TREATMENT OF DIABETES MELLITUS (DM) CAN BE QUITE FRUSTRATING. HUMAN RECOMBINANT LENTE AND ULTRALENTE PREPARATIONS, LONG USED TO TREAT DM IN VETERINARY MEDICINE, ARE NO LONGER AVAILABLE. VETSLIN™, A PORCINE LENTE, IS AVAILABLE AND IS THE ONLY INSULIN APPROVED FOR USE IN CATS. GLARGINE (LANTUS™) IS A GENETICALLY-ENGINEERED RECOMBINANT HUMAN INSULIN AVAILABLE NOW FOR A NUMBER OF YEARS. WITHIN THE LAST FEW YEARS, GLARGINE HAS BEEN USED IN CATS; REPORTS ARE VERY PROMISING FOR GETTING GOOD CONTROL AND, MORE IMPORTANTLY, FOR INDUCING DM REMISSION.

THREATMENT OF ANY DISEASE IS IDEALLY AIMED TOWARDS THE UNDERLYING ABNORMALITY. IN TYPE I DM, A LACK OF INSULIN EXISTS, SO TREATMENT PROVIDES AN EXOGENOUS SOURCE. TYPE I DIABETICS DO NOT HAVE THE METABOLIC ABNORMALITIES PRESENT IN TYPE II DM THAT ARE ADDRESSED BY ORAL HYPOGLYCEMICS. CONSEQUENTLY, ADMINISTRATION OF ORAL HYPOGLYCEMICS TO TYPE I DIABETICS IS INAPPROPRIATE, WITH THE EXCEPTION OF ACARBOSE. FOR TYPE II DM, ORAL HYPOGLYCEMIC AGENTS CAN BE USED INITIALLY, BUT AS TYPE II DM PROGRESSES, EXOGENOUS INSULIN INJECTIONS WILL BE REQUIRED. DOGS ARE MAINLY TYPE I DIABETICS. ACCORDINGLY, ORAL HYPOGLYCEMICS HAVE NOT BEEN USED WIDELY IN THIS SPECIES. CATS ARE BELIEVED TO BE MAINLY TYPE II, AT LEAST INITIALLY. IN ANY CASE, PATIENTS WITH ADVANCED TYPE II DM AND GLUCOSE TOXICITY, A POPULATION LIKELY TO REPRESENT THE MAJORITY OF DIABETIC CATS, WILL HAVE TOTALLY LOST INSULIN SECRETORY ABILITY. ACCORDINGLY, SOME DIABETIC CATS WILL RESPOND TO ORAL HYPOGLYCEMIC AGENTS BUT MOST WILL REQUIRE INSULIN THERAPY.

FOR CATS, THE BEST CASE SCENARIO IS TO HAVE THE DM RESOLVE. HOW LIKELY THIS IS IN GENERAL IS UNCLEAR. OLDER ESTIMATES WERE THAT 10-25% OF CATS HAD TRANSIENT DM. INITIAL DATA ON GLARGINE (WHICH INVOLVED ONLY 14 CATS) INDICATES THAT IT COULD BE MUCH HIGHER – 100% IN NEWLY DIAGNOSED CATS ON GLARGINE AND THE APPROPRIATE DIET. I DOUBT THAT IT REALLY WILL BE 100%, BUT 14/14 CATS TREATED IN THIS MANNER IS STILL IMPRESSIVE!

IN ORDER FOR THE DM TO RESOLVE, AS GOOD CONTROL OF BG CONCENTRATION AS QUICKLY AS POSSIBLE IS NEEDED. DIET DOES PLAY A ROLE IN THIS. FOR A NUMBER OF YEARS NOW, THE RECOMMENDATION FOR DIABETIC CATS IS A HIGH PROTEIN, HIGH FAT DIET, E.G. PURINA DM OR HILL’S M/D. FOLLOWING A HIGH CARBOHYDRATE MEAL, CATS HAVE PROLONGED POSTPRANDIAL HYPERGLYCEMIA. CATS ALREADY ON INSULIN PLACED ON A HIGH PROTEIN, HIGH FAT, LOW-CARBOHYDRATE DIET HAD THEIR DM RESOLVE OR EXPERIENCED A MARKED REDUCTION IN INSULIN DOSE. THE 14 CATS ON GLARGINE MENTIONED ABOVE THAT HAD THEIR DM RESOLVE WERE ON SUCH A DIET. IN GENERAL, THE CANNED VERSION OF DM OR M/D IS PREFERRED AS THAT IS THE LOWEST IN CARBOS, BUT DRY IS FINE. CANNED KITTEN FOOD WOULD BE ALL RIGHT AS WELL.

