THE PROBLEM DIABETIC DOG AND CAT

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The veterinary medical literature abounds with information regarding the regulation of the diabetic dog and cat. For more than 20 years, we have become increasingly aware of circumstances surrounding the difficult-to-regulate diabetic pet. This paper will review several of the common conditions in order to facilitate their recognition and appropriate management. Those discussed include problems occurring during the acute and chronic phases of this disorder.

ACUTE COMPLICATIONS

Hypoglycemia -- Hypoglycemia will occur when the amount of insulin administered exceeds the needs of the patient during the treatment of acute ketoacidosis. This occurs most commonly when intravenous boluses of insulin are used instead of slow low-dose infusion or subcutaneous injections. This problem can be avoided by focusing more closely on the blood glucose levels instead of the ketones because the former will decrease within hours while it may take 2-3 days before ketogenesis abates. It is safe to titrate the patient's blood glucose level by a rate of 70-100 mg/dl/hr while remembering to begin a 2.5% to 5% dextrose infusion when the blood glucose level declines to < 250 mg/dl. The blood glucose level can be accurately and conveniently monitored with commercial reagent strips or any of the other rapid diagnostic electronic devises currently available. Hypoglycemia should be immediately treated with 1 ml/kg of 50% dextrose solution given by i.v. push followed by a glucose-containing maintenance solution.

Hypokalemia – Most ketoacidotic patients have lost substantial amounts of their total body potassium from the catabolic effects of insulin deficiency, through the osmotic diuresis that accompanies hyperglycemia, and through vomiting or diarrhea. During treatment there will be a further decline in serum potassium from: (1) the plasma diluting effects of intravenous fluids; (2) improved renal function and the secondary hyperaldosteronism that accompanies hypovolemia; (3) the lessening of metabolic acidosis and (4) the tendency for insulin to transfer extracellular potassium into the intracellular space.

Hypokalemia should be treated parenterally with potassium chloride. In the absence of oliguria, the potassium-containing infusion should begin after hydration is improved and adequate urine output is demonstrated. The amount of potassium chloride needed over a 24-hour period varies from 3-5 mEq/kg for mild-moderate hypokalemia (2.5-3.5 mEq/l) to 5-10 mEq/kg for marked hypokalemia (< 2.5 mEq/l). Usually the maximum infusion rate should not exceed 0.5 mEq/kg/hr, but as much as 1.5 mEq/kg/hr can be given with life threatening hypokalemia (<2.0 mEq/L).

Cerebral Edema. This rare complication is thought to occur from a too rapid decline in the blood glucose level. The gradual elevations of blood and cerebrospinal (CSF) glucose levels in the untreated diabetic will increase their respective osmolalities. In order to offset the resulting osmotic gradient between the brain and the blood, idiogenic osmols will accumulate within the brain parenchyma thereby helping to retain its water component. These idiogenic osmols in the brain can create an osmotic gradient where plasma water will flow into the parenchyma causing edema if insulin treatment

causes a too rapid decline in blood glucose concentration. This complication can occur quickly and the result can be fatal. It must be rapidly detected and expediently treated with i.v. mannitol solution (0.5 to 1 gm/kg). Plasma volume expansion using 0.9% NaCl will help offset the osmotic shift of water.

Paradoxical Cerebrospinal Fluid Acidosis. CSF acidosis occurs rarely and is caused by a too rapid rise in blood pH from parenteral sodium bicarbonate administration. The elevation in blood pH allows for a decreased minute ventilation rate, therefore allowing the $PaCO_2$ level to increase. While the i.v. bicarbonate diffuses poorly across the blood brain barrier, the PCO_2 can readily pass into the CSF, thereby acting as an available source for H^+ accumulation. Paradoxical CSF can cause coma and rapid death.

Sepsis and Acute Pancreatitis. Either of these conditions can pose a great threat to the diabetic. They can cause a hypersecretion of the stress hormones (glucagon, epinephrine, cortisol, growth hormone), thereby causing insulin resistance. Sepsis is especially life-threatening to the immunologically impaired ketoacidotic diabetic. Treatment should entail the use of bactericidal antibiotics and ample surgical drainage where appropriate.

CHRONIC COMPLICATIONS

Insulin Preparations

Most clinicians are familiar with the various types of commercial injectable insulin preparations. It should be stated that the times for peak onset and duration of action are simply estimates, and that there is a great deal of variability in these values from patient to patient as a result of various factors including anti-insulin antibodies, variation in subcutaneous absorption, individual responses, and other factors such as illness, diet, appetite and exercise. Finally, the effect of exogenous insulin in the type 2 diabetic cat will also be affected by concomitant endogenous insulin secretion. Some of these abnormal patient responses to insulin are described.

