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ISSUES IN ENDOCRINOLOGY

Treating and Managing Diabetes Mellitus in Dogs

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Diabetes mellitus (DM) is a common endocrine disease in dogs; the reported worldwide prevalence ranges from 0.3% to 1.3%.[1-4] This disease results from an absolute or relative lack of the hormone insulin. Most commonly, dogs get insulin-dependent DM, similar to type 1 DM in people. This type of DM results from a presumed immune-mediated attack on the pancreatic beta cells, which are responsible for synthesizing and secreting insulin, although it can also result from vacuolar degeneration of the pancreas or pancreatitis.[5-7] The loss of pancreatic beta cells results in an absolute decrease in circulating insulin. Other risk factors for DM in dogs include concomitant diseases such as hypothyroidism, hyperadrenocorticism, and obesity, or other hormonal or iatrogenic insulin-resistance triggers (e.g., diestrus or medications such as steroids or progestins).[8,9]

SIGNALMENT AND CLINICAL SIGNS

DM usually affects middle-aged dogs, especially Samoyeds, poodles, schnauzers, and bichon frises.[10,11] Common clinical signs include polyuria/polydipsia, polyphagia, weight loss, persistent or recurrent urinary tract infections, decreased muscle mass, cataracts, and, rarely, peripheral neuropathy. If the disease is not treated, signs can progress to inappetence, lethargy, and vomiting. Because pancreatitis is often associated with DM (as a causative or resultant factor), clinical signs of abdominal pain may also be present.

DIAGNOSIS

DM is relatively easy to diagnose by recognition of clinical signs and persistent fasting hyperglycemia and glucosuria. However, one factor that may confound diagnosis is stress. Stress alone can cause hyperglycemia, and if sufficiently elevated in the serum, glucose can spill over into the urine. In dogs, the renal glucose threshold at which glucose will spill into the urine is approximately 180 mg/dL. Should the practitioner have any doubt as to whether hyperglycemia and glucosuria are the result of DM or stress, checking the serum fructosamine

A BREED APART
The incidence of canine diabetes mellitus appears to be increased in certain small breeds, such as schnauzers, though any breed can be affected.

level can be helpful. Fructosamine is a compound formed by a nonenzymatic covalent bond between a sugar (fructose or glucose) and a protein (largely albumin). The measurement represents the average of the blood glucose over the preceding 2 to 3 weeks and is not affected by rapid increases and decreases of blood sugar, such as those caused by a stressful event.[12] If the serum fructosamine level is elevated, then a diagnosis of DM is appropriate; if not elevated, then stress is probably the cause of the hyperglycemia/glucosuria.

Initial evaluation of the patient should include a complete physical examination, complete blood count, chemistry profile, and urinalysis. Even if urinalysis and sediment parameters are within normal limits, consider culturing the urine since up to 35% of urinary tract infections can be microscopically silent (no bacteruria or white blood cells) in animals with DM, hyperadrenocorticism, or both, probably the result of the dilute urine and immunosuppression.[13] Abdominal imaging may be pursued if clinically indicated.

Coexisting medical conditions should be addressed early and aggressively so that the DM can be easier to regulate; clients may become frustrated and give up if the DM is not easily controlled. Any concurrent disease can cause insulin resistance by causing release of inflammatory mediators, which interfere with the action of insulin, or by release of adrenal hormones.[14] The most common concurrent diseases in dogs with DM include urinary tract infections, pancreatitis, and endocrinopathies (e.g., Cushing's disease and hypothyroidism).[8]

TREATMENT

Initial evaluation will determine how intensively the patient should be managed. If the dog is eating and drinking normally and is well hydrated, there is no reason to hospitalize it while insulin therapy is initiated. If the dog is dehydrated, acidotic, or hyperosmolar, it should be hospitalized and stabilized before institution of long-term insulin therapy.

