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Diabetes mellitus in canines: A concise review

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Abstract
Diabetes mellitus constitutes a major global public health problem in humans, and is also of concern in dogs. Diabetes mellitus (DM), or diabetes, is a condition that occurs when there is deficiency or absolute lack of insulin secretion. Insulin deficiency diabetes (Type I) is caused either by genetic disposition or autoimmune destruction of insulin producing beta cells, pancreatitis/ exocrine pancreatic disease or secondary chronic hyperglycemia. Insulin resistance or Type 2 DM adds a peripheral insulin resistance to the non-functional islets of Langerhans, where in addition to metabolic abnormalities and ambient factors, other contributing diseases play an important role, for example, hyperadrenocorticism in dogs where excessive cortisol production antagonizes insulin activity and acromegaly. The main clinical manifestations are polydipsia, polyuria, polyphagia, weight loss and glucosuria. The etiology of diabetes mellitus is similar in dogs, cats and humans and is probably multifactorial. An essential aspect of successful DM management is to ensure that the owner of a diabetic dog is capable of administering insulin, recognizing the clinical signs of inadequately managed DM, and monitoring blood glucose levels at home. Insulin therapy is the mainstay of treatment for clinical DM. Various biomarkers not only reflect well glycemic control in hematologic disorder, but also represent postprandial glucose fluctuation. Complementary treatments, notably the use of encapsulated islets, gene therapy, and others, are being investigated for their therapeutic utility in the effective management of diabetes. This review will highlight our existing understanding of canine diabetes diagnosis and management.

Keywords: diabetes mellitus, dogs, HbA1C, insulin, treatment

Introduction
Dogs are the closest to man because of their sophisticated social behavior and share the same living environment as humans, hence are exposed to similar noxae. Several human endocrine disorders are known to occur as similar, spontaneous endocrinopathies in companion animals also. Endrocrinopathies are an escalating global health problem both in humans as well as domestic animals that stem from imbalances in hormone levels. Diabetes mellitus is a common endocrinopathy in dog. Canine diabetes mellitus has been recognized for almost a century, but its aetiology, pathogenesis and underlying disease mechanisms are still poorly understood (Kumar *et al*., 2014, Fall *et al*., 2009) [61, 33]. However, spontaneous cases of canine DM have increased globally due to factors such as obesity, alteration in feeding habits, owner inattention, lack of awareness and advancement in diagnosis.

Epizootiology
Diabetes mellitus constitutes a major global public health problem in humans, and is also of concern in dogs. The incidence of diabetes mellitus (DM) in dogs has also been substantially rising (Feldman and Nelson 2004) [34]. Recent trends indicate a steep rise (32%) in cases of canine DM from 2006 to 2010 according to Banfield Hospital of USA (Anonymous, 2011) [4], with an incidence rising from 0.19% in 1970 to 0.64% in 1999 (Guptill *et al*. 2003; Herrtage, 2009) [43, 45]. In another study of over 120,000 dogs from UK first-opinion practices, the prevalence of DM was 0.34% (Mattin *et al*, 2014) [70]. During the same time period the case-fatality rate decreased from 37% to 5% signifying increase in incidence and understanding of diabetes management in canine. The etiology of diabetes mellitus in dogs is probably multifactorial (Nelson and Reusch, 2014) [76]. Diabetes can be defined as a group of metabolic (endocrine) diseases, resulting from a variable interaction of hereditary and environmental factors, which is presented by hyperglycaemia following absolute or relative insulin insufficiency that causes metabolic manifestations reflected in a tendency toward accelerated non – specific atherosclerosis, macro- and microangiopathy, neuropathy, increased susceptibility to infection (ADA, 2003) [1]. Although DM is a non-curable disease but the life expectancy of the diabetic patient can be increased by successful management of ongoing veterinary treatment and a long-term commitment by the owners (Aptekmann and Schwartz, 2011) [5].

