Classification of Diabetes Mellitus (Humans and Dogs/Cats)—Abstracted from Dr. Chen Gilor (ACE Endocrine course 2015)

**TYPE 1 DM**

**Key features:** Beta cell destruction (without destruction of other cell types in the islet) often leading to absolute insulin deficiency

**Immune (usually genetic)**

In people, markers of the immune destruction of the beta-cell include islet cell autoantibodies, autoantibodies to insulin, autoantibodies to GAD (GAD65), and autoantibodies to the tyrosine phosphatases IA-2 and IA-2b. One or more (usually more than one) of these autoantibodies are present in 85–90% of human Type I diabetics when fasting hyperglycemia is initially detected.

Diabetes mellitus in dogs is most commonly associated with permanent hypoinsulinemia, no increase in c-peptide in response to insulin secretagogues, and an absolute necessity for exogenous insulin administration to avoid ketoacidosis. This presentation is consistent with Type 1 DM; however, this presentation is also consistent with Type 3c (pancreatic disease). Many of the hallmarks of Type 1 DM in people are not present in the majority of dogs with diabetes. There is evidence of cellular-mediated autoimmune destruction of the b-cells in about 50% of diabetic dogs or less, depending on the study. In a recent study there was lack of evidence for a role of islet autoimmunity in 121 dogs of 40 different breeds. In that study, histopathologic evaluation was performed in only 5 dogs but none of these had lymphocytic inflammation in pancreatic islets. Previously, infiltrating mononuclear cells, predominantly lymphocytes, were observed in 6 of 13 dogs (46%) with diabetes while in 5 of 18 dogs (28%), extensive pancreatic damage appeared to be responsible for the development of DM. It has been previously suggested that canine DM is similar to Type 1 DM in the presence of susceptibility and protective major histocompatibility complex haplotypes in canine diabetes mellitus. This candidate gene approach has been criticized however because it runs a high risk of false positives in dogs, and the DLA locus may be particularly susceptible to false associations created by popular sires, inbreeding, or genetic drift. Further studies are necessary to confirm these findings.

**Idiopathic diabetes.**

At least 50% of diabetic dogs have etiologies other than with immune-mediated type 1. What is the most likely etiopathogenesis of DM in the other 50%? No evidence of autoimmunity. An absolute requirement for insulin replacement therapy in affected patients may come and go. In people, only a minority of patients with type 1 diabetes fall into this category and most of these are of African or Asian ancestry. This form of DM is strongly inherited, lacks immunological evidence for b-cell autoimmunity, and is not HLA associated.

**Type 2 DM**

**Key features:** Unknown etiology: a combination of an insulin secretory defect with insulin resistance.
Type 2 DM was previously encompassed by non-insulin dependent DM (or adult onset DM). It is characterized by the combination of insulin resistance and impaired insulin secretion. Impaired secretion results in insulin deficiency that is usually relative (rather than absolute) to the overall increased insulin requirement that is the result of insulin resistance. Most patients with this form of diabetes are obese. Patients who are not obese by traditional weight criteria may have an increased percentage of body fat distributed predominantly in the abdominal region. Although obesity itself causes some degree of insulin resistance it is not the cause of Type 2 DM. This is because for type 2 DM to develop a component of impaired insulin secretion and inability to compensate over insulin resistance are necessary. Whereas patients with type 2 DM may have insulin levels that appear normal or elevated, the higher blood glucose levels in these patients would be expected to result in even higher insulin values had their b-cell function been normal. Thus, insulin secretion is defective in these patients and insufficient to compensate for insulin resistance. Insulin resistance may improve with weight reduction and/or pharmacological treatment of hyperglycemia but is seldom restored to normal. The risk of developing type 2 DM increases with age, obesity, and lack of physical activity. It is often associated with a strong genetic predisposition, more so than is the autoimmune form of type 1 DM. Based on clinical presentation, the epidemiology of the disease and the association with amyloid deposition in the islet of Langerhans it has been previously suggested that the majority of diabetic cats suffer from a Type-2-like disease.\textsuperscript{5, 21}

Type 3 DM

- Genetic defects in beta cell function (MODY 1-7)
- Genetic defects in insulin action.
- Exocrine pancreatic disease ***
- Endocrinopathies

Recent studies suggest that hypersomatotropism is much more frequent than previously thought.\textsuperscript{23} In contrast to Type 2 DM, it is questionable whether a primary defect in beta cell function is present in hypersomatotropism.

- Drug- or chemical-induced diabetes
- Infections
- Genetic
- Other

*** Reported in dogs

Type 4: Gestational DM (GDM)

For many years, GDM has been defined as any degree of glucose intolerance with onset or first recognition during pregnancy, at any stage of pregnancy. Reported in dogs.

Prediabetes

Prediabetes is defined as a condition in which abnormal hyperglycemia is present but does not meet criteria for diabetes. Impaired fasting glucose (IFG): fasting plasma glucose (FPG) levels = 100 – 125 mg/dl (5.6 – 6.9 mmol/l). Impaired glucose tolerance (IGT): 2h values in the oral glucose tolerance test (OGTT) of 140 – 199 mg/dl (7.8 – 11.0 mmol/l). Above the laboratory "normal" range but below the diagnostic cut point for diabetes (6.0 to 6.5%) people are at very high risk of developing diabetes. Prediabetes probably occurs in cats, although we have limited ability to measure glycosylated hemoglobin or IGT and OGTT in clinical practice.

INSULIN THERAPY

Human recombinant insulin is the most available insulin preparation on the market and is perfectly acceptable as insulin therapy for all dogs. Porcine insulin is identical to canine insulin in its amino acid structure and human insulin is very similar to canine insulin. Insulin preparations may be short-acting (regular insulin), intermediate (Lente, NPH) or long-acting (Ultralente, PZI). NPH and PZI insulin is made from regular insulin by adding protamine in increasing concentrations to retard insulin absorption.

Protamine zinc insulin (PZI) was discontinued as a human preparation in 1991 and has just recently become available again to veterinarians as a U-40 insulin (Boeringer Ingelheim). Lente preparations control absorption by regulating the size and shape of the insulin crystals. Semilente is composed of small, amorphous zinc-insulin, and ultralente is composed of large zinc-insulin crystals which are more slowly absorbed. Lente insulin is a mixture of 30% prompt zinc-insulin suspension (semilente) and 70% extended insulin zinc (Ultralente). Lente insulin, because of the small zinc-insulin crystal component, may be used to attenuate postprandial hyperglycemia.

These traditional intermediate-acting formulations (Lente, NPH, PZI) are injected as suspension: They need to be re-suspended by gentle rolling (or thorough mixing in the case of Vetsulin) prior to drawing up a dose from the vial. The process of de-precipitation in the SQ depot is relatively erratic and unpredictable for Lente, NPH and PZI which also contributes to their relatively variable time-action profile when compared to novel insulin formulations. In contrast to traditional formulations, synthetic insulin analogs are supplied as solutions (and not suspensions) and have a more predictable time-action profile, a result of their more precise dosing and more predictable absorption from the SQ depot.

Glargine is a recombinant human insulin analog (Asparagine at A21 is replaced by glycine and 2 arginines are added at B31 and B32). This synthetic molecule does not tent to hexamerize at apH of 4.0 but strongly crystalizes at neutral pH. Considered in people long-acting and “peakless”.

Detemir is a recombinant human insulin analog (B30 replaced by myristic acid – a 14-carbon fatty acid). Considered in people long-acting but not “peakless" and still as effective as insulin glargine as basal insulin (fewer side effects because more predictable). The fatty acid bound to insulin Levemir prevents formation of regular hexamers and allows hydrophobic interactions between detemir molecules and with albumin. This allows more predictable absorption from the SQ depot; furthermore, the buffering of detemir concentrations by albumin leads to minimal variability a better safety profile (fewer hypoglycemic events).

