Spontaneous Diabetes Mellitus in Animals

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Additional information is available at the end of the chapter

1. Introduction

Diabetes mellitus is considered as a common metabolic disease diagnosed frequently in canine and feline pathology. On the other hand, clinical syndrome of diabetes is described rarely in other domestic species (cattle, small ruminants, swine and horses) [1-3]. Many similarities with human counterpart are clearly emphasized in the literature, considering the mechanism of this disease. This is the reason why the animals are frequently used in many research studies with respect to etiopathogenesis and treatment [4]. The most of the cases present as main clinical sign the failure of β-cells to produce insulin to support the metabolic needs of the organism. The insidious onset of diabetes may be induced by various causes: diminished synthesis of insulin, decreased sensitivity of target cells and organs to insulin, excess of other hormones and drugs or multiple combinations of these causes [1].

Polyphagia, polyuria and polydipsia are mentioned as the most common clinical signs of uncomplicated *diabetes mellitus* (non-ketoacidotic). The animal presents persistent hyperglycemia generated by a low cellular uptake of glucose, increased glycogenolisis and gluconeogenesis from amino acid source. All these metabolic disorders are linked with a diminished glucose oxidation. Abnormal gluconeogenesis from amino acids will be clinically expressed as atrophy of the muscles and weight loss. High level of serum lipids is generated by increased lipolysis and decrease entry of fatty acid into adipocytes. Subsequently, the liver exhibits large quantities of mobilized lipids that cannot be used or transformed in lipoproteins. Grossly, the liver appears enlarged, even with hepatomegaly. Prolonged hyperglycemia will generate persistent high level of glucose in primary urine; these levels exceed the threshold of glucose resorption in renal tubes, thus leading to subsequent glucosuria, osmotic diuresis, polyuria and compensatory polydipsia. Despite of persistent hyperglycemia, the animal presents an increased appetite generated by the failure of neurons from hypothalamic satiety center to uptake the glucose [1].

The classification of diabetes in animals is the one used for the humans, although it is not entirely applicable to domestic animals.

Type 1 (insulin dependent diabetes mellitus - IDDM) and 2 diabetes mellitus (non-insulin dependent diabetes mellitus - NIDDM) are generally accepted as the main form of this disease in animals. Specific types of diabetes (previously framed as type 3 or secondary diabetes mellitus) include the cases which are the consequence of insulin antagonism or other situation when destruction of pancreatic islets was generated by pancreatitis, pancreatic necrosis and tumoral processes. Gestational diabetes is a particular clinical expression of this condition, the occurrence being reported in dogs [5].

2. Diabetes mellitus in horses

Despite all the controversies reported in the literature, it is generally accepted that horses develop all three forms of diabetes: insulin dependent diabetes mellitus, non-insulin dependent diabetes mellitus and secondary diabetes. Recent observation and studies recommend paying further attention and investigation to the resemblance between human and equine insulin resistance, which particularly develops in horses with clinical signs of equine metabolic syndrome (EMS). This may be expressed as obesity, associated with prior or concurrent rhabdomiolysis, ostechondrosis and laminitis (inflammation of the hoof wall), the onset of diabetes being exceptional [6-10].

Diabetes mellitus was diagnosed in horse and pony, all cases being described in individuals with pancreatitis or pars intermedia pituitary tumors [11-13]. IDDM was reported mainly in young horses, but elderly horses are also affected (the age ranges between 5 and 18 years). Gender is not considered as a predisposing factor, but many of the cases were diagnosed in mare. Affected individuals with IDDM develop rapid weight loss despite polyphagia, as well as hyperglycemia, glucosuria, low insulin levels, high glycosylated hemoglobin and fructosamine, polydipsia and compensatory polyuria. Hepatomegaly due to hepatic lipidosis may occur. The pancreas exhibits segmental shrinkage, effacement of lobule demarcation by lymphocytic infiltrates and same inflammatory population into the pancreatic islets which causes severe decrease of β-cells [14]. Sometimes inflammation is not observed, especially in old individuals, the number of β-cells being reduced and confined to the periphery of the islets [15]. A case was featured by concurrent lymphocytic thyroiditis and adrenalitis. Thus, considering polyendocrine involvement it is postulated that autoimmune cause of IDDM may be suspected [14].

Non-insulin dependent diabetes mellitus in horse have less resemblance to human counterpart, comparing to cats. Particularly, insulin resistance as one of the major features of the type 2 diabetes in human and cats is less important for the onset of diabetes in a horse and more attributable to obesity, inflammation and vascular diseases. The factors which interfere with the effectiveness of insulin in horse are the excess of glucocorticoides, free fatty acids and adipokynes. Hyperinsulinemia as the result of insulin resistance may be maintained for years, without exhaustion of β-cell [7]. This is the reason why non-insulin dependent diabetes mellitus is rarely diagnosed in horses. A minimal model of analysis of type 2 diabetes in horse has been presented. Insulin versus glucose dynamics has been monitored, insulin resistance and impaired β-cell functioning being obtained [16].

Transient IDDM may occur in neonates. Concomitant hyperglycemia, hypoinsulinemia and intestinal infection with Coronavirus was reported, the foal becoming euglycemic in less than a year [17].

3. Type 1 diabetes mellitus in cattle

Diabetes mellitus has been reported in various breeds of cattle: Holstein Fresian and Hereford [18, 19], Aberdeen Angus and Jersey [20], Brangus cattle [21], Charolais [22], Japanese brown and Japanese black [23-26]. Young individuals are constantly affected, the age ranging between 6 months and 5 years of age. Although there is no evidence of sex predilection, most of the data report cases of diabetes in females. Mild weight loss to severe emaciation, polyuria, polydipsia, dehydration, hyperglycemia, glucosuria and kenonuria are the most important clinical signs described. Previous studies mention diagnostic tests used in cattle: glucose tolerance test and measurements of serum fructosamine to prove that the most important signs of diabetes (hyperglycemia, glucosuria and kenonuria) have been induced by insulin deficiency. The results of these tests proved that the glucose disappearance rate and half time were longer than in normal control cows. Elevated values of serum fructosamine were also observed [22, 25].