Pathogenesis and classification

Diabetes is indicated by a deficiency of insulin, a hormone released by the pancreas or a lack of insulin response. After each meal, the digestive system breaks down food (carbohydrates) into glucose, whereupon insulin regulates the transportation and uptake to various cells and tissues. It is incredibly challenging for a dog to metabolize glucose correctly in the absence of or poor response to insulin, and as a result, its concentration rises, leading to hyperglycemia (increased blood sugar levels). Pathophysiologically, it is a syndrome associated with protracted hyperglycemia due to loss or dysfunction of insulin secretion by pancreatic beta cells, diminished insulin sensitivity in tissues, or both (Audrey, 2012 and Wubie and Getaneh, 2015) [7, 110]. In the dog, beta-cell loss tends to be rapid and progressive, and is usually due to immune-mediated destruction, vacuolar degeneration, or pancreatitis (Behrend *et al*., 2018) [11]. The disease is characterised by hyperglycaemia and glucosuria when blood glucose concentration exceeds 180 – 220 mg/dl in dogs (Rand and Fleeman, 2012) [85]. Insulin deficiency diabetes (Type I) is suggested to be caused either by genetic disposition or autoimmune destruction of insulin producing beta cells, pancreatitis/ exocrine pancreatic disease or secondary chronic hyperglycemia (Papa *et al* 2011, Stoy 2014) [82, 101]. Insulin resistance, also known as Type 2 diabetes, causes peripheral insulin resistance in the non-functional islets of Langerhans, where, in addition to metabolic abnormalities and environmental factors, other disorders, such as hyperadrenocorticism in dogs, where excessive cortisol production inhibits insulin activity, and acromegaly, play a role (Blois *et al* 2011) [13]. Chronic pancreatitis can lead to exocrine pancreatic insufficiency and has been observed to cause diabetes. Additionally, pancreatic complication might arise from iatrogenic provocations, plus the common cause of an inactive lifestyle, leading to various degrees of obesity. Compensatory hyperinsulinaemia has been identified in obese dogs (Tvarijonaviciute *et al*, 2012) [103] but consequent overt DM is not yet reported. Dogs mainly manifest type 1 or insulin-dependent diabetes mellitus and generally require exogenous insulin treatment throughout their entire life (Ettinger & Feldman 2000; Bachem 2015) [30, 8]. The third form of DM though a type of IRD, has also been reported called as gestational DM (GDM), or diestrus-associated DM in dog which mainly affects middle-aged bitches in the latter half of gestation with a breed predisposition toward Nordic Spitz (Fall *et al* 2008) [32]. GDM has been reported to resolve within days to weeks after whelping or termination of pregnancy. GDM is attributed to reduced insulin sensitivity in healthy bitch after 1 month of gestation and increase levels of progesterone (Kim *et al* 2019) [58]. Higher level of progesterone during diestrus in bitches leads to Glucose intolerance and overt diabetes and it also stimulates increased production of growth hormone from the mammary gland of bitches, which is a potent inducer of insulin resistance (Mared *et al* 2012) [65]. Juvenile diabetes in canine, a form of IDD has also been reported and is particularly prevalent in Golden retrievers, German shepherd and Keeshonds. Pre-diabetic form in the dog has been suggested in non-diabetic dogs with chronic pancreatitis due to β-cell loss (Caney 2013) [94].

Signalment and risk factors

Various subtypes of canine diabetes mellitus (CDM) have been identified based on aetiopathogenesis (Nelson and Reusch 2014 and Gilor *et al* 2016) [76, 41]. The evidence for an islet autoimmune aetiology in canine diabetes mellitus was weekly unknown. (Ahlgren *et al*., 2014; Gilor *et al*., 2016) [2, 41]. DM tends to occur in middle aged to older dogs (five-12 years of age) (Davison *et al*., 2005; Hess, 2013) [25, 48]. Female dogs were traditionally thought to be affected twice as frequently as males (Guptill *et al*., 2003; Marmor *et al*., 1982) [43, 66], but in a 2005 UK survey, only 53 per cent of the dogs were female (Catchpole *et al*, 2005, Davison *et al*., 2005) [20, 25]. This trend is most likely because of the increasing practice of elective neutering. Das and Lodh (2015) [24] reported even higher (73.3%) prevalence among females. Intact female dogs may be transiently or permanently diabetic due to the insulin-resistant effects of the diestrus phase. Insulin antagonism as a result of pathological (endocrine or iatrogenic) or physiological (gestation or dioestrus) processes is also thought to be a component of the development of the disorder (Watson *et al*., 2007, Catchpole *et al*., 2008b, Fall *et al*., 2010) [106, 19, 31]. Some studies have shown a winter peak in the onset of canine diabetes (Davison *et al*., 2005; Atkins & MacDonald, 1987) [25, 6] whereas in other studies no seasonal predisposition has been found (Guptill *et al*., 2003; Marmor *et al*., 1982) [43, 66]. Dogs are thought to be resistant to disease comparable to type 2 diabetes in humans (Verkest *et al*., 2011) [105]. However, reversible insulin resistance and greater postprandial blood glucose concentrations were associated with canine obesity (German *et al*., 2009, Verkest *et al*., 2012) [40, 104]. Two studies reported an association between excess weight and canine DM (Klinkenberg *et al*., 2006, Wejdmark *et al*., 2011) [59, 107], but they should be viewed with some caution because body condition score was owner-perceived and recorded after DM diagnosis. Genetics is a suspected risk factor and certain breeds of dogs like Australian terriers, beagles, Samoyeds, Poodles, Keeshounds, Alaskan Malamutes, Finnish Spitzes, Miniature Schnauzers, Tibetan Terrier, Yorkshire Terrier, Cairn Terrier and English Springer Spaniels are more susceptible (Davison *et al*., 2005; Fracassi *et al*., 2004; Guptill *et al*., 2003; Hess *et al*., 2000a; Hess *et al*., 2000) [25, 38, 43, 50, 47]. DLA (dog leukocyte antigen) haplotypes were described with higher prevalence in predisposed breeds in comparison to less predisposed ones, and cell mediated autoimmune destruction of beta-cells has been previously described in up to 50% of diabetic dogs (Catchpole *et al*., 2008a) [18]. Although genetic predisposition is likely important in canine diabetes (Gilor *et al*., 2016) [41], some environmental factors seem to be risk factors for diabetes development such as obesity, lack of exercise, and overfeeding (Klinkenberg *et al*., 2006) [59]. Risk factors for developing DM include insulin resistance caused by obesity, certain diseases (e.g. acromegaly and hyperadrenocorticism [HAC], hypertriglyceridemia, and hypothyroidism (Blois *et al*., 2011) [13], dental disease, systemic infection and pregnancy/diestrus, or medications (e.g., steroids, progestins, cyclosporine). Extensive pancreatic damage, resulting from chronic pancreatitis, is responsible for the development of diabetes in approximately 28 per cent of diabetic dogs (Alejandro *et al*., 1988; Verkest *et al*., 2012) [3, 104]. However, diseases of the exocrine pancreas, progesterone controlled GH overproduction, and secondary to hypercortisolism have been known as other causative factors for diabetes mellitus (Hoenig and Dawe, 1992; Rand *et al*., 2004; Catchpole *et al*., 2005; Gilor *et al*., 2016) [52, 86, 20, 41].