Subcutaneous administration of insulin detemir resembles the physiological effect of insulin more than other insulin formulation. Insulin secreted from the pancreas and into the portal system reaches the liver in high concentrations where it is degraded by the liver and eventually reaches peripheral target tissues in much lower concentration. By mimicking this differential effect insulin detemir causes less weight gain while maintaining the same degree of glycemic control. \(^1\)

Insulin concentration

Insulin is commercially available in 40, 100, and 500 U/ml concentration which are designated U-40, U-100, and U-500 respectively. One unit of insulin is approximately equivalent to 36 µg. Regardless of the concentration of insulin used for therapy, it is absolutely essential that owners purchase the appropriate syringe for the concentration of insulin. PZI insulin is manufactured as U-40 concentration only. U-100 insulin syringes are manufactured as low-dose (0.3 ml, 0.5 ml), and 1 ml capacities; U-40 syringes are only available as 1 ml capacity. All insulin syringes are packaged with a fine 26 or 27 gauge injection needle. In small dogs (<10 kg), the use of low-dose (0.3 or 0.5 ml) syringes is recommended. These syringes are designed to accurately draw up a small dosage of U-100 insulin without the need for dilution.
**Insulin Dosage**

Intermediate-acting insulin tends to be more bioavailable and therefore, more potent and is most appropriately dosed at the lower end of the range. Therefore, intermediate-acting insulin (NPH, Lente) is administered twice daily, at a starting dosage of 0.4-0.5 U/kg in dogs. Long acting insulins, such as PZI, are dosed once daily at 0.8-0.9U/kg.

**Insulin: Frequency of Dosing**

In order to mimic the physiologic release of insulin, ideally insulin should be given with each meal. However, the timing of the insulin injection has recently been called in question by several veterinary endocrinologists. Some authors argue that insulin should be injected one-two hours PRIOR to feeding to attenuate the post-prandial effect. The obvious concern with this timing of insulin is what to do if the animal will not eat. However, many suggest that this is a more “physiologic” way to administer insulin. In dogs, this author would be concerned about injecting insulin in this manner; however, in cats since they spend most of their time in a “post-prandial” state because of hepatic gluconeogenesis, I believe this type of insulin injection timing could work. The author recommends feeding the animal and injecting the insulin at the same time. If the animal does not eat, the insulin dosage can be reduced (usually by one-half) or skipped entirely and the animal evaluated by the veterinarian to determine the cause of the anorexia.

**Factors contributing to apparent variability in time-action profile:**

1. Injection site (vasculature, temperature)
2. Injection technique
3. Dose inaccuracies (dependent on syringe type, insulin formulation, and operator proficiency)
4. Insulin absorption (dependent on the above but also inherent to each insulin formulation)
5. External factors: Meal composition and size, physical and emotional stress and activity level

**Minimizing day-to-day-variability of insulin action:**

Consider use of synthetic formulations over traditional formulations. Synthetic analogs have more predictable time-action profiles because: 1. They are supplied as solutions (and not suspensions): increased accuracy in dosing. 2. They have more predictable absorption from SQ depot. 3. Detemir and degludec are buffered by albumin.

Synthetic analogs are U100 while traditional formulations that are used in veterinary medicine are supplied as U40. U40 syringes are generally more convenient and more accurate than U100 but at low doses they are not as precise. Injection pens increase precision and accuracy regardless of the insulin formulation being used.

**Adjustments to Insulin Dosage at Home**

In general, the client should be instructed to monitor the insulin effect and gross regulation of hyperglycemia by noting changes in appetite, attitude, body condition, polydipsia, polyuria and urine glucose and ketone levels. Consistently high urine glucose readings coupled with uncontrolled clinical signs, such as PU/PD, indicate that the insulin dose may be inadequate. Consistently negative readings on urine glucose may indicate that insulin dosages are either adequate or excessive. A serial glucose curve is required to differentiate between adequate insulin therapy and excessive therapy that could result in hypoglycemic shock.

**Insulin Injection Location and Technique**

The author recommends administration of insulin at sites along the lateral abdomen and thorax. Clipping or shaving a 2 x 2” square of haired skin on the lateral thorax or abdomen will assist the owner in accurate insulin placement. It often helps to reinforce verbal instructions with written
comments that the owner can refer to if they cannot recall the veterinarian’s exact instructions. The owner should be instructed to draw up the insulin using the appropriate insulin syringe. The insulin bottle is first removed from the refrigerator and warmed to room temperature by gentle rolling or agitation. The insulin bottle is turned upside down and the appropriate number of units drawn into the syringe.

A common mistake that owners may make is to measure the insulin dosage by the bottom rather than the top of the plunger. The owner should be observed drawing up saline to determine if accurate insulin dosage is being measured. After the insulin is drawn up in the syringe, the client should be instructed to inject the insulin by lifting the loose skin over the abdomen or thorax and inserting the needle into the skin at a 45 degree angle and parallel to the long axis of the skin fold. If the needle is inserted perpendicular to the skin fold, the needle may penetrate the other side of the skin fold and the insulin will be deposited on the hair.

Table 1: Insulin formulations in cats and dogs: species source and type, syringe type, and typical dosing frequency.

<table>
<thead>
<tr>
<th>Insulin</th>
<th>Species source/Type</th>
<th>Syringe</th>
<th>Dog</th>
<th>Cat</th>
</tr>
</thead>
<tbody>
<tr>
<td>Humulin N</td>
<td>Human/NPH</td>
<td>U-100</td>
<td>q 8-12h</td>
<td>q 8h</td>
</tr>
<tr>
<td>Vetsulin</td>
<td>Porcine/Lente</td>
<td>U-40</td>
<td>q 12-24h</td>
<td>q 8-12h</td>
</tr>
<tr>
<td>Prozinc</td>
<td>Human/PZI</td>
<td>U-40</td>
<td>q 12-24h</td>
<td>q 12-24h</td>
</tr>
<tr>
<td>Lantus</td>
<td>Human recombinant /Glargine</td>
<td>U-100</td>
<td>q 12h</td>
<td>q 12-24h</td>
</tr>
<tr>
<td>Levemir</td>
<td>Human recombinant /Detemir</td>
<td>U-100</td>
<td>q 12-24h Starting dose 0.1U/kg</td>
<td>q 12-24h</td>
</tr>
</tbody>
</table>

REFERENCES

Alternatives to Insulin Therapy for Diabetes Mellitus in Cats
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Diabetes mellitus (DM) is one of the most common endocrine diseases of cats. Islet amyloid polypeptide (IAPP) is involved in the pathogenesis of feline non–insulin-dependent diabetes mellitus (NIDDM) (O’Brien, 1993). In fact, recent publications have determined that IAPP concentrations increase in obese cats in direct correlation with increased BCS. Early diagnosis of type 2 diabetes mellitus is the key to successful therapy of DM using non-insuline alternatives. Cats with early type II diabetes are most likely to respond to any oral hypoglycemic agent. Therefore, emphasis should be placed on identifying cats early in the development of the disease.

Physiologic abnormalities associated with early Type 2 DM dictate the approach to therapy, with the primary abnormalities being increased hepatic glucose production, insulin receptor and post-receptor resistance or defects, and impaired insulin secretion. Treatment is aimed at attenuating the physiologic abnormalities by decreasing hepatic glucose output and glucose absorption from the intestine, increasing peripheral insulin sensitivity, and increasing insulin secretion from the pancreas. This discussion considers non insulin therapy for diabetes mellitus in cats using a physiologic approach.