The Transient Insulin Response

The transient insulin response usually occurs with NPH (Humulin N) and Lente (Vetsulin) insulins in dogs and cats and may even occur with the ultralong acting insulin (PZI , glargine) in cats. It is characterized by early onset and peak action times of the insulin and a decreased duration of action. Consequently the patient shows a decline in blood glucose within a few hours after the injection and subsequently remains moderately hyperglycemic for the large remaining portion of the day. The owner often relates to (1) the detection of marked morning glycosuria, (2) the subsequent increased insulin dosage requirements, and (3) worsening episodes of hypoglycemia occurring 3-6 hours following the insulin injection. Frequent urine glucose monitoring can show an observed tendency toward marked morning glycosuria and diminished amounts in the early afternoon specimens. This early peak action and transient insulin response can occur with or without significant hypoglycemia (blood glucose < 70 mg/dl). With pronounced hypoglycemia, the clinician might detect a marked hyperglycemic rebound on serial blood glucose determinations due to the combined affects of increased counterregulatory hormone secretions (mainly glucagon and epinephrine) and the insulin's diminished duration of action (Somogyi effect).

The transient insulin response is treated by (1) splitting the total daily dose into two equally divided dosages 12 hours apart or (2) switching to the ultralong-acting insulin preparations (glargine, PZI) if they are truly long acting in that particular patient. Any transient effects of ultralong-acting insulin can be effectively managed in most situations by splitting the dose. The total day's insulin dose should be reduced by approximately 25% prior to splitting because the animal had usually been receiving an excess amount of insulin by the time this complication is diagnosed. Both NPH and Lente (Vetsulin) insulins can be effectively used on a twice daily basis while glargine or PZI are the recommended insulins of choice for diabetic maintenance in cats. These latter two should also be given on a twice daily basis in the cat.

I currently recommend that the owner of a diabetic pet purchase Glucagon Injection from the drug store in order to have it available for any hypoglycemic coma or seizure. Administer at 0.03 mg/kg IM. I call it "Brain Insurance."

Posthypoglycemic Hyperglycemia

Also known as the Somogyi reaction, posthypoglycemic hyperglycemia results from insulin overdosing causing hypoglycemia and the body's subsequent hyperglycemic compensatory response that occurs through the production and hypersecretion of counterregulatory hormones: Glucagon, epinephrine, cortisol, and growth hormone. Glucagon and epinephrine are mainly involved. The excess insulin dosages can be due to faulty client/veterinarian communications or as a result of the transient insulin response causing marked morning glycosuria and the clinician's or owner's misimpression that subsequent larger amounts of insulin are needed.

Detection of this problem is aided by recognizing the typical pattern of marked morning hyperglycemia and glycosuria, early afternoon hypoglycemia, and rebound hyperglycemia that usually persists for the remaining 24-hour period, especially if associated with a transient insulin effect. Sometimes the patient has diminished late morning or early afternoon urine glucose levels that accompany the decline in blood glucose. This will be more apparent with more frequent urine testing.

The treatment of posthypoglycemic hyperglycemia requires decreasing the insulin dosage, thereby avoiding hypoglycemia. A 50-75% insulin dosage reduction should restore improved diabetic regulation in the absence of the transient insulin response. The problem can be managed as previously described if the reaction is associated with the transient insulin response. The split-dosage insulin technique along with gradual increased amounts of insulin are indicated when persistent marked glycosuria and hyperglycemia accompany this treatment adjustment.

Exocrine Pancreatic Insufficiency

The diabetic animal that has concomitant exocrine pancreatic insufficiency, not only has depleted amounts of endogenous insulin, but also has insufficient amounts of the pancreatic digestive enzymes that are essential for normal food digestion. Consequently these animals are severely malnourished and in a catabolic metabolic condition. They are also insulin sensitive because of the unavailability of adequate amounts of food substrate.

Treatment is usually rewarding with the correct use of pancreatic enzyme replacement (Viokase or Pancreazyme Powder). Since this causes enhanced protein-calorie utilization, the clinician and the pet

owner should anticipate the pet's increased insulin requirements. Close patient monitoring will provide a satisfactory response to treatment.

