CHAPTER 30

DIABETES MELLITUS IN CATS AND DOGS: CLASSIFICATION AND ETIOLOGIES

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INTRODUCTION

Diabetes Mellitus (DM) is referred as a group of metabolic dysfunctions resulting from impaired synthesis or decreased insulin sensitivity and characterized by hyper-glycemia, hyper-lipedemia and hyper-chloestremia (Khan et al. 2013; Elimam and Baragob 2015). Diabetes is considered as a chronic disease which can affect humans, dogs and cats and other animals such as apes, pigs and horses. In veterinary field, the classification of DM is based on human DM and mechanism. Four types of DM has been described; DM type-1 (insulin deficiency diabetes), DM Type-2 (insulin resistant diabetes), gestational DM and specific type DM (American Diabetes Association 2021). In DM type-1, the pancreas is damaged or incapable to produce enough insulin while DM type-2 occurs when the enough insulin is produced, but body is failed to utilize the insulin due to exhaustion of insulin receptors on cells. Diabetes mellitus is one of the most common disorders among dogs and cats where a prevalence of 0.4-1.2 % has been reported. type-1 DM is particularly more common in dogs as compared to cats and is associated with an absolute insulin deficiency as a result of immune mediated destruction of pancreatic β-cells. Furthermore, gestational DM has also been reported in dogs whereas there are no case reports in cats. However, cats are generally more susceptible to DM type-2 as it accounts for approximately 90% of all the cases in cats (Gottlieb and Rand 2018). The most significant clinical signs associated with DM generally include polyphagia, polydipsia, polyuria and sudden loss of weight. The clinical signs are generally not evident until the blood glucose concentration surpasses the threshold level of glycosuria which is 180-220 mg/dL in dogs whereas 220-270 mg/dL in cats. The likelihood of prediabetic or subclinical disorder is generally rare in dogs and cats unlike humans. It's diagnosis is basically made on basis of typical clinical signs, glycosuria and persistent hyperglycemia (Nelson and Reusch 2014). Most importantly, late diagnosis or delayed therapeutic intervention may result in further complications such as hypercholesterolemia and hypertriglyceridemia followed by ketoacidosis and ketonuria (Gottlieb and Rand 2018). Contrary to humans, there is no elaborated consensus in the veterinary literature on the prevalence and pathobiology of different types of diabetes in dogs and cats. In this chapter, the pathology of diabetes with the prevalence in dogs and cats is discussed along with the associated risk factor.

Diabetes Mellitus in Cats (Feline DM)

The prevalence of feline DM varies from 0.25 to 1% (1 in 400 to 1 in 100) (0.25%) according to the studied population and area. Feline DM shows the similar characteristics of clinical and pathological signs as exhibited by humans. Type-2 DM or Non-insulin dependent diabetes limited to persons having characteristics such as obesity and median to older age following low insulin level or the accumulation of amyloids in pancreas and damaged beta cells (β-cells) that consequently lead to retinal and neuronal complications (Niaz et al. 2018). Feline DM is analogous or like different types of human DM and most commonly, in felines type-2 DM persists. Beta cells in healthy cats are capable of responding to the fluctuating pattern of insulin requirements in the body and stimulate the more insulin secretion in case of increased demand (Ahren and Pacini 2005). Factors related with type-2 DM, hamper the ability of insulin secretion (Ahren and Pacini 2005; Alejandro et al. 2015). Mechanisms that damage the beta cells lead to an overall reduced potential to proliferate to catch up the higher insulin demand of body, faulty or decreased insulin production, insufficient insulin gene expression followed by uncontrolled beta cell death. Long term hyperglycemia generally results in a continuous cycle of progressive loss of insulin production (Poitout and Robertson 2008; Link et al. 2013). Other specific types of DM involve all other causes of DM. In cats, it can be associated with loss of pancreatic cells by neoplasia or pancreatitis (adeno-carcinoma is reported in 8–19% of euthanized animals). More than 60% of the diabetic cats, pancreatitis may be present based on bio-chemical and imaging results (De Cock et al. 2007; Caney 2013; Zini et al. 2015). In literature, It is reported that pancreatitis alone does not only contribute severely to cause DM but also enhances the beta cell destruction and probability of DM remission (Zini et al. 2015). The other specific types of DM may include increased insulin resistance in hyper-somatotrophism (acromegaly) and hyperadrenocorticism (Cushing syndrome)(Niessen 2010; American Diabetes Association 2021) in which the use of prescribed insulin doses are not enough to control the blood glucose level (Niessen 2013).