Clinical Signs

Diabetic animals are subject to many of the same problems described in human diabetics. Diabetics are more susceptible to infection, and wound healing is often impaired. Decreased insulin promotes lipolysis and moderate hyperlipidemia, which can lead to falsely lowered fructosamine levels, impaired renal circulation, and atherosclerosis. Regardless of the underlying etiology, classic clinical signs of Polyuria/Polydipsia develop when the blood glucose concentration exceeds the renal tubular threshold (>180mg/l), in turn causing osmotic diuresis. Polyphagia (excess eating), hyperglycaemia (high blood glucose), Glucosuria (glucose in the urine), Weight loss, lethargy, Cataract, Hepatomegaly, Retinopathy, Urinary Tract Infection, occulusive vascular disease muscle wasting and infections of the respiratory tracts may be noted on clinical examination (Herrtage, 2009) [45]. Ulcerative skin lesions and cutaneous xanthomata have occasionally been reported. Hyperglycemic, hypoinsulinemic animals continue to lose weight despite an increased appetite and an increased intake because they are not able to use glucose (Bennett, 2002) [12]. This increased susceptibility to infection may be related to impaired chemotactic, phagocytic and antimicrobial activity due to decreased neutrophil function (Bruyette, 2013) [15]. Weight loss, although a significant feature of chronic DM, might not be noticed in dogs that have recently become diabetic (Hess *et al*, 2000) [47]. Many unregulated diabetic animals would present with vomiting and diarrhoea that can exacerbate electrolyte abnormalities seen with the osmotic diuresis present in an uncontrolled state. Without effective treatment, dogs will develop ketonaemia, ketonuria and eventually ketoacidosis. Such cases are presented with lethargy, anorexia, vomiting and dehydration. Ketoacidosis is a life-threatening complication of DM that requires immediate intervention (Hess *et al*, 2000) [47].

Polyuria: Due to high levels of solutes in the renal tubule, a passive osmotic diuresis (solute diuresis) occurs, resulting in an increase in urine volume. When urinary glucose levels (> 250 mg/dl) surpass tubular reabsorption capability, high glucose levels in the renal tubules result, and water follows passively, resulting in glucosuria and increased urine volume (Maddukuri, 2012) [63].

Polydipsia: Dehydration results from osmotic diuresis which leads to decreased circulating blood volume and decreased blood pressure. The fall in blood pressure triggers homeostatic mechanisms for maintaining blood pressure, including secretion of ADH, thirst that causes constant drinking (polydipsia) and cardiovascular compensations. (Sillverthorn, 2010) [98].

Polyphagia: The metabolism of the brain is not insulin dependent, however, neurons in the brain's satiety center are insulin sensitive. Thus, in the absence of insulin, the satiety center is unable to take up plasma glucose. The center unable to take up glucose perceives itself as experiencing starvation and allows the feeding center to increase food intake (Sillverthorn, 2010) [98].