At necropsy, the pancreas presents normal volume or various degree of atrophy, granular surface due to interstitial fibrosis and yellowish-brown color of the parenchyma. The liver is friable and pale. The kidneys present the same discoloration, observed mainly in the cortex. Histologically, lymphocytic insulitis is the most important feature diagnosed. Pancreatic islets are reduced in size and number. The inflammatory infiltrate is represented dominantly by lymphocytes, few plasma cells and neutrophils being occasionally observed. The atrophied islets are composed by small cells, without aldehyde-fucsin and Masson-Goldner positive granules, proving that insulin secretion is ceased. This was supplementary proved by immunohistochemical investigation, almost all cells of atrophied islets being rarely reactive to anti-insulin antibody and poorly reactive to anti-glucagon and anti-somatostatin. Residual pancreatic islets present vacuolization of cytoplasm and a decreased synthesis of insulin. Unaffected islets may contain mitotic figures of cell nuclei. The lesions of exocrine components are interlobular and interacinar fibrosis, lymphocytic infiltrates around small pancreatic ducts and glycogen accumulation into the cytoplasm of ductal epithelial cells [23, 25].

Several possible mechanisms of insulin-dependent diabetes mellitus onset in cattle are described, such as viral infection, metabolic disorders (fatty liver, fat cow syndrome), parturition and chronic insulitis [2].

Considering viral infection, many studies were focused on foreign antigens exposure of genetically susceptible individuals. These molecules have similar biochemical structure with some of the components of β-cells. This way, a cell-immune mediated response is triggered also against islet cells. The viruses are the most suitable source of antigenic protein, bovine viral diarrhea virus (BVDV) and foot and mouth disease virus (FMDV) being subjected for extensive studies [2].

It is suspected that human IDDM is strongly related with viral infection as in bovine counterpart and include group B Coxsackie, Epstein-Bar, cytomegalovirus, herpesvirus, enteric rotavirus, influenza virus, rubella viruses, and mumps. This concept is highly supported by the results which prove epitope homology between Coxsackie B viral protein and glutamic acid decarboxylase – GAD (this enzyme mediates decarboxylation of glutamate and forms γ-aminobutiric acid - GABA). Furthermore, the cattle with IDDM do not express GAD in the cytoplasm of cells of atrophied islets [27-29].

Destruction of β-cells via apoptosis seems to be controversial, generated by many pathways (perforin/granzyme, FasL, and other members of the necrosis factor superfamily), each of those mentioned being dominant or redundant in initial or late stage of cell death. Thus, perforin/granzyme pathway mediated by CD8+ T-lymphocytes is preferentially active during onset of autoimmunity. FasL is dominant in CD4+ T-cell mediated insulitis [30-32]. In addition, ongoing lymphocytic insulitis is preceded by releasing of many cytokines (IL-1β, INF-γ, TNF-α) and free radicals [18, 27, 33]. Damaged proteic structures of β-cells result in molecules with enhanced antigenic properties, being initiated a self-perpetuating destruction of the cells. INF-γ and TNF-α are both responsible for increased expression of class I MHC molecules on β-cells [34, 35]. Combined effects of those molecules results in expression of class II MHC molecules on β-cells surface. Elevated expression of MHC molecules induces homing of lymphocytes into the islets. Activation of lymphocytes is initiated by INF- γ, engaging this way the responsiveness of these cells to local antigens. Differentiation of T-lymphocytes in IDDM shifts towards T helper lymphocytes type 1 (Th1) pathway. Although, Th2 pathway cytokine (IL-10) may be also involved by the effect on local vessels and promoting local release of other cytokines [33].

4. Type 1 diabetes mellitus in dog

Spontaneous cases of insulin-dependent diabetes mellitus in dog were mentioned for the first time in 1861 by Leblanc and Thiernesse [36]. Later, in depth studies subjected on dog considered a large numbers of individuals and concluded that this condition is specific for older dogs and also for females [36]. Sex predilection in diabetes was further associated with increased incidence shortly after estrus period and in pregnant females [36-38]. A major breakthrough in canine diabetes mellitus was the identification of the diabetogenic effect of progesterone induced mammary growth hormone (GH) [39]. During the last ten years a big number of studies have focused on etiology of dog diabetes, especially on dog leukocyte antigen (DLA) and their association, candidate genes and autoantibodies [40-43].

Epidemiological studies on canine diabetes conducted in different part of the world concluded that the disease is diagnosed mainly in Samoyed, Cairn Terrier, Tibetan Terrier, Australian Terrier, Miniature Poodle and Schnauzer, Bichon Frise, Border Collie and some of the Scandinavian breeds (table 1) [37, 44, 45]. In addition, other papers complete the list with Labrador retriever, Yorkshire terrier, Spitz, Lhasa Apso, Beagle and Dachshund. Keeshonds and probably Golden retriever are potential candidate breeds due to islet hypoplasia, the onset of diabetes being recorded in the first months of life. Popular breeds as

Boxer and German shepherd seem to be resistant. Generally, canine diabetes mellitus is clinically diagnosed in dogs with 4-18 years of age, the median age at diagnosis being 7-9 years [37, 44-46].

Swedish study [37]	UK study [44]	North America study[45]
Australian Terrier	Samoyed,	Miniature Schnauzer
Samoyed	Tibetan Terrier	Bichon Frise
Swedish Lapphund	Cairn Terrier	Miniature Poodle
Swedish Elkhound		Samoyed
Border Collie		Cairn Terrier

Table 1. The breeds commonly affected by diabetes mellitus

Juvenile onset of the disease is an uncommon event and it has been recorded in dogs with less than 12 months of age [47-49]. Several studies concluded that females are prone to diabetes (more than 70% of diagnosed cases) [37]. These results are controversial with other studies which conclude that the number of females and male with diabetes is almost equal [44]. The aforementioned studies highlight that ovariohisterectomy in the first year of life seems to eradicate diabetes, the particular hormonal status of the dam being the cause of diabetes onset. These can also explain the high incidence of this condition in diestrous and pregnant bitches.

The etiopathogenesis of diabetes mellitus in dog remains unclear for the majority of diagnosed cases. The difficulties in framing the type of diabetes come from the possible multifactorial etiology of the condition. Unfortunately, the human system of classification of diabetes is not entirely applicable to dog. The existence of NIDDM in dog is questionable, being known that insulin must be provided sooner or later for almost all diabetic dogs. In this context, it was suggested that classification of diabetes in dog would consider the underlying pathogenesis rather than response to insulin treatment [50]. Current diagnosis and therapy consider a classification system based on underlying cause of hyperglycemia: insulin deficiency diabetes and insulin resistance diabetes (Table 2). It is noteworthy that insulin resistance diabetes will be replaced progressively by insulin deficiency diabetes due to glucotoxicity and β-cell exhaustion [50].