WHETHER GLARGINE WOULD BE AS EFFECTIVE WITHOUT A CONCOMITANT HIGH PROTEIN, HIGH FAT DIET IS UNKNOWN. DIET IS NOT THE ONLY FACTOR IN REMISSION, AS SOME CATS HAD THEIR DM RESOLVE HISTORICALLY WHILE ON HIGH FIBER DIETS. HOWEVER, GDP, GLARGINE IS NOT EXPECTED TO BE AS EFFECTIVE WITHOUT A HIGH PROTEIN DIET. 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. THROUGH UNKNOWN MECHANISMS, DIETARY FIBER CAN DELAY GASTROINTESTINAL GLUCOSE ABSORPTION, REDUCING POSTPRANDIAL FLUCTUATIONS IN BG AND ENHANCING GLYCEMIC CONTROL. INSOLUBLE FIBER CAN BE BENEFICIAL IN DIABETIC DOGS. HOWEVER, THE RESPONSE OF DIABETIC DOGS TO FIBER CAN VARY BETWEEN INDIVIDUALS, AND 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 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 THE DM WILL RESOLVE. INSULIN THERAPY IS YOUR BEST CHANCE OF GETTING CONTROL OF THE BG QUICKLY!

THE “LATEST AND GREATEST” FOR THE LAST FEW YEARS FOR FELINE DIABETICS IS USE OF INSULIN GLARGINE. GLARGINE IS PRODUCED BY RECOMBINANT DNA TECHNOLOGY AND IS “PEAKLESS” IN PEOPLE. THE CHEMICAL STRUCTURE OF GLARGINE HAS BEEN ALTERED SLIGHTLY FROM NATIVE HUMAN INSULIN. IT COMES AS A CLEAR AQUEOUS SOLUTION IN 100U STRENGTH WITH A VERY ACIDIC pH (pH=4). WHEN GLARGINE IS INJECTED SUBCUTANEOUSLY INTO A MORE NEUTRAL pH, THE INSULIN FORMS MICRO-PRECIPITATES WITH A RELATIVELY CONSTANT ABSORPTION INTO THE SYSTEMIC CIRCULATION. THE MICRO-PRECIPITATE FORMATION AND SLOW ABSORPTION ARE DEPENDENT ON THE pH OF THE GLARGINE, SO GLARGINE CANNOT BE MIXED WITH OTHER INSULINS OR DILUTED.

IN DIABETIC CATS, THE USE OF GLARGINE APPEARS EXTREMELY PROMISING. GLARGINE HAS A LONG DURATION OF ACTION AND A PREDICTABLE BLOOD GLUCOSE LOWERING EFFECT. IN 14 NEWLY DIAGNOSED CATS TREATED WITH A HIGH PROTEIN-LOW CARBOHYDRATE DIET (PURINA DM CANNED), THE DIABETES RESOLVED IN ALL WITHIN 4 MONTHS. 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 BID TO 8 CATS EACH, ALL 8 ON GLARGINE WENT INTO REMISSION AS COMPARED TO 3 OF 8 ON PZI AND 2 OF 8 ON LENTE. Thus, I recommend glargine BID 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. Cost-wise, insulin glargine is comparable to PZI from Idexx.

**Note:** although glargine is my 1st choice insulin in a newly diagnosed cat or a cat not well regulated on another insulin, if a cat has been a long-term diabetic and is well regulated, I would not switch to glargine. In long-term diabetics, obtaining diabetic remission with glargine is much less likely, and if the cat is controlled, I would not “mess with success”.

Recommendations are to start cats on glargine BID at 0.5 U/kg if BG is >360 mg/dL or 0.25 U/kg if BG is <360 mg/dL. For the first 3 days, 12-hr blood glucose curves should be performed (i.e. the curve should be performed for the interval between the a.m. and p.m. dose). The purpose of the blood glucose curve is to detect hypoglycemia, if present, and lower the dose of glargine as needed. Many cats require dose reduction within the first 3 days. The insulin dose should not be increased for the first week no matter what the curves look like!!! After the first 3 days, the cat should be sent home and then return for a curve 7 days later. Subsequent blood glucose curves should be performed 1, 2 and 4 wks later and then as required.

Recommendations for dose adjustment are based on the pre-insulin blood glucose (compared to other insulins where we change dose based on the nadir). If at recheck, the pre-insulin BG is >290 mg/dL, increase the glargine dose 1.0 U/cat. The dose should not be changed if the pre-insulin BG is 220-290 mg/dL. In either of these first 2 scenarios, a curve should be done the following day to ensure that hypoglycemia is not occurring. The dose should be decreased 0.5-1.0 U/cat if the pre-insulin BG is <180 mg/dL. If biochemical hypoglycemia is present, the dose should be decreased 1.0 U/cat. If clinical signs of hypoglycemia are present, the dose should be decreased 50%. Administration of glargine should not be discontinued within 2 weeks of starting treatment regardless of the curve – decrease the dose if needed, but do not stop the insulin (J. Rand, personal communication).