Cataract: It has been reported that diabetic dogs, which have poor glycemic control and wide fluctuations in blood glucose, have higher risks of rapid development of cataracts (Bennett, 2002) [12]. Cataracts develop frequently as a result of the unique sorbitol pathway by which glucose is metabolised in the lenses, leading to oedema and opacification. The development of cataracts can be rapid, with owners reporting a sudden onset of blindness, however, it has been reported in 50% of dogs within five to six months of diagnosis, with the number increasing to 80% after 16 months regardless of the appropriateness of diabetic control (Beam *et al*, 1999) [9]. Out of 132 diabetic dogs referred to a university referral hospital, cataract formation in 14% of diabetic dogs was diagnosed (Beam *et al*., 1999) [9] with osmotic changes in the lens, glycosylation of structural proteins, and a decreased concentration of antioxidants. In dogs there is cataract, rapid lens intumescence and spontaneous lens capsule rupture which is associated with DM (Hess *et al*, 2000; Comazzi *et al.*, 2008) [47, 21].

Urinary Tract Infections: UTIs are seen, in 21% to 37% of dogs with DM being culture-positive at presentation. Potential mechanisms suggested to increase the risk of UTI in dogs with DM include enhanced bacterial growth in urine due to the presence of glucosuria and decreased neutrophilic chemotaxis secondary to the glucosuria (Forrester *et al*, 1999; Hess *et al*, 2000) [37,47].

Diagnosis

Diabetic dogs are often undiagnosed in Asian countries including India attributed to lack of awareness amongst both pet owners and veterinary clinicians. Over the years, Diagnosis of Diabete mellitus has changed. Initially, the diagnosis of DM was mainly based on glycosuria. Indirect ways of monitoring canine diabetics include assessment of water intake, quantification of urine glucose, ketones, and measurement of glycated/ glycosylated protein concentrations. Direct monitoring methods include serial blood glucose measurements (BG "curve") or continuous BG monitoring (Cook 2012) [23]. Diabetes mellitus is diagnosed by demonstration of persistent fasting hyperglycaemia and glycosuria with consistent clinical signs. Normal reference values for blood glucose in healthy dogs range from 75 to 120 mg/dl. The renal threshold for glucose is 180 mg/dl (Bruyette, 2013) [15]. Glycosuria is clinically present when blood sugar level exceeds the renal threshold. The use of glucometers and urine reagent strips allow a rapid and relatively inexpensive method of diagnosing canine DM.

The initial evaluation of the diabetic dog should be done as (Behrend *et al*., 2018) [11]:

1. The overall health including the history, diet and concurrent medications with complete physical examination should be made.
2. Complications that may be associated with the diabetes like cataracts, ketoacidosis should be identified.
3. Identify any concurrent conditions typically associated with the disease (e.g., urinary tract infections, pancreatitis).
4. Identify any conditions that may interfere with the patient's response to treatment (e.g., hyperthyroidism, renal disease, hyperadrenocorticism).
5. Evaluate for risk factors such as obesity, pancreatitis, insulin-resistant disease, diabetogenic medications, and diestrus in female dogs.

However, after the diagnosis has been made, a more complete examination of the dog is recommended, since it is critical to identify any concurrent illnesses that require treatment or that may interfere with long-term diabetic stability. The minimum laboratory evaluation in any newly diagnosed diabetic dog should include haematology, serum biochemistry and urinalysis with bacterial culture. The haematology is often unremarkable, but a stress leucogram may be present. On

biochemistry, hypercholesterolaemia, hyperglycaemia, hypertriglyceridaemia, and increased alanine aminotransferase and alkaline phosphatase activities are commonly present. Widespread hepatic hydropic changes could result in abnormally elevated liver enzymes ALP, ALT and AST. Hepatomegaly could lead to slight hepatic cholestasis and electrolytes imbalances. Affected animals may also have elevated serum concentrations of triglyceride and cholesterol due to increased lipolysis. In severe cases, urine test results may also show evidence of abnormally high levels of ketone bodies hence causing ketonuria.

Glycosuria is consistently found on urinalysis, while the presence of proteinuria, bacteriuria and ketonuria are more variable. Diabetic dogs have more viscous urine than normal and often have a sweet odor and high specific gravity with increase in blood glucose levels (Wubie and Getaneh, 2015) [110]. In dogs diagnosis of immune-mediated DM can be evaluated by β-cell specific antibodies and C-peptide concentration. The introduction of diagnostic testing of blood samples for fructosamine and glycosylated haemoglobin (HbA1C) has provided additional option for monitoring of glycemic control in veterinary patients (Kumar *et al* 2014) [61]. There are several alternative biomarkers to HbA1c in use nowadays, including fructosamine, Glycated Albumin (GA), 1,5-AG, and continuous glucose monitoring. Serum fructosamine and GA have been proposed useful tools for monitoring of short-term glycemic control. These biomarkers not only reflect well glycemic control in hematologic disorder, but also represent postprandial glucose fluctuation. Serum 1,5-AG may be useful for estimating within-day glucose variation. Use of these nontraditional tests can be more helpful in the management of diabetes as complement traditional measures (Lee *et al*, 2013) [62].

