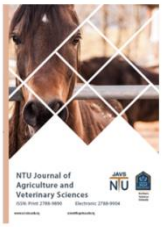
NTU Journal of Agricultural and Veterinary Sciences (2024) 4 (1) : 38-43
DOI: https://doi.org/10.56286/ntujavs.v2i2

IRAQI Academic Scientific Journals

P-ISSN: 2788-9890 E-ISSN: 2788-9904
NTU Journal of Agricultural and Veterinary Sciences
Available online at: https://journals.ntu.edu.iq/index.php/NTU-JAVS/index



Diabetes mellitus in pet animals

1st Muttaa Abdalmutalib Alhayali[1], 2nd Ahmed Ali Hussein[2], 3rd Nashaat G. Mustafa[3]
1.2.3. Department of Physiology, Biochemistry and Pharmacology, College of Veterinary Medicine, University of Mosul, Mosul, Iraq

Article Informations

Received: 14-10- 2023,
Accepted: 02-02-2024,
Published online: 28-03-2024

Corresponding author:
Name: Ahmed Ali Hussein
Affiliation : College of Veterinary Medicine, University of Mosul
Email: ahmvet@uomosul.edu.iq

Key Words:
Diabetes mellitus
Hyperglycemia,
Pet animals,
Insulin,
Cats,
Dogs.

A B S T R A C T

Diabetes mellitus (DM) is a recurrent trouble found in humans and animals, especially dogs and cats. Clinical symptoms include hyperglycemia with glycosuria, and using the documentation of their persistencefor diagnosis. The insurance that the owners of cats or dogs have the ability to administer of insulin, perceive the clinical symptoms of deficiency control DM, and observe of glucose concentrations in blood, are important steps in the successful management of DM. Treatment by using insulin twice daily with the diet diversity is very useful in the management insulin resistance and obesity in dogs. In cats, the first treatment includes moving to a diet of low-carbohydrates accompanied by an injection of insulin twice daily. Amnesty rates in cats can be more than 90%, while in dogs the disease, with the omission of a bias disorder, is usually life-long. This manuscript aim to detail the achievable classification, pathogenesis and etiology of impulsive DM in pet animals and spotlight innovative conducted research in this area.

©2023 NTU JOURNAL OF AGRICULTURAL AND VETERINARY SCIENCES, NORTHERN TECHNICAL UNIVERSITY. THIS IS AN OPEN ACCESS ARTICLE UNDER THE CC BY LICENSE: https://creativecommons.org/licenses/by/4.0/

Introduction

Diabetes mellitus (DM) is a chronic metabolic disorder that occurs when of the body's capability to generate or respond to insulin is defective, leading to an abnormal carbohydrate metabolism and increased glucose concentrations in urine and blood. DM it is the most remarkable and common metabolic disorder identified in cats and dogs after humans. The description of clinical characteristics and diagnosis are barely realized in other large livestock which are horses, buffalo, cattle, pigs and other small ruminants [1-3]. An essential clinical sing of DM is assumed to be the inability of beta cells to produce enough insulin in body's metabolic demands. Deceiving onset of DM rely on several factors: (a) Reduced insulin synthesis, (b) Reduced insulin sensitivity of targeted cells or organs, and (c) Exaggerated synthesis of other reliable hormones that are accountable for inducing DM [4,5]. Diabetes in a canines and felines recorded a hospitalization frequency of 0.4 - 1.2%. Typical medical manifestations of diabetes are weight loss, polydipsia and polyuria. These remarkable results appear only when hyperglycemia reaches level by pass renal threshold of concentrations that lead to glycosuria, at 220 -270 and 180-220 mg/dL in cats and dogs, respectively [6].

Classification

The categorization of DM is distinct between small and large animals, though it shares similarities with humans. The natural and common kinds of DM are called insulin-dependent DM (IDDM) (DM type 1) and non-IDDM (NIDDM) (DM type 2) in animals. In addition, minor DM type 3, which is a complexity of insulin antagonism, was established [7]. This is caused by the destruction of the pancreatic islets caused by pancreatitis, tumor evolution and pancreatic necrosis. The metabolic DM is a distinct preliminary expression of this form, mainly identified in cats and dogs [2].

Etiology

Type 1 DM is characterized by the collapsing of beta cells in the pancreas, which is naturally secondary to autoimmune activity. The outcome is complete destruction of beta cells which leads to low insulin production [8].

