administering half the usual dose of insulin and monitor for signs of hypo- or hyperglycemia or other systemic illness.
- Help clients recognize the signs of low BG, such as lethargy, sleepiness, strange behavior, abnormal gait, weakness, tremors, and seizures, and know what to do if they occur
 - If their pet is conscious, feed a high-carbohydrate meal (e.g., rice, bread, pasta, a regular diet with added corn syrup).
 - If their pet is poorly responsive or has tremors, rub 1–2 teaspoons of corn syrup onto gum tissue. Some experts use a dose of 0.125 mL/kg. Advise client of the risk of

aspiration in an obtunded animal. Feed if there is a response within 5 min. Take the pet to a veterinarian.

- Home BG monitors should be veterinary-approved products calibrated for dogs and cats.
- Client is empowered to decrease or skip an insulin dose if hypoglycemia is noted, but should never increase the dose or frequency of insulin without clear instructions from the attending veterinarian.

Conclusion

Management of DM requires the commitment and coordinated efforts of the veterinary healthcare team and the pet-owner client. For this reason, proactive client education is an essential component of a DM treatment plan. Client education includes instruction on insulin administration, signs of favorable clinical response or lack thereof, measuring BG levels, and the importance of non-insulin therapies, including dietary management.

Diabetes mellitus has a multifactorial etiology, requiring practitioners to consider and assess the possible roles of the patient’s body condition score, diet, concurrent diseases, medications, neutering status, and genetic predisposition. When the relevant DM-causative factors have been identified, a well-defined, case-specific treatment plan can be developed with a reasonable expectation for control, and in the case of cats, a chance for remission.

The distinction between clinical and subclinical DM and transient hyperglycemia is an important factor in the approach to treatment. Insulin therapy is reserved for patients with clinical DM. Patients at risk for developing DM should be managed using monitoring strategies and non-insulin modalities, with an emphasis on dietary management. Diagnosis of DM focuses on a combination of predisposing factors, characteristic clinical signs, and laboratory diagnostic values outside the reference ranges. These factors should be considered in their totality rather than as isolated indicators.

The mainstay of treatment for clinical DM in dogs and cats is insulin along with dietary modification. Goals include controlling BG below the renal threshold for as much of a 24 hr period as possible, which will improve clinical signs of DM, and avoiding clinically significant hypoglycemia. There are many insulin formulations currently commercially available, two of which are approved for veterinary use: lente (Vetsulin) in dogs and cats and PZI (Prozinc) in cats. The choice of insulin is often based on duration of effect in the respective species. Dietary management is an essential cotherapy in clinical DM cases, although non-insulin medications may be useful adjuncts to insulin therapy.

The goal of DM monitoring is to confirm the absence of clinical signs and avoidance of hypoglycemia, the definition of a controlled diabetic. Monitoring of BG levels is best done by obtaining a BGC

rather than by “spot-check” BG measurements. Diabetes mellitus is probably well controlled if the pet is not showing persistent signs of PU, PD, or PP and is not experiencing unintended weight loss. ■