Insulin deficiency diabetes (progressive destruction of β-cells, absolute insulin deficiency)	β-cell hypoplasia Immune mediated β-cell destruction β-cell cell loss associated with exocrine pancreatic lesions (pancreatic necrosis, pancreatitis) Idiopathic processes
Insulin resistance diabetes (relative insulin deficiency produced by insulin antagonists or concurrent disorders)	Diestrus/gestational diabetes Secondary to other endocrinopathies (acromegaly, hyperadrenocorticism) Obesity Iatrogenic (synthetic progestagens and glucocorticoids)

Table 2. Classification system of diabetes mellitus in dog [50]

Most of the diabetic dogs present unspecific destruction of Langerhans islets. Destruction of β-cells via autoantibodies may be considered, this being characteristic for 50% of newly diagnosed dogs [51]. Comparing with IDDM in human and cattle some diabetic dog express serological reactivity to 65kDa isoform of GAD and/or insulinoma antigen 2 (IA-2) [44, 52].

Furthermore, there have been described some gene associations with increase susceptibility to diabetes in dog similar with human counterpart such as INF-γ, IL-10, IL-12β, IL-6, insulin, protein tyrosine phosphatase non-receptor type 22 (PTPN22), IL-4 and TNF-α, comparing with protective association between IL-4, PTPN22, IL-6, insulin, IGF2, TNFα [43]. Canine major histocompatibility complex gene known as dog leukocyte antigen (DLA) is also linked with the onset and progression of diabetes. Samoyed, Cairn Terrier and Tibetan Terrier known as prone to diabetes express DLA-DRB1*009/DQA1*001/DQB1*008 haplotype of MHC, comparing with resistant breeds [50].

Inheritance of IDDM was studied and previously mentioned in Keeshonds, the genotype being described as autosomal recessive [41, 53].

Statistical analysis on a large canine population established a significant correlation between obesity and diabetes mellitus in Shetland Sheepdog, Dachshund, and Golden Retriever [54]. Hyperinsulinemia and glucose intolerance reaches the highest values in dogs with the highest degree of obesity [55]. The same authors concluded later that obese diabetic dogs can be subdivided in two groups according to the response to glucose administration: first group with fasting hypeinsulinemia which have a good response to glucose by increasing the level of insulin secretion and a second one with decompensate status featured by fasting hyperinsulinemia and lack of response to glucose administration. The results of the same study highlight that the obese dogs from this study present lower levels of insulin comparing with obese non-diabetic dogs [56]. It was also concluded that a high-fat diet generates subsequent insulin resistance which is not followed by compensatory hyperinsulinemia and create the premises for the onset of glucose intolerance and diabetes [57]. Despite to these reports, diabetes induced by insulin resistance and hyperinsulinemia in dog seems to be a rare condition.

Gestational diabetes mellitus (GDM) and diestrus diabetes are rare conditions in dog, thus being reported only in few cases [38, 58, 59]. Pregnancy is essentially dominated be tremendous metabolic changes which are set for supporting fetal development. Thus, caloric intake, insulin secretion, peripheral insulin resistance and lipid metabolism record higher levels and values in pregnant dam. These metabolic changes are focused to direct glucose and amino acids towards fetal development, lipids being used as alternative energetic supply for the female. Considering this new metabolic status, β-cells from the existing Langerhans islets undergo hypertrophy and hyperplasia [60]. These morphological and functional adaptations permit high level of insulin which maintains normal glycemia. GDM results from the failure of this adaptive process. It is described that peripheral insulin resistance is upregulated by hormones such as progesterone, prolactine, cortisol and placental lactogens. Progesterone induced mammary growth factor hormone (GH) generates anti-insulin activity, being one of the most important diabetogenic hormones

involved in the pathogenesis of GDM [61]. Destruction of β-cells and termination of insulin secretion is engaged by glucotoxicity. Both pregnant and diestrous nonpregnant dams have higher levels of GH and lack of GAD-65 autoantibodies [38]. These findings prove that the onset of the diabetes is induced via ovarian hormones. Furthermore, ovariohisterectomy and/or termination of gestation provide a substantial improvement of the prognosis, almost a half of affected animals returning to normal after these surgical procedures. It is possible for diabetes to become a permanent status in aging animals, because of senile diminishing of β-cells secretion and a shortened period of tolerance to hyperglycemia [38].

Similar pathogenic pathways to gestational diabetes mellitus are described in females with persistent corpora luteal and associated pseudopregnancy. Long term administration of synthetic progestagenes (medroxyprogesterone and megestrol acetate) initiates diabetes by vacuolization of β-cells [62].

5. Type 2 diabetes mellitus in cat

Non insulin dependent diabetes mellitus (NIDDM) is one of the most frequently encountered endocrinopathy in cats. Many research studies concluded that diabetic cat mimic some of the clinical and pathological features of human diabetes type 2: occurrence in obese, indoor confined, middle-aged and old individuals (highest incidence in cats with 8 years of age), with residual and subsequent decline of insulin secretion, deposits of amyloid in Langerhans islets associated with loss of β-cells and onset of complications such as peripheral neuropathy and retinopathy. Diseases or drugs which increase the risk of insulin resistance such as hyperadrenocorticism, acromegaly, hyperthyroidism, renal and cardiac disease, administration of corticosteroids and progestagenes were also considered. Cats express supplementary ketoacidosis and insulin-dependence [63-67]. It is quite difficult to estimate the incidence of IDDM in cat: β-cell antibody did not prove any involvement in pathogenesis of diabetes in cat [68] and require further investigation and lymphocytic insulitis is rare [69].

The synergy between hyperinsulinemia and exaggerated response to glucose feature the early stages of the disease and countervail basal insulin resistance. When diabetes becomes overt, the compensatory insulin synthesis and secretion decline, this being usually accompanied by exhaustion of β-cells and amyloid deposition into the islets. Cats may express clinically insulin independence at the beginning of the condition, but insulin requirement is very probable later [67].