THERAPEUTIC GOALS OF NON-INSULIN THERAPIES
Therapeutic goals in the treatment of cats with DM include amelioration of the metabolic abnormalities of diabetes and extension of life. However, early diagnosis does permit a greater choice of therapuetic options than insulin-dependent diabetes). Human type 2 diabetic patients can be divided into three therapeutic categories according to beta-cell function: (1) those with advanced disease who require exogenous insulin to control hyperglycemia , (2) those who require only dietary therapy because of sufficient islet reserve and insulin sensitivity to maintain relatively normal glucose levels, and (3) those with sufficient islet reserve and insulin sensitivity to respond to oral hypoglycemic agents or incretins. Human beings with type 2 diabetes are often classified according to their beta-cell function based on provocative testing. In cats, the differentiation of these categories is almost impossible prior to treatment; therefore, the clinician must rely on response to therapy as a guide to whether the cat has sufficient beta-cell function to be managed without insulin. Dietary therapy is the key to success with non-insulin alternatives, and the diet should be restricted in carbohydrates (<10% DM), and high in protein (50% DM) in order to allow the drugs to improve insulin sensitivity and insulin secretory capacity.

NON-INSULIN ALTERNATIVES: INDICATIONS
Oral hypoglycemic agents include the sulfonylureas (glipizide, glyburide, glimepiride), biguanides (metformin), thiazolidinediones (troglitazone), alpha-glucosidase inhibitors (acarbose), transition metals (chromium, vanadium), and more recently the incretins (exenatide) (Table 1). Most of these agents work either by increasing insulin secretion or by decreasing insulin resistance, glucose absorption, or hepatic glucose production. Indications for non-insulin therapy in cats include normal or increased body weight, lack of ketosis, probable type II diabetes with no underlying disease (pancreatitis, pancreatic tumor), and in some cases, the owner’s willingness to administer oral medications.

Drugs That Enhance Insulin Secretion
The mechanism of action of the sulfonylureas is to increase insulin secretion and reduce insulin resistance; however, some of these agents, such as glipizide, also cause an increase in hepatic glucose output. This leads to delayed hyperinsulinemia, weight gain, and atherosclerosis in humans undergoing sulfonylurea therapy (Kahn and Shechter, 1990). By provoking insulin release, sulfonylureas may promote the progression of pancreatic amyloidosis and hence increase the risk of long-term complications of diabetes. However, this has not been proven to be the case in either humans or cats with naturally occurring DM.

In cats, glipizide has been used successfully to treat patients with diabetes mellitus at a dosage of 2.5 to 5 mg b.i.d. (see CVT XII, p. 401, for a full discussion). An outline for monitoring and managing cats undergoing glipizide therapy is shown in Figure 2. Note that the evaluation of effectiveness should not be made until a cat has been on the drug for 16 weeks, as long as the cat is doing well. Side effects of oral hypoglycemic agents include severe hypoglycemia (rare in cats), cholestatic hepatitis, and vomiting. Gastrointestinal side effects, which occur in about 15% of cats treated with glipizide, resolve when the drug is administered with food (Ford, 1995). The author has noted that use of a lower dosage (2.5 mg/cat) of glipizide is associated with fewer side effects. Furthermore, glipizide does not have a taste so the author has had success adding it as a top dressing to canned food. The next generation sulfonylurea, glimepiride (Amaryl), has fewer side effects than glipizide and causes less fasting hyperinsulinemia.

The first long-term prospective study of glipizide in fifty cats studied for 50 weeks, showed 35-40% initial response rate (after 22 weeks); at the end of the study, 7 cats remained regulated on glipizide, 6 experienced hypoglycemia and went into remission so glipizide was discontinued, 6 showed initial response but no further improvement in glucose concentrations and 3 cats had recurrence of clinical signs that did not respond to further glipizide therapy. (Feldman 1997) In a more recent retrospective study of fifty cats on a low carbohydrate (< 10% on a dm basis) diet combined with either PZI insulin or glipizide, the response to glipizide was the same as with PZI insulin (about 70% response);(Moeller 2005). The difference in response between the two studies may have been the diet the cats were receiving. In the study by Feldman et al, cats were fed a dry or canned high fiber, high carbohydrate diet (15-40% on a DM basis) whereas the cats in the more recent study by Moeller et al were consuming a very low carbohydrate diet (<5%on a DM basis). As in humans, the use of an ultra-low carbohydrate, high protein canned diet is the key to success with oral hypoglycemic agents.

Drugs That Inhibit Hepatic Glucose Release
Metformin belongs to the biguanide group of oral hypoglycemic agents. These agents work by inhibiting hepatic glucose release and by improving peripheral insulin sensitivity (Kahn and Shechter, 1990). Biguanides may be used alone or in conjunction with other oral hypoglycemic agents to treat humans with type II diabetes mellitus (DeFronzo and Goodman, 1995). One advantage of the biguanides is that they do not promote insulin release; therefore, there is little potential for the development of hypoglycemia when metformin is used as a sole agent. A study of the pharmacokinetics of metformin in healthy cats revealed that 2 mg/kg twice daily was a safe dosage; however, because of renal excretion of the drug caution should be used in cats with chronic renal failure. (Michels 1999). Metformin has been studied in diabetic cats with poor results (Nelson 2004). Five newly diagnosed diabetic cats were given 50 mg/dog BID with only one cat responding to treatment; one cat died unexpectedly during the study and 3 others showed no response to the drug and required insulin therapy to control hyperglycemia and diabetic signs. (Nelson 2004) Contraindications for metformin therapy in humans, and presumably in cats, include concurrent renal disease, liver dysfunction, and cardiac disease.

Drugs That Impair Intestinal Glucose Absorption
The alpha-glucosidase inhibitors impair glucose absorption from the intestine by decreasing fiber digestion and hence glucose production from food sources. These drugs were initially developed as starch blockers to control obesity in humans and may be applied to the treatment of obese diabetic cats. Acarbose is used as initial therapy in obese prediabetic patients suffering from insulin resistance or as adjunct therapy with sulfonylureas or biguanides to enhance the hypoglycemic effect in patients with diabetes mellitus. Side effects include flatulence, loose stool, and diarrhea at high dosages. One advantage of these medications is that they are not absorbed systemically and may be used in conjunction with other oral hypoglycemic agents. They are not indicated in patients of low or normal body weight because of their effects on nutrition.

The author has had limited experience with acarbose at a dosage of one-quarter to one-half tablet per cat with meals; side effects are more common at the high end of the dose and include semi-formed stool or in some cases overt diarrhea. (Mazzaferro 2003) The glucose-lowering effect of acarbose is mild, with blood glucose concentrations decreasing only into the 250 to 350 mg/dl range.

