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Diabetes mellitus in small animals

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Abstract
In both cats and dogs, diabetes mellitus is a prevalent condition. Canine type 1 diabetes is similar to human type 1 diabetes in that it is more prevalent in canines. Research indicates that diabetes in dogs may be influenced by environmental variables, immune-mediated processes, and heredity. In dogs, gestational diabetes also has a variant. Variations in a different breed's vulnerability to diabetes mellitus point to a hereditary basis for the disease's etiology. One of the prevalent endocrinopathies is diabetes mellitus, which is characterised by weight loss, hyperglycemia, and glycosuria. Though the precise mechanism underlying the loss of pancreatic β-cells in diabetes remains unclear. β-cell loss most likely has multiple causes. For cats, basal insulins are the recommended course of action, while for dogs, lente is the preferred insulin.

Keywords: Islets, ketones, cataract, insulin, pancreas

Introduction
A common endocrine condition called diabetes mellitus (DM) is characterised by persistent hyperglycemia brought on by insufficient insulin synthesis, action, or both. A chronic condition of the metabolism of carbohydrates caused by a partial or total lack of insulin is called diabetes mellitus. There are two main types of diabetes mellitus: Type 1 is known as "juvenile-onset" DM or "insulin-dependent" (IDDM) and Type 2 is known as "adult-onset" DM or "non-insulin-dependent" (NIDDM). Type 1 diabetes, which affects dogs most frequently, is characterised by permanent hypoinsulinemia, lack of rise in endogenous serum insulin or C-peptide concentrations after insulin secretagogue (such as glucose, glucagon, or amino acids) is administered and the requirement for exogenous insulin to maintain survival and control blood sugar levels (Montgomery *et al.*, 1996; Rosenfield *et al.*, 2017) [12, 19]. All dogs with diabetes need exogenous insulin therapy to control their hyperglycemia, with very few exceptions (Catchpole *et al.*, 2005) [3]. Similar to type 2 diabetes in humans, feline diabetes is the most prevalent type of the disease. Obesity is a significant threat factor for cats.

Etiopathogenesis
Primary causes include decreased number and size of islets in the pancreas, as well as vacuolization, hypertrophy, and degeneration of beta cells (Ahlgren *et al.*, 2014; Gilor *et al.*, 2020) [2, 9]. It can happen as a result of exocrine pancreatic problems or any other process that causes pancreatitis (Nelson and Reusch, 2014; Davison, 2015) [14, 4]. The etiopathogenesis of diabetes mellitus in dogs involves both insulin deficiency and tolerance. The symptoms of insulin deficiency include beta-cell reduction, congenital hypoplasia, immune-mediated beta-cell death, pancreatitis-related beta-cell loss, and beta-cell exhaustion or glucose toxicity brought on by chronic insulin resistance. The cause of insulin resistance is the interaction between other hormones that inhibit the function of insulin and the occurrence of infection or inflammation, diestrus or pregnancy, associated hormonal disease such as Cushing's syndrome, hypothyroidism, acromegaly, iatrogenic (glucocorticoids, progestagens), obesity, infection, concurrent illness, heart diseases, hyperlipidemia, renal failure, etc. In dogs with diabetes mellitus, beta-cell activity is irreversibly lost, and survival requires lifetime insulin administration. Reversible diabetes mellitus (quite rare in dogs) is identified in subclinical diabetics who were administered an insulin antagonistic medication (glucocorticoids) and who also had a coexisting insulin-antagonistic condition (diestrus, pregnancy). All bitches whether pregnant or not, enter the luteal, progesterone-dominated diestrus phase of their ovarian cycle after estrus every six to twelve months. Diestrus lasts 60 to 90 days. Growth hormone (GH) is secreted by mammary tissue in response to progesterone (Pg). Pg and GH both counteract the effects of insulin (Selman *et al.*, 1994; Abdelmegeed and Mohammed, 2018) [20, 1]. When in