The frequency of diabetes mellitus in cats records different values in a given population, ranging to 0.43 to 2.24%, with significant prevalence in Burmese cats. The mean age was significantly higher for the same breed (more than 13 years of age) comparing with short and longhaired domestic breeds. Males seem to be prone to diabetes, comparing with the incidence of the disease in females [70-72]. Juvenile diabetes is rarely described. The condition is clinically featured by classical symptoms, islet hypoplasia and diabetic bilateral cataract with both cortex and nucleus involvement [73].

As in humans, diabetic cats present islet amyloidosis, progressive loss of number of β and α-cells and normal number of δ-cells. Nevertheless, these lesions are not capital for inducing impaired glucose tolerance in cat and also for the onset of diabetes, but it have an important contribution to the progression of the disease [74].

Early stages of the disease are particularly featured by a first-phase attenuated secretion of insulin as response to glucose administration, followed by an exaggerated second-phase response. Deleterious effects as glucose toxicity, lipotoxicity and islet amyloidosis are the mechanism incriminated in gradual onset of diabetes.

The onset of type 2 diabetes in cats is strongly related with glucose toxicity. Intraperitoneal administration of the glucose for a long time produce vacuolation of islet cells and even diabetes mellitus, this being one of the first experimental model in cats which prove toxic effect of glucose on Langerhans islets [75]. Glucotoxicity may be used as a major target of handling the therapy protocol of hyperglycemia, allows obtaining further preservation of β-cells and even succeed remission of the condition. In normal individuals, glucose stimulates synthesis of insulin via initiating transcription of insulin gene by phosphorylation of PDX1. Downregulation of glucose transporters on the membrane of β-cells and decreased expression of insulin and PDX1 genes usually mediate hyperglycemia and subsequent glucose toxicity. Persistence of hyperglycemia (for at least 10 days) leads to overloading of β-cells with glycogen and cell death. Toxic effect of glucose is enhanced by overburden secretion of insulin and initiation of β-cells destruction [76, 77].

Lipotoxicity concerns disturbances provoked by the excessive quantities of triacylglycerol and subsequent deposition in other non-adipose tissues (myocardium, liver, pancreas, skeletal muscle). Furthermore, the excess of triacylglycerol in β-cells will be expressed as loss of these cells and impaired synthesis of insulin; accumulation of triacylglycerol in muscles and liver leads to insulin resistance. The presence of triacylglycerol in the cytoplasm may be not sufficient to induce low levels of insulin and insulin resistance. It is presumed that lipolysis and synthesis of triacylglycerol are prone to produce fatty acids generating peroxidation compounds or other toxic lipid intermediates. Finally, these will initiate the expression of death receptor gene and alter insulin signaling in liver and β-cells. Long-chain acyl coenzyme A has been suggested as a major mediator of lipotoxicity and insulin resistance in non-adipose tissues [78]. The most reliable proof of this mechanism is offered by the skeletal muscles. High level of long-chain acyl coenzyme A into the sarcoplasm was correlated with decreased glucose entry. In addition, intramuscular content is higher in insulin-resistant animals and human [78].

Islet amyloidosis is the dominant feature in non-insulin dependent diabetes mellitus, being diagnosed in more than 80% of affected domestic and wild cats [79, 80]. Amyloid deposition is usually detected in healthy cats, the amount increasing with the age. The prevalace of amyloidosis is higher in diabetic animals than in non-diabetics. The presence of amyloid is a hallmark for impaired β-cells function and proves previous overstimulation and exhausting of β-cells. The deposits are mainly extracellular, although intracellular amyloid is possible in non-endocrine cells of the islets, generating further disruption of the cellular membrane and

cell death [81]. The major component of islet amyloid is islet amyloid polypeptide or amylin (IAPP), based on identification of a residual fragment of this hormone [82-84]. High levels of IAPP are identified in obese cat and also in euglicemic cats with impaired glucose tolerance. Although, increased concentration of IAPP is mandatory but not exclusive in insular amyloid formation, other accompanying mechanisms such as defective synthesis of β-cells and failure of secretion, transport and degradation of IAPP are probably implicated [85]. There is a strong correlation between IAPP levels and pathogenesis of type 2 diabetes in human and cats. As a premise of the onset of diabetes in cat, increased body condition score in correlated with increased levels of circulating IAPP and insulin in non-diabetic cats [86].

Increased levels of IAPP will generate impaired glucose tolerance. Inhibitory effect of IAPP on glucose-stimulating insulin synthesis and increased gluconeogenesis will contribute to hyperglycemia. Insulin resistance of the muscle is also induced by IAPP and it results in inhibition of glucose uptake and further glycogenolysis. Fat tissue seems to be insensitive to IAPP. It is suspected that glucose resulted from muscle glicogenolysis is used in lipogenesis causing secondary obesity [87].

Obesity is rightly considered as an important predisposing factor to NIDDM, being equally involved in the individual genetic predisposition to insulin resistance and impaired glucose tolerance [88]. The risk of disease results from obesity induced low sensitivity of tissues to insulin and compensatory hyperinsulinemia. The onset of obesity is multifactorial, with genetic and environmental origin. One of the cause is the presence of active "thrifty genotype" which allows lipogenesis when the food is plentiful and lipid mobilization when the food supply is diminished or absent [89]. Still, intake of large amount of highly palatable food with high concentration of carbohydrates, aging, neutering, and low physical exercises are considered important [90]. The onset of obesity is responsible of high levels of leptin and resistin, inflammatory cytokines such as tumor necrosis factor alpha (TNFα), interleukins 1β and 6, and C-reactive protein. Particularly, TNFα interfere insulin sensitivity by blocking activation of insulin receptors [88]. It is documented that weight gain in lean cats is followed by insulin sensitivity comparable with the range recorded in cats with overt diabetes. Furthermore, fasting-induced hyperinsulinemia in lean cats is considered to be the greatest risk for the onset of impaired glucose tolerance with obesity.

Male cats have a propensity to become obese comparing female, adipose tissue mass being larger than obese female [70, 91]. The lack of effectiveness of insulin to reduce basal glucose level is proportional with mass of adipose tissue. Lean male are less insulin sensitive than lean female, these sensitivity recording decline when the male have weight gain. Fasting hyperinsulinemia is more likely to develop in obese male than obese female cats.

Abdominal fat deposition is correlated with a more severe insulin resistance. This is also observed in diabetic Burmese cats which particularly have large amount of abdominal fat tissue and less subcutaneously [71].