**Drugs That Enhance Peripheral Insulin Sensitivity**

A new class of oral hypoglycemic agents that is receiving attention in medicine consists of thiazolidinedione compounds (Saltiel and Olefsky, 1996). These drugs facilitate the action of insulin in skeletal muscle and adipose tissue. Although the exact mechanism of action is unknown, thiazolidinediones facilitate insulin-dependent glucose disposal and inhibit hepatic glucose output through attenuation of gluconeogenesis and glycogenolysis. In addition, the thiazolidinediones have been shown to have beneficial effects on the lipid disturbances associated with NIDDM. Troglitazone is the thiazolidinedione compound that has progressed to clinical development for use in humans with NIDDM. In fact, some authors have suggested that the use of this drug early in the course of NIDDM may slow the progression of NIDDM (Saltiel and Olefsky, 1996). Side effects of troglitazone were minimal and included transient mild decreases in white blood cells, platelets, and hemoglobin (Berkowitz et al, 1996). No hypoglycemic reactions were described. The only study of troglitazone in cats was a pharmacokinetic study determining a dosage of 20-40 mg/kg BID in normal cats. (Michels 2000)

Compounds that contain the metals vanadium and chromium have been shown to have extensive insulin-like properties when administered in the drinking water of mice suffering from experimentally induced diabetes mellitus (type I and type II). A U.S. Department of Agriculture study of 180 patients with early type 2 DM found that administration of 1,000 μg of chromium picolinate once daily resulted in amelioration of the classic signs of diabetes and normalization of blood levels of hemoglobin A1c. In type I diabetes, vanadium decreases but does not eliminate the need for insulin (Cam et al, 1993). In type II diabetes, constant suppression of blood glucose is achieved with vanadium (Brichard et al, 1989). Studies have documented restoration of secretion of insulin in patients with type II diabetes treated with vanadium, suggesting reversal of "glucose toxicity" and disease progression. Oral vanadate causes marked and sustained improvement in glucose homeostasis in NIDDM by exerting an insulin-like effect on peripheral tissues; furthermore, vanadium prevents the exhaustion of insulin stores in the pancreas. Vanadium compounds are currently being investigated as insulin-mimetic agents in humans, thus their promise as a future therapy for type II diabetes is being documented.

Despite the efficacy of oral vanadium and chromium compounds in lowering blood glucose levels, the exact mechanism of action is unknown. Current research indicates that vanadium bypasses the insulin receptor and activates glucose metabolism within the cell (Shechter, 1990). By acting
at a post-receptor site, vanadium provides ideal treatment for type II diabetes mellitus that results from a lack of insulin receptor responsiveness. Unlike insulin, vanadium and chromium do not lower blood glucose concentrations in normal animals.

Studies in our laboratory indicate that low doses (0.2 mg/kg/day) of oral vanadium will decrease blood glucose and serum fructosamine concentrations and alleviate the signs of diabetes (polydipsia, polyuria) in cats with early type II diabetes mellitus. Initial side effects include anorexia and vomiting; however, most cats showed no ill effects when vanadium therapy was reinstalled. Long-term toxicity of vanadium is related to accumulation of the metal in organs such as bone, kidney, liver, adipose tissue, and pancreas. We have observed acute renal failure (blood urea nitrogen >100 mg/dl, creatinine >12 mg/dl) in one patient after 1 year of vanadium therapy; however, the cat recovered renal function (blood urea nitrogen <40 mg/dl, creatinine <3 mg/dl) after discontinuation of the metal. Humans ingest vanadium as a solution in juice and chromium as a tablet; however, cats ingest vanadium and chromium more readily in food than in water.

INCRETINS

In humans and animals, the incretin effect refers to the phenomenon of a greater insulin response to oral than intravenous glucose. Incretin analogues, such as exenatide (originally derived from the salivary secretions of the Gila monster (Heloderma suspectum), have been used in human diabetic patients to improve the post-prandial first-phase of insulin secretion which is impaired in early type 2 diabetes mellitus. Recent studies in the cat show that exanitide potentiates insulin secretion in healthy cats; however. (Gilor 2011) Ongoing studies are examining the response of diabetic cats to exenatide as an adjunct therapy to insulin. (Brunker 2011)

The peptide exendin-4 was first isolated from the poisonous venom of the Gila Monster. Exenatide has been shown to be as effective as insulin glargine in the treatment of DM but with less side effects (e.g. hypoglycemia and weight gain).14 In a 2-year follow-up of patients receiving exenatide, patients achieved sustained and significant reductions in glycosylated hemoglobin, accompanied by significant weight loss (instead of weight gain commonly seen in diabetics receiving insulin) and improvement in serum liver enzyme activity and blood pressure. Most importantly, treatment with exenatide improved beta cell function as measured by homeostasis model assessment of beta cell function (HOMA-B).15 Exenatide is commercially available in the USA under the trade name Byetta®.

In healthy cats, exenatide was quickly absorbed after a SQ injection and caused glucose-dependent insulin secretion. Increased glucose tolerance, however, was not observed after a single SQ injection.19,20 At a dose of 1.0 mcg/kg SQ (about 10 times the dose that is used in diabetic people), exenatide injection did not cause any side effects in healthy cats, except for hypoglycemia in 1 out of 9 cats.19 Exenatide has led to significant weight loss in healthy cats of 7.0 ± 4.9% (from 4.78 ± 1.5 kg to 4.48 ± 1.5 kg) with a dose of 1.0 mcg/kg SQ BID for 28 days.20

A long-acting sustained-release formulation of exenatide (Bydureon®) has recently been approved by the FDA as the first once-weekly subcutaneous injection for treatment of type 2 diabetes people. It consists of injectable microspheres of exenatide and poly(D,L-lactic-co-glycolic acid), a common biodegradable medical polymer with established use in absorbable sutures and extended-release pharmaceuticals, that allows gradual drug delivery at controlled
rates. In people, Exenatide plasma concentrations are sustained at an effective concentration (50 pg/mL) for longer than 60 days after a single injection at doses of 5mg, 7mg or 10mg. It has been shown in a recent clinical study to be more effective than once-a-day insulin glargine in achieving glycemic control with decreased risk of hypoglycemia and with reduction (instead of gain) in body weight. This extended release formulation was also more effective than regular exenatide (Byetta) in achieving glycemic control with no increased risk of hypoglycemia, decreased side effects like nausea, and with similar reductions in body weight.

**INSULIN AND ORAL HYPOGLYCEMICS: DO THEY MIX?**

A change from insulin to oral hypoglycemic agents or vice versa may be necessary in some diabetic cats. If a cat is particularly sensitive to insulin (becomes hypoglycemic on less than 1 U) but is unable to remain in remission on diet alone, a change to an oral hypoglycemic agent, such as glipizide, may be considered. Conversely, if a cat is treated with oral hypoglycemic agents and ketosis develops, the cat should be switched to insulin therapy. Agents that impair glucose absorption from the intestine (acarbose) or increase insulin sensitivity (vanadium, metformin, troglitazone) may be combined with insulin to improve glucose control. In human patients, acarbose and metformin are commonly used in conjunction with insulin and other oral hypoglycemic agents (sulfonylureas) that cause insulin release. Caution should be used in combining any oral hypoglycemic agent with insulin as hypoglycemic reactions may occur.

**MONITORING HYPOGLYCEMIC AGENT THERAPY IN CATS**

It appears that methods of assessing long-term glycemic control are better indicators of response to therapy with oral hypoglycemics than are spot glucose determinations or blood glucose curves. In humans, the response to treatment is measured by a decrease in hemoglobin A1C with most oral hypoglycemic agents yielding a modest decrease of about 1-2%. (Kimmel 2005) The author prefers to monitor the resolution of clinical signs of diabetes mellitus, such as polydipsia and polyuria, and serum fructosamine concentrations in cats undergoing oral hypoglycemic therapy. Serum fructosamine concentrations lower than 400-450 micromol/L are consistent with moderate to good long-term control of hyperglycemia. Body weight should increase or remain stable, appetite should remain good and polydipsia/polyuria (as blood glucose drops below the renal threshold for glucose) should resolve with effective oral hypoglycemic therapy.
REFERENCES AND SUGGESTED READING


Table 1.
Oral Hypoglycemic Drugs Used in the Treatment of Type 2 Diabetes Mellitus in Cats