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REFERENCES

- Rucinsky R, Cook A, Haley S, et al. AAHA diabetes management guidelines for dogs and cats. *J Am Anim Hosp Assoc* 2010;46(3):215–24.
- Davison LJ, Ristic JM, Herrtage ME, et al. Anti-insulin antibodies in dogs with naturally occurring diabetes mellitus. *Vet Immunol Immunopathol* 2003;91(1):53–60.
- Goossens MM, Nelson RW, Feldman EC, et al. Response to insulin treatment and survival in 104 cats with diabetes mellitus (1985-1995). *J Vet Intern Med* 1998;12(1):1–6.
- Bloom CA, Rand J. Feline diabetes mellitus: clinical use of long-acting glargine and detemir. *J Feline Med Surg* 2014;16(3):205–15.
- Caney SM. Management of cats on Lente insulin: tips and traps. *Vet Clin North Am Small Anim Pract* 2013;43(2):267–82.
- Hess RS, Kass PH, Ward CR. Breed distribution of dogs with diabetes mellitus admitted to a tertiary care facility. *J Am Vet Med Assoc* 2000; 216(9):1414–7.
- Rand JS, Bobbermien LM, Hendrikz JK, et al. Over representation of Burmese cats with diabetes mellitus. *Aus Vet J* 1997;75(6):402–5.
- Gilor C, Niessen SJ, Furrow E, et al. What’s in a name? Classification of diabetes mellitus in veterinary medicine and why it matters. *J Vet Intern Med* 2016;30(4):927–40.
- Link KR, Rand JS. Changes in blood glucose concentration are associated with relatively rapid changes in circulating fructosamine concentrations in cats. *J Feline Med Surg* 2008;10(6):583–92.
- Davison LJ. Diabetes mellitus and pancreatitis—cause or effect? *J Small Anim Pract* 2015;56(1):50–9.
- Scott-Moncrieff JC, Moore GE, Coe J, et al. Characteristics of commercially manufactured and compounded protamine zinc insulin. *J Am Vet Med Assoc* 2012;240(5):600–5.
- Roomp K, Rand JS. Management of diabetic cats with long-acting insulin. *Vet Clin North Am Small Anim Pract* 2013;43(2):251–66.
- Hess RS, Drobotz KJ. Glargine insulin for treatment of naturally occurring diabetes mellitus in dogs. *J Am Vet Med Assoc* 2013;243(8):1154–61.
- Nelson RW, Henley K, Cole C, et al. Field safety and efficacy of protamine zinc recombinant human insulin for treatment of diabetes mellitus in cats. *J Vet Intern Med* 2009;23(4):787–93.
- Palm CA, Boston RC, Refsal KR, et al. An investigation of the action of Neutral Protamine Hagedorn human analogue insulin in dogs with naturally occurring diabetes mellitus. *J Vet Intern Med* 2009;23(1): 50–5.
- Hoelmkjaer KM, Spodsberg EM, Bjornvad CR. Insulin detemir treatment in diabetic cats in a practice setting. *J Feline Med Surg* 2015;17(2):144–51.
- Roomp K, Rand J. Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control. *J Feline Med Surg* 2012; 14(8):566–72.
- Fracassi F, Corradini S, Hafner M, et al. Detemir insulin for the treatment of diabetes mellitus in dogs. *J Am Vet Med Assoc* 2015;247(1):73–8.
- Martin GJ, Rand JS. Pharmacokinetic and pharmacodynamics study of caninsulin in cats with diabetes mellitus. *Internal Study Report*. 2000.
- Graham PA, Nash AS, McKellar QA. Pharmacokinetics of porcine insulin zinc suspension in diabetic dogs. *J Small Anim Pract* 1997;38(10):434–8.
- Fracassi F, Boretti FS, Sieber-Ruckstuhl NS, et al. Use of insulin glargine in dogs with diabetes mellitus. *Vet Rec* 2012;170(2):52.
- Maggiore AD, Nelson RW, Dennis J, et al. Efficacy of protamine zinc recombinant human insulin for controlling hyperglycemia in dogs with diabetes mellitus. *J Vet Intern Med* 2012;26(1):109–15.
- Sparkes AH, Cannon M, Church D, et al. ISFM consensus guidelines on the practical management of diabetes mellitus in cats. *J Feline Med Surg* 2015;17(3):235–50.
- Nelson RW, Robertson J, Feldman EC, et al. Effect of the alpha-glucosidase inhibitor acarbose on control of glycemia in dogs with naturally acquired diabetes mellitus. *J Am Vet Med Assoc* 2000;216(8):1265–9.
- Riederer A, Zini E, Salesov E, et al. Effect of the glucagon-like peptide-1 analogue exenatide extended release in cats with newly diagnosed diabetes mellitus. *J Vet Intern Med* 2016;30(1):92–100.
- Oda H, Mori A, Lee P, et al. Characterization of the use of liraglutide for glycemic control in healthy and Type 1 diabetes mellitus suffering dogs. *Res Vet Sci* 2013;95(2):381–8.
- Gilor C, Rudinsky AJ, Hall MJ. New approaches to feline diabetes mellitus: Glucagon-like peptide-1 analogs. *J Feline Med Surg* 2016; 18(9):733–43.
- Zoran DL, Rand JS. The role of diet in the prevention and management of feline diabetes. *Vet Clin North Am Small Anim Pract* 2013;43(2): 233–43.
- Briggs CE, Nelson RW, Feldman EC, et al. Reliability of history and physical examination findings for assessing control of glycemia in dogs with diabetes mellitus: 53 cases (1995-1998). *J Am Vet Med Assoc* 2000; 217(1):48–53.
- Martin GJ, Rand JS. Comparisons of different measurements for monitoring diabetic cats treated with porcine insulin zinc suspension. *Vet Rec* 2007;161(2):52–8.
- Cohen TA, Nelson RW, Kass PH, et al. Evaluation of six portable blood glucose meters for measuring blood glucose concentration in dogs. *J Am Vet Med Assoc* 2009;235(3):276–80.
- AlphaTrak 2 [product insert.] Zoetis, Parsippany, NJ. Available at: https://www.zoetis.com/contact/pages/product_information/msds_pi/pi/alphatrak_2.pdf. Accessed September 13, 2017.
- Behrend EN, Suchowersky ND, Carlson EA, et al. Comparison between glucose measurements in canine whole blood, serum, and plasma. *J Vet Intern Med* 2017;31:1271–2.
- Roomp K, Rand J. Rebound hyperglycaemia in diabetic cats. *J Feline Med Surg* 2016;18(8):587–96.
- Fleeman LM, Rand JS. Evaluation of day-to-day variability of serial blood glucose concentration curves in diabetic dogs. *J Am Vet Med Assoc* 2003; 222(3):317–21.
- Ristic JM, Herrtage ME, Walti-Lauger SM, et al. Evaluation of a continuous glucose monitoring system in cats with diabetes mellitus. *J Feline Med Surg* 2005;7(3):153–62.
- Casella M, Wess G, Hassig M, et al. Home monitoring of blood glucose concentration by owners of diabetic dogs. *J Small Anim Pract* 2003;44(7): 298–305.
- Van de Maele I, Rogier N, Daminet S. Retrospective study of owners’ perception on home monitoring of blood glucose in diabetic dogs and cats. *Can Vet J* 2005;46(8):718–23.