Although obesity alone cannot induce diabetes, it is known that small increases of body weight and size of adipocytes result in higher risk of overt diabetes. Thus, 25% of cats which have weight gain have values of insulin sensitivity comparable with diabetic cats [92].

Insulin resistance is the expression of internalization of insulin receptors, low affinity of these receptors to insulin and disturbances of intracellular oxidative glucose metabolism. Skeletal muscle and liver present the highest expression of insulin resistance, which finally results into a low glycogen synthesis within the sarcoplasm and hepatocyte cytoplasm. As it was previously mentioned, IAPP prevents glucose uptake, inhibits glycogen synthetase and induce glycogenolysis followed by lactate production. The liver take lactate and initiates gluconeogenesis. In addition, three important insulin signaling genes are downregulated in liver and muscle of the moderate obese cats: insulin receptor substrate (IRS)-1, IRS-2, and phosphatidylinositol 3'-kinase (PI3-K) p85alpha. These data add a new resemblance between human and feline insulin resistance specific for NIDDM [93].

6. Pancreatic disease and diabetes mellitus

The destruction of Langerhans islets via pancreatic necrosis, acute or chronic inflammation and tumors are presented in dogs, cats, cattle and horses.

Particularly, canine acute pancreatitis and acute pancreatic necrosis are differentially framed as long as inflammation or necrosis is dominant. Thus, necrosis may be consistently represented comparing with inflammation and supports using the term of acute pancreatic necrosis (APN). This lesion is considered the common cause of diabetes mellitus in dog, knowing that APN is occasionally encountered in cats and sporadic in pigs and horses. Interestingly, the most of predisposing factors of APN are generally considered in the pathogenesis of diabetes mellitus. Obesity, hyperadrenocorticism, prolonged therapy with glucocorticoids are linked with APN and also with impaired glucose tolerance, insulin resistance and insulin antagonism. Most of the dogs with fatal APN express ketonuria while diabetic ketoacidosis can coexist with acute inflammatory lesions of the pancreas. Usually, all ketonuric dogs with APN or acute pancreatitis are diabetic. It is important to bear in mind that diabetes mellitus may create conditions for an increased risk for developing pancreatitis. Diabetic dogs express hypertriglyceridemia, which is a risk factor for acute pancreatitis [94, 95].

Chronic pancreatitis is featured by fibrosis, atrophy of parenchyma, lymphocytic infiltrate and cyst of pancreatic ducts [96, 97]. The onset of chronic inflammation is a common consequence of the repeated mild episodes of APN or acute pancreatitis. Chronic pancreatitis in dogs, cats, cattle and horses is not always sufficient to induce massive destruction of the islets with subsequent onset of diabetes. If the magnitude of the fibrosis, atrophy and lymphoplasmacytic infiltrate is sufficient enough to involve large areas of the pancreas, than exocrine and endocrine insufficiency may develop. Nevertheless, it is considered that chronic pancreatitis claims an important percentage from the canine patients with diabetes mellitus, almost 30% of diagnosed cases were linked with histological features attributable to chronic inflammation of the pancreas [98]. The incidence can be higher when is correlated with breed predisposition [99].

Various morphological types of pancreatic adenocarcinoma may determine extensive destruction of the parenchyma and secondary diabetes in old cats and dogs [3]. The tumors

of islet cells are rarely described, most being diagnosed in dog. Adenomas and carcinomas of pancreatic islets induce hormonal hypersecretion. The dogs and also cattle, and ferrets can present more than one hormone in histological sections in the majority of diagnosed cases. Pancreatic or extrapancreatic glucagonoma is linked with diabetes mellitus and is featured by antagonism of glucagon with insulin. Although not pathognomonic, the condition is also clinically recognized by the superficial necrolytic dermatitis which affect muzzle, mucocutaneous junctions, ears and frictional and pressure points of the body. The excessive secretion of glucagon determines hyperglycemia due to the high level of hepatic gluconeogenesis and glycogenolysis [3, 95, 100].

7. Diabetogenic hormones and drugs

Antagonists of insulin such as hormones and drugs represent an important mechanism of diabetes in animals. Thus, glucocorticoids, growth factor, thyroxine, glucagon, epinephrine, progesterone and synthetic progestagens are frequently involved. Antagonic effect is triggered on peripheral tissues, followed by sustained hyperglycemia and further exhaustion of islets. Early clinical management to monitor diabetes may be followed by resolution of secondary diabetes if remaining β-cells are sufficient. Finally, when antagonism can no longer be controlled the animals present a permanent insulin-dependent status.

Hyperadrenocorticism (tumorally induced or by administration of corticosteroids as dexamethasone and prednisolone) [101] is one of the antagonist in dog and rarely encountered in cats [102-104], the new abnormal hormonal status being concurrent with insulin resistance. Functional adenomas or adenocarcinomas of either pituitary gland or adrenal cortex are responsible for hyperadrenocorticism, more than a half of affected animals being diabetic at the time of diagnosis. Systemic control of glycemia is poorly developed and expressed by classical signs. Supplementary, the animals present bad condition of hair coat (bilateral alopecia) and skeletal muscles, excessive fragility of the skin, enlarged abdomen (pot belly), bacterial infection of skin, urinary and respiratory tract [64]. ACTH secreting adenoma of pars intermedia associated with hyperplasia of adrenal cortex and reduced β-cell population was diagnosed in horse, although reference to hormonal antagonism is not discussed [105].

Acromegaly as consequence of pituitary acidophil adenoma results in excessive secretion of growth factor (GH) and also causes associated severe insulin resistance and diabetes mellitus [106]. The excess of GH will generate further synthesis of insulin growth factor 1 (IGH-1) which exerts anabolic effect and subsequent proliferation of connective tissue, cartilages, bones, and organs. Screening of IGH-1 provides valuable information for diagnosis of acromegaly in cats with overt insulin resistance, although both monitoring of GH and IGH-1 should be considered in addition with imaging diagnosis [107-109].

Hyperthyroidism generates excess of thyroxine and triiodothyronine, which increase the bodily demands of glucose. Thus, supplementary glucose is produced in liver via gluconeogenesis and Cori cycle. Furthermore, fasting period allows adipose tissue lipolysis

which provide glycerol and fatty acids. Under these metabolic circumstances gluconeogenesis is initiated, glycerol resulted from lipolysis and amino acids resulted from proteolysis being used as basic resources. Hyperthyroid status is featured by decreased insulin-stimulated glycogen synthesis and increased anaerobic glycolysis. Lactate resulted from muscle anaerobic glycolysis and conversion to glucose into the liver maintains high levels of glycemia and facilitates preservation of adipose reserves [110].

