

## Monitoring Methods for Dogs and Cats with Diabetes Mellitus

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### Abstract

Effective monitoring is essential for the management of dogs and cats with diabetes mellitus. However, methods for evaluating glycemic control must be tailored to meet both the needs of the patient and the expectations of the owner. This article discusses the philosophies that drive blood glucose monitoring in veterinary diabetics and review common practices. The advantages and limitations of the various options are presented.

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**D**iabetes mellitus is a common endocrinopathy in dogs and cats. Although the underlying etiologies differ for the two species, both are treated with exogenous insulin and require regular monitoring to ensure appropriate therapy.<sup>1</sup> Successful patient management is widely defined by the maintenance of a stable body weight and mitigation of clinical signs such as excessive thirst, urination, and hunger, along with the avoidance of ketosis or hypoglycemia. The latter is particularly important for veterinary diabetics, as these patients cannot assist themselves if blood glucose (BG) concentrations drop precipitously. Achieving euglycemia (BG approximately 60–130 mg/dl) is not the goal of insulin therapy because dogs and cats are spared many of the complications associated with sustained hyperglycemia in human diabetes patients, such as retinopathy, vascular disease, and renal injury.<sup>1</sup> Consequently, most canine and feline diabetics experience only short periods of euglycemia in the course of the day and instead live with mild to moderate hyperglycemia.

The frequency of monitoring for diabetic dogs and cats is variable, although some form of evaluation is generally recommended every 4–12 weeks.<sup>1</sup> Newly diagnosed patients are monitored more frequently, often every 7–14 days, while a suitable insulin type and dose is determined. A substantial percentage of feline patients undergo remission within the first few months of insulin therapy, and therefore require careful monitoring so that hypoglycemia does not occur.<sup>2–4</sup> Established diabetics require less attention; most are on a fixed dietary schedule (specific meals offered at set times) with consistent exercise routines and are effectively treated for long periods with minimal alterations in insulin dose. If the owner notices a change in thirst, appetite, weight, or activity levels or observes any changes in behavior that may suggest hypoglycemia, prompt evaluation is indicated. From the veterinary perspective, owner impressions regarding quality of life and the severity of clinical signs, along with patient body weight, are key parts of the assessment process; laboratory data of any kind are

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**Abbreviations:** (BG) blood glucose, (CGMS) continuous glucose monitoring system

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essentially supplemental and used to guide treatment changes when owner satisfaction is poor.<sup>1</sup>

Decisions about monitoring options are often influenced by the owner's financial situation, level of motivation, and overall expectations with regard to their pet. Some owners are willing and able to monitor their pets regularly and are highly compliant with clinical recommendations. Others may approach their responsibilities as pet owner with a different philosophy and may be reluctant to follow suggested protocols if substantial cost or time is required. In these circumstances, the veterinarian must carefully advocate for the needs of the patient while acknowledging the owner's position.

Monitoring methods can be broadly classified as indirect or direct. Indirect ways of monitoring canine and feline diabetics include assessment of water intake, quantification of urine glucose  $\pm$  ketones, and measurement of glycated/glycosylated protein concentrations. Direct monitoring methods include serial BG measurements (often called a BG "curve") or continuous BG monitoring via a subcutaneous probe. Most veterinarians encourage periodic direct measurements of BG, as the indirect methods may fail to identify periods of hypoglycemia. However, direct methods can have logistical limitations, in which case indirect assessments may be used.

Direct measurements of BG can be particularly challenging in feline patients due to a phenomenon called stress hyperglycemia.<sup>5</sup> This term describes a fear-induced physiologic response in which BG concentrations become acutely and severely elevated, often exceeding 300 mg/dl in a nondiabetic patient or 500 mg/dl in a cat with diabetes mellitus. These values may be maintained for several hours following the trigger event and can markedly confuse interpretation of direct BG measurements. For many feline patients, a simple trip to the veterinary hospital can trigger stress hyperglycemia.