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Frequency</th>
<th>Side Effects</th>
<th>Mechanism of Action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exenatide (Byetta)</td>
<td>1 μg /kg</td>
<td>bid SQ</td>
<td>Weight loss</td>
<td>Improves beta cell function and post-prandial insulin secretion.</td>
</tr>
<tr>
<td>Glipizide (Glucotrol)</td>
<td>2.5-5 mg/cat</td>
<td>bid-tid, PO</td>
<td>Hepatotoxicity, hypoglycemia, vomiting</td>
<td>Increases insulin secretion and sensitivity</td>
</tr>
<tr>
<td>Glimepiride (Amaryl)</td>
<td>1-2 mg/cat</td>
<td>q24hr PO</td>
<td>Same as above but lower incidence</td>
<td>As above</td>
</tr>
<tr>
<td>Metformin (Glucophage)</td>
<td>2 mg/kg</td>
<td>bid</td>
<td>Anorexia, vomiting</td>
<td>Inhibits hepatic glucose production</td>
</tr>
<tr>
<td>Precose (acarbose)</td>
<td>12.5 mg</td>
<td>bid-tid with meals</td>
<td>Flatulence, soft stool</td>
<td>Alpha1-glucosidase inhibitor, impairs glucose absorption from gut</td>
</tr>
<tr>
<td>Troglitazone</td>
<td>20-40 mg/kg</td>
<td>bid-q24hr</td>
<td>Mild decreases in WBC, platelet, and Hb counts</td>
<td>Increases insulin receptor sensitivity</td>
</tr>
<tr>
<td>Chromium</td>
<td>200 μg</td>
<td>q24hr</td>
<td>Anorexia at high dosages</td>
<td>Increases insulin receptor sensitivity</td>
</tr>
<tr>
<td>Vanadium</td>
<td>0.2 mg/kg/day</td>
<td>q24hr in canned food</td>
<td>Anorexia, vomiting</td>
<td>Increases insulin receptor sensitivity</td>
</tr>
</tbody>
</table>
Figure 1. Possible clinical consequences of glipizide treatment. (From Ford SL: NIDDM in the cat: Treatment with the oral hypoglycemic medication glipizide. Vet Clin North Am Small Anim Pract 25[3]:611, 1995, with permission.)
Diabetic Ketoacidosis and Hyperosmolar Nonketotic Diabetes Mellitus

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Abstract

Diabetic ketoacidosis and hyperosmolar nonketotic diabetes mellitus are life-threatening metabolic emergencies in dogs and cats with poorly controlled or undiagnosed diabetes mellitus or diabetic patients with other concurrent conditions, such as pancreatitis. Acute management of the ketoacidotic patient including fluid therapy, insulin therapy, and electrolyte supplementation to reverse metabolic acidosis is discussed in detail in this article. Treatment of hyperosmolar nonketotic diabetes mellitus, a less common condition, is similar but on a much slower time scale, and the prognosis is poor.

Key Facts

• Diabetic ketoacidosis (DKA) is the culmination of diabetes mellitus that results in unrestrained ketone body formation in the liver, metabolic acidosis, severe dehydration, shock, and possibly death.

• In hyperosmolar nonketotic diabetic mellitus, some beta cells are still functioning and producing insulin, preventing the formation of ketones. It is defined by extreme hyperglycemia, hyperosmolality, severe dehydration, central nervous system depression, no ketone body formation, and absent or mild metabolic acidosis.

• The most important part of urinalysis is measurement of glucose and ketones. A strongly positive glucose confirms diabetes mellitus and a positive result for ketones confirms DKA. A negative ketone result, however, does not definitively rule out ketosis.

Treatment of diabetic ketoacidosis includes the following steps in order of importance:

1) fluid therapy using 0.9% saline initially, followed by 2.5% or 5% dextrose as serum glucose falls;
2) insulin therapy (low-dose intramuscular or intravenous);
3) electrolyte supplementation (potassium, phosphorus, magnesium); and
4) reversal of metabolic acidosis.

In HONKDM, fluid therapy should be judicious and designed to slowly replace maintenance and dehydration deficits Correct fluid and electrolyte imbalances very slowly. The goal should be to correct dehydration over 36 hours. Hyperosmolar nonketotic diabetic mellitus requires similar treatment to DKA but on a much slower time scale. Insulin therapy may be delayed for 24 hrs to allow slow rehydration of cerebral tissues.

The prognosis for diabetic ketoacidosis in dogs is fair to good as long as the underlying disorder is treatable (eg, urinary tract infection, pneumonia). With acute pancreatitis, the prognosis depends on the severity of the pancreatic disease in both dogs and cats. Cats with hyperosmolar nonketotic or mixed ketotic syndrome have a very poor prognosis.
Diabetic ketoacidosis (DKA) is the culmination of diabetes mellitus that results in uncontrolled ketone body formation in the liver, metabolic acidosis, severe dehydration, shock, and possibly death. Hepatic lipid metabolism becomes deranged with insulin deficiency and nonesterified fatty acids are converted to acetyl-co-enzyme A (acetyl-CoA) rather than being incorporated into triglycerides. Acetyl-CoA accumulates in the liver and is converted into acetoacetate-CoA and then ultimately to ketones including acetoacetic acid, beta-hydroxybutyrate (primary ketone in dogs and cats), and acetone. As insulin deficiency culminates in DKA, accumulation of ketones and lactic acid in the blood and loss of electrolytes and water in the urine results in profound dehydration, hypovolemia, metabolic acidosis, and shock. Ketonuria and osmotic diuresis caused by glycosuria causes sodium and potassium loss in the urine exacerbating hypovolemia and dehydration. Nausea, anorexia, and vomiting, caused by stimulation of the chemoreceptor trigger zone via ketonemia and hyperglycemia, contribute to the dehydration caused by osmotic diuresis. Dehydration leads to further accumulation of glucose and ketones in the blood. Stress hormones such as cortisol and epinephrine contribute to the hyperglycemia in a vicious cycle. Eventually severe dehydration may result in hyperviscosity, thrombembolism, severe metabolic acidosis, renal failure, and finally death.

Hyperosmolar nonketotic diabetic mellitus (HONKDM) is a less common complication of DM. It has a similar pathogenesis to DKA with a relative deficiency in insulin. For the hyperosmolar syndrome to develop, some functioning beta cells must still be producing insulin. The existence of some insulin prevents the formation of ketones. Excessive dehydration leads to a decrease in glomerular filtration rate (GFR), which leads to a decrease in glucose excretion. Hyperglycemia worsens and causes an increase in plasma osmolality. Increased plasma osmolality draws water out of cerebral neurons resulting in obtundation and decreased water intake, which ends in a vicious cycle.

Historical Findings

Most dogs and cats with DKA present with a previous history of uncomplicated diabetes including polyuria and polydipsia and dramatic and rapid weight loss in the face of a good or even ravenous appetite (Figure 2). Additional more recent historical findings include anorexia, weakness, depression, vomiting, and diarrhea. Occasionally owners fail to notice the significance of the classical signs of diabetes mellitus and the animals are presented solely with an acute history of DKA. It is also possible for DKA to develop in previously well-controlled, treated diabetic patients. Patients with hyperosmolar nonketotic diabetic mellitus typically are quite depressed. They may be comatose upon presentation. The history of weakness may be for several weeks prior to presentation.

Physical Examination Findings

The most common physical examination findings in DKA are lethargy and depression, dehydration, unkempt haircoat, and muscle wasting. Hepatomegaly is common in both diabetic cats and dogs. Cataracts are commonly observed in diabetic dogs. A plantigrade rear limb stance resulting from diabetic neuropathy is often observed in diabetic cats. Other findings include tachypnea, dehydration, weakness, vomiting, and occasionally, a strong acetone odor on the breath. Cats can present recumbent or comatose and this may be a manifestation of mixed ketotic hyperosmolar syndrome (Figure 3). Icterus can develop as a result of the complicating factors of hemolysis, hepatic lipidosis, or acute pancreatitis.