The etiology of canine type 1 DM is definitely multifactorial. Genetic susceptibility has been proposed through familial affiliations, Keeshonds analysis of ancestry, and studies of genome that targeted determination of perceptivity and defensive major histocompatibility complex haplotypes [9]. Many genes associated with sensitivity to diabetes in humans were related to elevated danger of diabetes in dogs. Canine diabetes is combined with a class II major histocompatibility complex gene, with same haplotypes and genotypes that are found in the most sensitive breeds. Additionally, components that mediate immunity of diabetes development have been identified in some dogs [10,11].

In the last ten years, researchers have focused on canine etiological factors like dog leukocyte antigen (DLA) which encourages DM, liable genetic material, auto antibodies, and their relationships [1,12]. Studies on dogs less than 12 months of age affirmed that the compatible incident with (pubertal disease) was found to be an unusual event [13,14]. In addition, about 70% of confirmed female dog cases proposed that they would be highly susceptible to DM [7]. Conversely, other studies affirm that DM may occur at the same rate in females and males [15].

Generally, canine DM identification While the natural average is between 7 and 9 years old, DM can be administered to dogs between the ages of 4 and 18, yielding reliable results [7, 15, 16]. The common destruction of Langerhans isolates can mostly be observed in each type of dogs. About 50% of recently diagnosed dogs assumed that beta cell destruction could be result from auto-antibodies [17].

The genes associated with inaugurate DM in humans and canines like genes of tumor necrosis factor - alpha and gamma (TNF-α , TNF-γ), interleukins include (IL-4, IL-10, IL-6, IL-12β), insulin and type 22 of non-receptor protein tyrosine phosphatase and their preservative association joints have been defined [1]. DLA also known canine important histocompatibility complex gene is definitely involved in the induction and provoking of canine DM [2].

In comparison to dogs, DM- type 1 are uncommon in cats. Lymphocytic pervading insulitis is considered a marker of an immune-mediated illness, which was just mentioned in some cats [18.[

In cats, DM exhibits identical clinical and pathophysiological features as type-2 DM in human limited to individual features like obesity, midsize, and age, accompanied by low insulin concentration in blood or the assemblage of amyloids in Langerhans islets with destruction of beta cells, and lastly results in retinal and complexes. In the first stage of DM, production of insulin declines in response to glucose, followed by a distorted response in the second stage of the medical condition. Inductance of glucotoxicity, lipid toxicity and amyloid of Langerhans islets forcefully are concerned with the beginning and progression of the DM, specially NIDDM type-2 in the cats [19-21]. This confirmational models in cats showed influence of glucose in Langerhans islets following continued therapy of intraperitoneal giving of glucose to generate vacuole at cell of Langerhans which will result in DM [21]. Damaging in the structure and function of beta cells and targeting insulin tissue could be an essential goal of treatment of the hyperglycemia to protect beta cells as well as improve of DM.

However glucose is accountable for the stimulation synthesis of insulin via inducing transcription gene of insulin by phosphorylation of pancreatic and duodenal homeobox 1 (PDX1) [22,23].

Obesity is the most risky event for the progression of DM in cats, in addition to others that involve sex (females are less dangerous than males), physical lethargy, captivity, old age and the administration of progestin's along with glucocorticoids. Experiential studies in cats explained that a median gain of acquire about (1.9 kg) through consuming experimentation was related to decline in insulin perceptivity above 50%. The sensitivity to insulin varies between individuals and it will be proposed cats with innately low sensitivity to insulin have an increased risk of developing resistance after gaining weight [24]. Tumor necrosis factor (TNF) was the earliest adipose-derived factor assumed to describe the relationship between insulin resistance and obesity noticed in humans with type 2 DM. TNF has an aggressive negative impact on signaling of insulin. Hyperglycemia is another factor, that has a negative effect on function of beta cells and viability in cats, this condition is called glucotoxicity, while the term lipotoxicity will be used to describe the noxious effects of elevated circulation levels of the free fatty acids on function of beta cells [25,26].