To determine if a cat is in remission, insulin administration should be continued until the cat is receiving 1 U BID. Then, if the pre-insulin BG is <180 mg/dL, go to once-daily administration. If the next day, the pre-insulin BG is still <180, do not administer insulin and do a complete curve. If the pre-insulin BG is >180 mg/dL when receiving once-daily insulin, go back to BID. An attempt to wean the cat can again be made in a couple weeks.

If performance of a curve is impossible, start glargine at 2 U/cat SQ BID and have the owner monitor urine glucose concentration or water intake. A cat well-regulated on glargine should have trace glucosuria at most and urine glucose should be negative the majority of the time. If after 2 weeks of receiving glargine, urine glucose is > trace, the dose should be increased 1 U/cat/wk until urine glucose is negative or water intake is <20 ml/kg/24h if eating canned food and <70 ml/kg/24h if eating dry food. At this point, keep the cat on the same dose for 2 wks then decrease the dose by 1 U/cat/wk until urine glucose is positive or the insulin has been discontinued.

**Nothing has been published to date about Levemir® (insulin detemir) in diabetic cats**, another long-acting recombinant insulin similar to glargine. It lasts longer than glargine in normal cats. Similarly, **nothing has been published about detemir or glargine in dogs**, but neither appears to offer any advantage. Interestingly, in 2 of 9 healthy dogs, BG did not change after injection of glargine suggesting possible lack of efficacy in dogs.17

**Vetsulin™** (Intervet) is a purified pork Lente insulin relatively recently approved by the FDA for use in dogs. It has been available for many years in other countries under the name Caninsulin. Since the amino acid sequences of pork and canine insulins are identical, porcine insulin, at least in theory, may be the ideal form to use in dogs. (I don’t believe that it is the ideal form.) Vetsulin™ is the only insulin approved for use in dogs.

A study has been completed where 53 dogs with uncomplicated diabetes were treated with Vetsulin™ for 60 days after a variable initial dose determination period. Therapy was started once daily and was changed to twice daily as needed. The starting dose used was the one recommended in the product insert: 1 U/kg with a supplemental dose depending on body weight (dogs <10 kg received 1 U supplement, 10-11 kg 2 U, 12-20 kg 3 U and dogs >20 kg 4 U). Efficacy and safety were evaluated at the end of the dose determination period (time 0) and 30 (time 1) and 60 days (time 2) later. With treatment, 80-96% of dogs had resolution of polyuria, polydipsia and ketonuria. Mean BG was 370 mg/dL before treatment but was 151-185 mg/dL while receiving Vetsulin™. At time 0, 1 and 2, 100%, 66% and 75% of the dogs were judged to be adequately controlled based on BG and clinical signs, respectively. At the end of the dose determination period, 57% were receiving Vetsulin™ twice daily (43% were receiving once-daily injections) and by day 60, 66% were receiving twice-daily injections. Overall, the median number of days to achieve adequate glycemic control was 35 (range 5-151). No unexpected side effects were observed, but 22 dogs had signs at some time that could have been caused by hypoglycemia and 2 dogs died of presumed hypoglycemia. For 7 dogs, owners reported swelling and/or pain at the injection site, but neither were noted by investigators on physical examination.18 Thus, Vetsulin™ appears to be a good option for use in diabetic dogs.

**The starting dose of insulin deserves consideration.** Although some authors recommend a starting dose of 0.25 U/kg twice daily for dogs19, others recommend using 0.5 U/kg if the blood glucose is >360 mg/dL and 0.25
after 1 and 2 weeks. A history, complete physical examination, body weight, BG and urine glucose/ketones should be performed periodically from initiation of therapy until failure is unpredictable, ranging from weeks to >3 yrs.

Adverse effects can be treated with glipizide for life in 12-15% of responder cats. Icterus develop within 4 wks of initiating therapy in approximately 10%.

Patients that are emaciated, dehydrated, debilitated, have concomitant disease or have recently lost >10% of their body weight are not good candidates.

Sulfonylureas (e.g. glipizide) is to increase insulin release. Long-term success rate is estimated to be approximately 35%. Increased liver enzymes and icterus develop within 4 wks of initiating therapy in approximately 10%. Hypoglycemia occurs in approximately 12-15% of responder cats; usually these cats are transient diabetics. Most cats that respond without continued adverse effects can be treated with glipizide for life, but glipizide loses effectiveness in at least 5-10%.

The period from initiation of therapy until failure is unpredictable, ranging from weeks to >3 yrs.