Insulin antagonism was also described as being associated with excessive secretion of catecholamines in animals with pheocromocytomas. Catecholamines action as inhibitors of insulin release and generate mild to moderate glucose intolerance [111]. Diuretics (hydrochlorothiazide, furosemide) induce glucose intolerance by diminishing insulin-stimulated glucose transport into skeletal muscle and adipose tissue [112].

8. Diabetic ketoacidosis and non-ketotic hyperosmolar diabetes

Diabetic ketoacidosis features complicated diabetes mellitus in dog and cat, being one of the most severe complications. Concurrent diseases as pancreatitis, hypercorticosolism, tumoral diseases, infections, renal and heart failure or poor management of insulin therapy create a stressful status by enhancing circulating levels of insulin antagonists such as catecholamines, cortisol, glucagon and growth hormone. Bodily energetic demands are shifted to lipolysis, followed by an increase uptake of fatty acids into the liver. The absence of insulin and glucose into the cytoplasm will favor oxidation of fatty acids, β-hydroxibutiric and acetoacetic acids being released. Some of ketoacids are converted into acetone, volatilization through the lungs giving a specific ketone breath [113]. Clinically, the onset of ketoacidosis manifests as severe hyperglycemia, acidosis, ketonemia, ketonuria, hyperosmolarity, massive loss of magnesium, sodium, potassium, dehydration, and hypovolemic shock [114, 115].

Non-ketotic hyperosmolar diabetes is characterized by hypeglicemia, hyperosmolarity, osmotic diuresis and subsequent dehydration. Thus, deleterious effects on central nervous system activity are clinically expressed as ataxia, nystagmus, seizures, hyperthermia and coma [116].

## 9. Lesions of diabetes mellitus in dog and cats

Postmortem gross lesions are very little expressed in diabetic animals. Atrophy of skeletal muscle, dehydration and fatty liver are the principal findings. Usually, pancreas is normal, excepting the situation when postnecrotic scarring, chronic pancreatitis and tumors occur [3].

Juvenile onset of diabetes in dog is represented by lymphocytic insulitis in almost a half of total number of islets. Inflammatory infiltrate is represented chiefly by T-lymphocytes, disposed around and inside the islets [47]. The rest of Langerhans islets presented severe atrophy and massive loss of β-cells. In addition to islet inflammatory lesions, other cases are featured by cytoplasmic vacuoles in islets cell and ductal epithelium due to massive

glycogen accumulation (fig.1). Lees damaged islets may present mitotic figures (fig 2). When insulitis do not occur, histological examination reveals only a lower number of pancreatic islets [49]. Amyloid deposition is characteristic for cat diabetes. The deposits are mainly extracellular, with particular concentration at the periphery of islets and around the capillaries and concurrent with depletion of islet cells (fig. 3) [79, 117].
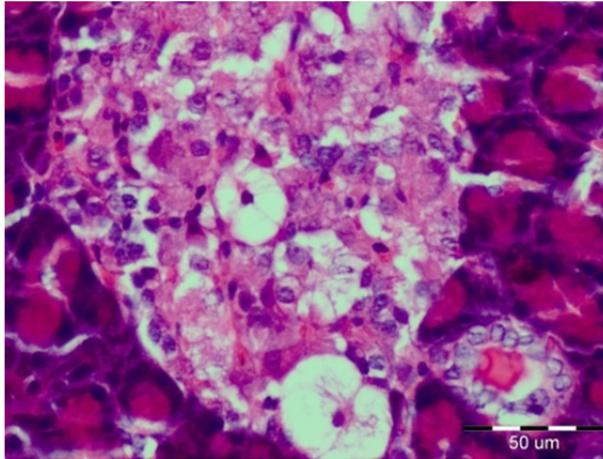

Figure 1. Cytoplasmic vacuoles in cells of Langerhans islets in a dog with diabetes mellitus
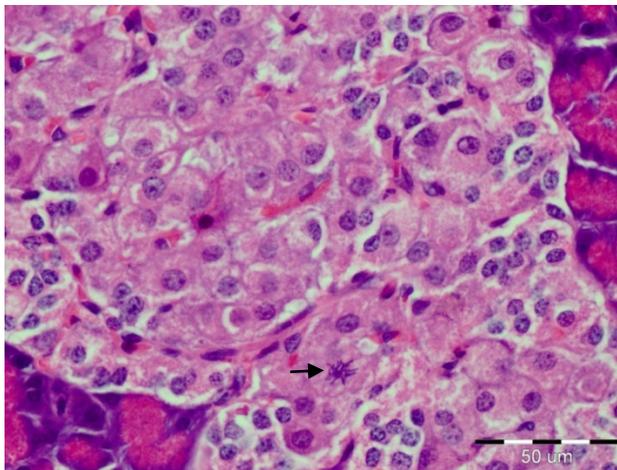
Figure 2. Mitotic figure (arrow) in a less damaged islets.

Hepatocytes and epithelium of bile ducts express also vacuolation of the cytoplasm due to lipid accumulation and glycogen, respectively. Renal epithelial cells show the same glycogen deposits, mainly in loops of Henle and distal convoluted tubules. Renal lipidosis is featured by vacuoles in proximal convoluted tubes and lipidic emboli in glomerular capillaries [3].
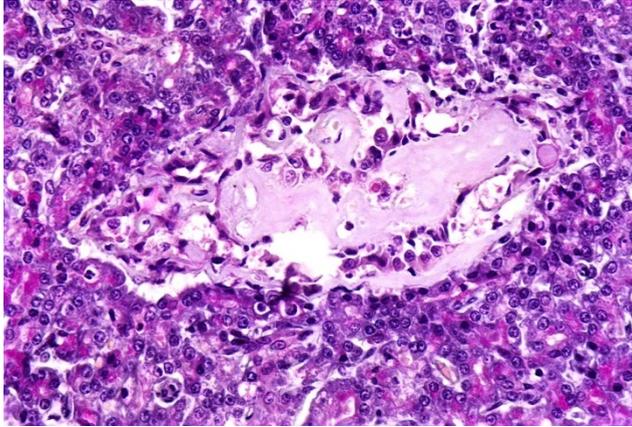
Figure 3. Islet amyloidosis, extracellular depositions and depletion of islet cells in cat diabetes mellitus. (Courtesy of M. Militaru)

The functional and structural disorders in other organs, chiefly in kidney and retina but also in other organs are attributable to altered vasomotor responsiveness, vasoactive mediators, plasma volume enhancement and tissue hypoxia, generating diabetic microangiopathy. Thus, increased vascular pressure and enhanced permeability in capillaries are followed by cell proliferation into the capillary walls and macromolecule transfer towards extravascular space respectively. Furthermore, these pathological effects are responsible for the thickening of basement membrane of the capillaries and vascular wall which induce compensatory dilation of less altered capillaries [118].