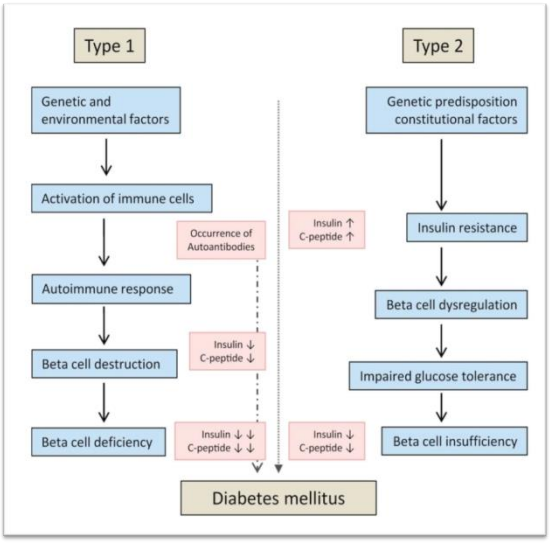


Fig. (1): Pathological events leading to type 1 DM and type 2 DM [27]

Pathogenesis

The pathological process of DM in cats is proposed to have a large correlatation to type 2 DM in humans, including lowered insulin perceptivity as a main character [28]. Instituted non-changeable risk aspects for DM in cats and dogs that involve sex, age and family will be analogous with risk factors for type 2 DM in humans [7,29]. However, dietary, obesity and physical activity levels impact the diabetic risk in both cats and dogs [30,31].

The pathogenicity mechanisms may not be fully similar, so it can be used as a 'human model' to supply a guide for confirmation and discrimination of the different kinds of DM in dogs and cats. Generally, diabetes in dogs and cats simulates type 2 and type 1 DM in humans, respectively [32].

Type-1 DM: diabetic dogs is defined by an immortally low level of insulin in blood (hypoinsulinemia), so there is no elevation in endogenous serum insulin or C-peptide levels after administrationof insulin and a complete demand for the exogenous insulin into conserve control the ketoacidosis and glycemia [33]. Reducing the size and number of islets in the pancreas, a decline in amount of beta cell in the islets, beta cell decadency and vacillation are the histological aberrations in dogs. An essential feature of immune – mediated insulitis is lymphocytic penetration into the islets [34].The onset of type 1 DM may be occurred in dogs aged eight (8) years or older. Diabetes canine seems to be more closely related to latent autoimmune diabetes in adult human. The inclination of lymphocytes to have a lot in diabetic cats compared to control group, when the lesions of islet are examined (5% of control cats vs. 20% of diabetic cats) [35,36].

Type- 2 DM: diabetic cats endure from the type 2-DM which is heterogeneous illness referable to association of impaired insulin activity in muscle, liver, adipose tissue and beta cell deficiency [37].

Diagnosis

The appearance of suitable clinical indications and insistent glycosuria and hyperglycemia are the essential steps for diagnosis of diabetes. However, both hypertriglyceridemia and hypercholesterolemia are common, whereas ketoacidosis and ketonuria may evolve when the owner connot idetify early symptoms or may be dilatory in searching for veterinary care [38].

Physical examinations could be performed for cats and dogs with clinical indicators of DM, also full laboratory experiments such as complete blood count (CBC), urine culture with analysis, urine protein: creatinine ratio (UPC), triglyceride (TG), thyroxine (T4) and blood pressure (BP), which can be used for diagnosis and to cancel other diseases [39].

Development glucosuria typically occurs when the level of glucose in blood transcends (250–300 mg/dL) in cats and (200 mg/dL) in dogs. Clinical symptoms of diabetes will appear while there is persistent glycosuria and hyperglycemia [40]. These symptoms are not found when glucose concentrations spanning through the high reference concentrations with the values of renal threshold. In the early stages of non-clinical DM dogs and cats seem healthy, have a constant weight, and can be discovered only by routine laboratory examination. In addition to the above some may present with inactivity, asthenia, and weak body condition [41].

The basic estimation standards for the diabetic dog and cat are [39-41]:

- Checking the common health of the animal (checking history involves dietary and concurrent drugs, and a full physical examination).
- Determine any complexities that could be related to the disease (e.g. peripheral neuropathy in cats and cataracts in dogs).
- Determine any concurrent dilemma generally linked to the disease (e.g. pancreatitis and infection of the urinary tract).
- Determine states that may be interfere with the patient's responses to treatment (e.g. kidney disease, hyperadrenocorticism and hyperthyroidism).
- Evaluation the risk aspects like pancreatitis, insulin-resistance, diestrus and obesity in female dogs.