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Table 1: Major risk factors associated with the development and etio-pathogensis of diabetes mellitus in cats and dogs

Cats	Dogs
Immune mediated insulitis	
Hyperlipidemia	
Islets amyloidosis	
Obesity	
Pancreatitis	
Genetic (breed like Burmese cats)	Genetic
Concurrent hormonal diseases	Concurrent hormonal diseases
1. Acromegaly	1. Hyperthyroidism
2. Hyperthyroidism	2. Diestrus-induced excess growth hormone
	3. Hyperadrenocorticism
Drugs	Drugs
4. Progestogens	6. Progestogens
5. Glucocorticoids	7. Glucocorticoids
Infection	Infection
8. Heart diseases	11. Cardiac and renal diseases
9. Renal diseases	12. Hepatic disorders
10. Concurrent illness	13. Concurrent illness

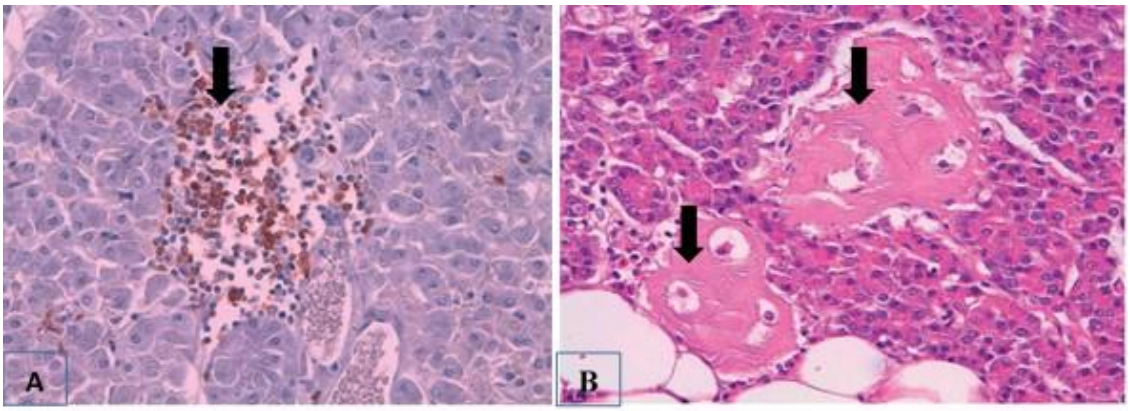

Figure 1: Histomicrograph of diabetic cat: A; Pancreatic beta cells showing infiltration oflymphocytes (black arrow) in 18 year-old hyperglycemic rats (A). Immunohistochemistry for CD3, counterstained with H&E (40 X). B; Islet amyloidosis (black arrow) in a sixteen year old female spayed cat with diabetes mellitus (B) (Hematoxylin & Eosin, 40 X). (Nelson and Reusch 2014)