Focal or diffuse diabetic glomerulosclerosis is one of the morphological expressions of diabetic microangiopathy. It is commonly encountered in dog and cats and indicate a long evolution of the disease. Basal membrane of glomerular capillaries present thickening caused by hyaline deposits, being followed by subsequent sclerosis of the tufts. Similar sclerosis occurs in mesangium and also thickening of the basement membrane of Bowman capsule and convoluted tubules. Dysfunctional filtration are clinically expressed in cats as microalbuminuria and proteinuria [119].

Diabetic lesions of the eye are represented by diabetic retinopathy and cataracts. As renal complications, retinal involvement proves a long evolution disease. Dogs and cats express retinopathy as microaneurysms and varicous dilations of capillaries, degenerative processes which result in loss of endothelial cells and pericytes and further formation of acellular non-perfused capillaries. Neovascularization within the retina may occur [120, 121]. Cataract onset in dog and cats is a common event and represent the reason for which diabetes is suspected. The incidence is higher in dogs than cats [122], suggesting that lens capsule in diabetic dogs is more permeable to circulating glucose [118, 123].

The cats express frequently diabetic neuropathy, being clinically revealed by plantigrade position, hindlimb paresis and subsequent muscle atrophy [124]. The lesions are usually confined to pelvic sensitive and motor nerves, but thoracic limb involvement was also

described in juvenile onset [125]. Axonal injuries (glycogen deposition, accumulation of membranous deposits or neurofilaments and loss of fibers) of both myelinated and unmyelinated fibers, degeneration of myeline sheath featured by discontinuity (rows of myelin balls and ovoids), and demyelination are frequently described in feline and canine diabetes [126]. Microvascular changes were noticed in feline diabetic neuropathy, those being consistent with endoneurial dilation of capillaries and thickening of basement membrane [127]. Remyelination may occur if the therapy management in glucose control is achieved and revealed by fibers with thin myelin sheaths [128].

Diabetic dog and cats are prone to secondary infections. Glucosuria creates good growth conditions for glucose and albumin fermenting bacteria (*E. coli, Clostridium sp, Proteus sp, Staphylococcus aureus, Aerobacter aerogenes*) [129] which creates gas accumulation in kidneys, ureters and urinary bladder. Urinary bladder wall has spongy consistency, with multiple cyst-like structures filled with gas, which confer floating ability when the tissue specimens are put into fixative solution. Hemorrhages and inflammatory cell infiltration are observed in lamina propria [130, 131].

Pulmonary lesions may occur in cats with diabetes mellitus. The lesions are diverse and require careful clinical assessment of the individuals. Furthermore, the onset of pulmonary lesions are linked to vascular disturbances (congestion, edema, smooth muscle hypertrophy), inflammatory (pneumonia, type II pneumocytes hyperplasia, fibrosis), degenerative (mineralization) and neoplasia [132].

Impaired pigmentation (vitiligo) and canine diabetic dermathopathy are rarely seen and may be expressed as erythema, erosions, ulcers and crusts which feature superficial necrolytic dermatitis. The lesions have bilateral disposal on muzzle, lips, periocular skin, pinae and extremities. The onset of the lesions is attributable to decreased levels of amino acids which are extensively used in hepatic gluconeogenesis [3].

10. Diabetes mellitus in wildlife

Spontaneous diabetes mellitus in humanoid and non-humanoid primates was described in captive animals and it is consistent with clinical and morphological features of type 2 diabetes mellitus [133-139]. Thus, previous results, comparative studies and creation of animal models emphasized many similarities with human non-insulin dependent diabetes mellitus (insulin resistance, long prediabetic status and impaired β-cell function). Furthermore, spontaneous amyloidosis is described in various species such as rhesus (*Macaca mulatta*), squirrel monkey (*Saimiri sciureus*), baboons (*Papio hamadryas), drills (Mandrillus leucophaeus, Mandrillus sphynx*) , macaques (*Macaca fascularis, Macaca cyclopis, Macaca nemestrina, Macaca nigra*), *Cercopithecus diana, Cercopithecus nictitans* , orangutan (*Pongo pygmaeus*) and chimpanzee (*Pan troglodytes*). Amyloid deposits appear not only in pancreas, but also in spleen, liver, kidney and adrenal gland. In this context islets amyloidosis was immunohistochemically positive for islet amyloid polypeptide (IAPP) and calcitonine gene-related peptide (CGRP) [138]. Histologically, the lesions present obvious resemblance with those described in cat: amyloid deposition around capillaries, with little or

severe deleterious effect on islet cell density [134, 138, 140-142]. Complications of diabetes mellitus in primates are cardiomiopathy, myocardial fibrosis, nephropathy and venous thrombosis [143]. Secondary diabetes mellitus is described in non-humanoid monkeys with pituitary adenoma which creates condition for insulin antagonism [144].

Diabetes mellitus was described in wild captive rodents, one of the broader studies being conducted on golden mantled ground squirrel (*Spermophilus lateralis*). Grossly, the animals present cataract (multifocal subcapsular areas of opacity), retinal atrophy, and islet cell vacuolation in both α and β cells [145]. Other species of captive rodents such as tuco-tuco (*Ctenomys talarum*) [146] and plains viscachas (*Lagostomus maximus*) [147] may develop diabetes mellitus in both adults and offspring which have been diagnosed with cataract, hepatic lipidosis and significant high level of glucose and fructosamine. High energetic diet and lack of physical exercises seem to be the cause of the onset of diabetes. Wild bank vole (*Clethrionomys glareolus*) developed type 1 diabetes mellitus in adults and offspring after few months of captivity. The animals express typical markers for insulin dependent diabetes mellitus such as GAD65, IA-2 and insulin autoantibodies and vacuolation of pancreatic islets. A novel Picornavirus (Ljungan virus) was identified in affected islets [148, 149].

