

Literary Approach to Glucose Metabolism Disorder in Dogs

Taysnara Keyla Gomes Silva Cavalcante¹, Elizabeth Simões do Amaral Alves² and João Manoel da Silva^{3*}

¹Veterinarian, Universidade Federal de Alagoas, Brazil

²Veterinarian and Biologist, Department of Animal Morphology and Physiology, Veterinarian, Federal Rural University of Pernambuco - UFRPE, Brazil

³Agronomist Engineer and Biologist, Northeast Network of Biotechnology, Universidade Federal de Alagoas, Brazil

***Corresponding Author:** João Manoel da Silva, Agronomist Engineer and Biologist, Northeast Network of Biotechnology, Universidade Federal de Alagoas, Brazil.

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Abstract

Endocrine diseases are clinical conditions present in routine veterinary medicine for dogs and cats. Hormones are necessary for the maintenance of organic homeostasis. Therefore, the dysfunction in its production or arrival in the action channels has consequences for the normal functioning of the organism, as well as the maintenance of the animal's healthy state. Blood glucose control is affected in some occasions in the animal's life and in the occurrence of some morbidities, such as Diabetes mellitus. Animals with changes in glycemic control have difficulty using or maintaining stored glucose, causing long periods of hyperglycemia. In this context, DM is an endocrinopathy resulting from the transient or definitive lack of insulin, characterized by a metabolic imbalance of fats, carbohydrates and proteins, due to the unavailability of this hormone. It is possible to conclude that among the endocrinopathies that can affect dogs, Diabetes mellitus has a high prevalence, and its diagnosis is quite common in routine veterinary clinics and hospitals. Due to its chronic nature and the need for periodic monitoring, the diagnosed animals start to establish a closer relationship with the veterinary medical professional, as well as with their guardians. Thus, this study aims to promote knowledge about aspects related to Diabetes mellitus, through the elaboration of a narrative review taking into account the historical return of diabetes mellitus in dogs diagnosed with this endocrine disorder.

Keywords: Animal Health; Endocrinopathy; Diabetes Mellitus; Insulin; Canine

Introduction

Endocrine diseases are clinical conditions present in routine veterinary medicine for dogs and cats. Due to their incidence, it is appropriate to understand that they result from some dysfunction in the metabolism of hormones in the body, whether due to failures in their production (excessive or deficient), establishment of immune-mediated or idiopathic resistance to their action, inadequate transport and /or disorders in the producing glands [1,2].

Hormones are proteins that have an action on tissues, necessary for the maintenance of organic homeostasis. Therefore, the dysfunction in its production or arrival in the action channels has consequences for the normal functioning of the organism, as well as the maintenance of the animal's healthy state. The endocrine pancreas is responsible for producing a hormone called insulin. More specifically, insulin is produced by β cells located in the islets of Langerhans, and it is a necessary hormone for the use of glucose in the body, that is, its transport to the tissues. The dysfunction and/or destruction of these specialized cells causes metabolic disorders that characterize Diabetes mellitus (DM) [3].

Blood glucose values considered within the normal range for the body of dogs comprise the range between 60 and 120 mg.dL⁻¹. Both, hypoglycemia and hyperglycemia cause injuries to the body. Hypoglycemic animals, for example, with blood glucose levels below normal present with tremors, disorientation and even convulsions [3]. It is possible to find cases in which the animal is in a state of coma, especially when dealing with patients with more severe stages, or when there is a delay in the search for a professional for the proper diagnosis, control and restoration of the animal's health [4].

Blood glucose control is affected in some occasions in the animal's life and in the occurrence of some morbidities, such as Diabetes mellitus. Animals with alterations in glycemic control have difficulty using or maintaining stored glucose, causing long periods of hyperglycemia. Therefore, a nutritional management that contributes to accelerating the reestablishment of normal blood glucose concentrations must be established by minimizing the postprandial response [5,6].