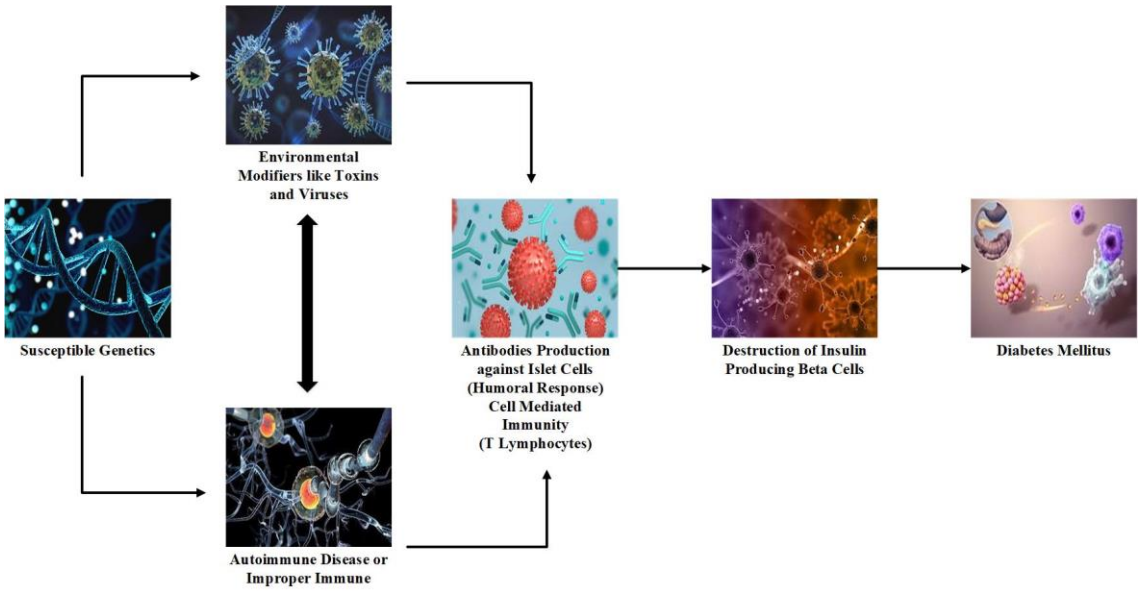

Figure 2: Genetic susceptibility and Development of diabetes Mellitus.

Pathogenesis of DM in Cats

Feline DM can also be classified under human classification system as they develop different types of DM related with acromegaly, hyper-adrenocorticism and pancreatic carcinoma (Rand 2013). Infiltration of inflammatory cells in the beta cells (Codner et al. 2012), commonly seen in human type-1 DM, is rarely seen in cats (Figure 1). Mostly the level of insulin is too low to diagnose that cannot be detected in diabetic cats (Zini et al. 2016). These results showed that fasting hyper-insulinemia is

