Canine Diabetes Mellitus

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Class of 2018

Clinicopathologic Conference

Presented on December 1, 2017

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Introduction

Diabetes mellitus is the most common disorder of the canine endocrine pancreas with insulin-dependent diabetes mellitus (IDDM) being the most recognized form in the dog.[12] Signalment and other disease processes can play a role in the development and/or the exacerbation of the disease. Epidemiologic studies have shown that 13 cases per 10,000 dogs or 1 of 100 dogs reaching the age of 12 will develop diabetes mellitus.[3,12] While clinical signs are often non-specific, with a thorough history, physical exam and proper diagnostic tests, an accurate diagnosis of diabetes mellitus can be made in a small animal private practice setting. Proper control of the disease, while sometimes challenging, is obtained through regular veterinary visits and owner compliance, and can result in a good quality of life for the patient.

Historically in human medicine, two forms of diabetes mellitus have been described: type 1 and type 2 diabetes. Type 1 diabetes is associated with immune-mediated destruction of beta cells, which in turn leads to an absolute insulin deficiency. Type 2 diabetes is characterized by impaired insulin secretion as well as insulin resistance, which is often seen in obese patients.[12] Studies have shown that canine diabetes mellitus is more comparable to type 1 diabetes in humans, while type 2 is rare to non-existent.[12] Even though canine type 1 diabetes mellitus is similar to that of human diabetes, canine diabetes is more than likely caused by other etiologies than just immune-mediated.[10] In fact, development of insulin autoantibodies does not seem to be a common feature in the disease of dogs.[18]

History and Presentation

Diabetes mellitus is a disease of middle-aged dogs with ages ranging between 5 and 15 years old with a peak prevalence between 7 and 9 years old.[3] Juvenile-onset diabetes occurs in dogs less than 1 year of age but is uncommon.[18] Originally, female dogs were thought to be

affected twice as often as males, but a recent study proved only 53% of dogs affected by diabetes mellitus were female.[2] This changing trend could be associated with an increase of elective spays.[19] Certain breeds are also predisposed to developing diabetes mellitus. Of the breeds listed, the Australian terrier, Standard Schnauzer and the Samoyed had the highest risk of developing diabetes mellitus.[17] While most diabetic dogs are overweight or obese, there is still very little evidence for a direct link between obesity and diabetes mellitus in the dog.[4]

The most common signs associated with diabetes mellitus in the dog are polyuria/polydipsia (PU/PD), polyphagia, and weight loss with PU/PD being the main reason patients present to the veterinarian.[18] Of course, the development of these signs depends on the amount of time between onset of hyperglycemia and when the patient is presented to the veterinarian.[21] At times, some patients present to the veterinarian due to rapid blindness caused by cataract formation.[18] There is also a chance that the presenting clinical signs go unnoticed by the owner, and the patient is at risk for the development of systemic illness such as vomiting, lethargy and anorexia.[17] These symptoms can be a sign of a more insidious onset of diabetes known as diabetic ketoacidosis (DKA), which carries a much poorer prognosis.[18]

Pathophysiology

In the normal, healthy canine patient, insulin is secreted by beta cells, which make up the majority of the endocrine pancreas.[9] When not needed, insulin is stored in secretory granules and circulates for the most part unbound.[13] When the intracellular blood glucose rises (hyperglycemia), beta cell membrane depolarization occurs followed by an influx of calcium ions, exocytosis of secretory granules, and increase in blood insulin concentrations.[9] Insulin is required for glucose transport into adipose tissue and muscles via GLUT-4 molecules.[9] When hyperglycemia occurs, insulin binds to insulin receptors causing translocation of intracellular

vesicles to the cell membrane, along with GLUT-4, and facilitates glucose uptake into the appropriate cells.[13] Once blood glucose levels return to normal, vesicles separate and are stored until needed again.[9] In patients with diabetes mellitus, hyperglycemia is sustained and not enough insulin is produced or insulin cannot act on its target tissues ultimately leading to the utilization of ketones, fatty acids and amino acids as an alternate source of energy.[8]