diestrus (pregnant or not), older bitches are often diagnosed with diabetes mellitus due to elevated serum levels of GH and Pg (Fall *et al.*, 2010; Mared *et al.*, 2012) [7, 11]. Ovariohysterectomy eliminates the Pg source, which in turn eliminates the trigger for GH release. It is advised that diabetic female dogs who have not been spayed undergo surgery to neuter them. Due to remaining beta-cell function, some dogs with recently diagnosed diabetes mellitus experience a period known as the "honeymoon period," which is characterised by remarkable glycemic control in relation to minimal insulin doses (<0.2 U/kg/injection). Within months of starting treatment, insulin dosages must be raised in these dogs due to the difficulty in maintaining glucose control (residual beta-cells fail to regenerate and die). Reduced secretion of endogenous insulin occurs (Nelson, 2003) [16]. In dogs, type 2 diabetes, also known as NIDDM, is uncommon and is typically treated in conjunction with an insulin antagonistic disorder.

Pathophysiology

Reduced tissue uptake of glucose, amino acids and fatty acids as well as increased hepatic glycogenolysis and gluconeogenesis are the results of insulin insufficiency (Nelson, 2015) [15]. Hyperglycemia, or a buildup of glucose in the blood, is the result. Glycosuria, glucose-induced osmotic diuresis, polyuria, water loss, stimulation of the thirst mechanism (polydipsia), negative calorie balance (inability to utilise glucose, some loss of calories via glycosuria & tissue catabolism), and polyphagia occur when renal tubular capacity for reabsorbing glucose is surpassed (when blood glucose concentrations are >180-220 mg/dL). The effects of DM are the same as those of hunger. Proteolysis rises and synthesis falls as a result of protein metabolism. Bioavailable amino acids boost hepatic gluconeogenes, which means the body responds well to hunger. However, it also increases the risk of hyperglycemia in diabetes mellitus at the expense of a negative nitrogen balance, muscular atrophy, and cachexia (Reusch *et al.*, 2010) [17]. Continued deficiency in intracellular glucose and insulin causes lipid breakdown to speed up and mobilise triglycerides. Elevations in plasma free fatty acids (FFAs) are the result. After being delivered to the liver, FFAs are beta-oxidized to produce acetyl CoA, which may be produced in excess of what is required for the Krebs cycle's oxidation to produce ATP. Thus, acetyl CoA is metabolised to produce ketone bodies, which are its alternate product. Furthermore, ketone bodies are a suitable short-term energy source in reaction to starvation. Ketosis and ketoacidosis in diabetics can result from the overproduction of ketones during extended fasting or diabetes mellitus. Hyperlipidemia and hepatic lipidosis are the results of increased hepatic production of triglycerids and very low density lipoproteins (VLDL) due to a rise in hepatic fatty acid content.

Signalement

Dogs 5-12 years old, who are middle-aged and older, are most frequently diagnosed with DM (Davison *et al.*, 2005; Fall *et al.*, 2007) [4, 6]. 7-10 years is the peak prevalence. In canines, females experience symptoms twice as frequently as males. Though any breed can be impacted, incidence seems to be higher in some tiny breeds, including Miniature Poodles, Dachshunds, Schnauzers, Cairn Terriers, and Beagles. Male cats who are obese appear to be more affected than female cats. Certain breeds seem more prone than others, including Burmese, Russian Blue, Norwegian Forest Cat, Abyssinian, and Tonkinese (Fracassi *et al.*, 2004) [8].

Clinical findings

Weight loss and the symptoms polyuria (PU), polydipsia (PD) and polyphagia (PP) are classic clinical indicators. PU and PD in dogs with diabetes is constant. Up to 50% of cats and certain dogs exhibit a reduced appetite. A coexisting illness that suppresses appetite (e.g., pancreatitis, ketosis, diabetic ketoacidosis) may lessen PP. Recent diabetic canines may not exhibit weight loss; other symptoms include a voracious hunger, abrupt cataract formation-related blindness in dogs, and diabetes neuropathy, which primarily affects cats. Diabetic ketoacidosis (DKA) symptoms, such as weakness, anorexia, vomiting, and lethargy. It might take days or months for DKA to develop after the onset of clinical symptoms. Dogs' peculiar sorbitol pathway, which causes edema in the lens and interferes with normal light transmission, is linked to the development of cataracts (Richter *et al.*, 2002) [18].