Commonly detected are glucosuria, hyperglycemia and stress leukograms in addition to elevated triglycerides and cholesterol. Dogs continually exhibit high levels of alanine aminotransferase (ALT) and alkaline phosphatase (ALP) whereas Cats, expose more changeability in the stress leukogram and increased(ALP). In cats, high levels of enzymes in liver may confirm more assessment for liver diseases [11]. Pancreatitis is prevailing concomitant disease and may be require treatment to have dealt. Diabetic dogs and cats with ketoacidosis may be exposed to extreme increases in blood glucose levels, azotemia and decline total minor carbon dioxide (CO2) due to metabolic acidosis, dehydration, osmotic diuresis and coma. Analysis of urine will indicate the presence of glucose, or protein, ketones, on bacteria, with/ without casts. In animals with glucosurine, a culture of urine should be applied because infection is commonly present [13,23].

Treatment

Actually, the options of treatment are the same as those used in diabetic humans, which involve insulin injections (twice per day at 12 h discontinuities), diet conversions, amendment of obesity, oral hypoglycemic drugs in cats and physical activity in dogs. The treatment method is different between cats and dogs, partially, due to the difference in essential etiology. Generally, the DM classification in cats and dogs may not follow the same pattern used in human medicine [6].

In cats, DM management embraces minimal symptoms via no clinical symptoms, owner acumen of well lifestyle quality and agreeable drug responses, delay or development of DM adverse effects especially, peripheral neuropathy, diabetic ketoacidosis and delay of hypoglycemia. Prognosticators of diabetic absolution in cats involve achieving admirable glycemic control through six months of diagnosis by deeply monitoring at home, ceasing anti-insulin drugs, and using insulin detemir (Levemir) or glargine (Lantus) along with a low-carbohydrate diet. The best method to manage the diabetic cats to start insulin therapy with protamine zinc insulin (PZI; Prozinc) or glargine (Lantus) at an initial dose of 1–2 U/kg q 12 hr [41,42].

In dogs, treatment of clinical DM usually require insulin therapy. U-40 pork lente (porcine insulin zinc suspension; Vetsulin) is the Task Force's best-choice that can be recommended for dog treatment using an initiate dose at 0.25 U/kg q 12 hr [43]. The time of activity is near to 12 hr in many dogs, and formless constituents of insulin aids that decrease postprandial hyperglycemia. As in the case with diabetic cats a clinically ill and ketotic dog should responds for 24 hr care for advanced treatments of ketosis and other basic diseases. An essential aim of therapy is to delay indicative hypoglycemia which may be occur when the dose of insulin is strongly elevated [44].

Therapy complications

The frequency or continuation of the clinical symptoms could be arduous and frustrating for the owner and for the veterinarian [45]. The activity of Insulin is usually due to concerns about the bioactivity of insulin, storage, or insulin response. Resistance to insulin should be suspicious when control of hyperglycemia existed against doses more than (1.5 - 2.0) IU/kg per injection [46]. Applicable examinations should be applied depending on further clinical symptoms or pathophysiological features. Hypoglycemia is typical complexity of insulin treatment, and it occur due to an unexpectedly high elevate in insulin dose or because of an extreme overlay of time of insulin, intervals of lack (loss) of appetite or arduous activities [47]. Symptoms of hypoglycemia involve inactivity, asthenia, ataxia, paroxysm and coma. This is a pathphysiological response to hypoglycemia, where the below glucose in blood induces increasing glycogenolysis, glucagon, growth hormone, glucocorticoids and epinephrine). All mentioned above, result in a notable hyperglycemia within 12 hours, lasting for 2-3 days with the clinical symptoms of the hyperglycaemia. The continuation of classic clinical symptoms of DM results in inference that the dogs are not under control, and negative presumption that the dogs require to an increasing dose of insulin. Detection of the Somogyi phenomenon (response) needs hospitalization and sequential blood glucose. When the Somogyi phenomenon is appears, the dose decrease is assured [46]. Exaggerated interference with insulin duration may elevate hypoglycaemia risks. It is commonly noticed when the (glucose lowest point) is occurs 10 hours or more than hours after the injection. Options of treatment are minimizing the administration frequence or altering insulin type with a shorter time of action.

Managing diabetes in pet animals can be difficult and frustrating, but with applicable owner training, monitoring, and appreciation of the variables that can be managed, diabetes can be controlled in all diabetic pet animals [44,46].

