International Journal of Recent Biotechnology **ISSN: 2322 – 0392**
Available online at www.ijrbp.com *Int. J. Rec. Biotech.* **2015,** 3 (4): 18-22
Review Article

IJRB

Diabetes Mellitus in Dogs and its Associated Complications: A Review

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ABSTRACT
Diabetes mellitus is a disease of the pancreas. This is a small but vital organ located near the stomach. It has two significant populations of cells. One group of cells produces the enzymes necessary for proper digestion. The other group, called beta-cells, produces the hormone insulin. Insulin regulates the level of glucose in the bloodstream and controls the delivery of glucose to the tissues of the body. In simple terms, diabetes mellitus is caused the failure of the pancreas to regulate blood sugar. Diabetes has evidence in ancient literatures, though recently is being considered as one amongst the most emerging disease condition in both human and companion animals. Diabetes mellitus is one of the common endocrinopathy of dog characterized by hyperglycemia, glycosuria and weight loss (Kumar et al., 2014).Although the exact mechanism of pancreatic β-cell loss in canine diabetes has not been determined, The cause of β-cell loss is likely multifactorial i.e.autoimmunity, genetics, environment, diseases resulting in insulin antagonism.Diabetes in most dogs is immune mediated and insulin dependent. Breed predisposition in canine is attributed to dog leukocyte antigen gene pool encoding form major histocompatibility complex-II molecules, however research is still underway.

Key words: *Diabetes mellitus,Dog, Hyperglycemia*

INTRODUCTION

Canine diabetes is a common endocrine disorder with an estimated breed-related prevalence ranging from 0.005% to 1.5% in pet dogs. Increased prevalence in some breeds suggests that diabetes in dogs is influenced by genetic factors and similarities between canine and human diabetes phenotypes suggest that the same genes might be associated with disease susceptibility in both species. Between 1-5% of human diabetes cases result from mutations in a single gene, including maturity onset diabetes of the adult (MODY) and neonatal diabetes mellitus (NDM) [1].

Diabetes is a common condition where sugar (glucose) levels of the body are poorly regulated, due to either lack of production of the hormone insulin, made in the pancreas, or an increase in resistance of tissues in the body to the effects of insulin [2]. Canine diabetes has been compared with human type 1 diabetes (T1D) [3]. canine insulin-deficiency diabetes (IDD) occurs more commonly in older dogs, aged 7–12 years [4]. Females are at increased risk, regardless of neuter status. Neutered males are at greater risk than intact males.

Breed Susceptibility

Pedigree dog breeds, similar to some ethnic groups in the human population [5], display

variability in diabetes susceptibility, with some breeds (e.g. Samoyed) being over-represented, whereas others (e.g. Boxer) seem to be relatively resistant to developing the disease [6]. These breed-related differences in diabetes susceptibility suggest that the pathogenesis of diabetes is influenced by genetic factors and similarities between canine and human diabetes phenotypes indicate that the same genes and/or genetic pathways might be involved in both species. Since some phenotypes also appear to be somewhat breed-specific [7], for example NDM, in Keeshond dogs [8] and dioestrus diabetes in female entire Elkhounds and Lapphunds [9], there could be differences in the individual susceptibility genes that contribute to the overall genetic risk for different dog breeds, as is seen with different ethnic groups and type 2 diabetes in humans [10].

Classification

In humans, there are two types of diabetes mellitus. Both types are similar in that there is a failure to regulate blood sugar, but the basic mechanisms of disease differ somewhat between the two. "**Type I Diabetes Mellitus** is the most common type of diabetes in dogs."

Type I Diabetes Mellitus (sometimes also caused Insulin Dependent Diabetes Mellitus), results from total or near-complete destruction of the beta-cells. This is the most common type of diabetes in dogs. As the name implies, dogs with this type of diabetes require insulin injections to stabilize blood sugar.

Type II Diabetes Mellitus (sometimes called Non-insulin Dependent Diabetes Mellitus), is different because some insulin-producing cells remain. However, the amount of insulin produced is insufficient, there is a delayed response in secreting it, or the tissues of the dog's body are relatively resistant to it (also referred to as *insulin resistance*). Type II diabetes may occur in older obese dogs. People with this form may be treated with an oral drug that stimulates the remaining functional cells to produce or release insulin in an adequate amount to normalize blood sugar. Unfortunately, dogs tend not to respond well to these oral medications and usually need some insulin to control the disease [10].

Canine diabetes mellitus (DM), classified as either type I or type II, is a generally treatable condition caused by insulin deficiency. At diagnosis, most diabetic dogs are suspected of having type I. Type I patients, characterized by permanent inability to produce insulin, often require exogenous insulin administration.DM has a potential immune-mediated cause (though this is not firmly established).Diabetogenic drugs, pregnancy, and chronic pancreatitis are also possible causes of canine DM.

