DIABETIC CONUNDRUMS: DIFFICULT-TO-MANAGE CASES

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Diabetes mellitus (DM) is the most challenging endocrine disease to treat. Good monitoring is essential to determining what to do. When all issues accounting for poor control have been exhausted, resistance should be considered. An orderly work-up will be needed.

Monitoring diabetic pets can be quite challenging in many ways. No technique is perfect. In one study, all blood glucose (BG) measurements, fructosamine and GHb were consistent with good glycemic control in 60% of dogs judged to have good clinical control or with poor control in only 39% of judged to have poor clinical control.[1] Furthermore, monitoring can become a financial burden to owners. Although somewhat controversial and not perfect, I am an advocate of monitoring through performance of BG curves. Their disadvantages need to be recognized (and in part can be overcome by having owners conduct curves at home), but they are the only technique that not only confirms poor control but indicates how an insulin dose should be altered. Measurement of urine glucose and glycosylated proteins as well as assessment of clinical signs is also recommended to get as much information as possible for complete evaluation. In the following manuscript, I will address questions commonly asked regarding diabetic monitoring.

One question to ask, is what are we looking for in monitoring diabetics, or, in other words, what is the goal of therapy? At all costs, hypoglycemia should be avoided. On the flip side, how high can BG go? The goal of therapy is to get rid of the clinical signs in order to provide a good quality of life for the pets and clients. The strict control aimed for in human diabetics is not practical and may not be necessary in veterinary patients. Strict control in humans is required to avoid serious diabetic complications such as nephropathy, retinopathy, vasculopathy, etc. For whatever reason, these complications are not prevalent in veterinary populations. To get rid of clinical signs, BG needs to be below the renal threshold the majority of the time, i.e. < approximately 200 mg/dL in dogs and approximately 250-300 mg/dL in cats.

Performance of in-hospital BG curves has long been the gold standard for assessing diabetic control. To construct a curve, BG is measured in general every 2 hrs for one interval between injections, i.e. for 12 hrs if insulin is administered twice daily and for 24 hrs if insulin is given once daily. When BG is <150 mg/dL, the concentration should be measured hourly. A normal insulin/feeding schedule must be maintained as much as possible. If a patient does not eat the normal amount of the normal food at the usual time, the serial glucose curve should probably not be performed. The patient should be fed its standard diet at the usual time and the insulin given by the owner in the hospital so the owner's injection technique can be assessed. Obtaining a fasting sample for measurement of BG prior to insulin injection can aid in appraisal of glycemic control, but this may not be possible if normal feeding time occurs before the hospital opens. Furthermore, feeding a dog or cat at home may ensure that the pet will eat. If the patient is fed at home, the insulin should then be given by the owner either at home or, especially if owner technique is questionable and needs to be assessed, in the hospital in front of a technician or veterinarian. Clearly, cooperation between client and veterinarian is necessary to maximize the information obtained with minimal disturbance to routine. When first trying to regulate a diabetic patient, assessment of the owner's technique is crucial.

A curve should be performed the first day insulin is given. Glucose concentrations may be lower than expected after the first 24 to 48 hours of insulin therapy, especially in cats as stress hyperglycemia resolves.[2] This first curve is done solely to ensure that hypoglycemia does not occur. If hypoglycemia is found, the insulin dose should be decreased 25% and another curve done the following day with the same goal in mind – to check for hypoglycemia. The insulin dose should not be increased based on the first day's curve. A patient requires 5-7 days on a dose of insulin to equilibrate and reach maximal effect, so another glucose curve should be performed at that time. Based on assessment of the curve after equilibrium, the insulin dose can be increased or decreased as deemed necessary.

A serial BG curve should establish the time to peak insulin effect, duration of effect and degree of fluctuation in BG. The pattern of insulin effect should be used to determine dose, interval, and feeding schedule. Ideally, glucose concentrations should reach a nadir at 80 to 150 mg/dL. The highest glucose concentration should be close to 200 to 250 mg/dL in dogs or 300 mg/dL in cats. Changes in insulin dose can usually be made without affecting the duration of effect. The glucose differential is the difference between the nadir and the BG prior to the next dose, and can be a measurement of insulin effectiveness.[3] If the curve is relatively flat, e.g. differential of 50-100 mg/dL, the insulin, with the exception of

glargine where such curves are expected, may not be having a desired effect. My definition of duration is the number of hours that the BG is in the desired range.