The High Insulin Dose Requiring Cat

Occasionally the cat will require insulin doses far in excess to the usual anticipated amounts (1-10 units/day). The amount required might range as high as 20-30 units per day. The reasons for this phenomenon might include (1) coexisting Cushing's disease or acromegaly (2) the transient insulin response with the owners being unaware of the cat's hypoglycemic reactions, (3) some peripheral insulin receptor or postreceptor defect, or (4) faulty insulin absorption from the injection site.

Any cat that requires progressively increased dosage increments should be evaluated for hyper-cortisolism and acromegaly if the history and signs suggest either of these syndromes. If blood glucose monitoring substantiates persistent hyperglycemia indicating minimal response to insulin, the insulin dose should be raised by 1 unit increments every day or every other day. Remember:

> THERE IS NO RULE THAT STATES THAT A CAT'S INSULIN DOSE MUST STOP AT 10 UNITS.

If the cat requires more, give more so long as it does not experience any hypoglycemia. The author recommends that the high dose-requiring patient receive its treatments on a split dosage regimen every 12 hours. Any predisposing condition should be treated appropriately. Occasionally switching to a different type of insulin or dosing from a new bottle might benefit the patient.

Diestrus

Diestrus in the dog is a well known cause of insulin resistance. This resistance results from progestagen-induced supraphysiologic secretion of growth hormone that can exert a profound peripheral insulin resistance. It is common to find where female diabetic dogs in diestrus show dramatic increased insulin requirements (up to 6-7 times their previous maintenance dosages). This problem is remedied with ovariohysterectomy and/or the cessation of any progestogen treatment.

The Diabetic Dog with Cushing's Syndrome

These two conditions can occur simultaneously or one might randomly precede the other. Typically, these patients are present with physical features characteristic of hyperadrenocorticism or because of the owner's concern over the onset of their pet's increased insulin requirement. They can show polydipsia, polyuria, polyphagia and daily insulin requirements in excess of 2 units/kg per day. Sometimes the animal shows anorexia, vomiting, and other signs of physical deterioration as a result of the onset of ketoacidosis or perhaps acute pancreatitis. Diagnosis depends on the index of clinical suspicion derived from the history and physical examination findings and serum biochemical confirmation with the dexamethasone suppression or ACTH stimulation tests. It is important to note, that false positive test results can occur if the patient is metabolically stressed.

Treatment requires the use of o,p'-DDD (mitotane) in conjunction with the dog's insulin treatments. Because of the anticipated hypoglycemia that might associate with decreased levels of glucocorticoid hormones, the standard recommended o,p'-DDD loading dose can be reduced to 25-35 mg/kg per day. Prednisone (0.3 mg/kg per day) is often given during the first seven days in order to offset any side effects caused by cortisol depletion. The ACTH stimulation test should be repeated after

this loading period in order to assess the patient's treatment response. Abnormally high post-ACTH serum cortisol levels (> 6 μg/dl) requires extending the loading period, while adequate adrenocortical suppression (2-6 μg/dl) allows for the o,p'-DDD weekly maintenance dosage of 25-35 mg/kg that can be administered in divided amounts every 3 days. Trilostane can be used in place of op'-DDD.

During the first 2-3 weeks of o,p'-DDD treatment, the clinician and the pet owner should anticipate the dog's diminished insulin requirement. This will be evident as less glycosuria, possible signs of hypoglycemia, and/or measurably decreased blood glucose levels. The insulin dosage should be decreased by approximately 50% at the onset of the earliest signs of increased insulin sensitivity.

Acromegaly

This condition in the cat is characterized by abnormally increased growth hormone production caused by a somatotropin-secreting anterior pituitary gland tumor. It occurs in the dog during diestrus through progesterone-induced endogenous growth hormone secretion by the mammary gland. Progesterone injections can also cause acromegaly in the dog.

Acromegaly is recognized by detecting insulin resistance in the presence of the characteristic physical changes that occur. The objective diagnosis rests on demonstrating (1) elevated plasma levels of growth hormone or insulin growth factor or (2) non-suppression of growth hormone with glucose infusion. Despite the high insulin requirements in the cat, they rarely become ketoacidotic.

Treatment entails removing the source or stimulus responsible for the elevated growth hormone levels; ie hypophysectomy, radiation treatment, ovariohysterectomy, discontinued progesterone injections.

Infections

This is a frequent cause of increased requirements in humans. It is associated with increased endogenous production of the stress hormones: Cortisol, epinephrine, and growth hormone that can cause insulin resistance. Effective management requires prompt diagnosis and treatment consisting of surgical drainage (where indicated), bacterial culture and sensitivity determinations, and the use of the appropriate bactericidal antibiotic.