1. C-peptide

In human patients measurement of C-peptide provides a sensitive and clinically valid assessment of β-cell function (Palmer *et al*., 2004) [81]. During the processing of proinsulin, a peptide called C-peptide is cleaved off to form insulin. Measurement of C-peptide provides a sensitive and clinically validated assessment of β-cell function (Palmer *et al*., 2004) [81]. Fall *et al.* (2009) [33] reported that diabetic dogs, had low concentrations of C- peptide and insulin and high concentrations of glucose.

2. Glycosylated Hemoglobin

In systemic circulation, glycosylated haemoglobin (GHb) is the result of an irreversible, nonenzymatic, and insulin-independent binding of glucose to haemoglobin. Glucose levels and red blood cell availability have a direct impact on glycosylation. The half-life of circulating GHb is proportional to the longevity of red blood cells. Canine red blood cells have a longer lifespan (100 days) than cats (<68 days). Thus, GHb is used to measure long-term glucose regulation over the previous 10- to 14-week period in the dog and 6- to 9-week period in the cat (Elliot *et al*., 1999) [29]. As such, this test is not appropriate for an animal that is still undergoing regular changes in insulin dosages. GHb has been proven to be a reliable indicator of long-term glucose control in both the dog and the cat (Hoenig and Ferguson, 1999; Marca and Loste, 2000) [53, 64]. Reusch (2009) [90] reported reference range of GHb for healthy and diabetic dog varying between 2.3-4.3% and 4.5-8.6%, respectively. (Elliot *et al.*, 1997; Marca and Loste, 2000) [28, 64]. Aldose reductase is detected in high amounts in the crystalline lens, neurons, and erythrocytes of diabetic dogs. With ketonuria, the sorbitol concentration in diabetic dogs' erythrocytes was shown to be considerably greater (Comazzi *et al* 2008) [21].

3. Fructosamine

Fructosamine is a ketoamine produced by the glycosylation of fructose to total serum protein, primarily albumin. The mean blood glucose concentrations over the past two to three weeks are reflected in serum fructosamine levels, which can be employed clinically as markers of recent glycemic control modifications (Jensen, 1995) [56]. The reported upper limit of serum fructosamine in dog is 374 µmol/L (Reusch *et al*, 1993) [89].When used in combination with other measures, it may play a role in identifying fluctuating glucose levels in DM patients with stable HbA1c. There is a good correlation between HbA1c values and serum fructosamine (Narbonne *et al*. 2001, Kumar *et al*., 2014) [75, 61].

4. Glycated albumin

GA refers to the ratio of serum GA to total albumin. GA levels are roughly three times greater than HbA1c levels. Considering albumin has a shorter half-life than RBC, GA reflects a shorter period of glycemic control (two to three weeks) than HbA1c (Koga *et al*., 2013) [60]. GA and fructosamine are strongly associated with HbA1c and fasting glucose (Juraschek *et al*., 2012; Lee *et al*., 2013; Shin *et al.*, 2013) [57, 62, 97].

GA is unaffected by aberrant RBC lifetime or variable haemoglobin, making it a particularly valuable glycemic control indicator in hematologic illnesses like anaemia, haemorrhage, renal anaemia, pregnancy, liver cirrhosis, and neonatal DM. GA will provide a more accurate picture of recent glycemia. The connection between GA and postprandial glucose levels and glucose excursions is stronger as compared to HbAIC (Koga *et al.*, 2013) [60]. Because the glycation speed of GA is ten times faster than HbA1c, GA is likely to reflect variations in blood glucose and postprandial hyperglycemia in combination with HbA1c and its value. It has been reported that GA is related to daily glucose fluctuation (Matsumoto *et al*., 2012) [69].

5. 1,5-anhydroglucitol

The 1-deoxy form of glucose known as 1,5-AG is a naturally occurring dietary polyol. During euglycemia, serum 1,5-AG concentrations are maintained at a constant steady state due to renal tubular reabsorption of all of the serum 1,5-AG. The normal serum concentration of 1,5-AG has been reported to be 12–40 µg/mL (Yamanouchi and Akanuma, 1994) [110]. Serum 1,5-AG competes with very high levels of glucose for reabsorption into the kidney. Within 24 hours of a rise in serum glucose to >180 mg/dL, serum circulating 1,5AG falls as urinary losses increase (Buse *et al*., 2003; Dungan 2008) [16, 27]. Lower serum 1,5-AG levels reflect high circulating glucose and the occurrence of glycosuria over the past 1 to 2 weeks (Stettler *et al*., 2008) [100]. Measurement of serum 1,5-AG may reflect postprandial glycemic excursion rather than HbA1c (Dungan *et al*., 2006) [26]. While 1,5-AG may have clinical implications for the evaluation and treatment of glycemic excursions in type 1 diabetes (Seok *et al*., 2015) [96], this test is affected by alteration in renal hemodynamics.