When BG concentration exceeds the reabsorptive capacity of the proximal convoluted tubules, glucose will persist in the renal filtrate and cause an osmotic diuresis. The renal threshold for dogs is usually between 160 and 220 mg/dl; the value for cats is not well established but appears to be higher, at 230–280 mg/dl. Animals consume water when driven by the sensation of thirst, not for taste or social reasons, so fluid intake crudely reflects BG status. As owners are accustomed to cleaning and refilling the pet's water bowl, measuring and recording consumption is quick and easy. A decrease in water intake is often used

initially in feline diabetics to document a response to insulin administration. Conversely, a substantial increase in water intake suggests sustained hyperglycemia. Periods of hypoglycemia may not be recognized, however, so increasing insulin dose solely on the basis of persistent polydipsia can be problematic and result in insulin overdose. It is also important to recognize that factors other than BG concentrations can impact water intake. These include concurrent renal disease, thyroidal disease, ambient temperature, and the moisture content of the food.

Detection  $\pm$  semiquantification of urine glucose is another indirect way to assess BG status. Owners of canine patients can simply hold a glucose reagent strip in the urine stream while the pet voids. Unfortunately, very few dogs will urinate on command and may not completely empty their bladder when voiding occurs. Urine glucose test results therefore reflect the events of many hours, and transient hypoglycemia may essentially be masked by periods of hyperglycemia. Both dogs and cats can experience the Somogyi effect, i.e., prolonged rebound hyperglycemia following an acute and profound decrease in BG concentrations. It is therefore inappropriate to increase an insulin dose simply on the basis of persistent glycosuria. A well-controlled canine diabetic may experience several hours of euglycemia during the course of a day but will generally be glycosuric for substantial periods. A prolonged interval without glycosuria is therefore suggestive of insulin overdose and should prompt investigation. For cats, indicator particles (Glucotest, Nestle Purina PetCare Company, St. Louis, MO) can be mixed with the litter and checked within a 12 h period for a color change. This product is particularly helpful for detection of onset of diabetic remission, and BG should be measured if prolonged periods without glycosuria are noted. Similarly, this product can be used once weekly to monitor for diabetic relapse if insulin is discontinued.

If owners opt to check for glycosuria using a reagent strip, it is prudent to purchase a product that also identifies ketonuria (e.g., KetoDiastix, Miles Laboratories Inc., Elkhart, IN). It is not unusual for newly diagnosed diabetes patients to have mild ketonuria in the first week or so, but this should not be a persistent finding.<sup>6</sup> Ketonuria in an established diabetes patient suggests substantial insulin deficiency or resistance and should prompt further investigation.

Serum fructosamine concentrations provide a quantitative indirect assessment of diabetic regulation in both dogs

and cats.<sup>7,8</sup> The fructosamines are a group of serum proteins, primarily albumin, which have undergone glycation/glycosylation while in the circulation. An elevated fructosamine concentration indicates persistent hyperglycemia over the previous 2 weeks. There are published target levels for canine and feline diabetics, although alterations in serum protein levels or increased protein turnover can impact the accuracy of this test.<sup>9</sup> For example, serum fructosamine concentrations in cats with hyperthyroidism are often lower than expected due to their catabolic state and may not appropriately reflect glycemic status.<sup>10</sup> If stress hyperglycemia prevents accurate BG measurement in a cat, serum fructosamine concentrations can be a useful monitoring tool. A low concentration suggests insulin overdose, probably due to the onset of diabetic remission. Elevated levels in either species indicate poor diabetic regulation but do not indicate the cause. In fact, some patients receiving too much insulin have high fructosamine levels due to the Somogyi effect.

Glycosylated hemoglobin concentrations can also be measured in dogs and cats and provide relevant information regarding glycemic control for the previous 6 weeks.<sup>7,11</sup> However, these assays are not commercially available for these species at the present time and have no apparent advantages over measurement of serum fructosamine.