The Exceptionally Insulin Sensitive Cat

This is a fairly common happening where a diabetic cat will show exquisite sensitivity to the smallest amount of insulin (1.0 unit) and then tend to be unacceptably hyperglycemic without the insulin treatment. This problem can possibly be caused by the cat's poorly controlled endogenous insulin release magnifying the hypoglycemic effects of the injected amount. The clinician will find this very difficult to manage because of the erratic swings in blood glucose levels. It is best to make any dosage increases slowly on alternate days using a split dosage regimen.

Faulty SQ Insulin Absorption

Rarely will the SQ route simply just not work in a particular patient. This can be proven by showing where the blood glucose will decline from an IM or IV injection of regular crystalline insulin.

TREATMENT OF DIABETES MELLITUS IN THE CAT AND DOG

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Diabetes mellitus is not a rare disease in the dog and cat. It results either from an inability of the pancreatic beta cells to synthesize and release adequate amounts of insulin or from a peripheral antagonism to the effects of insulin. Most of the time the cause is idiopathic, but some associated known predisposing factors include pancreatitis, glucocorticoid abuse, prolonged use of megestrol acetate, and acromegaly.

Diagnosis is made on the basis of history and clinicopathologic abnormalities as will be described in further sections. The practitioner should be aware that the cat often shows a transient hyperglycemia during times of stress where the blood glucose levels can elevate to 200-300 mg/dl. Therefore it is important to interpret the laboratory values within the context of the patient. When the significance of the hyperglycemia is questionable, the clinician should repeat the test and check for the presence of glycosuria.

The medical management of the diabetic pet will be divided into two sections. The first will discuss treatment in the non-ketoacidosic diabetic, and the second will discuss treatment for ketoacidosis.

THE NON-KETOACIDOTIC PATIENT

History and Physical Examination Findings

The history usually denotes polyuria, polydipsia, and gradual weight loss over a period of weeks to months. Polyphagia is sometimes evident. The usual physical examination abnormalities include evidence of weight loss and slight hepatomegaly. Dogs can get a rapid onset of diabetic cataracts.

Diagnosis

Persistent hyperglycemia and glycosuria are the classic clinicopathologic abnormalities. Occasionally the liver serum enzyme tests (ALT, AST, and alkaline phosphatase) are elevated due to hepatic lipidosis.

Most of the time, these patients are initially treated as outpatients following a special consultation session with the owner that provides specific instructions regarding insulin injection technique, feeding, insulin dosage adjustments, and the actions needed to counter any hypoglycemic reactions.

Treatment

NPH (Humulin N) insulin is the initial drug of choice in the compensated dog. It is initially dosed at ½ unit/kg (dog) or 1.0 unit total (cat) and should only be given subcutaneously on a divided dose basis BID. In man, the activity of NPH insulin is characterized as follows: Onset of action – three to four hours, peak

action -- eight to 12 hours, and duration of action 18-24 hours. In the cat and most dogs, however, experience has shown that the onset and peak action times of NPH can occur as early as a few hours following the injection thereby predisposing the animal to life-threatening episodes of hypoglycemia. To circumvent this misfortune, the insulin dose should be split where one-half of the total is given in the morning, and the other half is given 8-12 hours later. This split-dose method provides the patients total daily insulin requirement yet lessens the risk of hypoglycemic reactions. In situations where the animal is receiving only one dose of insulin per day, the clinician should suspect the need for splitting the dose when the following signs are present: (a) symptoms of hypoglycemia in the late morning or early afternoon accompanied by minimal glycosuria and (b) hyperglycemia and excess glycosuria on the following morning's blood and/or urine sample(s). The reasons explaining this reaction include the Somogyi reaction, shortened duration of insulin effect, and possibly the owner's administration of excessive carbohydrates on the preceding day to counter the hypoglycemic episode.

PZI has recently been shown to be suitable as a maintenance insulin for the dog (JVIM Feb 2012). However, unpredictable peak time hypoglycemia is still a potential concern and larger field studies are needed before a more definite recommendation can be made for its routine use in the dog.

The diabetic cat will maintain much more satisfactorily if it is treated with PZI or insulin glargine because of their longer action and duration of action times. These insulins are likewise given subcutaneously on a divided bid basis. I now recommend to all of my diabetic pet owners that they purchase Glucagon injection at the drug store and give it IM at a dose of 0.03 mg/kg for any hypoglycemic coma or seizure event. Oral glucose substitutes will adequately treat hypoglycemia so long as the patient is conscious.