Canine diabetes mellitus is the consequence of a relative or absolute insulin deficiency which results in decreased tissue utilization of glucose, amino acids and fatty acids, accelerated hepatic glycogenolysis and gluconeogenesis, leading to hyperglycemia.[18] Beta cell loss in the dog tends to be rapid and progressive and is most often due to immune-mediated destruction, vacuolar degeneration, and/or pancreatitis.[21] Hyperglycemia (> 200 mg/dL) ultimately causes many disturbances in the body's normal processes and in turn the clinical signs become apparent.[15] Usually the first organ system affected is the renal system. As blood glucose increases, the renal tubular cells exceed the amount of glucose removed from the glomerular filtrate, thus resulting in glucosuria.[18] In the dog, spillage of glucose into the urine occurs when the blood glucose concentration exceeds 180 mg/dL.[18] Due to osmotic diuresis caused by the glucosuria, polyuria is displayed with a compensatory polydipsia to prevent dehydration.[17] Dogs diagnosed with diabetes mellitus are at an increased risk for urinary tract infections due to the presence of glucose in the urine which acts as an ideal environment for bacterial growth.[19] At the same time, a decrease in peripheral tissue utilization of ingested glucose leads to weight loss because the body is compensating for the disease-induced starvation.[17] In a normal animal, glucose enters cells in the satiety center that directly affects the feeling of hunger.[17] With diabetes mellitus, the deficiency in insulin therefore keeps glucose from entering the cells and the patient becomes polyphagic.[18]

Another common clinical sign seen in the diabetic patient is the formation of cataracts. Diabetic cataracts is the second most common cataract in the dog.[14] Cataract is defined as the loss of transparency of the lens or its capsule.[20] About 80% of dogs diagnosed with diabetes mellitus will form cataracts within their first year of diagnosis.[15] Cataracts occur via an alteration in glucose metabolism by the lens metabolic pathways.[1] When hyperglycemia is sustained, sorbitol accumulates in the lens causing osmotic draw and disruption of the lens fiber.[14] Sorbitol, fructose and dulcitol then accumulate in the lens further adding to the hypersomolality.[20] While lens phacoemulsification is the treatment of choice for cataracts, the ability of the diabetic patients to withstand anesthesia should be considered.[20]

Differential Diagnosis

Of the all differentials for diabetes mellitus, hyperadrenocorticism (Cushing's Disease) is the most common in the dog.[12] Cushing's is characterized by an extreme increase in cortisol and leads to clinical signs such as PU/PD and polyphagia, much similar to diabetes mellitus. On a serum biochemistry panel, a mild elevation in liver enzymes of a "healthy" diabetic dog is a common finding and is presumed to be hepatic lipidosis.[17] If the serum alkaline phosphatase enzymes are above 800 U/L, suspicions of Cushing's should be high.[17] If this occurs, other bloodwork abnormalities typical of Cushing's will be evident and further diagnostics, such as an ACTH stimulation test, should be performed to rule out the disease process.

Other causes of hyperglycemia and PU/PD include postprandial, diestrus in the bitch, pheochromocytoma, pancreatitis, exocrine pancreatic neoplasia, renal insufficiency, drug therapy (e.g. glucocorticoids), and head trauma.[18] In the intact female, the primary hormone of diestrus, progesterone, stimulates mammary tissue to produce growth hormone and leads to insulin resistance and is commonly reversible.[7] To obtain a diagnosis of diabetes mellitus, it is important

to document both persistent hyperglycemia and glycosuria.[18] Hyperglycemia differentiates diabetes mellitus from primary renal glucosuria or other renal tubular problems, while glucosuria differentiates diabetes mellitus from the other causes of hyperglycemia.[18] Due to the fact that multiple disease processes cause similar symptoms to diabetes mellitus, special attention should be paid to trends on all diagnostic tests and further diagnostics should be pursued if warranted.

Diagnostic Approach/Considerations

Physical Exam and Initial Diagnostics

As with all cases, the initial work up of all disease processes should start with a history and physical exam. Initial physical exam might reveal dehydration, weight loss, dull coat, cataract formation, or abdominal pain.[18,21] While many diabetic patients are over-weight, others may be thin and show signs of muscle wasting.[12] The hair coat can be sparse, dull, lackluster and even brittle.[17] Hepatomegaly may be evident on abdominal palpation due to diabetes induced hepatic lipidosis and lenticular changes such as cataract formation, anterior uveitis and keratoconjuncitivitis sicca (KCS) may be present.[18] Unfortunately, there is no classic physical exam findings in a “healthy” diabetic dog.[12]

