Diet

In order for the diabetes mellitus (DM) to resolve, good control of blood glucose (BG) concentration is needed as quickly as possible. Diet does play a role. The recommendation for diabetic cats is a high-protein, high-fat diet. In general, the canned version of such prescription diets is preferred as it is lower in carbs. Although prescription diets are the first-choice dietary recommendation in most cats with DM, a carefully selected, over-the-counter, high-protein, low-carb diet can provide the same degree of effective glycemic control as a prescription diet when financial constraints are present or when a cat will not readily eat the prescription diet. Many canned over-the-counter diets are relatively low in carb content (< 5.0 g/100kcal), but information must be obtained from the manufacturer on specific brands and flavors to ensure that the goal nutrient composition is being met. Most dry over-the-counter diets are higher in carb content than prescription dry low-carb, high-protein diets, but it can be difficult to identify a good-quality dry food with low carb content when the prescription diet is not an option. Caution should be used with these diets in cats with renal disease due to the high protein content. If a high-protein diet is not a possibility, feeding a more standard diet and administering acarbose may achieve the same goal.

High dietary fiber for treatment of diabetic dogs is still recommended. However, a recent study showed that diets with high fiber and moderate starch were not advantageous for dogs with stabilized DM compared to a moderate-fiber, low-starch diet. Insoluble fiber, the type present in commercial feline high-fiber diets, can improve glycemic control in diabetic cats.

Although anecdotally I have heard of cats that appear to be early diabetics and that have their DM resolve with dietary management alone, I do not recommend this if the owners are willing to administer either insulin (much preferred) or glipizide, an oral hypoglycemic agent. The longer a cat has uncontrolled DM, the less likely it is that the DM will resolve. Insulin therapy is your best chance of getting control of the BG quickly!

Timing of feeding, especially as it relates to insulin administration, is important. In order to mimic physiological insulin release, insulin ideally should be given with each meal. The absorption of nutrients and development of postprandial hyperglycemia depends on numerous factors, but, ideally, calories should be ingested when insulin is still present in the circulation. Classically, the recommendation has been to feed patients b.i.d. to spread out caloric intake. In a patient receiving insulin b.i.d., giving the meals before the insulin also serves the purpose of ensuring that the patient is eating. If inadequate calories are consumed, the insulin dose should be halved.

Some dogs and (especially) cats as well as households are not amenable to a b.i.d. feeding schedule. At least when they are fed a high-carb meal, prolonged gastric emptying and prolonged postprandial hyperglycemia can result. Thus, animals that eat small amounts constantly throughout the day may actually best approximate the ideal situation, as postprandial hyperglycemia will likely never be profound in them. Judging an individual animal’s intake in a multi-animal household, however, can be difficult and may necessitate periodic isolation. Owners need to be very strongly advised about the possibility of hypoglycemia, as administration of a full dose of insulin in the face of inadequate caloric intake is more likely to occur using this method.

Insulin

At the current time, the insulins commonly used for maintenance in dogs or cats in the United States are NPH, PZIVet, glargine, and detemir. Glargine (Lantus) and detemir (Levemir) are produced by recombinant DNA technology. Glargine’s chemical structure has been altered slightly from native human insulin. In detemir, the insulin molecule is modified via addition of a fatty-acid side chain that facilitates reversible binding to plasma proteins, particularly albumin, from whence it is released slowly into plasma. It also self-associates at the injection site, which helps prolong its absorption and duration of action.

Nothing has been published about the use of detemir or glargine alone in dogs, but neither appears to offer any advantage. Interestingly, in two of nine healthy dogs, BG did not change after injection of glargine, which suggests possible lack of efficacy in dogs. Anecdotally, detemir can be used with success in dogs. It is very important to note that detemir is particularly potent in dogs, and the starting dose is 25% of what is recommended for other insulins. Glargine has a long duration of action and a predictable BG-lowering effect in cats. Although no difference was seen in control or remission in diabetic cats when lente or glargine was administered once daily, when lente, PZI, or
glargine were administered b.i.d. to eight cats each, all eight on glargine went into remission as compared to three on PZI and two on lente. Thus, I recommend glargine b.i.d. for treatment of newly diagnosed diabetic cats. Long-term diabetic cats have been switched to and treated with glargine as well with good success, but the diabetes has not resolved. Detemir is similar to glargine in diabetic cats, offering no advantage.