In this context, DM is an endocrinopathy resulting from the transient or definitive lack of insulin, characterized by a metabolic imbalance of fats, carbohydrates and proteins, due to the unavailability of this hormone. It is also characterized by an increase in blood glucose levels, a deficiency in the action or production of insulin, the hormone responsible for the use of glucose in cells and for maintaining its acceptable level for the body's homeostasis [7].

The disease is classified as type I DM, characterized by the destruction of the β cells of the pancreas, which are responsible for insulin production, and consequently, there is a deficiency in insulin production, due to genetic, immune-mediated or idiopathic factors [5]. In cases of type II DM, there is considerable production of normal levels of insulin, however there is evidence of a failure in its secretion, causing insulin resistance, in which the pathophysiological mechanism has not been fully elucidated, but it is believed that it can be related to factors such as obesity. Despite the different classification, both are similar with regard to the inability to regulate blood glucose levels [8].

Type I DM is quite common in dogs and is associated with immune-mediated destruction of β -cells, which results in absolute insulin deficiency in the animal body. Less common in dogs, it can also occur due to the development of insulin resistance, in general in obese or sedentary dogs, and even in bitches due to particularities in the reproductive cycle [8]. The onset of the pathology can be associated with comorbidities that start in the pancreas itself or in other glands, such as hyperadrenocorticism. It is a difficult disease for the tutor and for the veterinarian in search of stabilization and quality of life for the patient [9].

According to Nelson [10] the disease manifests itself clinically through polydipsia, polyphagia, weight loss and polyuria. However, many owners take the animal for consultation when they notice the presence of cataracts or sudden loss of vision, which already represent the progression of the disease. So, in addition to bilateral cataracts, the diabetic patient may have weakness and, depending on the progression of the disease, there may be ketosis and metabolic acidosis.

Females are at high risk of being affected in general. However, neutered males are more susceptible than whole animals. Canine DM most often refers to type I DM, as diabetic patients have an irreversible inability to produce insulin, there is a need for exogenous administration of the hormone [11], and type II DM is more frequent in cats.

DM is a disease that affects a lot of people, with a high prevalence worldwide and important for public health. Given the way people have treated their animals, for reasons of customs and the improper practice of offering leftover dog food, it has been observed that the number of cases that affect pets has increased. Although there is evidence that ancient civilizations already had the disease, there are established therapeutic protocols for the treatment, there are still significant incentives for research on this morbidity [8].

Through science and technological innovation, therapeutic protocols aimed at the maintenance and control of diabetic patients are already well defined. However, there is a need to produce and incite knowledge related to how to provide quality of life to the animal that

lives with the disease and its guardians. Provide guidelines that lead the tutor to adhere to and follow the protocols, properly, and the veterinarian to have more empathy about the problematization of the disease in the family environment that surrounds that pet. Thus, this study aims to promote knowledge about aspects related to Diabetes mellitus, through the elaboration of a narrative review taking into account the historical return of diabetes mellitus in dogs diagnosed with this endocrine disorder.

Diabetes mellitus

Diabetes mellitus is a disorder of endocrine origin, chronic and systemic that affects dogs and cats, becoming fatal when diagnosis and treatment are not carried out properly (IMAI, 2009). The disease is characterized by a set of metabolic disorders, has a multifactorial etiology and has a predisposition to certain racial groups [12,13].

The endocrinopathy that is present in the clinical practice of veterinarians with high worldwide prevalence, commonly affects animals of any age group, females are more affected than males, with a predisposition for dogs between 4 and 14 years old, and belonging to the following breeds: Cairn Terrier, Poodle, Samoyeda, Schnauzer, Tibetan Terrier, Yorkshire Terrier, among others [9-11]. Endocrinopathy is present in the clinical practice of veterinarians with a high worldwide prevalence, commonly affecting middle-aged patients to the elderly, being more frequent acquired as a result of insulin antagonism during the diestrus phase and the most predisposed breeds already reported are Toy Poodle and miniature, Australian Terrier, Schnauzer, Labrador, Pinscher and Dachshund, although this predisposition may vary depending on the region studied and thus, on the fad and racial preference of the place [14].