Undoubtedly, direct measurements of BG have numerous advantages over the indirect methods and provide the information needed for safe and effective dose adjustment, namely, duration of action of insulin, BG nadir, and an estimation of average BG. The targets for veterinary patients are very different from their human counterparts, as modest hyperglycemia is better tolerated than hypoglycemia. Most veterinarians are satisfied with a nadir in the 100–150 mg/dl range and an average BG below 250 mg/dl.<sup>1</sup> It is widely accepted that the majority of diabetic dogs will develop cataracts using these parameters, but other consequences of moderate persistent hyperglycemia (e.g., retinopathy, vascular injury, nephropathy) are not expected in this species.<sup>12</sup> Some diabetic cats develop a hind limb neuropathy; this may be present at the time of diagnosis or become clinically apparent while on insulin therapy.<sup>13</sup> Affected cats may have a plantigrade stance and impaired ability to jump but usually remain ambulatory. Due to innately low aldose reductase activity in the feline lens, cataracts are very uncommon in diabetic cats.<sup>14</sup>

A traditional BG curve requires the collection of a blood sample every 2 h, starting ideally just prior to insulin

administration and continuing to the time of the next dose. Patients should eat their standard diet at the usual time during this process. If the BG moves down rapidly or approaches 100 mg/dl, the next sample should be collected within 60 min. For cats on ultra-long-acting products such as insulin glargine, adequate information can often be obtained with a sample every 4 h, as BG fluctuations are often modest.<sup>15</sup>

In the past, patients were admitted to the veterinary hospital for a BG curve, as venipuncture was required for sample collection. In-clinic curves have some substantial limitations, including anorexia or hyporexia due to anxiety, disruption of normal exercise routines, and the effect of stress on feline BG values. Clients are also impacted by the inconvenience and expense of these visits and may postpone a recheck to avoid these issues. However, the newer handheld glucometers require much smaller blood samples, and pet owners are now able to collect an adequate volume of capillary blood using a lancet or a small gauge needle. In addition, improved test strip design means that the blood is essentially wicked from the puncture site, with the glucometer held at any angle. Studies have confirmed that BG concentrations obtained in this way are comparable to the standard venous values.<sup>16</sup> This has fostered a trend toward BG measurement in the home environment, and many veterinarians educate their clients about this at the time of diagnosis. Most owners quickly become comfortable with sample collection, and the majority of pets tolerate the process with little or no apparent discomfort.<sup>17</sup> Various sites can be used, including the edges of the ear (dogs and cats), paw pad (dogs and cats), elbow callus (dogs), and outer lip (dogs). Optimal sampling sites can vary from patient to patient, and it is often helpful to identify a good location before demonstrating the technique to the owner. In addition, online resources such as videos can be used to encourage client confidence and compliance.

At-home monitoring of feline diabetics has particular advantages, including the prompt identification of remission and avoidance of stress hyperglycemia. In addition, frequent BG monitoring and careful adjustment of insulin dosage appears to facilitate the onset of diabetic remission, most likely due to reversal of glucose toxicity. In one study, intensive BG monitoring of newly diagnosed diabetic cats (i.e., <6 months postdiagnosis) resulted in a remission rate of 84%.<sup>13</sup>

Selection of an appropriate glucometer is important because devices designed for the human market are variably

discrepant when used on canine and feline patients.<sup>18,19</sup> Handheld units use electrochemical or photometric methods to determine whole BG concentrations, i.e., glucose within erythrocytes plus glucose dissolved in plasma. Serum/plasma glucose concentration is then extrapolated from this number and displayed by the machine. Human erythrocytes contain a large amount of glucose, accounting for over 40% of the measured amount. However, canine and feline erythrocytes contain substantially less glucose and, therefore, contribute much less to the total amount measured. Consequently, glucometers designed for use in humans tend to underreport plasma/serum levels in dogs and cats.<sup>18,19</sup> When BG concentrations are high, this error has little clinical impact, but it becomes more significant when BG is below 200 mg/dl. This can have a critical impact on identification of the BG nadir and may result in inappropriate insulin dose reduction.