Radiographic studies, including x-rays and ultrasonography, can be helpful for the diagnosis of concurrent diseases and complications due to diabetes. Abdominal X-rays and

ultrasound will help to determine the presence of kidney stones and/or inflammation of the pancreas and liver as well as other associated abnormalities

Treatment

The mainstay of treatment for clinical DM in dogs is insulin along with dietary modification to maintain the quality of life of the patient. The major goal is to eliminate indications that are visible to the owner (e.g., reduced PU/PD and steady body weight). Clinical symptoms can be reduced by limiting large fluctuations in blood glucose concentration and keeping it below the renal threshold. It is not as critical to keep blood glucose levels within the reference interval 24 hours a day, seven days a week (Rucinsky *et al*, 2010) [92].

These goals are achieved through

a. Proper insulin administration
b. Dietary therapy
c. Exercise
d. Avoidance or management of concurrent inflammatory, infectious, neoplastic or hormonal diseases

Insulin Therapy: Insulin therapy is the cornerstone of management for diabetic dogs and many insulin types have been shown to be effective (Schoeman and Herrtage 2007 and Qadri *et al*., 2015) [95, 84]. Insulin is a polypeptide hormone synthesized in humans and other mammals within the beta cells of the islets of Langerhans in the pancreas (Anonymus, 2011) [4]. The ability of insulin to mediate tissue glucose uptake is a critical step in maintaining glucose homeostasis and in clearing the postprandial glucose load (Ginsberg *et al*., 1975; Reaven, 1988) [44, 87]. Insulin regulates blood glucose levels by its effects on the liver and skeletal muscles. Normal blood glucose levels are maintained by sustenance of balance between hepatic glucose production and glucose utilization by the peripheral tissues. Insulin regulates hepatic gluconeogenesis and promotes glucose catabolism by the skeletal muscles. In type 2 diabetes mellitus, post-absorptive hepatic glucose production is increased, which positively correlates with fasting plasma glucose concentration. Between gluconeogenesis and glycogenolysis, gluconeogenesis appears to be drastically increased in type 2 diabetes mellitus (Consoli, 1992) [22]. Various insulin is classified according to its promptness, duration and intensity of action.

Short acting insulin: It is used chiefly in the management of DKA. It may be given by any route intramuscular/ intravenous. It has a rapid onset of action (minutes) and a short duration of effect (hours) and is very potent.

Intermediate acting insulin: Intermediate insulin injections are commonly used for glycemic control in insulin dependent diabetic dogs acting as a replacement for natural insulin. They are used mainly on a twice daily basis given subcutaneously. They have an intermediate duration of effect in dogs (lasting 6–8 hours usually) and are moderately potent.

Long acting insulin: It has a long duration of effect (usually between 12 and 18 hours). It is the least potent of all the insulins.

In diabetic dogs, the Behrend *et al*. (2018) [11] recommends a starting dose of 0.25 U/kg q 12 hr. Most dogs are well controlled on insulin at an average dose of 0.5 U/kg q 12 hr with a range of 0.2–1.0 U/kg.

Initiation of Insulin Therapy

For the treatment of non-ketoacidotic animals, intermediate- or long-acting insulin should be used. This type of insulin must be administered with a 40 international units (I.U.) syringe. The recommended starting dosage is 0.25-0.5 I.U./kg of the optimal body weight twice daily, although most dogs are safely started on 0.5 I.U./kg twice daily (Fleeman and Rand, 2003; Behrend, 2006) [36, 10]. Two injectable insulin preparations commonly used are neutral protamine Hagedorn (NPH) insulin and insulin glargine. NPH insulin is also known as human isophane insulin, and was created by Novo Nordisk, one of the world's leading companies in diabetes care, in 1946. It is considered to be an intermediate acting insulin with an approximate time of onset of 2 h and duration of action of 18 h (Mori *et al*., 2008) [73]. Its original formula consisted of porcine insulin being reacted with zinc chloride and protamine to form a protein complex with a ratio of free and bound insulin, providing action between regular insulin and protamine zinc insulin. It was discovered that protamine was able to prolong the effects of injected insulin. Currently though, animal insulin have been replaced by synthetic recombinant human insulin in NPH insulin formulations.

Alternatively, insulin glargine is a recently developed, long-acting, human synthetic basal insulin analogue. It has a 24 h duration of action with a peakless profile thus, it more closely resembles the basal insulin secretion of normal pancreatic β-cells. Insulin glargine differs from human insulin in that the amino acid asparagine at position A21 is replaced by glycine and two arginines are added to the terminal B-chain. Insulin glargine is formulated at pH 4.0, where it is completely water soluble. However, after subcutaneous injection, the body, at physiological pH levels, slowly neutralizes the solution causing insulin microcrystals to gradually precipitate from the insulin glargine solution, which then release insulin in biologically active form (Hilgenfeld *et al*. 1985) [51]. This gradual process ensures that small amounts of insulin glargine are released into the body continuously, giving an almost peakless profile, and prolonging the duration of action (Murphy *et al*. 2003; Rossetti *et al*. 2003) [74, 91].