Glipizide treatment should be instituted at a dosage of 2.5 mg/cat per os BID with food, and the cat examined after 1 and 2 weeks. A history, complete physical examination, body weight, BG and urine glucose/ketones should be performed periodically.
be evaluated. If no problems occurred during the first 2 weeks, the dosage should be increased (5.0 mg/cat BID). If ketonuria is found, the medication should be discontinued and insulin therapy initiated. If vomiting or icterus is present, the drug should be discontinued until the problem resolves. Most cats will tolerate the medication if started at a lower dosage and gradually increased. If hepatic enzyme elevation or icterus occurred with the first administration, liver enzymes and serum bilirubin concentration should be checked periodically after reinitiation. If problems recur, the drug administration should be stopped and the cat placed on insulin.

Once a dosage of 5 mg BID has been given for 2 wks, the previously mentioned parameters and a 10-12 hr glucose curve should be checked every 4 wks. Response to therapy is evidenced by resolution of clinical signs, BG during the curve ≤200-300 mg/dL and lack of glycosuria. Time until response varies, so therapy at the full dosage should continue for 12 wks unless a contraindication develops.

If no response is seen after 12 wks, glipizide administration should be stopped and insulin therapy instituted. **To me, this is the big problem with glipizide.** We really do not know at what point glucose toxicity becomes irreversible. The length of time this requires after development of DM probably varies between cats. Empirically, wasting 12 weeks trying glipizide worries me. If glipizide does not work, you may get control of the DM when you try insulin, but may be less likely to obtain remission.

If clinical signs and glycosuria resolve and blood glucose levels ≤200 mg/dL, glipizide therapy should be stopped and the glucose concentration re-evaluated in 1 week. If hyperglycemia is present then, glipizide should be reinitiated. If normoglycemia is present, no medication is warranted. Glipizide can be used again, however, at any time if hyperglycemia recurs. The patient should be rechecked every 3 months to ensure ongoing control.

Cats that have resolution of clinical signs according to the owner, stable body weight and normal physical examinations but serial blood glucose levels ≥300 mg/dL present a clinical dilemma. Either the clinical signs have not truly resolved or the hyperglycemia is due to stress. Cats such as this should ideally be monitored by serum glycated hemoglobin (GHb) or fructosamine concentrations to determine overall glycemic control. If these tests are not available, urine glucose can be monitored at home when the cat is not stressed. If glycosuria is absent or GHb or fructosamine concentrations are normal, glipizide therapy can proceed. If glycosuria is present or glycated protein levels are elevated, insulin should be used instead.

**Other oral hypoglycemic agents do not hold much promise for treatment of DM in veterinary patients.** Transition metals are insulin-mimetic. Low doses (0.2 mg/kg/day) of vanadium decrease blood glucose and alleviate clinical signs in cats with early type II DM (D.S. Greco, personal observation). Unfortunately this is not a population we see often. In cats treated with vanadium, mild gastrointestinal signs may occur and 1 cat developed reversible renal failure. Vanadium is available commercially as Vanadyl Fuel ( capsule daily on food). In one study, chromium had no effect in concert with insulin treatment in diabetic dogs. Large clinical studies on the effect of vanadium or chromium in diabetic cats are lacking.

The biguanides (e.g. metformin) inhibit hepatic glucose release and improve peripheral insulin sensitivity. Doses of 25-50 mg/cat BID should attain plasma concentrations used for treating human DM, but results in diabetic cats are not promising. In the single published study, 6 cats (5 newly-diagnosed, 1 insulin-treated) received metformin at a gradually increasing dosage. One cat was found dead after 2 weeks and no response was seen after 6-7 weeks in 4 cats. In 1 cat, glycemic control improved after 7 weeks (dose = 50 mg daily) and metformin was used successfully for 5 months. Side effects noted in healthy cats include inappetence, weight loss and vomiting.

α-glucosidase inhibitors (e.g. acarbose) impair intestinal glucose absorption by decreasing fiber digestion and hence glucose production from food sources. In 5 dogs, a combination of acarbose and insulin provided better glycemic control over insulin alone. However, the final conclusion was that, due to expense and adverse effects, acarbose is primarily indicated for poorly controlled diabetic dogs for which the cause for the poor control cannot be identified. Acarbose may be administered at a dosage of 25-200 mg/dog or 12.5-25 mg/cat BID with meals. Side effects include flatulence, semi-formed stools or diarrhea.

Thiazolidinediones increase target tissue sensitivity to insulin by binding to a novel receptor called the peroxisome proliferator-activated receptor-γ (PPAR-γ); they have received little attention for use in diabetic cats. Recent work suggests that darglitazone has beneficial effects in obese non-diabetic cats to decrease insulin secretion and glucose concentrations in a glucose tolerance test, but no work has been done in diabetic cats.

References available from the author.