Pathophysiology

Insulin deficiency results in hyperglycemia by causing:Uninhibited hepatic glucoseproduction, impaired entry of glucose into tissues, accelerated protein and lipid catabolism. Persistent hyperglycemia results in glucosuria when the renal tubularthreshold for glucose excretion >180–220 mg/dL. Increased proteolysis leads to muscle wasting and poor wound healing. As the accelerated lipid catabolism persists, hepatic lipidosis develops and ketoacidosis can result secondary toenhanced ketone body production, endothelial damage and immunesuppressionultimately occur[11].

Clinical Signs

The clinical signs seen in diabetes mellitus are related to the elevated concentrations of blood glucose and the inability of the body to use glucose as an energy source. They arepolyuria, polydipsia, polyphagia, weight loss, owners occasionally report acute blindness secondary to cataract formation.

Diagnosis

Diabetes mellitus is diagnosed by the presence of the typical clinical signs (excess thirst, excess urination, excess appetite, and weight loss), in addition the presence of a persistently high level of glucose in the blood stream, and the presence of glucose in the urine. The normal level of glucose in the blood is 80-120 mg/dl (4.4-6.6 mmol/l). It may rise to 250-300 mg/dl (13.6-16.5 mmol/l) following a large or high-calorie meal. However, diabetes is the only common disease that will cause the blood glucose level to rise above 400 mg/dl (22 mmol/l). Some diabetic dogs will have a glucose level as high as 700-800 mg/dl (44 mmol/l), although most will be in

the range of 400-600 mg/dl (22-33 mmol/l).To conserve glucose within the body, the kidneys do not filter glucose out of the blood stream into the urine until an excessive level is reached. This means that dogs with a normal blood glucose level will not have glucose in the urine. Diabetic dogs, however, have excessive amounts of glucose in the blood, so it will be present in the urine. After the blood sugar reaches 180 mg/dl, the excess blood sugar is removed by the kidneys and enters the urine. This is why dogs and people with diabetes mellitus have sugar in their urine (called glucosuria) when their insulin is low [12].

Prognosis for a dog with diabetes mellitus

Once the diabetes mellitus is properly regulated, the dog's prognosis is good as long as treatment and monitoring are consistent. Most dogs with controlled diabetes live a good quality of life with few symptoms of disease.

Treatment

Short-acting insulin (eg, regular insulin, insulin lispro) is predominately used in the hospital for clinically ill diabetics or DKAs, as increased potency increases risk for hypoglycemia.

- Intermediate-acting insulin is the common choice, as it results in the best glycemic control.
- Human recombinant neutral protamine Hagedorn (NPH) insulin. Comparable with NPH insulin,lente insulin is currently unavailable.
- Long-acting insulin effectively reduces the blood glucose level but varies in absorption, time to nadir, and duration of action, increasing risk for hypoglycemia and Somogyi effect.
- Insulin detemir, insulin glargine, and protamine zinc insulin (PZI).
- Treatment should be initiated q12h, although starting doses differ forinsulin types.

Insulin therapy in dogs

The two most effective insulin formulations in dogs are NPH and Lente insulins. Use of human recombinant insulin or pure pork insulin, appear to avoid the complications that can occur due to development of anti-insulin antibodies in dogs treated beef/pork insulin. Lente insulin (Caninsulin/Vetsulin) and NPH insulin (Humulin N) are used at a starting dose of 0.25 to 0.5 IU/kg twice a day. Most dogs treated with NPH and Lente insulin require twice daily treatment, and twice daily therapy should be recommended in all dogs, but because Lente insulin is a mixture of ultralente and semilente insulin, the duration tends to be longer than the duration of NPH. For this reason up to 30% of dogs have adequate glycemic control with once a day therapy. Long acting insulins such as PZI, glargine, and detemir are unpredictable in dogs and are not appropriate for the initial management of most diabetic dogs; however treatment with these products may be necessary in dogs that have a very short duration of action when treated with NPH insulin or Lente insulin. The analogue insulin, detemir has only been evaluated in a small number of diabetic dogs. It is important to be aware that this insulin is much more potent in the dog than other insulin products with the dose needed for good glycemic control ranging from 0.07-0.23 U/Kg.

Table: Starting dose and dose range for insulin products used in diabetic dogs

Insulin	Starting dose	Median dose	Dose range
NPH	0.25-0.5 U/kg	0.5 U/kg	0.2-1.0 U/kg
Lente	0.25-0.5 U/kg	0.7 U/kg	0.3-1.4U/kg
PZI	0.5 U/kg	1.0 U/kg	0.4 -1.5U/kg
Glargine	0.5 U/kg	0.6 U/kg	0.1-1.1 U/kg
Detemir	0.1-0.2 U/kg	---	0.07-0.23 U/kg