Laboratory Findings
The average blood glucose in patients with DKA is 25 mmol/L. Values can range from 10 to more than 50 mmol/L, but the latter is more characteristic of hyperosmolar coma (1). Although portable glucose meters are commonly used to monitor glucose concentrations in DKA, caution is advised in relying on these monitors for baseline glucose concentrations because of inaccuracies in the face of severe hyperglycemia. All DKA patients have a relative or absolute deficiency of insulin and excessive hepatic production of glucose resulting in hyperglycemia. Hyperglycemia is further exacerbated by dehydration and the corresponding reduction in glomerular filtration rate (GFR) and these factors are important determinants of its severity. This is supported by the findings that glucose concentrations exceed 25 mmol/L only when dehydration is severe enough to reduce GFR and thus the ability of the kidneys to excrete glucose, and that fluid administration alone can significantly reduce blood glucose concentrations (2).

Osmolality is usually mildly to markedly increased in the DKA patient as a result of hyperglycemia, but may not be detected, in part because of concurrent hyponatremia (3,4). Sodium and to a lesser extent, potassium, glucose, and urea concentrations are the determinants of the calculated serum osmolality. Reference values for serum osmolality in dogs and cats are approximately 290 to 310 mOsm/kg. Hyperosmolality is generally mild enough to resolve with intravenous fluid and insulin therapies.

Nonketotic hyperosmolar diabetes is defined by extreme hyperglycemia (>30 mmol/L, 600 mg/dL), hyperosmolality (>350 mOsm/L), severe dehydration, central nervous system (CNS) depression, no ketone body formation, and absent or mild metabolic acidosis (5). Affected patients are more likely to have underlying renal or cardiovascular disease and are more likely to be non-insulin-dependent (4). Although this specific syndrome, as defined in humans, is uncommonly encountered in veterinary medicine, it is not uncommon to have ketotic or nonketotic diabetic cats with significant hyperosmolality and CNS alterations (6).

Most patients suffering from DKA have a total body potassium deficit due to urinary (osmotic diuresis), anorexia, and gastrointestinal (vomiting and anorexia) losses. The metabolic acidosis, relative or absolute insulin deficiency, and serum hypertonicity combine to cause a shift of potassium from the intracellular to the extracellular compartment. This is capable of masking the severity of total body hypokalemia when plasma concentrations are measured. Insulin therapy, as well as correction of the acid-base disturbance with fluids and/or bicarbonate will drive serum potassium intracellularly, potentially causing marked circulating hypokalemia (7). Polyuric patients are predisposed to severe hypokalemia, while oliguric or anuric patients are predisposed to severe hyperkalemia.

In general, DKA causes significant total body sodium deficits. Excessive urinary loss of sodium results from the osmotic diuresis induced by high glucose and ketone concentrations and the lack of insulin, which usually aids in reabsorption of sodium from the distal nephron. Hyperglucagonemia, vomiting, and diarrhea also contribute to the total body sodium loss. Hyperosmolality may contribute to a low sodium concentration because as osmolality increases, water is drawn from the interstitium into the vascular space, thus diluting plasma sodium and chloride.

Phosphorus is the major intracellular anion and is important for energy production and for maintenance of cell membranes. Concentrations are regulated by dietary intake, renal elimination, factors promoting its movement into and out of cells, and vitamin D and parathyroid interactions. In DKA, circulating concentrations are usually within reference range or increased initially because of dehydration and/or renal disease. Phosphorus may also be low at presentation because of urinary loss due to osmotic diuresis (8). As long as renal function is not compromised, a significant decrease in phosphorus should be anticipated with therapy. Following insulin
administration, phosphorus shifts to the intracellular compartment with glucose. Clinical signs of hypophosphatemia such as hemolytic anemia (also seen with Heinz bodies in DKA), lethargy, depression, and diarrhea may develop once concentrations reach 0.32 mmol/L. Oversupplementation of phosphorus should be avoided as hypocalcemia or metastatic calcification may result (9).

Magnesium (total serum) is not usually measured routinely, but concentrations may be abnormal in DKA. A recent study in cats demonstrated high total serum magnesium concentrations at presentation in patients with DKA; however, after 48 hours of therapy, total serum magnesium concentrations were significantly decreased (10). Magnesium deficiency may be caused by poor oral intake, decreased intestinal absorption, increased renal loss, or changes in distribution as it is the second most abundant intracellular cation (11). Clinical signs of hypomagnesemia include neuromuscular weakness and cardiac arrhythmias, signs that can be seen with other electrolyte alterations. Hypomagnesemia can also cause decreases in other electrolytes such as potassium and calcium. Correction of deficits may resolve electrolyte disturbances and may improve clinical outcome in the severely deficient patient (Table 1).

Liver enzyme elevations are common in diabetes mellitus. Further increases potentially occur in DKA. Alanine aminotransferase and aspartate aminotransferase are most commonly affected and these increase secondary to hypovolemia and poor hepatic blood flow, and subsequent hepatocellular damage (3). Further increases in serum alkaline phosphatase concentration may occur if pancreatitis and secondary cholestasis ensue. Cholesterol and triglycerides may be elevated secondary to derangements of lipid metabolism due to decreased insulin.

Metabolic acidosis is one of the most prominent features of DKA. As ketone bodies accumulate in the blood and overwhelm the body’s buffering capabilities, there is an increase in hydrogen ions and a decrease in bicarbonate. As dehydration worsens, blood flow to peripheral tissues decreases and the resulting lactic acidosis may contribute to the acid–base derangement. Acidosis can be manifested as lethargy, vomiting, hyperventilation, decreased myocardial contractility, peripheral vasodilation, stupor, and coma. Initiation of insulin therapy to stop ketogenesis and fluid therapy to correct dehydration will help improve the metabolic acidosis in most patients. Bicarbonate supplementation should be pursued with caution and is generally not recommended unless the patient’s blood pH is less than 7.1 or the serum bicarbonate is less than 12 mmol/L (Table 1).

In DKA, ketones become unmeasured anions as they dissociate from ketoacids (12). If, however, significant dehydration is present secondary to the osmotic diuresis and vomiting, lactic acidosis secondary to tissue hypoxia may contribute to the unmeasured anions, thus increasing the anion gap. Anion gap may be normal or elevated. An elevated value further characterizes the metabolic acidosis caused by DKA. The anion gap is a representation of the circulating anions not routinely measured on biochemical analyses. The normal anion gap ranges from 10 to 20 and is calculated by the following equation:

\[
\text{Osmolality (mOsm)} = 2(\text{Na} + \text{K mEq/L}) + (\text{glucose mmol/L}) + (\text{BUN mmol/L})
\]

Circulating urea and creatinine concentrations may be within reference range or high. These values are high in most patients as a reflection of severe dehydration, but renal insufficiency or failure is also a possible cause for the elevation. Elevations of urea and creatinine must be evaluated in light of the urine specific gravity. A low urine specific gravity at presentation does not always guarantee a diagnosis of renal insufficiency or failure, as osmotic diuresis and chronic hypokalemia can contribute to low specific gravities in diabetic patients. Therefore, re-evaluation of urea, creatinine, and urine specific gravity must be done after treatment of the crisis. If urea and creatinine are initially elevated and remain static or increase with appropriate therapy, concurrent renal disease is strongly suspected.
The most important part of urinalysis is measurement of glucose and ketones. A strongly positive glucose confirms diabetes mellitus and a positive result for ketones confirms DKA. A negative ketone result, however, does not definitively rule out ketosis. The nitroprusside reagent used in urine sticks detects only acetoacetate and acetone. It is not as sensitive for beta-hydroxybutyrate, the most prevalent ketone body, and therefore may be negative in the face of ketosis. A recent study reported that beta-hydroxybutyrate concentrations above 1.9 mmol/L were the most sensitive indicator of DKA and that values above 4.8 mmol/L were highly specific for its diagnosis (13). Using a cut-off value of 3.8 mmol/L was associated with the best combination of specificity (95%) and sensitivity (72%) for DKA.