References

[1]. Catchpole, B., Adams, J.P., Holder, A.L., Short A.D., Ollier, W.E. and Kennedy, L.J. (2013) Genetics of canine diabetes mellitus: Are the diabetes susceptibility genes identified in humans involved in breed susceptibility to diabetes mellitus in dogs? Vet. J., 195: 139-147. https://doi.org/10.1016/j.tvjl.2012.11.013

[2]. American Diabetes Association. (2014) Diagnosis and classification of diabetes mellitus. Diabetes Care, 37: S81-S90. https://doi.org/10.2337/dc14-S081

[3]. Robinson, W.F., Robinson, N.A. and Maxie, M.G. (2016) Jubb, Kennedy, and Palmar's Pathology of Domestic Animals. Elsevier, St. Louis, MO. p1-101.

[4]. Akash, M.S., Rehman, K. and Chen, S. (2013) An overview of valuable scientific models for diabetes mellitus. Curr. Diabetes Rev., 9(4): 286-93. DOI: 10.2174/15733998113099990062

[5]. Ganguly, S. (2014) Canine diabetes mellitus: Diagnosis, adequate care and overall management practices involved. Int. J. Pharm. Life Sci., 5: 4022-4023. https://www.researchgate.net/publication/269037220

[6]. American Diabetes Association(2013) Standards of medical care in diabetes –2013. Diabetes Care 36 (Suppl 1) S11–S66. doi:10.2337/dc13-S011. https://doi.org/10.2337/dc13-S011

[7]. Fall, T., Hamlin, H.H., Hedhammar, A., Kämpe, O., and Egenvall, A. (2007) Diabetes mellitus in a population of 180,000 insured dogs: incidence, survival, and breed distribution. J. Vet. Intern. Med., 21: 120. DOI: 10.1892/07-021.1

[8]. Rucinsky, R., Cook, A., Haley, S., et al.(2010) AAHA diabetes management guidelines for dogs and cats. J Am Anim Hosp Assoc;46(3):215–24. DOI: 10.5326/0460215

[9]. Gilor. C. (2019) Discussing prognosis for canine diabetes mellitus: do we have relevant data? Vet Rec.,185(22):689 –91. DOI: 10.1136/vr.l6719

[10]. Link. K.R., Rand, J.S.(2008) Changes in blood glucose concentration are associate with relatively rapid changes in circulating fructosamine concentrations in cats. J Feline Med Surg .,10(6):583–92. DOI: 10.1016/j.jfms.2008.08.005

[11]. Davison, L.J.(2015) Diabetes mellitus and pancreatitis–cause or effect? J Small Anim Pract .,56(1):50–9. https://doi.org/10.1111/jsap.12295

[12]. Mattin, M.J., O'Neill, D.G., Church, D.B., McGreevy, P.D.Thomson, P.C. and Brodbelt, D.C. (2014) An epidemiological study of diabetes mellitus in dogs attending first opinion practice in the UK. Vet. Microbiol., 174: 349. DOI: 10.1136/vr.101950

[13]. Roomp, K., Rand, J. (2012) Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control. J Feline Med Surg .,14(8):566–72. DOI: 10.1177/1098612X12446211

[14]. Alvarez, M.S., Herrería-Bustillo, V., Utset, A.F. and Martínez, J. (2015) Juvenile diabetes mellitus and concurrent exocrine pancreatic insufficiency in a Labrador retriever: long-term management. J. Am. Anim. Hosp. Assoc., 51: 419-423. DOI: 10.5326/JAAHA-MS-6283

[15]. O'Kell, A.L., Wasserfall, C., Catchpole, B., Davison, L.J., Hess, R.S., Kushner, J.A. and Atkinson, M.A. (2017) Comparative pathogenesis of autoimmune diabetes in humans, nod mice, and canines: Has a valuable animal model of Type 1 diabetes been overlooked? Diabetes,66: 1443-1452. doi: 10.2337/db16-1551

[16]. Bellumori, T.P., Famula, T.R., Bannasch, D.L., Belanger, J.M. and Oberbauer, A.M. (2013) Prevalence of inherited disorders among mixed-breed and purebred dogs: 27, 254 cases (1995-2010). J. Am. Vet. Med. Assoc., 242: 1549-1555. DOI: 10.2460/javma.242.11.1549

[17]. Gilor, C., Niessen, S.J., Furrow, E. and Di Bartola, S.P. (2016) What's in a name? Classification of diabetes mellitus in veterinary medicine and why it matters. J. Vet. Intern. Med., 30: 927-940. DOI: 10.1111/jvim.14357