THE DIABETIC KETOACIDOTIC PATIENT

The diabetic ketoacidotic pet is usually a medical emergency requiring immediate therapy based on the understanding of the underlying pathophysiology. The amount of knowledge regarding the pathogenesis of ketoacidosis has increased considerably over the past several years and a thorough understanding of the pathophysiology is essentail to appropriate treatment.

History and Physical Examination Findings

The history can be acute and characterized by a sudden onset of anorexia, depression, weakness and vomiting of only several days duration. In other situations, the history is more chronic as characterized by polydipsia, polyuria, and weight loss of several weeks or months duration with the subsequent onset

of weakness, depression and vomiting which finally arouses the pet owner's concern.

The physical examination can reveal an entire spectrum of findings ranging from an essentially normal animal to one that is prostrate and nearly comatose, extremely dehydrated, and often times cachectic. A smooth symmetrically enlarged liver due to hepatic lipidosis is often detected with abdominal palpation.

Diagnosis

Insulin treatment should not be given until the hallmark signs of hyperglycemia and ketonuria or marked glycosuria and ketonuria are substantiated with laboratory tests. In a previously published survey by this author describing the clinicopathologic abnormalities in 30 diabetic cats, the following abnormalities were frequently found in the sick ketoacidotic patient: Azotemia, hypobicarbonatemia, elevated serum liver enzyme tests, and hypokalemia. Additional clinicopathologic abnormalities included hyponatremia, hypophosphatemia and anemia.

A qualitative assessment of hyperketonemia can be made using the nitroprusside test (Acetest Tables - Ames Division, Miles Laboratories Inc., Elkart, Indiana, 46514) when a urine sample is not initially available. This serum

ketone test is first performed on an undiluted sample and then subsequently on serial serum dilutions ranging from 1 in 2 to 1 in 32.

Treatment

The type of treatment must be tailored according to each patient's need. A hyperglycemic pet with mild ketonemia that presents with a good appetite and no signs of debilitation can safely receive NPH or Vetsulin (if available) and be treated as an outpatient as described in the previous section. However, the depressed, dehydrated patient should be hospitalized for more intense treatment and observation. The following sections describe the principles of therapy for the sick ketoacidotic diabetic animal.

(a) Intravenous Fluid Therapy:

The calculated fluid requirements include the patient's dehydration deficits, the 24-hour maintenance needs, and extra losses that result from vomiting or diarrhea. The dehydration status is approximated on a scale ranging from a mild (5%) to extreme (10%). The needed isotonic replacement volume is calculated by either of the following two methods based on either pounds or kg body weight:

(1) dehydration volume deficit (ml) =

dehydration x kg body wt x 1000

(2) dehydration volume deficit (ml) =

dehydration x lb body weight x 500

The 24-hour maintenance volume is roughly estimated (assuming adequate urine output) at 30 ml/lb (60 ml/kg). Therefore, the initial first 24-hour total fluid volume is the sum of the dehydration and the maintenance volumes.

If the animal is 8-12% dehydrated ½ of the estimated dehydration deficit should be administered intravenously over the first two- to four-hour period of hospitalization with the remaining replacement and maintenance volumes given over the following 20- to 22-hour period.

Lactated Ringer's solution (LRS) is the initial fluid of choice, however 0.9% saline can be given as an alternative or when the patient is significantly hyponatremic (<135 mEq/L). The lactate in LRS is not associated with a H+ and therefore will not promote the onset of lactic acidosis. Acetate containing parenteral fluids should not theoretically be given to the ketoacidotic patients in order to avoid possible increases in acetoacetate blood levels.

(b) **Insulin:**

Regular crystalline insulin is used when the patient has signs of depression, dehydration, anorexia, and vomiting. The advantages of regular insulin include: (1) various routes of administration (IV, IM and SQ); (2) rapid onset of action; and (3) short duration of action. These properties allow

adequate insulin titration throughout the day according to the animal's needs. The clinician must acknowledge that blood glucose levels decline much earlier than ketone levels and so anticipate the persistence of some ketonemia and ketonuria for the first 48-72 hours.

Bolus intravenous doses of insulin offer the advantage of an immediate onset of action for the critically hypotensive patient. The recommended dose for a medium-sized to large dog is 1-2 units/kg. In the small dog and cat, the dose is reduced to 0.5 units/kg. Subsequent doses are given at the same amount every two to three hours until the blood glucose levels decrease to less than 250 mg/dl, at which time the patient is switched over to subcutaneous insulin injections given approximately every six hours. The disadvantages of this technique include the need for intensive care monitoring with frequent (every one to two hours) blood glucose determinations, the likelihood of hypoglycemia and hypokalemia, and the possibility of cerebral edema resulting from a too-rapid fall in blood glucose levels. Mannitol is the preferred treatment should this complication occur. This author does not prefer this method.