A diagnosis of diabetes mellitus requires appropriate clinical signs and the evidence of fasting hyperglycemia and glucosuria.[18] This is achieved with a portable blood glucose monitoring device and urine reagent test strips. Fructosamine, a glycosylated protein, can be used to determine a persistent hyperglycemia over a longer period of time than one single blood glucose check.[6] Beware that fructosamine levels can be in the high normal range in a diabetic dog if the patient recently developed diabetes mellitus.[17]

Clinicopathologic Abnormalities

Once the diagnosis of diabetes mellitus has been established, a thorough clinicopathologic evaluation is warranted. Minimum laboratory evaluation in a newly diagnosed diabetic patient should include a complete blood count (CBC), serum biochemical panel and urinalysis with bacterial culture.[17] If the patient is an intact bitch, progesterone concentration should be checked, and also, if available, abdominal ultrasound should be performed to evaluate for concurrent pancreatitis, adrenomegaly, and/or abnormalities affecting the liver and urinary tract[17]. Due to the high prevalence of pancreatitis in dogs with diabetes mellitus, it is recommended pancreatic lipase immunoreactivity (cPLI) be measured, especially if ultrasound is unavailable.[18]

The CBC of a diabetic patient is usually normal but can be affected if a comorbid condition is in play.[12] On serum biochemistry panel, other than a hyperglycemia, the most common abnormalities seen are elevated serum alanine aminotransferase (ALT), alkaline phosphatase (ALP) and hypercholesterolemia.[18] If the ALT is in excess of 600 U/L, suspicions should be high for a hepatopathy other than diabetes-induced hepatic lipidosis.[17] Blood urea nitrogen (BUN) and serum creatinine are often normal, but if elevated, this maybe associated with primary renal failure or pre-renal uremia secondary to dehydration.[17]

Abnormalities found on urinalysis in a patient with diabetes mellitus are glycosuria, ketonuria, proteinuria and/or bacteriuria.[12] While all diabetics, complicated or uncomplicated, have glycosuria, small amount of ketones may be present in the “healthy” diabetic.[17] If large amounts of ketones are observed and the animal is symptomatic, a diagnosis of DKA should be made and treated accordingly.[17] In the untreated diabetic, urine specific gravities usually range from 1.025 to 1.035 likely due to glucosuria.[17] If a urine specific gravity less than 1.020 in the

presence of 2% glucosuria is observed, a concurrent disorder such as Cushing's or chronic kidney disease (CKD) should be investigated.[17] Proteinuria along with pyuria, hematuria and bacteriuria is suggestive of a urinary tract infection, but if lacking, does not rule out a urinary tract infection.[17] All diabetes mellitus patients should have urine obtained via cystocentesis for culture.[17] Of the organisms isolated from bacterial culture, *E. coli* is the most commonly isolated.[11]

Treatment and Management Options

The ultimate goal of therapy for canine diabetes is to control clinical signs, maintain the patient in a euglycemic state, and to consider the quality of life of both the animal and their owner. Of the top 10 negative impacts of canine diabetes mellitus, most of the issues were directed towards the owner's quality of life.[16] In the initial phase of treatment, the main goal is to avoid symptomatic hypoglycemia, which can be life threatening, caused by too aggressive or inappropriate therapy.[21] The mainstay therapy is lifelong administration of insulin. The ideal insulin formulation should accurately mimic the insulin secretion of a normal, healthy animal.[7] There are various formulations of insulin, but only two are approved by the Food and Drug Administration (FDA) for use in animals. In veterinary medicine, the two main classes of insulin used are intermediate-acting insulin preparations and long-acting basal insulin preparations. Rapid-acting insulin analogs are not used for the long-term management of diabetes mellitus but are useful in the treatment of diabetic ketoacidosis.[7,12]

Of the intermediate-acting insulin preparations, the most commonly used insulin in veterinary medicine is lenti insulin (Vetsulin) and is a purified pork-source insulin.[18,21] This formulation is also approved by the FDA for use in animals.[15] Lenti insulin is a U-40 preparation and must be used with U-40 syringes for proper dosing. A mixture of three parts short-acting,

amorphous zinc insulin and seven parts long-acting crystalline zinc insulin are used to create the insulin.[17] Studies have shown that appropriate euglycemia is obtained with twice daily subcutaneous administration of lenti insulin and is least likely to cause hypoglycemia.[10,15] In fact, in some animals, plasma insulin concentrations remained longer than 14 hours after subcutaneous administration.[17] Starting dosage for lenti insulin is 0.25 U/kg twice daily.[10]