Dietary management

Dietary management should be instituted at the same time as insulin therapy in the diabetic dogs. The goal of dietary therapy is to minimize postprandial fluctuations in blood glucose and to potentiate the action of insulin. Studies support the feeding of a high complex carbohydrate (> 50% dry matter), high fiber diet (> 10% dry matter) to dogs with DM. Diets containing increased amounts of soluble fiber (fruits, legumes, oats) delay gastric emptying alter intestinal transit time and potentiate the actions of insulin in tissues. Increased amounts of

insoluble fiber (cellulose, vegetables, and grains) alter intestinal transit time and slow starch hydrolysis. The net effect of a high fiber diet is to slow glucose absorption from the intestinal tract, reduce postprandial fluctuations in blood glucose and enhance glycemic control of the diabetic dog. Reduced fat diets are probably appropriate in diabetic dogs due to their susceptibility to hepatic lipidosis, pancreatitis and hypercholesterolemia. Canned or dry foods are the diet of choice in diabetics since they contain predominantly complex rather than simple carbohydrates. Canned diets tend to be lower in carbohydrates than dry diets. Since complex carbohydrates require digestion before absorption, they minimize postprandial fluctuations in blood glucose concentration. Soft moist foods contain simple carbohydrates which are rapidly absorbed. These diets may result in rapid fluctuations in blood glucose 30-45 min after eating. Soft moist foods also contain large quantities of propylene glycol which cause postprandial hyperglycemia. The daily caloric intake should be designed to correct obesity and maintain ideal body weight. Obesity has been shown to cause reversible insulin resistance in dogs due to its effects on insulin receptors. In dogs reversal of obesity may improve glycemic control and decrease the requirement for insulin, but is unlikely to replace the need for insulin therapy. The feeding schedule is also very important in diabetic dogs. Feeding should occur when insulin is present in the bloodstream in order to utilize glucose as it is absorbed. If this does not happen, severe postprandial hyperglycemia will occur. Also multiple feedings are preferable since this will help minimize the hyperglycemic effect of each individual meal. Ideally 3 - 4 small meals/day should be fed, however the schedule of most owners limits the ideal feeding schedule. For dogs receiving once a day insulin (which rarely results in good glycemic control in dogs), one meal should be given at the time of insulin administration, and a second meal given in the late afternoon at the time of peak insulin effect. For those dogs receiving insulin twice a day, at least 4 meals would be ideal. In most cases, however, two meals are fed at the same time as insulin is administered. As in every aspect of management of the diabetic patient a regular and consistent feeding schedule is the most important factor [13].

Poor response to insulin

Clinical signs suggestive of inappropriate response to insulin therapy include recurrence or persistence of clinical signs of DM, disorientation or seizures due to hypoglycemia, an insulin dose higher than 2 U/Kg/dose in the dog or recurrent ketoacidosis. Adequate assessment of the cause of the problem requires performing a blood glucose curve. Measurement of fructosamine may also be helpful. Once this data has been evaluated, appropriate changes in treatment or further diagnostic testing can then be instituted. In dogs receiving twice daily insulin, most glucose curves can be performed during working hours (8 am to 6 pm). Common problems that may lead to a poor response to insulin include problems with owner administration, inappropriate insulin dose or formulation, insulin induced hypoglycemia, rapid metabolism of insulin, and insulin resistance. It is important to take into consideration the level of stress of the dog while in the hospital when interpreting the results of blood glucose curves. It is also important to appreciate that blood glucose curves show significant day to day variability. Other factors such as clinical signs, results of urine blood glucose measurements, serum fructosamine concentrations, and changes in physical examination (especially body weight), should be taken into account when interpreting the results of a blood glucose curve.

Problems with owner administration

Diagnosis of problems of owner administration of insulin may be detected either by a thorough history or by administration of insulin from a new bottle in the clinic by a clinician or veterinary technician, followed by a repeated blood glucose curve. Care should be taken to monitor the patient carefully in this setting however, because severe hypoglycemia can result if the insulin dose has been escalated due to problems with administration. If hypoglycemia does occur, the dose of administered insulin should be decreased by 25-75 % depending upon the severity of hypoglycemia and a blood glucose curve repeated after 7 days of the new dose.

Prevention and control

Prevention and controlinvolve a healthy diet, physical exercise, being a normal body weight. Blood pressure control and proper foot c

also important. Type 1 diabetes m
managed with insulin injections. Type 2 diabetes may be treated with medications with or without insulin.

Nutritional Aspects

- Minimizing postprandial blood glucose fluctuations is the principal goal of dietary therapy.
- Most studies suggest that fiber-rich diets, particularly insoluble fiber, resultin improved glycemic control.
- The ideal dietary composition is debatable, as improved glycemic control may be attributed to the high-fiber, low-carbohydrate, lowfat, or combination content.
- Diet change is not recommended during stabilization.
- If diabetes is difficult to regulate, increase fiber.
- Diets should be palatable to ensure predictable consumption.
- Equal-sized meals should be offered q12h (with insulin administration).
- Overweight dogs require weight reduction programs, as obesity contributes to insulin resistance.

SUMMARY

Uncontrolled diabetes can lead to cataract formation, bacterial infections (usually urinary tract), ketoacidosis, hepatic lipidosis, persistent weight loss, DM can also be complicated by morbid conditions (e.g., pancreatitis, infections, hyperadrenocorticism).Attempting to control diabetes with insulin therapy can lead to iatrogenichypoglycemia.

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