Although some authors recommend a starting dose of 0.25 U/kg b.i.d. for dogs, others recommend 0.5 U/kg if the BG is > 360 mg/dL and 0.25 U/kg if it is < 360 mg/dL. In one study of dogs, 94% of dogs required b.i.d. dosing regardless of insulin type used for adequate control. Human recombinant NPH may have a shorter duration of action than the animal-source NPH previously available, further increasing the need for b.i.d. therapy. Absorption of insulin from various sites in the body differs. In dogs and cats, the dorsal neck or scruff has commonly been used as a site for injection, but this site may not be ideal due to low blood flow and increased fibrosis caused by repeated injections. A better option may be to administer the insulin at sites along the lateral abdomen and thorax. The chosen area should be rotated daily in order to prevent fibrosis at an injection site.

A good practice is to make the injections part of a good experience. For diabetics that are meal fed and are very into their food, inject them as they are eating. For others, you can give the injections when doing a pleasurable activity. For any patient that needs a small amount of insulin, 0.3 ml syringes should be used for accurate dosing. These are referred to as low-dose syringes. The scale on the syringe is easier to read for small doses. Although this seems like a minor detail, believe me, giving insulin can be nerve wracking! The syringes are not that easy to read and a small error can have big consequences when you are giving small doses!

**Monitoring**

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 while avoiding hypoglycemia. To get rid of clinical signs, BG needs to be below the renal threshold the majority of the time, that is, less than approximately 200 mg/dL in dogs and approximately 250 to 300 mg/dL in cats.

**Urine Glucose Monitoring**

Measurement of urine glucose at home can aid in monitoring. First, urine glucose levels can be determined as needed to aid in assessment of glycemic control, especially when other data are conflicting. Second, consistently negative readings on urine glucose may indicate that insulin dosages are either adequate or excessive. Remember, a negative urine close only means that in the period since the last urination, the BG was below the renal threshold. So, for example, the BG could be 150 mg/dL, or it could be 40! A serial glucose curve will 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 high. Third, uniformly high urine glucose readings, coupled with unresolved clinical signs, indicate that the insulin dose may be inappropriate. Fourth, 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.

A good option for monitoring urine glucose at home in cats is the Purina Glucotest. The Glucotest tends to overestimate urine glucose concentrations in the midranges (50–300 mg/dL). However, the overestimation is by one category—for example, 50 read as 150 mg/dL—and would likely be clinically irrelevant. The color change read at 8 hours is more accurate than the initial readings; the change over time is, again, typically by one category. It should be noted that the Multistix are not highly accurate, at least in dogs, as they tend to underestimate urine glucose (unpublished data). To get the most accurate measurement and to ensure that glucose is really present in the urine, based on these results it is best to have the lab measure urine glucose concentration as it would serum.

**Glycosylated Proteins**

Glycosylated hemoglobin (GHb) and fructosamine are formed by the binding of glucose to hemoglobin and serum proteins, mainly albumin, respectively. They form at a rate proportional to the average BG present, so the higher the mean BG 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 two to three months, while fructosamine reflects control over the previous two to three weeks. 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.
**Home Monitoring**

Home monitoring of clinical signs has been advocated as a useful adjuvant tool in assessing glycemic control. One study evaluated the usefulness of a variety of different clinical and biochemical measurements in twenty-three cats treated with lente insulin. No single measurement best correlated with the level of clinical control identified. The amount of water drunk over 24 hours, maximum BG concentration, mean BG concentration, and urine glucose were the most useful practical indicators of clinical control. Owners were often happy with the level of control in their cats despite not having laboratory evidence of tight glycemic control, which shows the importance of remembering that the long-term aim of treatment in diabetic cats is to control the clinical signs associated with hyperglycemia.

**Glucose Curves**

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 hours for one interval between injections, that is, for 12 hours if the insulin is administered b.i.d. and for 24 hours if the insulin is given once daily. For glargine, the suggestion has been made to only measure BG every 4 hours, but I still measure BG q 2 hours. 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. If possible, the insulin should be given by the owner in the hospital so the injection technique can be assessed. Obtaining a fasting blood sample prior to insulin injection can aid in appraisal of glycemic control, but may not be possible if the normal feeding time occurs before the hospital opens. Furthermore, feeding a dog or a cat at home may ensure that the pet will eat. If the patient is fed at home, the insulin should 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. If given a choice between obtaining a fasting sample or assessing owner injection technique when first trying to regulate a diabetic patient, choose to assess technique.