[18]. Verkest, K.R., Rand, J.S., Fleeman, L.M., Morton, J.M. & Herrtage, M.E.(2012) Spontaneously obese dogs exhibit greater postprandial glucose, triglyceride, and insulin concentrations than lean dogs. Domestic Animal Endocrinology 42 103–112. DOI: 10.1016/j.domaniend.2011.10.002

[19]. Hoenig, M. (2014) Comparative aspects of human, canine, and feline obesity and factors predicting progression to diabetes. Vet. Sci., 1(2): 12. https://doi.org/10.3390/vetsci1020121

[20]. Reusch, C.E. (2014) Feline diabetes mellitus. In: Feldman, E.C., Nelson, R.W., Reusch, C.E., ScottMoncrieff, J.C.R. and Behrend, E.N., editors. Canine and Feline Endocrinology. 4th ed. Elsevier, St. Louis, MO. p258-314.

[21]. Will, S.E., Júnior, J.C., Alcântara, D., Fratini, P., Favaron, P.O., Miglino, M.A. and Neto, A.C. (2017) Stem cell therapy to restore pancreatic function in dogs and cats. Braz. J. Vet. Pathol., 5: 99-105.

[22]. Zini, E., Lunardi, F., Zanetti, R., Heller, R.S., Coppola, L.M., Ferro, S., Guscetti, F., Osto, M., Lutz, T.A., Reusch, C.E. and Cavicchioli, L. (2016) Endocrine pancreas in cats with diabetes mellitus. Vet Pathol., 53: 136-144. DOI: 10.1177/0300985815591078

[23]. Zheng, S., Zhou, H., Han, T., Li, Y., Zhang, Y., Liu, W. and Hu, Y. (2015) Clinical characteristics and beta cell function in Chinese patients with newly diagnosed Type 2 diabetes mellitus with different levels of serum triglyceride. BMC Endocr. Disord., 15: 21. DOI 10.1186/s12902-015-0018-1

[24]. Slingerland, L.I., Fazilova, V.V., Plantinga, E.A., Kooistra, H.S. & Beynen, A.C.(2009) Indoor confinement and physical inactivity rather than the proportion of dry food are risk factors in the development of feline type 2 diabetes mellitus. Vet J. 179(2) 247–253. DOI: 10.1016/j.tvjl.2007.08.035

[25]. Hoenig, M., Thomaseth, K., Waldron, M. & Ferguson, D.C.(2007) Insulin sensitivity, fat distribution, and adipocytokine response to different diets in lean and obese cats before and after weight loss. American Journal of Physiology. Regulatory, Integrative and Comparative

Physiology.292 227–234. DOI: 10.1152/ajpregu.00313.2006

[26]. Radin, M.J., Sharkey, L.C. & Holycross, B.J.(2009) Adipokines: a review of biological and analytical principles and an update in dogs, cats, and horses. Veterinary Clinical Pathology 38 136–156. doi:10.1111/ j.1939-165X.2009.00133.x.

[27]. Hörber,S., Achenbach,P., Schleicher,E. And Peter,A.(2020) Harmonization of immunoassays for biomarkers in diabetes mellitus. Biotechnology Advances 39 (2020) 107359. DOI: 10.1016/j.biotechadv.2019.02.015

[28]. Henson, M.S., O'Brien, T.D.(2006) Feline models of type 2 diabetes mellitus. ILAR J,47:234-42. doi:10.1093/ilar.47.3.234.

[29]. 8ii8iÖhlund, M., Fall, T., Ström Holst ,B., Hansson-Hamlin, H., Bonnett, B.and Egenvall, A.(2015) Incidence of Diabetes Mellitus in Insured Swedish Cats in Relation to Age, Breed and Sex. J Vet Intern Med, 29:1342. doi:10.1111/jvim.1358.

[30]. Öhlund, M., Egenvall, A., Fall, T., Hansson-Hamlin, H., Röcklinsberg, H. and Holst, B.S.(2017). Environmental Risk Factors for Diabetes Mellitus in Cats. J Vet Intern Med;31:29-35. doi:10.1111/ jvim.14618.

[31]. Pöppl, A.G., de Carvalho, G.L.C., Vivian, I.F., Corbellini, .LG.and González, F.H.D. (2017) Canine diabetes mellitus risk factors: A matched case-control study. Res Vet Sci;114:469-73. doi:10.1016/j.rvsc.2017.08.003.