The absolute BG must also be taken into consideration. If all BG are < 200 mg/dL, the insulin is very effective. However, if all BG are between 350-400 mg/dL, then the insulin is ineffective at that dose, stress hyperglycemia is present or you have caught a patient post- Somogyi (for a number of hours after a Somogyi phenomenon, insulin resistance will be present). In assessing a glucose curve, whether it is the first curve performed on a patient or the last of many, two basic questions need to be asked. First, has the insulin succeeded in lowering BG? And, second, how long has the insulin lasted? By answering these questions, logical changes in dosing regimen, if necessary, can be made.

For all insulins but glargine, the first aim in regulating a diabetic is to achieve an acceptable nadir. (For insulin glargine, dose adjustment is made based on the pre-insulin BG concentration.) In general, if an acceptable nadir is not achieved, the insulin dosage should be adjusted depending on the size of the animal and the degree of hyperglycemia. Usually changes of approximately 10% are appropriate. Obtainment of an acceptable glucose nadir may not be possible in some animals, however, if insulin with a short duration of activity is used. In these patients, the BG is typically quite high in the morning since there has been inadequate control for most of the previous day. Even if an insulin injection is capable of lowering BG, it does not have a long enough effective period to lower BG into an acceptable range. In other words, a glucose curve in this situation shows a noticeable but brief decrease in BG after the insulin injection. Increasing dosing frequency from once to twice a day or changing to a longer lasting insulin type is indicated.

Hypoglycemia should always be avoided. No matter what other BG concentrations are during the day, if the value of the BG nadir is <80 mg/dL, a reduction in insulin dosage is indicated. Decrease the dose 25% if there are no signs of hypoglycemia and 50% if there are signs, and then do another curve to ensure hypoglycemia does not recur.

Once an acceptable nadir is accomplished, duration of action, roughly defined as the time from the insulin injection through the lowest glucose and until the BG exceeds 200 to 250 mg/dL, can be determined by a glucose curve. The total time of BG control also needs to be considered. For example, if the BG is not controlled for the first 6 hrs after insulin administration, control is inadequate. If the dose of insulin is inadequate and the target glucose nadir has not yet been achieved, the dose must be increased until the nadir is acceptable before duration of effect of the insulin can be determined.

The Somogyi phenomenon, also called hypoglycemia-induced hyperglycemia, refers to hypoglycemia followed by marked hyperglycemia. The phenomenon results from a normal physiological response when BG declines to less than 60 mg/dL in response to an insulin dose that is too high or when BG concentration decreases rapidly regardless of the nadir. In either case, a number of reflexes are triggered that act to increase BG. Counter-regulatory hormones such as epinephrine, cortisol, glucagon and growth hormone (GH) are secreted, and the resultant hyperglycemia usually occurs rapidly, thus preventing a hypoglycemic seizure. Insulin secretion does not occur in response to the rise in glucose, however, as would occur in normal dogs and cats, and diabetics become extremely hyperglycemic (400 to 800 mg/dL). If the Somogyi phenomenon is observed, the insulin dosage should be decreased so the nadir is > 80 mg/dL; counter-regulatory hormones will no longer interfere with the action of the exogenous insulin and the true duration of effect will become apparent. If the duration of insulin action is truly < 8 hours, adequate therapy with that type of insulin requires injections more frequently than twice daily, which is impractical for most owners. A switch between different types of intermediate-acting insulin can also be beneficial. For example, a dog or cat may metabolize NPH insulin quickly, resulting in too short of an effect, but lente insulin may have a longer duration.

Admittedly, glucose curves are not perfect. Results of a serial glucose curve should always be interpreted in light of clinical signs. Glucose curves can be affected by deviation from normal routine. Curves in dogs and cats can vary from day to day.[4,5] (One related important point is that due to the variation, predicting the timing of a diabetic's nadir on the basis of previous serial glucose curves and obtaining a single sample at that time is unlikely to give a reliable result[4], i.e. spot checking does not provide helpful information.) Stress hyperglycemia can also falsely elevate results.

However, curves serve 2 very useful purposes that other techniques do not. First, they can clearly show clinically undetectable hypoglycemia. A phenomenon exists in human diabetics referred to as "hypoglycemic unawareness". In this situation, the body does not respond to mild or even moderate hypoglycemia as in normal patients and clinical signs do not develop. However, when moderate to severe hypoglycemia occurs, profound clinical signs appear acutely without warning. Although unproven, I believe the same occurs in veterinary patients. A glucose curve will hopefully document mild hypoglycemia that can be fixed before a seizure occurs. Thus, periodic curves can be helpful even in a seemingly well-controlled patient. Secondly, and more importantly, other techniques and clinical signs can suggest that control is

lacking, but multiple reasons for poor control including too low and too high a dose of insulin exist. The only way to know how to change the therapy to gain control is by performance of a curve.