Insulin

The definitive therapy for DM in dogs is insulin, to replace the deficiency caused by lack of functional pancreatic beta cells.[9] A short-acting insulin such as regular insulin has a rapid onset of action; is degraded quickly; and may be given by the intravenous, intramuscular, or subcutaneous routes. It is used to treat diabetic animals in unstable condition, such as those who are dehydrated, ketotic, or hyperosmolar. For dogs in stable condition, the practitioner can start with intermediate or long-acting insulins that generally require subcutaneous administration and thus are not appropriate for dehydrated animals. The many types of insulin on the market differ according to the pharmacologic mechanism by which they are made into a repository form. Dogs may have a differential response to a singular insulin. In the United States, the insulins most commonly used in dogs are porcine lente (Vetsulin, merck-animal-health-usa.com) and isophane insulin (also known as NPH) (Novolin-N, novonordisk-us.com; Humulin-N, lilly.com/products), which are optimally given twice daily.[9] The human basal insulins glargine (Lantus, sanofi.us) and detemir (Levemir, novonordisk-us.com) have also been used in dogs and may be longer-lasting, although current recommendations are to initiate therapy twice daily. Human recombinant protamine zinc insulin (ProZinc, bi-vetmedica.com) has recently been licensed for use in dogs; in a field trial, it was shown to be effective in 72% of over 200 dogs given the drug once daily. Factors to consider when choosing insulin are price (NPH is the least expensive), U.S. Food and Drug Administration approval for veterinary use (the U-40 insulins Vetsulin and ProZinc), availability of dosing pens (Lantus, Levemir, Vetsulin), and possible once-daily dosing (Lantus, Levemir, ProZinc). Regardless of insulin type, the initial dose for dogs is 0.5 U/kg q12h, except for determir, which should initially be given at 0.25 U/kg q12h.

For most diabetic dogs, insulin therapy will improve clinical signs soon after initiation. However, it may take several weeks for the animal to fully adjust to insulin therapy. Because the average time for initial DM control is 4 to 6 weeks (C.R. Ward, unpublished data), remind clients to be patient.

Feeding

Dogs receiving insulin should be fed twice daily. The optimal diet for diabetic dogs is high in insoluble fiber.[15] This diet slows glucose absorption from the gut and reduces postprandial hyperglycemia. Many clients give insulin while the dog is eating; doing so associates the insulin injection with a pleasant experience for the dog, which makes it easier for clients to administer. To avoid obesity in the dog, clients should ensure that the dogs are not receiving more than their caloric needs. The daily caloric intake should be divided into 2 equal

meals. A small snack calculated into the daily caloric requirements may be given at peak insulin activity time, usually 4 to 8 hours after insulin administration. If the dog does not eat its meal, insulin should be given at half the normal dose. If the dog misses another meal, the client should contact the veterinarian.

Exercise

Exercise is beneficial for diabetic dogs; it helps lower insulin requirements and provide better glycemic control. Daily walking or play exercise for dogs with DM can be an effective ancillary treatment to help achieve glucose control at a lower dose of insulin.

Treatment of DM in dogs can be frustrating, expensive, and time-consuming for clients. In a recent worldwide study, 10% of dogs with DM were euthanized at or within the first year of diagnosis.[16] The reason for 32% of euthanasia cases was cited as the effect on the client's lifestyle; therefore, be flexible when establishing a treatment plan. The long-lasting sequelae of DM in people (e.g., glomerlular disease, retinal degeneration, and hypertension) are not problematic for veterinary patients.[9] Perhaps our patients do not live long enough for these problems to surface, or perhaps they are protected in some way. Regardless, the veterinarian and client should not strive for perfect blood glucose control; rather, the goal should be good clinical control. Good rapport with clients with diabetic dogs is helpful because clients will be asked to provide invasive (injections) and time-consuming (glucose monitoring) care for their dog. It is beneficial to have an in-depth discussion with clients as to the time, effort, and financial resources they can realistically commit to treatment for their diabetic dog.

Remember that the goals for DM therapy should be correction of clinical signs, restoration of normal musculature and energy level, control of concurrent diseases, and avoidance of emergency situations (e.g., hypoglycemia, ketosis, and hyperosmolality).

MONITORING

After insulin therapy has been started, wait 7 to 14 days to monitor any effects since it takes that long for the dog to adjust to the therapy. During that period, clients can measure urine glucose and ketones with Keto-Diastix (pharma.bayer.com). These strips can be put on any area that contains urine moisture, such as grass or gravel; as long as the strip is wet, it will provide ketone and glucose readings. Clients should notify the veterinarian if more than 2 urine glucose readings are negative, especially if the dog shows clinical signs of hypoglycemia or if the ketone readings are positive. If urine glucose is negative, hypoglycemia may be present since the strip will only show glucose if the blood glucose is greater than 180 mg/dL (the renal threshold).

Because DM is so common among people, many veterinary clients may be familiar with glucometer use. For those willing to obtain spot blood glucose measurements at home, the Alpha-Trak2 glucose monitor (zoetisus.com) may be helpful. It is specially calibrated for use in dogs and requires substantially less blood to obtain a reading, therefore making it more convenient to use than human glucometers. Although glucose measurements using serum chemistry analyzers are more accurate, glucometer measurements are easily obtained in the home environment with rapidly available results. Trends in glucose measurements can

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HEART-TO-HEART TALK
Though most cases of canine diabetes mellitus are uncomplicated and can be treated at home, pet owners can be overwhelmed by the diagnosis. When talking to these clients, it is important to explain that dogs with DM—even those with other complicating diseases—can live a full and healthy life.