The presence of pyuria and hematuria on urinalysis, along with confirmation by examination of urine sediment, supports the presence of a urinary tract infection. Urine culture should be performed, however, regardless of urine sediment activity. The hemogram may be normal at presentation, but usually reveals a leucocytosis with a mature neutrophilia (common in cats), or a stress leukogram. There may be a regenerative or degenerative left shift suggestive of a severe inflammatory and/or infectious process. The red blood cell count and hematocrit may be elevated due to dehydration. Heinz bodies, with or without anemia, may be noted in cats, as feline hemoglobin is uniquely susceptible to oxidative damage (14).

**Treatment**

Treatment of diabetic ketoacidosis is outlined in Table 1 and includes the following steps in order of importance: 1) fluid therapy using 0.9% saline initially, followed by 2.5% or 5% dextrose as serum glucose falls; 2) insulin therapy (low-dose intramuscular or intravenous); 3) electrolyte supplementation (potassium, phosphorus, magnesium); and 4) reversal of metabolic acidosis.

**Fluid Therapy**

Fluid therapy should consist of 0.9% NaCl supplemented with potassium when insulin therapy is initiated; however, hypernatremic patients may be rehydrated with lactated Ringer’s solution to limit sodium load. Placement of a large central venous catheter is preferred for intravenous access because central venous pressure (CVP) may be monitored thereby providing the means to avoid overhydration. In addition, the need for repeated venipuncture necessary for frequent monitoring of glucose, electrolytes, and blood gases is eliminated. Rapid initiation of fluid therapy is key for successful treatment of the DKA patient. Fluid rates vary depending on degree of dehydration, maintenance requirements, continuing losses such as vomiting and diarrhea, and presence of diseases such as congestive heart failure and renal disease. Extreme caution should be exercised when considering initiating fluid therapy with a hypotonic solution as this increases the risk of cerebral edema. Fluids containing dextrose may be required to maintain blood glucose concentrations as insulin treatment for the DKA is continued.

**Insulin Therapy**

In dogs, insulin therapy should be initiated using either intravenous insulin or low-dose intramuscular methods. Intravenous constant rate infusion (CRI) of regular insulin therapy is accomplished by placement of two catheters: a peripheral catheter for the insulin infusion, and a central catheter for sampling blood and administration of drugs and other fluids. A dosage of 2.2 U/kg for dogs or 1.1 U/kg for cats of regular (neutral, soluble) insulin is diluted in 250 mL of saline. Approximately 50 mL of fluid and insulin are allowed to run through the intravenous drip set and is discarded because insulin binds to the plastic tubing. The species of regular insulin (beef, pork, or human) does not affect response; however, the type of insulin given is very important. Regular or synthetic short-acting insulin must be used; lente, glargine, isophane, or protamine zinc insulins should never be given intravenously. Using intravenous insulin administration, blood glucose decreases to below 15 mmol/L by approximately 10 and 16 hours in dogs and cats, respectively. Once this has been achieved, the animal is maintained on subcutaneous (SC) regular insulin.
(0.1–0.4 U/kg SC every 4–6 hours) until it starts to eat and/or the ketosis has resolved. Often, the transition from hospital to home maintenance therapy can be made by using a low dose (1–2 U) of regular insulin combined with the intermediate or long-acting maintenance insulin at the recommended dosages.

**Electrolyte and Acid–Base Therapy**

Potassium should be supplemented as soon as insulin therapy is initiated. While serum potassium may be normal or elevated in DKA, the animal actually suffers from total body depletion of potassium. Correction of the metabolic acidosis tends to drive potassium intracellularly in exchange for hydrogen ions. Insulin facilitates this exchange and the net effect is a dramatic decrease in serum potassium which must be attenuated with appropriate potassium supplementation in fluids. Refractory hypokalemia may be complicated by hypomagnesemia. Supplementation of magnesium along with potassium as outlined in Table 1 may be indicated in cats or dogs with hypokalemia that is unresponsive to potassium chloride supplementation.

Serum and tissue phosphorus may also be depleted during a ketoacidotic crisis and some of the potassium supplementation should consist of potassium phosphate (one third of the potassium dose as potassium phosphate), particularly in small dogs and cats who are most susceptible to hemolysis caused by hypophosphatemia. Caution should be used as oversupplementation of phosphorous can result in metastatic calcification and hypocalcemia. Bicarbonate therapy may be necessary in some patients with blood pH less than 7.1 or if serum HCO₃ is less than 12 mmol/L. Caution is recommended as metabolic alkalosis may be difficult to reverse.

Hyperosmolar nonketotic diabetic mellitus requires similar treatment to DKA but on a much slower time scale. Correct fluid and electrolyte imbalances very slowly. Fluid therapy is typically either 0.9% NaCl or 0.45% NaCl which replaces Na⁺ for glucose in the extracellular fluid (ECF) spaces. Caution must be exercised to not decrease osmolality too quickly: decrease osmolality by ½ to 1 osmol/hour. The goal should be to correct dehydration over 36 hours. While patients may still be hypokalemic, this abnormality does not tend to be as severe as in DKA because they do not have as great of an osmotic diuresis. Patients with hyperosmolar diabetes may be hyperphosphatemic depending on the azotemia. Hypophosphatemia is less of a concern in hyperosmolar nonketotic diabetic mellitus. Insulin therapy is the same as for DKA but should be monitored very closely! Monitor urine output, electrolytes, and renal values one to three times daily.

**Monitoring Response to Treatment**

Fluid therapy is one of the cornerstones of treatment of the diabetic patient but overhydration is a concern, especially in cats or if renal or cardiac disease is present. With a central venous catheter in place, CVP can be monitored intermittently. Oscillometric or Doppler measurements can be used to monitor systemic blood pressure. Monitoring lead II electrocardiograms (ECGs) can also be helpful not only if cardiac disease is present, but in alerting the clinician that serious electrolyte abnormalities may be developing, warranting more frequent electrolyte analyses and alteration of electrolyte replacement therapy.

Hypokalemia may cause supraventricular and ventricular arrhythmias such as premature atrial and ventricular contractions, sinus bradycardia, paroxysmal atrial or junctional tachycardia, atrioventricular block, ventricular tachycardia, and ventricular fibrillation. Other ECG changes include ST segment depression, QT prolongation, and decreased amplitude and biphasic T waves (15). Electrocardiographic signs of hyperkalemia include decreased P wave amplitude,
prolonged PR and QRS intervals, decreased R wave amplitude, ST segment depression and increased amplitude and sharply pointed T waves, bradycardia, atrial standstill, and ventricular fibrillation.

Blood glucose should be checked every one to two hours during initial therapy, especially if administering insulin via CRI or hourly intramuscular (IM) injections because hypoglycemia is a common and avoidable complication of therapy. Use of glucometers, which require only a drop of blood, allows measurement of glucose without induction of anemia. Electrolyte values can change rapidly with initiation of therapy and thus should be monitored every 4 hours. For the first 24 to 48 hours of therapy, blood glucose concentrations should not decline below 12 mmol/L as lower values may predispose the patient to development of cerebral edema. After the first day or two, if the patient is responding to therapy, or if giving injections only every 4 to 6 hours, the frequency of blood glucose determinations can be reduced (ie, every 4 to 6 hours). More objective measurements of hydration status include direct or indirect blood pressure measurements, as well as measuring CVP, urine output and specific gravity, body weight, serum osmolality, PCV, and total solids. Assessing the PCV and plasma for evidence of hemolysis in the hypophosphatemic patient is important to evaluate for hemolytic anemia.