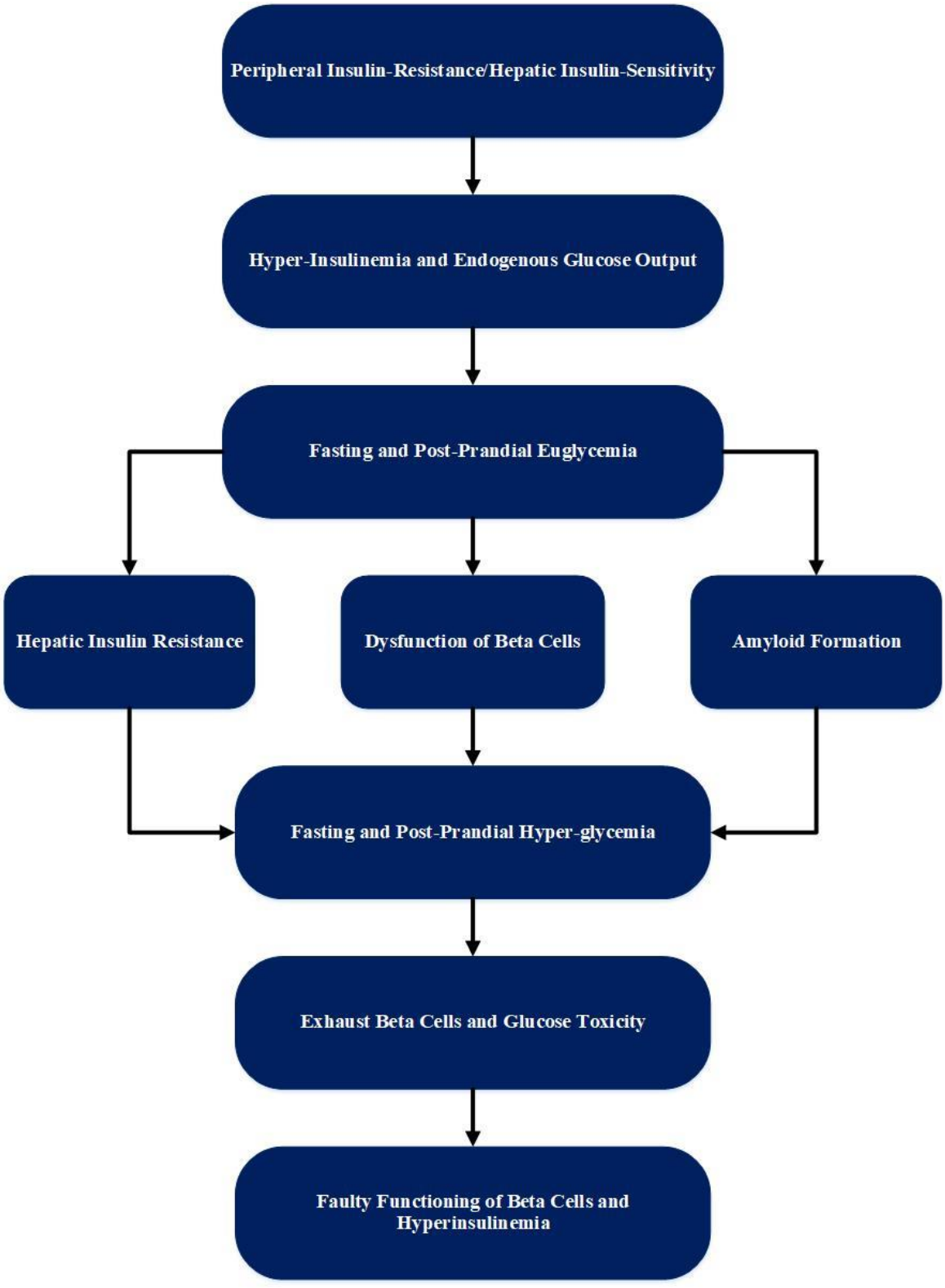

Figure 3: Sequential events in the development of Type 2 diabetes from obesity in cats

not found in case of overt diabetes in cats unlike what is observed in hyper-glycemic patients during early stage of type-2 DM in which the levels of fasting insulin are usually seen elevated in comparison to healthy individuals (Hecking et al. 2013). This fact can be linked with the more rapid beta cells destruction in cats than the humans, however, insulin deficiency is not permanent character in many cats and beta cells are seen to recover to a small degree that enables them to maintain normal glycemic level. The remission rate of diabetic cats has been reported to vary between 25 and >80%, supporting the ability of beta cells to recover (Hoenig 2014; Zini et al. 2016). The exact understanding of insulin resistance or exhaustion of its cellular receptor and their relationship with different factors are not yet clear. In obese cats, glucose transporter (GLUT4) expression on insulin sensitive cells (muscles and fat) were seen significantly lower compared to non-obese cats, whereas the expression of GLUT1, not-insulin sensitive, remained unchanged. Expression of different genes of

insulin signalling in hepatic and skeletal muscles was observed to be lower in obese than in lean cats, identical to humans with insulin-resistance (Nelson and Reusch 2014). The fat cells in cats generally act as complex endocrine glands like humans that secrete adiponectin which decreases in obese condition. Adiponectin improves sensitivity of insulin and also possess strong anti-inflammatory characteristics; and a decline in it, therefore, can contribute to development of insulin resistance and inflammation (Radin et al. 2009). The fat tissue is involved in secretion of adiponectin along with different types of proinflammatory cytokines and obesity is thus regarded as a low grade chronic inflammatory state. It is reported that insulin resistance developed in response to obesity may revert after decrease in the body weight. Though obesity induces development of DM in cats but not all obese cats are susceptible to DM. Beta cells dysfunction leading to impaired glycaemic control is the main pre-requisite for diabetes development in cats. Beta cells dysfunction occurs as a result of amyloid deposition in cats as well as in humans whereas nonhuman possess an amyloidogenic amino acid based structure that potentiates the formation of amyloid aggregates within the pancreatic islets (Hull et al. 2004; Henson et al. 2011). It is generally unclear why some but not all hyperglycemic cats develop amyloid aggregates and whether its accumulation could lead to disease development. Hyperglycemia is known as an additional potential factor, which has a definite negative impact on the physiological performance of beta cells and survival in cats, a mechanism generally known as glucotoxicity (Link et al. 2013). However, the cellular mechanisms involved in insulin sensitivity and its impaired secretion through chronic hyperglycemia are poorly understood.