The risk of hypoglycemic episodes is higher when insulin is administered once daily, and most dogs need a twice-daily administration for an adequate glycemic control (Hess and Ward, 2000; Fleeman and Rand, 2001; Davison *et al*., 2005; Monroe *et al*., 2005; Behrend, 2006) [46, 35, 25, 72 10]. Newly diagnosed dogs can be closely observed by the owner at home or can be hospitalized for 24 to 48 hours to evaluate the insulin response. During hospitalization, blood glucose concentrations can be measured at the time of administration and three, six and nine hours later, while further diagnostic tests are performed. The goal is to identify dogs that might be at risk for hypoglycemia (Miller, 1995; Fleeman and Rand, 2001; Behrend, 2006) [71, 35, 10]. Patients, in which the glucose concentration drops below 5.6 mmol/l (100 mg/dl) during the first 24 to 48 hours of monitoring, should be discharged on a dose that is reduced by 25%. Since it takes several days for the diabetic dog to adjust to the insulin dose or type, the dosage in persistently hyperglycemic dogs is not raised until the first recheck five to seven days later (Miller, 1995; Fleeman and Rand, 2001; Monroe *et al*., 2005; Behrend, 2006) [71, 35, 72, 10]. A crucial part in the initiation of therapy is a good owner communication and education. Dog owners should be aware of the lifelong commitment, feel comfortable administering the insulin, and they should be taught to recognize possible life-threatening complications of the disease. It is important to explain to the owner that it might take at least one to two months to establish an adequate

insulin treatment protocol in uncomplicated diabetes mellitus (Fleeman and Rand, 2001; Bennet, 2002; Mathes, 2002) [35, 12, 68].

Dietary therapy

Life style management is apparently the cornerstone of management of diabetes mellitus. It is recognized as being an essential part of diabetes and cardiovascular disease prevention. Meta-analyses demonstrate that lifestyle interventions, including diet and physical activity, led to a 63% reduction in diabetes incidence in those at high risk (Rebecca *et al*., 2009) [88]. The dietary management of diabetes mellitus is a complement of lifestyle management. It has a positive effect on long term health and quality of life. Dietary management aims at optimal metabolic control by establishing a balance between food intake, physical activity, and medication to avoid complications. In type 2 diabetes, the dietary objective is for improved glycemic and lipid levels and correcting obesity, maintaining consistency in timing of feeding and caloric consent and minimizing post-prandial glycaemic swings (Piero *et al*., 2006) [83].

Dietary fibre and complex carbohydrates (CHO): Diets high in fibre and complex carbohydrates (CHO) are optimal for weight loss because they decrease glucose absorption, reduce postprandial glucose swings, and promote weight loss. Studies show that offering a high complex carbohydrate (> 50% dry matter) and high fibre (> 10% dry matter) diet to dogs with DM is beneficial (Qadri *et al*., 2015) [84]. Supplementation of a canned food with insoluble or soluble fibre reduced the magnitude of postprandial glycaemia in diabetic dogs (Nelson *et al*., 1991, Graham *et al* 2007) [77, 42]. High fiber diets are often not all that palatable and time for gradual adaptation should be allowed. These benefits of dietary fibre are most likely mediated through reduction of postprandial glycaemia, which can be attributed to delayed gastric emptying, slowed starch hydrolysis, interference with glucose absorption and altered intestinal transit time (Qadri *et al*., 2015) [84]. These mechanisms also contribute to the lowering of plasma cholesterol and triglycerides by dietary fibre, along with interference with bile acid circulation (Ide *et al*., 1990) [50]. A diabetes patient may be overweight and need to reduce weight to reach ideal weight, but should not be skinny. Insulin resistance is induced by obesity. Because diabetic dogs are prone to hepatic lipidosis, pancreatitis, and hypercholesterolemia, low-fat diets are likely to be beneficial. Canned or dry foods are the diet of choice in diabetics since they contain predominantly complex carbohydrates that require digestion before absorption, they minimize postprandial fluctuations in blood glucose concentration (Ganguly, 2014) [39]. There are no firm recommendations regarding protein content and a low restricted fat diet is usually recommended.

Feeding schedule: Feeding must be regular, scheduled and always the same amount. Routine is the key to managing diabetic animals. Traditionally feeding occurs twice daily with injections, i.e., food in the gut should be providing glucose to the blood at the same time that the injected insulin has its peak effect (Pillay and Aldous, 2016; Sullivant, 2017) [93, 102].