Another commonly used intermediate-acting insulin preparation is neutral protamine hagedorn (NPH). NPH, also known as Humulin N or Novolin N, is a recombinant human insulin which contains the fish protein protamine and zinc which delays insulin resorption and prolongs its effects.[17] This insulin formulation is U-100 preparation and must be used with U-100 syringes for proper dosing. NPH is also used as a twice-daily subcutaneous administration but the duration of action is often less than 12 hours is most dogs.[21] Previous studies have shown, of the intermediate-acting insulin preparations, NPH was the most likely to have problems with hyperglycemia caused by a shortened duration of inulin.[17] Starting dosage for NPH range from 0.3 to 0.4 U/kg twice daily.[10]

When it comes to long-acting insulin preparations, the most commonly used in veterinary medicine are protamine zinc insulin (PZI), insulin glargine (Lantus), and insulin detemir (Levemir). PZI, also known as ProZinc, is similar to NPH in the fact that they are both recombinant human insulin and is prepared in the same way.[17] PZI differs from NPH because it has a larger amount of protamine that gives the insulin a longer duration of action, and it is a U-40 preparation.[10] Reports have shown that due to the long duration of action of PZI, blood glucose nadirs inappropriately occur and cause difficulty of correcting hyperglycemia.[17] Although not suitable for use in the newly diagnosed diabetic patient, PZI has been proven

effective in controlling the disease process in dogs that did not respond well to NPH or lenti insulin.[10,17] The starting dose for PZI is 0.25-0.5 U/kg twice daily.[10]

Both glargine and detemir insulin are long-acting insulin preparations produced by recombinant technology.[10] Of the long-acting insulins, detemir has the longest duration of action in the dog.[10] Very few studies have been done to look at the efficacy of both of these products, but overall, detemir is a favorite among veterinarians when treating patients that did not respond well to lenti, NPH or PZI.[7] Starting dose for glargine is 0.1 U/kg twice daily and 0.25-0.5 U/kg twice daily for detemir.[10] Both of the preparations are U-100 and must be administered with a U-100 syringe for proper dosing.

In addition to insulin therapy, there are various other treatment options and lifestyle changes that can be instituted to help control unwanted clinical signs and concurrent disorders. Most veterinarians considered insulin plus the addition of dietary management to be a mainstay therapy.[19] The addition of fiber to the diet has been show to improve glycemic control by decreasing the amount of glucose absorbed from the intestinal tract.[5,12] Fiber can be added to the diet through supplementation such as psyllium, guar gum and coarse wheat bran.[5] There are also commercial diets that are used in diabetic patients due to their increased levels of fiber and weight loss support.[21] Another dietary option is a low-carbohydrate diet. As fewer carbohydrates are consumed, peaks in glucose absorption will be decreased. Low carbohydrate diets can also decrease the amount of insulin needed as well as aid in weight loss.[5] If the patient is not obese but is actually thin, it is important that a high quality food be fed that is not designed for weight loss.[21] The most important aspect of dietary management of the diabetic dog is supplying a well-balanced diet that the patient will eat consistently.[17]

Other options for management of diabetes mellitus in the dog are exercise and oral supplementations. Exercise, paired with a healthy diet, combats obesity and has a glucose-lowering effect by increasing the absorption of insulin from the injection site.[17] Exercise levels should be kept constant with activity at the same time everyday.[15] Other medications include oral hypoglycemics. Oral hypoglycemic drugs work by stimulating pancreatic insulin secretion, enhancing tissue sensitivity to insulin or slowing the postprandial intestinal glucose absorption.[18] These drugs work best with non-insulin dependent diabetes mellitus (NIDDM), which is rare in the dog, and are not efficacious in IDDM.[17] Another option for oral drugs is oral sulfonylurea which work by directly stimulating insulin secretion from the beta cells.[18] Oral sulfonylurea drugs are used in humans and cats with diabetes mellitus but are not efficacious in the dog.[17]