In the presence of the disease, there is evidence of chronic hyperglycemia resulting from decreased tissue sensitivity to the action of insulin and/or deficiency in its secretion. Due to the lack of international consensus for the classification of DM in dogs and cats, the classification of the disease in humans as Diabetes mellitus type I and Diabetes mellitus type II is taken into account, based on the need for treatment with exogenous administration of insulin. It has been acceptable to consider that dogs are mostly affected by DM type I (insulin-dependent), and cats, in turn, affected by DM type II (insulin-independent), they have the possibility of remission of the disease after treatment [7,11].

Etiology

The occurrence of canine diabetes mellitus can be attributed to a variety of genetic, inflammatory, hormonal and immunological factors. However, it is believed that the most common causative agents are genetic predisposition, presence of autoimmune mechanisms against the insulin molecule, continuous administration of drugs considered diabetogenic, such as glucocorticoids and progestins, obesity, pregnancy, infectious agents and secondary mechanisms to chronic pancreatitis, acromegaly and hyperadrenocorticism [11,15,16].

To Gonçalves [17] the offer of excessive or inadequate food for dogs, such as leftovers from human food, along with sedentary lifestyle, lack of space for the animal to move and spend its energies have resulted in the increase of new cases of obesity in the canine population, which represent around 25 - 35% of the total number of dogs. Once obesity is installed, the risk of occurring so-called endocrine diseases, which includes DM, becomes significant. To Silva, *et al.* [18] dietary factors such as high energy density, amount of food offered, number of meals, supply of snacks, change in the animals' lifestyle, genetic, social, cultural, metabolic and endocrine factors, determine the multifactorial character of Diabetes Mellitus.

Glucocorticoids, adrenaline, glucagon and growth hormone are considered to have a diabetogenic action in the body. Thus, when there is an increase in plasma levels, either as a result of exaggerated secretion, damage to degradation or via exogenous administration, an antagonism to insulin is established in peripheral tissues, together with the triggering of the mechanisms of gluconeogenesis, hepatic glycogenolysis, hyperinsulinemia, and impaired glucose tolerance. The most common DM in dogs is type I, in which the causative factors are

responsible for the destruction of pancreatic β cells and the establishment of resistance to the action of insulin in the body [12,15]. In DM, hyperglycemia is the result of a relative or absolute deficiency in insulin synthesis and secretion by β islet cells (type 1 DM), or a failure of target cells to recognize and respond to insulin (type 2 DM). canines, predominantly affected by type 1 DM, unlike felines and humans, knowing that type 1 DM can be primary (autoimmune) or secondary to extensive pancreatic lesion [27].

Clinical manifestations

The clinical manifestations evidenced by the patient are related to hyperglycemia, together with the body's inability to use glucose as a source of energy, resulting in polyuria, polydipsia, polyphagia, weight loss, weakness and bilateral cataracts. It is very common for the owner to report acute blindness secondary to cataract formation as the main complaint. However, this is due to lack of attention, as the four symptoms mentioned above, which are widespread in practice as the 4 P's of DM, mostly precede the ophthalmic condition [11,18].

Therefore, it is important to carry out the differential diagnosis and not only consider the symptoms to make the diagnosis. They manifest with different pathogenesis according to each case, whether it is the lack of secretion of antidiuretic hormone (ADH), lack of response to ADH, osmotic diuresis and primary polydipsia [19].

Cataract is characterized by lens opacity and represents one of the main causes of blindness in dogs. Its occurrence in dogs, despite being present in some diabetic patients, is linked to other initial causes, such as trauma, intraocular inflammation, nutritional or being of congenital origin, so the clinician must associate clinical symptoms with complementary tests to conclude the diagnosis of the disease. DM induces a series of ophthalmic disorders, which culminate in bilateral cataracts of acute onset and rapidly progressive, with blindness being the resulting clinical manifestation [19,20].