When laboratory facilities are unavailable, blood glucose reagent strips (Chemstrip bG reagent strips, Boehringer-Mannheim or Dextrostix reagent strips, Bayer, Alphatrack , Abbott) can be used for approximate blood glucose

determinations. Several reflectance colorimeters are now commercially available to enhance the accuracy of these reagent strips.

To circumvent the occurrence of the aforementioned side effects, a continuous low-dose insulin infusion can be used. One successfully applied technique in the dog involves the addition of 5 units of regular insulin to a 500 ml bottle of lactated Ringer's solution which produces an insulin concentration of 0.01 unit/ml. After the first two to four hours of rehydration, the insulin infusion can be administered at a dosage of 0.1 unit/kg/hr. Care must be taken to avoid intravascular fluid overload in the small animal which might result from the technique. This can be accomplished by infusing the insulin containing solution through a separate intravenous catheter. Blood glucose determinations should be made every one to two hours. Reduce the insulin infusion to 0.05 unit/kg per hour when the blood glucose level is reduced to 250 mg/dl.

Low-doses of regular insulin can also be given intramuscularly. Initially 2 units are given into the thigh muscles of cats and dogs weighing less than 10 kg. For dogs weighing more than 10 kg, the initial dose is 0.25 unit/kg. Subsequent hourly injections of 1 unit for cats and small dogs and 0.1 unit/kg for larger dogs are given until the blood glucose level is less than 250 mg/dl, at which time the subcutaneous route can be used on an every six hours or as

needed basis. The low doses used in this technique can be accurately measured with low-dose calibrated syringes (Lo-dose Insulin Syringe, Becton Dickinson, Rutherford, NJ 07070).

Subcutaneous regular insulin treatment is a suitable alternative to the intravenous and intramuscular methods when intensive care monitoring is unavailable and when the patient is not in hypovolemic shock. The initial dose is 0.5 unit/kg followed by subsequent doses every six to 10 hours depending on need.

Dextrose 2.5% or 5% solution is instituted when the blood glucose decreases to < 250 mg/dl.

The patient is regarded as stable and able to receive intermediate action (NPH, Vetsulin) or ultralong-acting (Glargine, PZI in cats) insulin when normal hydration is restored, blood glucose levels are below 350 mg/dl, serum or urine ketones are minimal to absent, and oral feedings are accepted.

Electrolyte Supplementation

Assessment of the patient's serum electrolyte levels and correction of any abnormalities are extremely important for a successful outcome. As mentioned earlier the most common abnormalities include hypokalemia, hyponatremia and hypophosphatemia. Hypokalemia will be emphasized here because it is the

most common and most debilitating serum electrolyte abnormality in the ketoacidotic diabetic.

The major causes of potassium depletion in diabetic ketoacidosis include (1) lean tissue breakdown (nitrogen loss), tissue glycogen depletion and cellular water loss which cause potassium to leave the cell and eventually be excreted in the urine, (2) hypoinsulinemia allowing cellular potassium to enter the plasma and be lost in the urine, (3) secondary hyperaldosteronism in response to hypovolemia, and (4) gastrointestinal loss from vomiting. To complicate matters even further, the serum potassium level will usually fall after treatment commences via (1) dilution from rehydration, (2) continued urinary losses which are enhanced by excess Na^+ delivery to the renal distal tubule, (3) correction of acidosis and the cellular influx of K^+, and (4) increased cellular uptake of K^+ due to insulin.

A ketoacidotic, dehydrated, normokalemic diabetic usually has significant total body potassium depletion. When hypokalemia is initially present, the total body potassium losses are even more substantial.

Although these patients are acidotic, very few are ever found to be hyperkalemic. The onset of hyperkalemia in this setting of metabolic acidosis is offset by the continuing body loss of potassium by the mechanisms shown above. Furthermore the recent literature has shown that hyperkalemia is only

rarely associated with an organic anion acidosis as opposed to a predictably higher incidence with an inorganic anion type of acidosis. Hyperkalemia will more commonly accompany oliguria and anuria.