A few aspects of glucometers should be considered. First, a glucometer should be easy to use. Glucometers that require minimal amounts of blood as well as those that "sip" the blood into the strip are desirable. Second, they need to be accurate. Two recent studies[6,7] suggest the Abbot AlphaTRAK® is the most accurate meter for dogs and cats. Care must be taken to code the machine for sample source, i.e. whether the sample is from a dog or a cat. Although in general glucometers are commonly believed to underestimate BG concentration, the AlphaTRAK can either over- or underestimate BG in dogs[7], while, in cats, it tends to underestimate low and normal BG and overestimate high BG concentrations.[6] The inaccuracies, however, are of little clinical significance.

Measurement of urine glucose can be helpful for monitoring, especially cats where stress hyperglycemia prevents obtaining an accurate curve. First, urine glucose levels can be determined as needed to aid in assessment of glycemic control, especially when other data are conflicting. Consistently negative urine glucose readings may indicate that insulin dosages are either adequate or excessive. Remember, a negative urine glucose reading only means that in the period since the last urination, the BG was below the renal threshold. So, for example, the BG could be 200 mg/dL or it could be 40! The only way to know is to measure BG. With consistently negative readings, a serial glucose curve can be performed to differentiate between adequate insulin therapy and use of excessive doses that could result in hypoglycemic shock. If BG measurement is not an option, the risk of hypoglycemia is higher. Uniformly high urine glucose readings coupled with unresolved clinical signs indicate that the insulin dose is inappropriate.[8] Second, urine glucose concentrations can be determined regularly (at least weekly) to help in the assessment of ongoing control. Changes in urine glucose levels may alert the owner and clinician to loss of glycemic control and a need for reevaluation. Third, for cats receiving glargine insulin, a protocol exists for altering insulin dose based on urine glucose measurements.

Another possible means for monitoring is measurement of glycosylated proteins, either glycosylated hemoglobin or fructosamine. Glycosylated hemoglobin (GHb) is formed by non-enzymatic, irreversible binding of glucose to hemoglobin.[9] Fructosamine refers to glycosylated serum proteins, mainly albumin.[10] Both GHb and fructosamine form at a rate proportional to the average BG present, so the higher the mean BG concentration over time, the greater their concentrations should be. The levels of glycosylated proteins are also affected by the half-life of the native protein. Thus, GHb reflects glycemic control over the previous 2-3 months, while fructosamine reflects that over the previous 2-3 weeks.

Both parameters correlate with BG and are typically not affected by stress. However, the value obtained from the laboratory must be interpreted in conjunction with all other data. Normal animals or well-controlled diabetics can have elevated concentrations of either GHb or fructosamine, and, conversely, uncontrolled diabetic animals can have normal levels of either.[11,12] Fructosamine may be elevated in sick, hyperglycemic, but non-diabetic cats.[19]

Given the overlap in GHb or fructosamine concentrations that can occur between well and poorly controlled diabetics, in general, I think one of the best uses of glycosylated proteins is to evaluate trends in glycemic control if measured at each recheck. Current recommendations are not to try to normalize serum concentrations of glycosylated proteins but to aim, in general, for a concentration slightly above normal. A fructosamine below normal indicates chronic hypoglycemia.

Lastly, home monitoring of clinical signs has been advocated as a useful adjuvant tool in assessing glycemic control. Observation of clinical signs is crucial. If a patient is not polyphagic, polydipsic or polyuric and body weight is stable or increasing, diabetic control is likely good. Although owner observation of the presence or absence of clinical signs is very important, judgment of adequacy of control should not rely solely on owner reports.

Insulin resistance should be suspected in any pet in which marked hyperglycemia persists throughout the day despite insulin doses of more than 1.5 U/kg per injection or when large doses of insulin (i.e. >2.2 U/kg per injection) are needed to maintain adequate glycemic control. However, use of these doses does not mean that insulin resistance is present. The problem could lie with owner technique of insulin administration, patient management (e.g., exercise, diet), or insulin choice. Lack of response to high doses of one insulin type does not mean all insulins will be ineffective; for example, 20% of cats did not respond to high doses of ultralente insulin but could be effectively managed by twice-daily lente. In addition, longer-acting insulin (PZI) will be more slowly absorbed and less bioavailable than shorter-acting insulin; thus slightly more than 2.2 U/kg of long-acting insulin may be required.