DM may appear more discreetly in some dogs with more controlled clinical manifestations, whose animals are controlled with regard to dehydration and the presence of ketonuria. In these cases the animals are active and do not present emesis. However, there are cases in which the animal arrives at the clinic with decompensated signs of DM, such as convulsion, emesis, respiratory distress and excretion of ketone bodies in the urine. These signs precede Diabetic Ketoacidosis, therefore, the clinician must act with the appropriate conduct to stabilize the animal before the disease progresses to CAD, which is one of the most reported emergencies in diabetic patients [21,22].

Pathophysiology

The control of blood glucose levels in the body effectively represents an important mechanism of hormonal homeostasis, and its mechanisms of action begin to act during the intestinal absorption of nutrients and after a few hours of its decline. The energetic substrate is produced from glycogenolysis and gluconeogenesis, mechanisms that occur in the liver [23].

The liver is the main effector organ of glycemic control, as it is the primary tissue included in glucose metabolism. Glucose secretion from it into the bloodstream occurs through glycogenolysis and gliogenesis [24], which are mechanisms responsible for the accumulation of glucose, which generates hyperglycemia.

The lack of insulin or resistance to its action in the body causes hyperglycemia to the detriment of the non-utilization of glucose by tissues. Filtered glucose is rapidly reabsorbed in the proximal renal tubules. However, when in excess in the blood, it exceeds the capacity of renal tubular reabsorption (180 mg.dL^{-1}), and this starts to be eliminated in the urine, together with water and other electrolytes by osmotic diuresis [18].

Thus, polyuria is evidenced and polydipsia sets in in a compensatory way, as the diabetic patient loses water and triggers the thirst mechanisms. The loss of glucose, which is an energy source, triggers a catabolism of fats (lipolysis) and proteins (proteolysis), which re-

sults in the loss of weight/muscle mass. Polyphagia, in turn, occurs due to the lack of nutrient input in the hypothalamic areas that signal satiety, so the animal remains continuously with the feeling of hunger [18,24].

The body's fluid and electrolyte balance is the result of the control carried out in the normalization of factors, such as thirst and urinary output, usually in response to changes in plasma osmolality and blood volume. In addition to being present in DM, increased urinary output (polyuria) and excessive thirst (polydipsia) are common clinical manifestations in the routine of small animal veterinary medicine [25].

Sudden vision loss in diabetic patients is frequently reported in dogs, which are susceptible to the development of diabetic cataract. This develops as a result of the association of increased membrane permeability and loss of lens cell function, favoring the entry and accumulation of osmotic products, such as sorbitol and fructose, glycolysis and oxidative degeneration of lens proteins [21,26].

Diagnosis

Diagnosis is based on anamnesis, animal history and identification of clinical manifestations considered classic of DM, such as polyuria, polydipsia, polyphagia and weight loss, together with evidence of hyperglycemia ($> 200 \text{ mg.dL}^{-1}$) and persistent glycosuria through laboratory tests [10]. According to Borin-Clivellenti and Malta [26], the occurrence of polyuria and polydipsia guides the diagnostic investigation of endocrine diseases, also serving as a parameter for evaluating the effectiveness of the treatment instituted, especially in the case of diabetic dogs.

The diagnosis of DM must be performed early with the determination of fasting blood glucose concentrations. To measure blood glucose, a blood sample from the animals' ears is used, after collection from the medial surface of the animal's external ear using a disposable hypodermic needle (25 x 0.7 mm). Then a test strip is inserted into the glucometer device, the blood sample is deposited on the test strip within a maximum period of fifteen seconds. The diagnosis of DM must be performed by measuring fasting glucose to observe hyperglycemia, fructosamine dosage, and performing urinalysis to prove glycosuria, as well as confirming concomitant ketonuria to lead to the diagnosis of diabetic ketoacidosis [27].