Potassium supplementation for moderate to severe hypokalemia is best provided with potassium chloride solution which is added to the parenteral fluids. If concurrent hypophosphatemia is present, potassium phosphate solutions are available which can also be added to the intravenous fluid bottle. Potassium supplementation is best begun after the first two hours when rehydration, blood pressure, and adequate urine output are present. When the patient is initially markedly hypokalemic, the potassium can be supplemented in the initial volume of intravenous fluids but care should be taken to slow down the rate of infusion where the replacement of one half of the dehydration deficit is best delivered over an extra one- to three-hour period. The recommended amount of supplemented potassium chloride is provided:

(a) mild hypokalemia (serum K^+ = 3.0 to 3.5 mEq/L): give 1-3 mEq KCl/kg B.W. over 24 hrs or you can add 25-30 mEq KCl/L of solution.

(b) moderate hypokalemia (serum K^+ = 2.5 to 3.0 mEq/L): give 3-5 mEq KCl/kg B.W. over 24 hours or you can add 40 mEq KCl/L of solution.

(c) severe hypokalemia (serum K^+= < 2.5 mEq/L.): give 5-10 mEq KCl per kg B.W. over 24 hours or you can add 60 mEq KCl/L of solution.

It is important to recheck the serum electrolyte levels on the following day in order to further adjust electrolyte supplementation. The intravenous fluids and potassium supplementation are usually discontinued when euhydration and normal serum electrolyte levels are restored, and when the patient is able to eat and drink without vomiting.

Acidosis

Diabetic ketoacidosis is metabolic in origin and characterized by the accumulation of organic acid anions (acetoacetate and beta-hydroxybutyrate) which buffer and thereby lower the plasma bicarbonate levels. The body compensates the acidosis quite efficiently by (1) tissue and blood protein buffering (2) increased ventilation rate which blows off CO_2 and (3) renal mechanisms which regenerate bicarbonate and excrete the acid via increased $HP0_4^-$ and NH_4^+ activity.

The diagnosis of metabolic acidosis in this disorder is characterized by a low blood pH, low total CO_2 level, and the presence of a base deficit and an elevated anion gap. The anion gap is equal to: $(Na^+ + K^+) - (HCO_3^- + Cl^-)$. A value greater than 30 mEq/L is clinically significant.

The use of sodium bicarbonate solutions should be reserved for those patients with a blood pH of less then 7.1. The complications of excess sodium bicarbonate therapy include: Extracellular fluid hyperosmolarity, cerebrospinal fluid acidosis, intracranial hemorrhage, metabolic alkalosis, hypokalemia, and a left shift of the oxygen-hemoglobin dissociation curve. When the blood pH is between 7.2-7.3, the patient will usually counter the acidosis with its own compensatory mechanisms once the insulin and IV fluids are administered. Furthermore the body will convert acetoacetate and beta-hydroxybutyrate to bicarbonate once adequate amounts of insulin are administered.

When the acidosis is severe (pH < 7.1), sodium bicarbonate treatment should be given. The amount needed is determined by the following formula: mEq NaHCO3 needed for extracellular replacement = 0.3 x B.W.k_g x base deficit in mEq/L. The sodium bicarbonate should be administered slowly, and the blood pH should be re-evaluated a few hours later. When the blood pH returns to levels of approximately 7.25 or greater, the alkaline supplement should be discontinued to avoid the above mentioned side effects.

Feeding

Once the animal is able to hold down food, it should be fed or gently forced fed every six hours. A multivitamin supplement should also be given.

MANAGEMENT OF THE DIABETIC PET

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Dear Mr./Mrs. _____:

Your pet has a disease called Diabetes Mellitus (sugar diabetes). Since your pet does not have enough natural insulin to maintain normal body function, you must provide the insulin by daily injection.

At your pharmacy, you will purchase Humulin N (NPH) insulin (or another particular type preferred by your veterinarian) (100 units per cc), insulin syringes (100 unit), and needles with the accompanying prescriptions. Other insulin products can be obtained, but these will best be left to your doctor's discretion. The U-100 syringes are available in the following calibrations 0 to 100, 0 to 50, and 0 to 30 units. They have "painless" 29 gauge needles attached. Note that insulin and insulin syringes can be purchased without prescriptions. Insulin should be refrigerated or kept in a cool and shaded environment at all times, and the bottle must be gently swirled prior to withdrawal of the insulin into the syringe. The injection must be given subcutaneously (beneath the skin). Your doctor or technician will demonstrate the correct injection technique.

If your veterinarian chooses to use PZI (for cats and dogs), this only comes in a concentration of 40 units per cc. Note that PZI requires U-40 syringes.