When initially treating the diabetic patient, frequent veterinary visits to measure blood glucose are necessary to ensure the appropriate dose and insulin preparation has been chosen. Due to the frustrating nature of the first few months of controlling the disease, veterinarians should be sure to discuss in full detail with the owner what goes into the management of the diabetic patient before pursuing treatment.[12,16] At the first appointment, the owner should perform the initial administration of insulin therapy after a meal. Blood glucose samples are taken every 2 hours for at least 8 to 12 hours or until the nadir (80-150 mg/dL) is established.[21] If blood glucose remains greater than 150 mg/dL, the patient is sent home and another blood glucose curve is performed in one week.[15] If the blood glucose is less than 150 mg/dL, the dose is decreased by 10%-25% and rechecked again in 1 week.[21] Weekly visits are continued until clinical signs are controlled and blood glucose concentrations are under control. If problems controlling blood glucose persist, instituting a new insulin preparation should be considered.[18]

Once the appropriate dose and preparation of insulin is determined, long-term management is tailored to the individual patient by focusing on weight, physical exam, and the presence of clinical signs.[21] Every 3 months, appointments should include weight, physical exam and ocular exam.[21] A fructosamine level may also be used to clinically evaluate the diabetic patient.[21] If the fructosamine is abnormal, a blood glucose curve should be performed.[21] Every 6 months, full laboratory work should be performed including a urinalysis and urine culture.[21]

Sometimes when managing the diabetic patient, there is an underlying cause that must be addressed and treated successfully in order to obtain a euglycemic state and resolution of clinical signs. Initially, attention should be paid to the owner's administration of insulin and if the medication is being handled appropriately.[11] The veterinarian should take appropriate time to instruct the owner on how to give insulin subcutaneously and how to store and handle the medication properly. If the problem is with owner compliance, a few simple instructions and teaching opportunities can result in an appropriately managed diabetic patient. If clinical signs persist, further diagnostics should be pursued to track down an underlying cause of insulin resistance. Responsiveness to insulin can be affected by concurrent inflammatory, infectious, neoplastic or hormonal disorders.[18] Studies directed towards this phenomena have suggested that the most commonly identified concurrent disorders of the diabetic patient are hyperadrenocorticism, urinary tract infection, dermatitis, otitis, acute pancreatitis, neoplasia and hypothyroidism.[11] Further diagnostic tests including measurement of pancreatic lipase enzymes, ACTH stimulation, total T4 levels and abdominal ultrasound should be performed. Once the underlying disease process is determined, appropriate treatment, such as antibiotics for urinary tract infection, should be instituted and a blood glucose curve should be reassessed.

Expected Outcome and Prognosis

Prognosis for diabetes mellitus is dependent up several factors: owner compliance, ease of glycemic regulation, presence and reversibility of concurrent disorders, and avoidance of chronic complications associated with diabetes mellitus.[18] Most dogs live for a few years with diabetes with the average survival time being 3 years.[15] Sadly, a rather high mortality rate exists in the first 6 months of diagnosis due to the high probability of a concurrent life-threatening disease.[17] Most dogs develop cataracts within 5 to 6 months of diagnosis while 80% develop cataracts within 16 months.[15] Overall, the prognosis is fair to good with diligent care and monitoring.[12]

Conclusion

Canine diabetes mellitus is a disease of middle-aged to older dogs that results in an absolute insulin deficiency. The disease itself is non-reversible, but with appropriate treatment and care from both veterinarian and owner, the clinical signs associated with the disease may be diminished. Once a diagnosis of diabetes mellitus is made through a history, physical exam and various diagnostics, owners must be made aware of the long-term care and financial restraints that comes with the disease. The mainstay therapy for diabetes mellitus is lifelong insulin administration, along with dietary changes, and life-style alteration. While there are many different types of insulin, lente insulin (Vetsulin) appears to be the insulin of choice with newly diagnosed diabetics. Regular veterinary visits should be performed the first few months of the diagnosis to ensure a proper dosage is being achieved. Successful control is achieved once clinical signs are diminished and the patient maintains a euglycemic state. Due to the age of dogs diagnosed with diabetes mellitus, there is a high likelihood of concurrent disease that should be

treated in order to achieve appropriate results of insulin therapy. Prognosis is fair to good with the average survival being 3 years post diagnosis.

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