Handheld glucometers targeted for veterinary use have appeared on the market. A species-specific code is used to adjust the algorithm for the patient in question, thereby improving reliability and accuracy. Pet owners should be encouraged to use a device that is validated and approved for the species in question. Peer-reviewed studies have supported the use of these monitors in veterinary patients.<sup>20,21</sup>

Variations in patient hematocrit can also impact the accuracy of the oxidase-based testing systems, even if a validated veterinary device is used. Some breeds of dog such as greyhounds and dachshunds routinely have higher hematocrits than others (55–65% versus 32–45%), which causes a downward error in BG measurement.<sup>22</sup> Conversely, an anemic patient will have an upward error in which hypoglycemia may be missed.

Several studies have highlighted the poor repeatability of BG curves in both dogs and cats.<sup>23,24</sup> Even in well-controlled circumstances with respect to diet, exercise, and external stimulation, there is substantial day-to-day variation in BG readings. This may be due to subtle variations in insulin absorption or reflect alterations in the secretion of counter-regulatory hormones such as cortisol. For this reason, data collected on a BG curve should never be considered in isolation from other clinical information, such as thirst, urination, and body weight.

Continuous glucose monitoring systems (CGMSs) are not widely used in veterinary medicine, although several studies have demonstrated their clinical utility.<sup>25–27</sup> This is

due, in part, to cost; most veterinary clinics treat a small number of their diabetic patients and cannot justify the capital investment. In addition, a traditional BG curve provides enough information to allow appropriate dose adjustment in most instances.

A CGMS is a useful alternative if a patient requires close monitoring of BG concentrations, but frequent sampling would be technically challenging or cause substantial distress. Examples would include fractious animals or patients with diabetic ketoacidosis. Many referral institutions use a CGMS in these circumstances, although technical issues can be problematic. Although most dogs and cats do not resent insertion of the subcutaneous sensor, many patients will attempt to remove it by scratching, biting, or rolling. For this reason, sensors are usually placed on the dorsal cervical area, out of reach of the mouth. Some practitioners have suggested securing the neck of the sensor to the patient's skin with a drop of tissue glue, although concerns have been raised about potential interference with sensor function. Instead, a light adhesive dressing may be used to prevent dislodgement.

Devices that remotely transmit data to a distant receiver are generally preferred, as this eliminates the need to attach the display device to the patient. Instead, this can be attached to the animal's cage or run, where the data can be viewed by the caregiver. In the home setting, it may be possible to attach the display device to a collar or harness, thereby permitting the patient to move freely around the house and yard and perform its usual activities. The data collected can be downloaded later for analysis.

Using a CGMS does not eliminate the need for blood collection, however, as two or three BG measurements are needed for initial calibration when the device is first activated. In addition, CGMSs have a limited working range and cannot be calibrated when BG exceeds 400 mg/dl or is below 40 mg/dl. As many poorly regulated or ketoacidotic veterinary patients have values substantially above this ceiling, these devices may not be used until the BG enters the required range.

Acceptable correlation has been reported between BG values and interstitial glucose concentrations measured by CGMSs in several species, including the cat and dog.<sup>28</sup> Discrepancies seem to be more likely when BG is higher, and it has been suggested that postprandial hyperglycemia may not be effectively demonstrated with a CGMS.<sup>27</sup> However, compromised accuracy at high BG concentrations has little clinical relevance and

would not preclude the use of one of these devices. More importantly, a CGMS might identify transient hypoglycemia, which could be missed with a standard BG "curve."<sup>29</sup>

Although treating dogs and cats with diabetes mellitus can be challenging, many patients do well, and owner satisfaction is usually high. Effective communication between the veterinary team and the client is essential, as owner perceptions regarding the quality of life of the pet will ultimately determine outcome.

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