The amount of insulin required each day may be subject to change depending on various factors such as alterations in diet, exercise and certain environmental stresses. The dose is determined by monitoring the amount of sugar in your pet's urine. This will be measured each morning prior to insulin administration. To measure urine sugar, purchase Diastix® or Ketodiastix® at your pharmacy. Do not confuse these with Ketostix® which does not measure urine sugar. The instructions on these tests are simple to follow.

Split Injection Method – This is my preferred method for dogs and cats when using NPH, PZI (note that PZI-feline is 40 units/ml concentration and requires U-40 insulin syringes), and glargine (the latter two are used in cats).

(a) In the morning, determine the urine sugar level and determine the necessary insulin dosage adjustment.
(b) Administer ½ of the total dose SQ; then feed ½ of the daily total diet.
(c) In the evening, administer the other ½ dose of insulin and feed the other one half of the daily diet. Allowing free choice food throughout the day is permissible for your cat.

The following chart will guide you in making total daily insulin dose adjustment. Note that the colors are meant to coordinate with the Ketodiastix® or Diastix® reagent tests.

FOR A LARGE OR MEDIUM SIZED DOG: _____
[above 30 lb (15 kg)] (Patient's Name)

If urine sugar is 4+ (2%)	..... (brown)	increase 2-3 units over previous day's dose.
If urine sugar is 3+ (1%)	..... (brown)	increase 2 units over previous day's dose.
If urine sugar is 2+ (½%)	..... (green/brown)	increase 1 unit over previous day's dose.
If urine sugar is Trace (1/10%) or 1+ (1/4%)	..... (green)	repeat previous day's dose.
If urine sugar is Negative	..... (blue)	decrease 2 units from previous day's dose

FOR A CAT AND SMALL DOG: _____
[less than 30 lb (15 kg)] (Patient's Name)

If urine sugar is 3+ (1%) or 4+ (2%)	..... (brown)	increase ½-1 unit over previous day's dose.
If urine sugar is 2+ (½%)	..... (green/brown)	increase ½ unit over previous day's dose.
If urine sugar is Trace (1/10%) or 1+ (1/4%)	..... (green)	repeat previous day's dose.
If urine sugar is Negative	..... (blue)	decrease 2 units from previous day's dose

The ultimate objective is to maintain the morning urine sugar at the Trace to 1+ level. In the small pet, adjustments for dosage increase can be made on an alternate day basis.

Infrequently your pet may experience an insulin reaction due to a marked decrease in its blood sugar. When using NPH (Humulin N) insulin, this reaction is most likely to occur 3-8 hours following the morning's injection but may occur as soon as 1-2 hours after the injection. When using PZI or glargine, the hypoglycemia can occur a bit later (8-12 hours postinjection). The signs accompanying such a reaction will mimic a drunken state; that is, your pet will be weak and walk with a wobbly incoordinated gait. Should this occur, administer 1-2 tablespoons of Karo Syrup (or 0.25-0.5 ml/lb) orally. If no improvement is seen after 15 minutes or if the signs worsen, seek out veterinary assistance immediately. If you were instructed to purchase Glucagon severe hypoglycemic seizures or coma, the dose is 0.03 mg/kg IM or SQ. Glucagon can be purchased at the drugstore with a doctor's prescription.

Dietary changes are unnecessary other than feeding your pet twice daily so long as the diet is nutritionally balanced and avoids obesity. Prescription diets can be used at your veterinarian's discretion.

Should your pet become ill or acquire any type of trauma, your doctor should be contacted immediately.

COMMON PROBLEMS FREQUENTLY ENCOUNTERED

(1) If you attempt to give the morning injection and your pet gets only part of its dose because of its sudden movement causing slipping of the needle from under the skin, do not attempt to approximate its dose by giving another injection. Simply wait until the next day and repeat the previous day's dose. It is safer to err by not giving enough for 24 hours rather than giving an overdose.

(2) If your pet is unable to eat after insulin is given (for example, vomiting), try to administer a semi-liquid diet such as baby food about one hour later. If vomiting persists, your pet should receive veterinary attention immediately.

(3) If you have a female pet, we strongly urge that she be spayed prior to her next heat since loss of diabetic control frequently occurs during the heat period.

If any problems or questions arise, please call your veterinarian as soon as possible.

Sincerely,

Dr. _____
Medical Service _____

This morning your pet received ____ units and this evening he/she should receive ____ units.

Tomorrow morning you will administer the next dose according to the above chart.