Fig 1: A nine years old dog was diagnosed with diabetes mellitus and was subsequently photographed.

Fig 2: After four months, the same dog. The owner stated sudden loss of vision and the diabetic cataract had progressed quickly.

Cats appear to have the similar sorbitol route, but cataract formation is uncommon. A kind of decompensated diabetes mellitus known as diabetic ketoacidosis occurs when cells are unable to access glucose (due to absolute or relative insulin shortage) and instead use free fatty acids (FFAs) as an energy source. FFAs are converted to ketoacids when increased glucagon and other counter-regulatory hormones are present. A build-up of glucose and ketoacids in the blood can cause life-threatening metabolic disruptions. Weakened resistance to fungus and bacteria that cause dermatitis, prostatitis, bronchopneumonia, and cystitis. Reduced neutrophil function is linked to an increased vulnerability to infection. Diabetes mellitus is suggested by radiographic evidence of emphysematous cystitis, which is caused by glucose-fermenting organisms such *Proteus sp*., *Aerobacter aerogenes* and *E. coli* and results in gas production in the bladder's wall and lumen. In dogs with diabetes, emphysema can also form in the gallbladder wall. In diabetic dogs and cats, lipid buildup frequently results in hepatomegaly. Increased adipose tissue fat mobilisation is the cause of the fatty liver. The formation of many neutral lipid droplets significantly enlarges

individual liver cells. A further syndrome associated with decompensated diabetes mellitus is hyperosmolar hyperglycemic state. It is characterised by hyperosmolality (> 320 mOsm/kg) and extreme hyperglycemia (serum glucose > 600 mg/dL), with a normal pH and either little or no ketonemia or ketonuria. Compared to diabetic ketoacidosis, it is less frequent. Animals are neither acidotic nor ketotic in the classical form. On the other hand, mixed forms happen when there is severe hyperosmolality and ketoacidosis.

Physical examination

Dogs with simple DM are often in good health. Dogs with diabetes may weigh normal, underweight, or fat. There can be obvious lethargy. The hair coat could be dull. Hepatomegaly can often be felt. Cataracts also occur often. There could be keratoconjunctivitis sicca and anterior uveitis. Cats with diabetes often exhibit neurologic symptoms (e.g., weakness in hindlimbs, ataxia, plantigrade stance).

Diagnosis

Glycosuria and chronic fasting hyperglycemia (>200 mg/dL) are the basis for a diagnosis of diabetes mellitus. In dogs and cats, the typical fasting blood glucose range is 75-120 mg/dL. Complete Blood Count generally appears normal. Neutrophilic leukocytosis or toxic neutrophils may be observed if pancreatitis or infection is present. Biochemistry panel reveals hyperglycemia, hypercholesterolemia and hypertriglyceridemia. Urinalysis indicates urine specific gravity typically >1.025, glycosuria and variable ketonuria. Stress-associated hyperglycemia is a common issue in cats, and confirmation of the diagnosis may need several blood and urine samples (Junaid, 2018) [10]. Serum fructosamine measurement can help distinguish between diabetes mellitus and hyperglycemia brought on by stress. When there is hyperglycemia brought on by stress, fructosamine concentrations are normal. In practice, diabetes mellitus is diagnosed using random measures of glycosylated haemoglobin (HbA1C). A random glucose value > 200 mg/dL (> 11.1 mmol/L) may be diagnostic, but values can be affected by recent meals & must be confirmed by repeat testing; testing twice may not be necessary in the presence of symptoms of diabetes. HbA1C measurements reflect glucose levels over the preceding 3 months. HbA1C measurements are now included in the diagnostic criteria for diabetes: HbA1C ≥ 6.5% = diabetes (in humans). HbA1C 5.7 to 6.4% = prediabetes or at risk of diabetes (in humans). However, HbA1C values may be falsely high or low and tests must be done in a certified clinical laboratory with an assay that is certified. The average blood HbA1c concentration in non-diabetic dogs - 3.48±0.28%, ranging from 3 to 4.1% median 3.5%. In diabetic dog group - 5.41±0.84%, ranging from 3.7 to 7.5%, median 5.1%. Compared with the non-diabetic dogs, the diabetic dogs had significantly higher HbA1c levels in their blood. Point-of-care is HbA1C measurements should not be used for diagnostic purposes, although they can be used for monitoring diabetes control.