In a maximum of five seconds, the equipment expresses on its display the concentration of glucose in the sample in mg.dl^{-1} . In case the diagnosis is confirmed, tutors must be instructed to perform this procedure daily to monitor blood glucose and when necessary in the preparation of blood glucose curves required by the veterinarian [28]. In addition to the medial surface of the ear, blood sample collection can be performed on the inner surface of the labial mucosa and/or on the plantar pads.

Fructosamine consists of a glycolized enzyme resulting from the link between glucose and a serum protein. Therefore, the level of fructosamine in the blood shows the serum glucose concentration related to the last 2 or 3 weeks. Thus, the measurement of fructosamine is an important diagnostic tool and to monitor the diabetic patient [3,22].

When analyzing the blood count of a diabetic animal, but which does not present other clinical complications, parameters are usually found to be within the normal range. However, mild anemia and stress WBC may be present, with an increase in segmented neutrophils and lymphopenia. In cases of pancreatitis or concomitant infection, there is leukocytosis due to neutrophilia, with the presence of toxic neutrophils. The serum biochemical profile usually presents elevated levels of triglycerides, cholesterol, alkaline phosphatase and alanine aminotransferase. Urinalysis, in turn, presents glycosuria, increased density and, sporadically, proteinuria and ketonuria [7,10].

Complementary tests should be performed in order to confirm and/or rule out comorbidities, as these can negatively influence the patient's glycemic control. The concomitant occurrence of urinary tract infection can prevent the establishment of good glycemic control. The clinician, then, must make use of all the diagnostic tools he has to assess the animal's health. This includes urinalysis, urinary protein/creatinine ratio, SDMA (symmetric dimethylarginine), blood count, kidney and liver function, blood pressure and abdominal ultrasound.

Many tutors are resistant to performing the complementary exams requested by the veterinarian, often due to the economic impossibility. However, the risks must always be exposed, and if possible, negotiate their realization gradually, in order to investigate comorbidities that may hinder the proper treatment of the animal. If there is a urinary infection concomitant with DM, it must be treated, otherwise it will be quite difficult to achieve the animal's recovery.

The chronic and complex nature of the disease, as well as its series of complications, should not prevent the animal from receiving quality of life and adequate treatment. There must be good communication between the veterinarian and the tutor so that there are no doubts about all aspects involving the disease and for the latter to be committed to complying with the prescribed protocol and the periodic return for reassessment of the animal [6]. Furthermore, as it is a chronic disease, the sooner it is diagnosed, the faster treatment can be started and the better the chances of promoting the animal's quality of life [29].

Final Considerations

It is understood that among the endocrinopathies that can affect dogs, Diabetes mellitus has a high prevalence, and its diagnosis is quite common in routine veterinary clinics and hospitals. Due to its chronic nature and the need for periodic monitoring, the diagnosed animals start to establish a closer relationship with the veterinary medical professional, as well as with their guardians.

This relationship must be harmonious, secure with the necessary mutual trust so that information is not omitted by the tutors and the dog is not exposed to the risk of worsening the clinical condition, with uncompensated signs or even the emergence of diabetic ketoacidosis, which puts it at risk the patient's life. Thus, the treatment of DM has to be seen as a continuous challenge, precisely because it is complex and dependent on the adoption of therapeutic, nutritional, physical and psychological protocols, associated with full dedication by the owners of the animals.

The owner must be committed to the veterinarian's guidelines for the improvement of the diabetic patient's condition. Despite being a chronic disease and difficult for the tutor to manage his pet, the challenge for the veterinarian is even greater. In routine, it is common, but not normal, to observe tutors who do not follow medical guidelines or even abandon treatment. As a professional, it is necessary to empathize with time constraints and with the family's feelings, so that viable protocols can be found or established, always aiming at patient stabilization.

DM is a disease that has no cure, but there are alternatives for the animal to live with the disease and have quality of life. This is the great challenge for the tutor and the veterinarian. Keep the animal stable, promote blood glucose control and symptom remission, so that the animal has at least quality of life, well-being and longevity with a favorable prognosis. For this, your home environment must be surrounded by people who understand the risks that the disease presents, especially if it is not controlled.

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