[32]. Nelson,R. W. and Reusch, C. E. (2014).ANIMAL MODELS OF DISEASE Classification and etiology of diabetes in dogs and cats. Journal of Endocrinology, 222, T1–T9. DOI: 10.1530/JOE-14-0202

[33]. Catchpole, B., Kennedy, L.J., Davison, L.J.and Ollier, W.E.R. (2019) Canine diabetes mellitus: from phenotype to genotype. J Small Anim Pract.:4–10. DOI: 10.1111/j.1748-5827.2007.00398.x

[34]. Usui, S., Yasuda, H.and Koketsu, Y. (2015).Characteristics of dogs having diabetes mellitus; analysis of data from private Japanese veterinary clinics. Vet Med Anim Sci.;3(1):5. http://dx.doi.org/10.7243/2054-3425-3-5

[35]. Miceli, D.D., Pignataro, O.P. and Castillo, V.A. (2017).Concurrent hyperadrenocorticism and diabetes mellitus in dogs. Res Vet Sci. :115:425–31. DOI: 10.1016/j.rvsc.2017.07.026

[36]. Miller, E.J. and Brines, C.M. (2018) Canine diabetes mellitus associated ocular disease. Top Companion Anim Med.;33(1):29-34. DOI: 10.1053/j.tcam.2018.03.001

[37]. Chatterjee. S., Khunti, K. and Davies, M.J. (2017) Type 2 diabetes. Lancet;389:2239-51. doi:10.1016/S0140-6736(17):30058-2.

[38]. Kumar, P., Kumari, R.R., Kumar, M.,Kumar, S. and Chakrabarti, A.(2014) Current practices and research updates on diabetes mellitus in canine. Veterinary World,7(11):952-959. DOI: 10.14202/vetworld.2014.952-959

[39]. Tardo, A.M., Baldo, F.D., Dondi, F., Pietra, M., Chiocchetti, R. and Fracassi, F. (2019). Survival estimates and outcome predictors in dogs with newly diagnosed diabetes mellitus treated in a veterinary teaching hospital. Vet Rec. , 185(22):692. DOI: 10.1136/vr.105227

[40]. Palm, C.A., Boston, R.C., Refsal, K.R., et al. (2099) An investigation of the action of Neutral Protamine Hagedorn human analogue insulin in dogs with naturally occurring diabetes mellitus. J Vet Intern Med .,23(1): 50–5. DOI: 10.1111/j.1939-1676.2008.0249.x

[41]. Valentin, S.Y. (2014) Clinical findings, diagnostic test results, and treatment outcome in cats with spontaneous hyperadrenocorticism: 30 cases. J Vet Intern Med:28(2):481–7.

[42]. Hess, R.S.and Drobatz ,K.J.(2013) Glargine insulin for treatment of naturally occurring diabetes mellitus in dogs. J Am Vet Med Assoc.;243(8):1154–61

[43]. Nelson, R.W., Henley, K., Cole, C., et al.(2009) Field safety and efficacy of prot amine zinc recombinant human insulin for treatment of diabetes mellitus in cats. J Vet Intern Med;23(4):787-93. doi: 10.1111/j.1939-1676.2009.0342.x .

[44]. Heeley,A.M., O'Neil', D.G., Davison, L.J., Church, D.B., Corless, E.K. and Brodbelt, D.C. (2020) Diabetes mellitus in dogs attending UK primary-care practices: frequency, risk factors and survival. Canine Medicine and Genetics .7:6. https://doi.org/10.1186/s40575-020-00087-7

[45]. Nelson, R.W., Feldman,E.C., Reusch,C.E., Scott-Moncrieff, J.C.and Behrend,E.N. (eds)(2015) Canine diabetes mellitus. In: Canine and Feline Endocrinology. 4th edition. Elsevier, St Louis, Missouri, p213-153.

[46]. Hess, R.S.(2010) Insulin resistance in dogs. Vet Clin N Am: Small Anim Pract.; 40: 309-316. DOI: 10.1016/j.cvsm.2009.12.001

[47]. Ettinger, S.J., Feldman, E.C.and Côté, E. (2017) Canine diabetes mellitus. In: Textbook of Veterinary Internal Medicine. SJ Ettinger and EC Feldman (eds). 8th edition. Elsevier, St Louis, Missouri, p1767-81.