Treatment

Treatment consists of insulin injections, diet, weight loss, and potentially oral hypoglycemics. Neutering intact females is a good idea. Recent research has validated the usage of low-carb, high-protein diets for cats. Diets rich in complex carbohydrates and high in fibre are recommended for dogs (Nelson *et al.*, 1998) [13]. Insulin therapy must be used as an initial treatment because diet and weight loss alone will not be enough to control the illness. The majority of dogs need two daily insulin shots. The first insulin of choice is typically NPH or lente, administered twice daily at a dose of 0.5 U/kg. When receiving twice daily injections, insulin is administered at the same time as two meals of equal caloric content. Diets heavy in semi-moist foods, or simple sugars, ought to be avoided. After the first five to seven days of stabilisation at home, therapy is monitored using clinical symptoms and serial blood glucose measurements. When giving NPH or lente insulin to dogs with poor glycemic control, detemir should be used as a basal insulin. Detemir's potency dictates that its beginning dosage be 0.1 U/kg, twice day, with a glycemic control and clinical sign review after one week.

High-protein meals and insulin therapy are started for cats, and they are reevaluated after 5-7 days. Insulin glargine is the recommended insulin for cats with recent diagnoses. Long-acting basal insulin, such as glargine, is administered in combination with low-carb, high-protein diets. These insulins do not, however, appear to be linked to high rates of diabetic remission. Cats with diabetes may take oral hypoglycemic medications, such as glipizide. A sulfonylurea, glipizide induces functioning β cells to release more insulin. When extreme insulin shortage is expected and exogenous insulin therapy is necessary, glipizide should not be administered to thin or ketonuric cats. The starting dose of glipizide is 2.5 mg PO, b.i.d. each day. For cats, the recommended doses of glimepiride are 2 mg/day and glyburide are 0.625 mg/day. In cats, acarbose, an oral α-glucosidase inhibitor, has also been used to manage hyperglycemia at a dose of 12.5-25 mg, two to three times a day, in combination with diet and/or insulin.

Diabetes mellitus can have major complications, including ketoacidosis, which needs to be treated as an emergency. One aspect of therapy is treating dehydration with intravenous fluids, such as lactated Ringer's solution. lowering blood sugar levels and preventing ketosis by the use of regular, crystalline zinc insulin. keeping serum electrolyte levels stable by giving electrolyte solutions in excess. diagnosing and managing underlying and concomitant conditions, such as infections or acute pancreatitis. Ketoacidotic diabetes mellitus has been treated with a variety of insulin regimens. In the intermittent insulin regimen, the first dosage is standard insulin at 0.2 U/kg, IM, and it is then administered hourly at 0.1 U/kg. When the serum glucose level falls below 250 mg/dL, insulin is given subcutaneously (SC) at a rate of 0.25-0.5 U/kg, every 4-6 hours, while the serum glucose level is closely monitored every 1-2 hours. Blood glucose levels may drop quickly during vigorous insulin treatment; in such cases, adding 2.5%-5% dextrose to the IV fluids may be necessary. With good results, recent studies recommend using glargine instead of normal insulin for the therapy of ketoacidotic diabetes mellitus.

Conclusion

In clinical settings, diabetes is a prevalent endocrine medical condition. Diabetes mellitus (DM) can be made worse by dreadful conditions e.g., pancreatitis, urinary tract infections, hyperadrenocorticism, cataract formation, ketoacidosis, hepatic lipidosis, and persistent weight loss. Some breeds and coexisting medical conditions have been linked to a higher risk of diabetic mellitus. In addition to a suitable diet and exogenous insulin administration, treatment includes regular blood glucose monitoring adequate dose adjustment, a consistent daily routine, and the removal of triggers for

insulin resistance. Education of the client is crucial.

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