Diabetes Mellitus in Dogs

Type-1 DM

Clinically type-1 DM is diagnosed more frequently in dogs in which the patient is totally dependent on the exogenous insulin. Specially dogs have adapted to diets like grains and vegetables. Dogs, like cats, don't have salivary amylase however amylase, secreting from the exocrine part of the pancreas, is present in sufficient amounts and are able to digest starch (Murray et al. 2001; Hoenig 2014). Generally, at the time of DM diagnosis, most dogs are found to be insulin dependent. The histological investigation revealed a decline in pancreatic beta cells population and an overall reduced size of pancreatic islets. In addition, the pancreatic beta cells appeared to be degenerated and vacuolated in the DM affected dogs. The juvenile dogs are considered highly susceptible to the lethal form of DM where the pancreas becomes totally deficient of beta cells along with hypoplasia or aplasia of pancreatic islets. Adult dogs with mild changes in pancreatic islets and beta cells are more likely to develop DM after exposure to some environmental factors like insulin antagonistic conditions, pancreatitis and various drugs. Numerous reports have highlighted the role of immune mediated insult in development and occurrence of DM, particularly in dogs. In DM affected dogs, immune mediated insulitis is identified to be based upon cellular infiltration by inflammatory cells in pancreatic islets along with evidence of immunoglobulins against islet cells, insulin, insulinoma antigen and intracellular glutamic acid decarboxylase. Therapeutic control of diabetes and an extensive life-long insulin therapy is crucial for maintenance of a normal diabetic state.

type-2 DM

Insulin resistance in obese dogs has been reported but it seldomly develops type-2 DM in the dogs. Some of the etiopathogenic factors involved in the development of type 2 DM in human beings and cats are generally non-existent in dogs. Some mechanisms such as sensitivity of pancreatic beta cells to variations in glucose concentration and beta cell's derived insulin secretory response have been lost in human beings and cats unlike dogs despite of obesity years leading to induced insulin resistance and compensatory insulinemia (Hoenig 2014; Nelson and Reusch 2014).

Gestational Diabetes in Dogs

This type of special DM is found in human model diagnosed firstly as carbohydrate intolerance with the onset of recognition or during gestation period (American Diabetes Association 2021). A similar condition reported in old female dogs but not in cats. Due to long oestrous cycle, the female dogs ovulate almost seven months apart leading to the elevated level of progesterone after the formation of corpora lutea. Elevated progesterone stimulates the secretion of growth hormone form mammary glands which results in causing the carbohydrate intolerance and insulin resistance in older female dogs. The female dogs diagnosed with gestational diabetes are frequently observed with elevated level of progesterone and growth hormone. Documenting increased baseline blood insulin concentration supports the presence of functional beta cells. These dogs presumably have a suitable mass of intact beta cells to maintain carbohydrate tolerance when insulin-resistance is not present (during the periods of ovarian inactivity when progesterone level remain low (0.5 ng/ml) but they are unable to secrete a satisfactory amount of insulin to maintain euglycemia in the presence of insulin resistance (Fall et al. 2008). Early diagnosis and ovariectomy lead to improve the insulin resistance, while some functional beta cells are present, may restore normal glycemic level without the use of any insulin therapy. Failure in early diagnosis and correction of insulin-resistance may result in loss of beta cells function greater likelihood for long-term dependency of insulin therapy for glycemic control.

Risk Factors

Different factors that are involved in the development of DM includes obesity, lack of exercise, old age and the use of different drugs like glucocorticoids and progestins. It has been reported that males are more prone to DM than females. Furthermore, obese cats are at four times more risk of contracting DM as compared to other cats (Slingerland et al. 2009; Nelson and Reusch 2014). Sensitivity of insulin receptors differs significantly among the individuals which is directly related with the development of DM. Cats and dogs with low insulin sensitivity along with increasing age are at a significantly higher risk of contracting hyperglycemia with weight gain. The male cats having an overall lower insulin sensitivity, when subjected to a feed trial resulted in a comparatively more weight gain as compared to female cats which could be a reason of a higher risk of DM development in male cats. At cellular level, the underlying mechanisms of development of insulin resistance and its interrelations specially with gender are not yet clearly understood. Phenotypes of specific breeds result

from selective-breeding for chosen characteristics like morphology, texture and coat colour along with body size. The desired breed specific characters are frequently accompanied by susceptibility to genetic disorders in comparison with out-bred populations. In cats and dogs, inbreeding coefficients and extensive linkage disequilibrium are reported which are more prone to genetic disorder (Figure 1). Detailed characterization of the genetic and other risk factors involved in the pathogenesis of DM and their interrelations are not yet clear with their underlying mechanism and detailed research work is needed yet to explore this issue (Samaha et al. 2020).

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