Exercise: Regular scheduled exercise helps glycaemic control through weight management and enhanced insulin sensitivity.

Monitoring

When it comes to managing diabetes, good outcomes depend on regular monitoring (Sullivant, 2017) [102]. Effective monitoring is essential for the management of dogs and cats with diabetes mellitus. However, methods for evaluating glycemic control must be tailored to meet both the needs of the patient and the expectations of the owner (Cook, 2012) [23]. The outcomes of monitoring can help make better medical decisions and improve patients' treatment efficacy and quality of life. Although normalising clinical symptoms (such as resolution of PU/PD/PP and attaining appropriate body weight) takes precedence over all other monitoring indicators, diabetic patients should have their blood glucose levels monitored as well. After diagnosis and initiation of insulin, a few “spot” checks over the next week are helpful to monitor for hypoglycaemia. New management strategies and therapies for canine DM are currently being developed, which may alter the outcome of affected animals and subsequently impact on the future epidemiology of the disease. Clients may measure water consumption at home and keep a log of water intake to document trends. Dog owners should be encouraged to leash walk, so they can better estimate urination (Bennett, 2002) [12]. Older pets are often more frequently diagnosed with diabetes, which will then require lifelong treatment and management with long-term medications and/or special or restricted diets. Therefore, once the disease is diagnosed, implementing a monitoring program that includes regularly scheduled diagnostic testing tailored to the individual patient is crucial to judge the efficacy of treatment plans. Frequent communication between the veterinary healthcare team is critical to the successful care of a diabetic patient, as are regularly scheduled recheck examinations, during which clinical signs and body weight are assessed. Management of a diabetic pet may be stressful for owners and may impair their own quality of life. A survey revealed areas with the most negative impact, such as “difficulties leaving dog/cat with family or friends”, “boarding difficulties” “vision (dog)”, “hypoglycemia”, “work life”, “social life”, “costs”, “wanting more control” (Niessen *et al* 2012) [79]. It is, therefore, advisable to discuss with every single owner his/her biggest worries and curtail the treatment and monitoring plan accordingly. For instance, if hypoglycemia is the biggest worry one should avoid aggressive treatment protocols, if costs are a major concern it may be necessary to simplify the treatment, if more control is desired home-monitoring should be introduced (Sparkes *et al* 2015) [100]. Therapy of the diabetic patient is monitored by assessing clinical response, evaluating blood glucose curves and determining fructosamine concentrations. Evaluation of clinical improvement or lack thereof is crucial for evaluating response to therapy. In addition, periodic monitoring of urine glucose levels by the owner can provide valuable additional information. Serial blood glucose curves are used concurrently with fructosamine levels to monitor the effectiveness of insulin therapy. Blood glucose curves can provide valuable information about insulin dose, including duration of insulin action, blood glucose nadir and presence or absence of rebound hyperglycemia (Behrend *et al*, 2018) [11]. Determination of fructosamine levels has come to be an integral part of the monitoring of insulin therapy of diabetes mellitus in both dogs. In a review of 53 cases of canine DM, BG measurements and fructosamine concentrations were consistent with good glycemic control in only 60 percent of dogs judged to have good clinical control (Briggs *et al*., 2000) [14]. Recheck evaluations, fructosamine levels and BG curves are determined every 2–4 weeks during the initial regulation

of the diabetic patient and then every 3–6 months during long-term management. Lastly, underlying or concurrent disease states that complicate diabetes management or cause insulin resistance should be addressed if possible; examples include hyperadrenocorticism and acromegaly.

The goals of any therapy for Insulin-deficient diabetes are to attain normoglycemia and avoid hypoglycemia. With conventional replacement therapy, the first aim requires the use of high doses of Insulin, which increases the likelihood of hypoglycemic episodes (The United Kingdom Prospective Diabetes Study). Various alternative remedies for canine diabetes mellitus have been tried, but only a few have proven to be highly efficacious. Single intramuscular dosages of adeno-associated virus (AAV) vectors could be leveraged to engineer the skeletal muscle and decrease diabetic hyperglycemia (Mas *et al* 2006; Callejas *et al*., 2013) [67, 17]. Using AAVs of serotype 1 (AAV1) encoding the insulin (Ins) and glucokinase (Gck) genes, had shown long-term control of hyperglycemia and prevention of secondary complications in mice with streptozotocin-induced diabetes (Otaegui *et al*., 2003) [81]. Hence it was reported that the successful control of diabetic hyperglycemia after a single delivery of the human Insulin and rat Glucokinase genes to the muscle of dogs, with therapeutic efficacy demonstrated for a period that essentially covered the lifetime of the animals. Glycemia was successfully controlled over a long period of time without the need of exogenous insulin. Multiple samples from treated muscles with normal morphology indicated the survival of vector genomes and therapeutic transgene expression years after vector delivery (Jaen *et al.*, 2017) [55].

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