A curve should be performed the first day that insulin is given. It is done solely to ensure that hypoglycemia does not occur. If hypoglycemia is found, the insulin dose should be decreased 25% and a curve should be 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 five to seven days to equilibrate to a dose of insulin, so another glucose curve should be performed at that time. Based on assessment of the curve, the insulin dose can be increased or decreased as 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. The actual nadir and peak concentrations in a patient will probably be lower or higher, respectively, than measured, because the exact time of nadir and peak effects of insulin are not known. Changes in the dose of insulin can usually be made without affecting duration of effect. The glucose differential is the difference between the nadir and the BG prior to the next dose; it can be a measurement of insulin effectiveness. If the curve is relatively flat, e.g., differential of 50 to 100 mg/dL, the insulin, with the exception of glargine, where such curves are expected, may not be having a desired effect.

The absolute BG must be considered. If all BGs are < 200 mg/dL, the insulin is very effective. However, if all BGs are between 350 and 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 the assessment of 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? With answers to 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 pre-insulin BG concentration.) In general, if an acceptable nadir is not achieved, the insulin dosage should be adjusted based on the size of the animal and the degree of hyperglycemia. Usually changes of approximately 10% are appropriate. Obtaining an acceptable nadir may not be possible, 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 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 that hypoglycemia does not recur.

Once an acceptable nadir is accomplished, duration of action, roughly defined as the time the BG is in the ideal range, can be determined by a curve. It should be as close to 24 hours per day as possible. 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—that is, duration and nadir cannot be assessed at the same time if one or the other is insufficient.

The Somogyi phenomenon, or overswing, refers to hypoglycemia followed by marked hyperglycemia. If the Somogyi phenomenon is observed, the insulin dosage should be decreased so the nadir is > 80 mg/dL; counterregulatory 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 less than 8 hours, adequate therapy with that type of insulin requires injections more frequently than twice daily, which is impractical for most owners.

Once control has been achieved, glucose curves should be performed to assess adequacy of glycemic control every three to six months or earlier if clinical signs suggest that control has been lost. The more precarious the control, the more frequently rechecks should be done. As during the initial curves, if the nadir is unacceptable, the insulin dose must be lowered or raised accordingly. If duration of action appears to have changed, then the same modifications as discussed above can be made.

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 and can vary from day to day. (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, i.e., spot checking does not provide helpful information.) Stress hyperglycemia can also falsely elevate results. However, curves serve two very useful purposes that other techniques do not. First, they can clearly show clinically undetectable hypoglycemia. A glucose curve can document mild hypoglycemia before a seizure occurs. Thus, periodic curves can be helpful even in a seemingly well-controlled patient. Second, and more important, 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 doing a curve.

To avoid some of the problems associated with in-hospital curves, performance curves at home are an option. Capillary blood can be used from the ear, gum, footpads, or elbow callus. I do not recommend the gum and footpads owing to associated pain. I have not tried using the callus. It should be recognized that glucose curves can vary day to day when done at home as well. Training owners to perform home glucose curves takes time. Not all owners are suited to perform such a task.

The CGMS (continuous glucose monitoring system, Minimed) is a device that can be strapped onto a patient so that a small needle can be inserted into subcutaneous tissue. Interstitial glucose concentrations are sampled every 5 minutes for up to 72 hours. Using such a device avoids the stress of multiple venipunctures or catheterization, and it could potentially be worn at home. However, three BG concentrations must be measured in every 24-hour period. In normal and diabetic dogs and cats, interstitial and serum glucose concentrations were highly correlated overall. The working range of the CGMS is approximately 40 to 400 mg/dL, i.e., BGs outside the range cannot be measured. In certain cases, postprandial increases in BG were not detected in the interstitial fluid. Some variation existed between patients, and the differences between serum and interstitial glucose concentrations were more marked in some patients than others. The greatest discrepancies occurred at higher BGs. No irritation resulted from sensor placement.

References available upon request.