To capture the optimal glucose lowering effects, clients should optimally check blood glucose levels 4 to 8 hours after injecting insulin.

be followed. Blood samples can be obtained by pricking the ear pinna, gum, paw pad, or elbow areas.

During the initial insulin acclimation period, insulin doses should not be changed as a result of glucose readings, but clients should notify the veterinarian if the animal is ketotic or hypoglycemic. To capture the optimal glucose lowering effects, clients should optimally check blood glucose levels 4 to 8 hours after injecting insulin.

At the initial recheck after insulin therapy has been initiated, ask the client about resolution of clinical signs and perform a physical examination, weight measurement, and determination of body condition score. Examine muscle mass and record a muscle condition score. These parameters measure the most important goal of DM therapy in dogs: resolution of clinical signs and normalization of physical examination parameters. For many patients, these factors are more predictive of diabetic control than glucose measurements.[17]

Another useful aid for monitoring response to therapy is serum fructosamine.[12] For fructosamine values to be interpretable, the dog should have received a stable insulin dose for at least 3 weeks before the serum fructosamine level is measured. Although fructosamine levels can be useful for monitoring long-term response to insulin therapy, they are inappropriate for use in animals in unstable condition or those in which a hypoglycemia-induced hyperglycemic (Somogyi) response is suspected. For these patients, a glucose curve must be completed.

A glucose curve is the only way to truly evaluate the body's response to insulin. Serum glucose levels directly reflect insulin activity. Information obtained from glucose curves includes insulin onset of action, duration of action, time of peak activity, and lowest glucose level (nadir). The first 3 parameters indicate whether the right type of insulin is being used; the last parameter provides information about the appropriate dose of insulin.

Obtaining a traditional in-hospital glucose curve requires measuring blood glucose levels, usually by glucometer, every 2 hours over a 9- to 12-hour period. These curves have many limitations, including disruption of the patient's normal activity and eating routine, introduction of stress-related hyperglycemia, and labor intensiveness of the procedure. Furthermore, diabetic dogs experience significant variations in day-to-day glycemic control.[18] Intermittent blood sampling over a 12-hour period only may grossly overestimate or underestimate a patient's glycemic control, and glucose peaks and nadirs may be missed if they occur between samplings. Some clients can complete glucose curves at home and send the data to the veterinarian. Although such home-generated curves minimize the change in the dog's normal routine, the daily variance in data can lead the clinician to make different insulin recommendations, depending on the curve examined.[19]

Continuous glucose monitoring and flash glucose monitoring systems provide minimally invasive ways to continuously evaluate glycemic control for up to 14 days.[20] They measure interstitial glucose and record an average value every 5 minutes. The systems comprise an external sensor with a flexible electrode that is inserted into the subcutaneous tissue. The electrode emits a small electrical current proportional to the amount of glucose in the interstitium. The electrical charge is then calibrated to a glucose measurement that is read on a monitor.

Two systems that have been validated for use in veterinary patients—the MiniMed iPro2 (continuous, professional.medtronicdiabetes.com) and the Abbott Freestyle Libre (flash, freestylelibre.us/index.html) systems—have been used successfully and can be sent home with the patients.[21,22] The iPro2 sends data continuously from the disposable sensor to a recorder attached to the end of the sensor. Clients are blinded to the glucose results until the device is removed and downloaded onto the MiniMed website. The iPro2 requires calibration by blood glucose measurement every 8 to 12 hours. The Abbott Freestyle Libre consists of a disposable sensor and recorder attached to the skin of the patient. The interstitial glucose data are stored in

the recorder until a reader is passed over it, which will show the glucose level and download updated information to the reader. The glucose information can be shared with the practitioner via a website. The Freestyle Libre is factory calibrated and does not require blood sample calibration at home.

Both of these systems have the advantage of being able to evaluate the response to insulin therapy in the patient's home environment and during its usual routine. The stress of frequent blood sampling is avoided and glucose data can be captured at all times during the day. Flash glucose monitoring has the advantage of allowing clients to see glucose measurements, thereby relieving concerns of extreme hyper- or hypoglycemia. This monitoring can make it easier to manage diabetic dogs with concurrent diseases, such as hyperadrenocorticism, for which insulin therapy needs to be tailored to adrenolytic therapy.

PROGNOSIS

Because veterinary patients do not experience the detrimental long-term effects of DM-associated hyperglycemia experienced by people, target blood glucose ranges can be more relaxed than those necessary for managing DM in human patients. However, veterinary practitioners should be vigilant in monitoring for urinary tract infections, pancreatitis, and other endocrinopathies, such as hyperadrencorticism.

With client commitment and appropriate veterinary care, dogs with DM—even those with other complicating diseases—can live a full and healthy life. TVP

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