Secondary diabetes mellitus was also described in rock hyraxes (*Procavia capensis*) diagnosed with pancreatic islet fibrosis [150] and in California sea lion due to chronic pancreatitis [151].

Wild carnivores develop diabetes in captive or captive-born individuals such as jaguar [152] and african spotted leopard [153]. Thus, secondary diabetes occurred in a female of jaguar (*Panthera onca*) with prolonged administration of megestrol acetate for preventing pregnancy and subsequent metastatic uterine scirrhous adenocarcinomas [152].

A case of diabetes mellitus is described in a 50 years of age captive elephant. The bull had a medical history of necrotizing laminitis, poliarthritis and preputial edema treated with phenylbutazone, prednisolone, dexamethasone and diuretics (chlorothiazide). Pancreas presented atrophy and fibrosis of the islets. The authors mention that a previous infection with endotheliotropic elephant herpes virus should be considered as a potential cause of this case. Therapy protocol is also important. Although is not discussed, the usage of insulin antagonists in the therapy protocol may be envisaged [167].

Glucose metabolism in granivorous birds presents important differences comparing with mammals. Normal glycemia records higher values than other vertebrates with corresponding body weight, intracellular glycogen reserve is lower and plasma glucose concentration is not regulated via insulin intervention. Glucagon, insulin, somatostatin and avian pancreatic polypeptide are synthesized in three different types of islets [154]. The levels of glucagon in pancreas and plasma are higher than in mammals, this being essential for glucose metabolism. The absorption of glucose from gastrointestinal tract is performed by sodium-glucose co-transporters and glucose transport protein. These mechanisms are very efficient in kidneys, avian urine being glucose-free [155]. Finally, it is postulated that the onset of avian diabetes is probably a consequence of glucagon excess and less due to insulin deficiency. This has been supported by studies in ducks which have developed hypoglycemia after total pancreatectomy. Controversially, some experiments conducted in

duck and goose proved the onset of diabetes after administration of anti-insulin serum or subtotal pancreatectomy respectively [154]. Furthermore, some cases of avian diabetes mellitus have been managed successfully by insulin therapy for a long time. Carnivorous birds have the same insulin-coordinated glucose metabolism as described in mammals [156].

Spontaneous diabetes mellitus in birds is rarely reported and it is consistent with type 1 diabetes mellitus. Small parrots such as nanday conure (*Nandayus nenday*) [157] or in chestnut-fronted macaw (*Ara severa*) [158] present diabetes clinically expressed as polyuria, polydipsia, hyperglycemia, hypoinsulinemia, glucosuria and ketonuria. Pancreatic islets were almost totally destructed with absent immunohistochemical reaction to insulin. Lymphoplasmocytic pancreatitis features the lesions of exocrine pancreas in almost all cases described [157]. A similar situation was described in African grey parrot (*Psittacus erithacus erithacus*), in which destructions produced by pancreas inflammation were concurrent with compensatory proliferation and hypertrophy of the islets cells [159]. Negative results were obtain for identification of concurrent bacteriological and viral infection in almost all reviewed cases. A cockatiel (*Nymphicus hollandicus*) diagnosed with type 1 diabetes mellitus present chronic pancreatitis and associated viral inclusions in acinar and ductal epithelial cells due to Psittacid herpesvirus infection which indicates the diagnosis of Pacheco's disease [160]. This condition is specific for Psittaciforme and it is featured by hepatic, renal and splenic coagulative necrosis, syncitial cells into respiratory epithelium, intestinal crypts, parathyroid, thymus and both intracytoplasmic and intranuclear inclusions [161, 162]. Although Psittacid viral infection in pancreas is rarely mentioned, the authors recommend differential diagnosis in avian pancreatitis with or without diabetes mellitus. It is noteworthy that diabetes mellitus was associated with excessive iron storage, this being a condition described in chestnut-fronted macaw (*Ara severa*), military macaw (Ara militaris) and also in humans [163]. This association is well documented in humans and rodent models of haemochromatosis, iron being preferentialy stored in β-cells and generating insulin deficiency [164]. Although pancreatic biopsies revealed no lesions attributable to iron storage in pancreatic islets, specific long term therapy succeeded to prolong survival of the birds more than 20 months [163].

Diabetes mellitus in raptors is little documented. Experimental pancreatectomy in a great horned owl was followed by hyperglicemia and subsequent death, proving that carnivorous birds develop a similar disease with humans [165]. Spontaneous diabetes mellitus was described in a female of red-tailed hock (*Buteo jamaicensis*). Kidneys, lungs and air sacs present different types of inflammation, as interstitial lymphocytic nephritis associated with cysts of proximal tubules and suppurative bronchopneumonia and aerosaculitis. Hepatic lipidosis was featured by isolated foci. Severe degeneration of pancreatic islets was confined to β-cells, characteristic glycogen granules being absent. Although bacteriological investigation did not identified any bacterial colonies, histological section detected cocci in kidneys and lungs. Postmortem examination of pituitary and adrenal glands did not identified tumoral lesions attributable, the etiology of the condition remaining unknown [166].

11. Conclusions

Spontaneous diabetes mellitus in animals includes all types of diabetes described in humans. Although rarely diagnosed, the horses express IDDM, NIDDM and secondary diabetes. Cattle and dogs present IDDM, while the cat is the animal prototype of spontaneous NIDDM featured by islet amyloidosis. Gestational, diestrus and persistent corpora luteal diabetes were described in dog. The onset of diabetes in wildlife is frequently correlated with captivity, diet changes, low physical exercises or concurrent lesions of the pancreas followed by endocrine insufficiency.

Diabetes mellitus in animals represent not only a generous field for research purpose due to numerous resemblances with human conditions, but also an important area in practice of veterinary medicine. The surveillance and treatment of diabetic animals include many issues to be considered, beginning with the diagnosis, continuing with causes which are responsible for the onset of diabetes and finishing with the setting of the most appropriate therapeutical protocol. Although the human diagnosis and classification of diabetes mellitus is not entirely applicable to animals, spontaneous onset of this disease represented the first steps in creating adequate animal models which became more refined to meet the various requirements of the research.

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