39. Alt N, Kley S, Haessig M, et al. Day-to-day variability of blood glucose concentration curves generated at home in cats with diabetes mellitus. *J Am Vet Med Assoc* 2007;230(7):1011–7.
40. Behrend EN, Tapia J, Welles EG, et al. Evaluation of a conventional urine glucose test strip method for detection of glucosuria in dogs and cats [abstract]. *J Vet Intern Med* 2008;22:790a.
41. Greco DS, Broussard JD, Peterson ME. Insulin therapy. *Vet Clin North Am Small Anim Pract* 1995;25(3):677–89.
42. Miller E. Long-term monitoring of the diabetic dog and cat: clinical signs, serial blood glucose determinations, urine glucose and glycated blood proteins. *Vet Clin North Am Small Anim Pract* 1995;25(3):571–84.
43. Crenshaw KL, Peterson ME, Heeb LA. Serum fructosamine concentration as an index of glycemia in cats with diabetes mellitus and stress hyperglycemia. *J Vet Intern Med* 1996;10(6):360–4.
44. Caney SM. Pancreatitis and diabetes in cats. *Vet Clin North Am Small Anim Pract* 2013;43(2):303–17.
45. Behrend E. Canine hyperadrenocorticism. In: Feldman ED, Nelson RW, Reusch CE, et al, eds. *Canine and Feline Endocrinology*. 4th ed. St. Louis: Elsevier; 2015:403–5.
46. Valentin SY. Clinical findings, diagnostic test results, and treatment outcome in cats with spontaneous hyperadrenocorticism: 30 cases. *J Vet Intern Med* 2014;28(2):481–7.
47. Niessen SJ, Petrie G, Gaudiano F, et al. Feline acromegaly: an under-diagnosed endocrinopathy? *J Vet Intern Med* 2007;21(5):899–905.
48. Berg RI, Nelson RW, Feldman EC, et al. Serum insulin-like growth factor-1 concentration in cats with diabetes mellitus and acromegaly. *J Vet Intern Med* 2007;21(5):892–8.
49. Mooney C. Canine hyperthyroidism. In: Ettinger SJ, Feldman EC, Cote E, eds. *Textbook of Veterinary Internal Medicine*. 8th ed. St. Louis: Elsevier; 2017:1731–42.
50. O'Neill DG, Gostelow R, Orme C, et al. Epidemiology of diabetes mellitus among 193,435 cats attending primary-care veterinary practices in England. *J Vet Intern Med* 2016;30(4):964–72.
51. German AJ, Hervera M, Hunter L, et al. Improvement in insulin resistance and reduction in plasma inflammatory adipokines after weight loss in obese dogs. *Domest Anim Endocrinol* 2009;37(4):214–26.
52. Keith K, Nicholson D, Rogers D. Accuracy and precision of low-dose insulin administration using syringes, pen injectors, and a pump. *Clin Pediatr (Phila)* 2004;43(1):69–74.