Before a thorough and costly workup for insulin resistance is initiated, factors that mimic insulin resistance should be ruled out. The owner's technique and insulin handling should always be evaluated first. Possible causes for an unsatisfactory response to insulin include inadequate mixing of insulin before withdrawal into the syringe; use of the incorrect syringe (e.g., using a U100 syringe with U40 insulin); misunderstanding of how to read the insulin syringe; problems with insulin injection technique; inactivation of insulin as a result of improper handling; and, if diluted insulin is being used, improper dilution. A bottle of insulin should be discarded after 2 to 3 months of use because activity may begin to decrease. If owner issues are suspected, a glucose curve should be performed after the owner administers insulin using a new, undiluted bottle and while being observed. Second, the owner should be questioned to ensure consistent and appropriate diet and exercise. If hyperglycemia is believed to be due to a postprandial surge from feeding a meal when the insulin's effects are waning, timing of meals should be adjusted. Alternatively, addition of an oral hypoglycemic agent such as acarbose can be considered. Third, if no response is seen to one type of insulin, then another should be tried to see if it might be effective. Fourth, absorption of insulin can vary among subcutaneous sites, so another injection site should be used; the lateral thorax or abdomen is recommended. Lastly, a glucose curve should be performed to eliminate other possible mimics of insulin resistance, such as the Somogyi phenomenon and inadequate duration of insulin action.

Once true insulin resistance has been documented, a number of differential diagnoses should be considered. Insulin antibodies are a commonly discussed cause of insulin resistance. The clinical significance of anti-insulin antibodies (AIAs) remains unclear. Although antibodies may form against exogenous insulin, associated clinical insulin resistance appears rare. If AIAs are believed to be causing insulin resistance, the insulin source should be switched to a different one. Glycemic control should improve within 2 weeks of changing the species of insulin if AIAs are causing resistance.

Infection, ketoacidosis, and concurrent illness can cause insulin resistance. The urinary tract and oral cavities are common sites of infection; a urinalysis and urine culture, regardless of urinalysis findings, and complete oral examination should always be performed. Renal disease, hepatic insufficiency, cardiac insufficiency, pancreatitis, and starvation should be considered as possible causes of insulin resistance. Malnutrition can lead to insulin resistance and diminished insulin secretion. Obesity has been linked to glucose intolerance and abnormal insulin secretion in cats and dogs, but its role in creating insulin resistance is unclear insofar as obese diabetic pets generally remain insulin responsive. Hyperthyroidism, hypothyroidism, and hyperadrenocorticism can cause insulin resistance through diverse mechanisms.

Certain drugs can cause insulin resistance, most notably progestogens and glucocorticoids. Although cats are resistant to development of many of the common adverse effects of glucocorticoids, such as polyuria and polydipsia, they may develop glucocorticoid-associated glucose intolerance readily. If possible, use of these medications should be slowly discontinued in diabetic patients. Otherwise, the patients may need to be treated as insulin-resistant. Neoplasia has been associated with insulin resistance in 5% to 10% of diabetic cats and dogs. Hyperlipidemia should be considered as a possible cause of insulin resistance.

When a cause for insulin resistance is sought, the easiest causes to rule out and the most likely should be eliminated first, proceeding through to the least likely. The following order, in general, has been recommended in cats: concurrent drugs, obesity, concurrent disease (including infection and ketoacidosis), hyperthyroidism, acromegaly, hyperadrenocorticism, and insulin antibodies. The order to use in dogs, in general, is as follows: concurrent drugs, diestrus/acromegaly, obesity, concurrent disease (including infection and ketoacidosis), hyperadrenocorticism, hypothyroidism, hyperlipidemia, and insulin antibodies. This order is not absolute. If strong evidence exists for a differential diagnosis lower in the order, that possibility should be ruled out first.

Management of insulin resistance requires correcting the underlying disorder, if possible. For causes such as a simple bacterial infection or concurrent administration of diabetogenic medications, eliminating the underlying problem can be relatively easy; other problems, such as acromegaly, may be more difficult to correct.

If the cause cannot be determined or eliminated, the following guidelines are suggested: (1) Administer insulin at least twice daily. (2) Avoid long-acting insulins, unless regular insulin is added. Intermediate-acting insulins are more effective in overcoming insulin resistance and lowering blood glucose concentrations. (3) Consider using mixtures of short-acting and longer-acting insulins. (4) Administer insulin shortly before or at the time of feeding to help control postprandial hyperglycemia. Large insulin doses may be required, but it will be necessary to determine the actual dosage using serial blood glucose curves, as for any diabetic.

References available from author upon request