Initially monitoring urine output via an indwelling urinary catheter connected to a closed system is also optimal to ensure the patient is not oliguric or anuric; this is especially important for the hyperosmolar patient as severe hyperglycemia (> 30 mmol/L) is unlikely to occur without significant renal impairment or severe dehydration and subsequent poor renal perfusion. A minimum of 1.0 to 2.0 mL urine per kilogram of body weight per hour should be produced. If output is less than optimal, check patency of the catheter, adequacy of fluid administration (CVP, arterial blood pressure, subjective signs, PCV/total solids, urine specific gravity), and adjust therapy as needed.

Serum electrolytes and blood gas analyses should be performed four to six times daily during the first 24 to 48 hours when the patient is most critical. Electrolyte composition of the fluids may need to be altered several times daily depending on results of electrolyte analyses. Performing a urine dipstick test daily is also important to assess degree of glucosuria and ketonuria. An increase in dipstick ketones may actually be indicative of successful therapy as the dipstick measures acetoacetic acid, the metabolite of the most prevalent ketone body, beta-hydroxybutyric acid.

Prognosis

The prognosis for diabetic ketoacidosis in dogs is fair to good as long as the underlying disorder is treatable (eg, urinary tract infection, pneumonia). With acute pancreatitis, the prognosis depends on the severity of the pancreatic disease in both dogs and cats. Cats with hyperosmolar nonketotic or mixed ketotic syndrome have a very poor prognosis.

References


**Table 1: Stepwise Treatment of Diabetic Ketoacidosis (*)**

**STEP ONE: FLUIDS**

a. Place intravenous catheter, preferably central venous

b. Fluid rate: Estimate dehydration deficit (%) x BW (kg) x 1000 mL = no.of mL to rehydrate

Estimate maintenance needs: 2.5 mL/kg/hr x no. of hours required to rehydrate (24 hours)

Estimate losses (vomiting, diarrhea):

Dehydration deficit + maintenance + losses = no. of mL of fluid/24 hours = hourly fluid rate

c. Fluid composition

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Fluids</th>
<th>Rate</th>
<th>Route</th>
<th>Monitor</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;15 mmol/L</td>
<td>0.9% NaCl</td>
<td>up to 90 mL/kg/hr to rehydrate</td>
<td>intravenous</td>
<td>osmolality</td>
<td>q 4 hr</td>
</tr>
<tr>
<td>12–15</td>
<td>0.45% NaCl</td>
<td>same</td>
<td>intravenous</td>
<td>CVP, urine output</td>
<td>q 2 hr</td>
</tr>
<tr>
<td>6–8</td>
<td>plus 2.5% dextrose</td>
<td>(see above)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>same</td>
<td>see above</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>plus 5% dextrose</td>
<td>see above</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**STEP TWO: INSULIN**

Intravenous (Regular only), mixed in 250 mL NaCl 0.9%, discard 50 mL through IV tubing

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Rate</th>
<th>Route</th>
<th>Dose</th>
<th>Monitor</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;15 mmol/L</td>
<td>10 mL/hr</td>
<td>IV</td>
<td>1.1 U/kg C</td>
<td>BG</td>
<td>q 1–2 hrs</td>
</tr>
<tr>
<td>12–15</td>
<td>7 mL/hr</td>
<td>IV</td>
<td>2.2 U/kg D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6–8</td>
<td>5 mL/hr</td>
<td>IV</td>
<td>5 mL/hr</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;6</td>
<td>Stop IV, SC</td>
<td>0.1–0.4 U/kg</td>
<td></td>
<td>q 2 hrs</td>
<td></td>
</tr>
</tbody>
</table>

Intramuscular (Regular only)

<table>
<thead>
<tr>
<th>Blood glucose</th>
<th>Rate</th>
<th>Route</th>
<th>Dose</th>
<th>Monitor</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;15 mmol/L</td>
<td>q 1 hr</td>
<td>IM</td>
<td>0.1 U/kg</td>
<td></td>
<td>Hourly</td>
</tr>
<tr>
<td>&lt;15</td>
<td>q 4–6 hr</td>
<td>IM</td>
<td>0.1 U/kg</td>
<td></td>
<td>q 4–6 hr</td>
</tr>
<tr>
<td>q 6–8 hr</td>
<td>SC</td>
<td>0.1–0.4 U/kg</td>
<td></td>
<td>q 6–8 hr</td>
<td></td>
</tr>
</tbody>
</table>

**STEP THREE: ELECTROLYTES**

<table>
<thead>
<tr>
<th>Electrolyte concentration</th>
<th>Amt (mmol/L) added to 1 L of fluids</th>
<th>Maximum rate (mL/kg/hr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Potassium</td>
<td>3.6–5.0 mmol/L</td>
<td>20</td>
</tr>
<tr>
<td>2.6–3.5</td>
<td>40</td>
<td>9</td>
</tr>
<tr>
<td>2.1–2.5</td>
<td>60</td>
<td>7</td>
</tr>
<tr>
<td>&lt;2.0</td>
<td>80</td>
<td></td>
</tr>
</tbody>
</table>

Phosphorus

<table>
<thead>
<tr>
<th>Phosphorus</th>
<th>0.32–0.65 mmol/L</th>
<th>0.01 mmol phosphate/kg/hr</th>
<th>Monitor phosphorus</th>
<th>q 6 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.32</td>
<td>0.03 mmol phosphate/kg/hr</td>
<td>Monitor phosphorus</td>
<td>q 6 hr</td>
<td></td>
</tr>
</tbody>
</table>

Magnesium

| Magnesium | 0.36–0.5 mmol/kg/day CRI | Use 5% dextrose | |
|-----------|--------------------------|-----------------| |
| <0.6 mmol/L | | | |

**STEP FOUR: ACID–BASE BALANCE**

<table>
<thead>
<tr>
<th>pH</th>
<th>Bicarbonate concentration</th>
<th>Dose of bicarbonate</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;7.1</td>
<td>&lt;12 mmol/L</td>
<td>mL IV = 0.1 x BW (kg) x (24 –HCO₃⁻)</td>
<td>over 2 hrs</td>
</tr>
</tbody>
</table>

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Abbreviations: C, cat; D, dog; BW, body weight; PCV, packed cell volume; TS, total solids; CRI, constant rate infusion; IV, intravenous; IM, intramuscular; SC, subcutaneous.
Beta-hydroxybutyrate (BOHB) concentrations have not been quantified in dogs with acute pancreatitis (AP). Objective: The aim of this study was to investigate BOHB concentrations in dogs with AP.

Methods: Prospective clinical study. Dogs were enrolled into 1 of 3 groups: AP, sick without an AP diagnosis, or fasted. BOHB was measured on whole blood with a portable ketone meter. The Kruskal-Wallis test was performed to compare BOHB in the 3 groups. Pair-wise comparisons were performed using the Mann-Whitney test and Bonferroni corrected P-values are reported.

Results: Median BOHB concentration was significantly higher in dogs with AP (0.3 mmol/L, range 0–2.9 mmol/L) compared to sick dogs without AP (0.20 mmol/L, range 0–0.9 mmol/L, P = .007) and fasted dogs (0.1 mmol/L, range 0–0.4 mmol/L, P = .0001). Median BOHB concentration was significantly higher in sick dogs without AP compared to fasted dogs (P = .0002).

Conclusions and clinical importance: In dogs without DM, BOHB is significantly higher in dogs with AP compared to other dogs. The diagnostic utility of this finding remains to be investigated.

Key words: Anorexia; Diabetic ketoacidosis; Ketone; Vomiting.