



SUMMARY PhD. Stud. Madalina ROSCA

RESEARCH REGARDING THE ETIOPATHOGENESIS, DIAGNOSIS AND THERAPY OF DIABETES MELLITUS IN CAT

The current state of knowledge on the etiopathogenesis, diagnosis and treatment of diabetes mellitus in cats, comprise the first part of the thesis, divided in three chapters. Data regarding the epidemiology, pathophysiology of disease, paraclinical tests commonly used for the diagnosis of diabetes mellitus and related conditions, and also the current specific therapy are presented on 31% of the paper. *Chapter I*, entitled "*Current data regarding the etiopathogenesis of diabetes mellitus in cats*" reveals general information on pancreas anatomy, glucose intake by insulin-dependent and non-insulin-dependent tissues and the pathophysiology of persistent hyperglycemia. Disease character is completed by the general classification in type I and type II diabetes mellitus, pathophysiological description and worldwide occurrence rate. *Chapter II*, as indicated by the title "*Current diagnostic panel used for the detection of diabetes mellitus and underlying diabetogenic endocrinopathies*" presents an overview of the clinical and physical examination, also general and special paraclinical investigations used to confirm diabetes mellitus or associated pathologies. Chapter III summarizes the "*Therapeutic protocol of feline diabetes mellitus*". The section outlines the main insulin analogues and oral hypoglycemic agents commonly used for the therapy of feline diabetes mellitus, in respect to the conditions and complications related to the primary disease. The second part includes the original research conducted in the thesis, comprised in three main chapters, divided into subchapters, presented in 69% of the work. The section presents personal research results which regard feline diabetes epidemiology, establishment most important causal factors and difficulties encountered by clinicians in patient assessment. In chapter V, new diagnostic methods with high applicability in the clinical and laboratory veterinary field are developed. Important research contributions on the specific therapeutic protocol and glucose homeostasis equilibration of diabetic patients are made in chapter VI.

"*Etiopathogenesis study of feline diabetes mellitus*" is structured in chapter IV, divided in three subchapters which include the incidence, involvement of insulin antagonists in increasing the rate of occurrence of the disease and evaluation of clinical status in relation to the disease progression.



"Epidemiologic study on diabetes mellitus in cats" in subchapter IV.1 was conducted on a total of 5175 cats registered in retrospective, on a period of nine years, from the database of a private practice and the Medical Clinic of the Faculty of Veterinary Medicine.

The prevalence of diabetes showed a linear increase ($R^2 = 0.98$) from 4 cases in 2006 to 12 cases in 2014. Cumulative incidence in the studied population showed a progression from 6.9 cases on each 1000 consulted cats (1 on 143 cases) to 12.5 cases per 1000 consulted cats (1 to 79 cases), on a nine year period, with an incidence of 1.25% referred to the total number of cases. The higher proportion of males in the total studied population (2898 males - 56%, 2277 females - 44%) explain the increased proportion of diabetes cases to this gender. However, males predisposition was statistically proven ($P < 0.001$) and correlated with their higher average weight ($M = 5.16$ kg, $F = 4.51$ kg) and also a lower average age ($M = 10.85$ years, $F = 11.16$) when compared to females. The data is explained by a naturally decreased sensitivity to insulin than females and higher adipogenetic capacity, which makes males more prone to develop insulin resistance. Burmese breed revealed a risk of developing diabetes 2.7 times higher than other breeds. During the nine year period, 19% ($n = 983$) cases belonged to the Burmese breed, of which 34 have been diagnosed with diabetes, resulting in a prevalence significantly higher compared the other breeds. The cumulative incidence indicated a number of affected individuals of 34.5 to 1000 or 1 to 29 cats for the Burmese breed. The increased breed predisposition has been explained by a series of defects of lipid metabolism, a reduced activity of lipoprotein lipase, regulated primarily by insulin and the absence an apolipoprotein. All these factors lead to higher levels of lipoproteins and chylomicrons, with following hypertriglyceridemia and insulin resistance. Average age of Burmese females was 3.6 years higher when compared to the Domestic Short Hair breed (Burmese/F - 13.3 years; Domestic Short Hair/F - 9.7 years), while the males showed a difference of only 0.7 years (Burmese/M - 11.47 year; Domestic Short Hair/M - 10.69 year). The late trend of occurrence of diabetes mellitus in the Burmese breed was attributed to a reduced amyloid secretion and pancreatic inflammation compared to other breeds.

Recorded anamnesis data showed a major association of diabetes with the administration of synthetic progestagens and steroidal anti-inflammatory drugs, a finding which motivated the research in chapter IV.2.



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"Synthetic progestagens and steroidal anti-inflammatory drugs involvement in the epidemiology and etiopathogenesis of feline diabetes mellitus" (Chapter. IV.2.) was evaluated through descriptive epidemiological analysis of diabetes mellitus in relation to the administration of these insulin antagonists.

Out of the total cases in the database, a number of 750 (14.5%) entire individuals were treated annually with synthetic progestagens in two to four episodes. Of these (n=750), a total of 21 cases were subsequently diagnosed with diabetes mellitus, indicating a prevalence of 0.4% for the total analyzed population. By reporting the patients diagnosed with diabetes (n=21) only to those treated with progestagens (n=750), diabetes prevalence increases significantly to 2.8%. Individuals treated with progestagens (n=21) represented 32.3% of diabetic patients. Of these, 14 were entire females (21.5% of 65) with a mean age of 11.12 years and an average weight of 3.1 Kg. Entire males, in a total of 7 cases (10.7% of 65) had an average age of 9.5 years and an average weight of 4.5 kg. Steroidal anti-inflammatory drugs were administered in 802 (15.5% of 5175 cases), both neutered and entire cats. Of these, a total of 13 cases were subsequently diagnosed with diabetes mellitus, indicating a prevalence of 0.2% for the total population (n = 5175). However, if reported to the population of interest (n = 802), the prevalence for the steroidal anti-inflammatory treated cases was 1.6%. This group represented 20% of diabetes mellitus cases (n=65), of which 9 (11.22%) were males and 4 (4.98%) females.

Cumulative incidence results were an important indicator regarding the impact of administered insulin antagonists on the rate of occurrence of feline diabetes mellitus. The established cumulative incidence of diabetes mellitus in association with synthetic progestagens was of 28 cases on every 1000 cases, or 1 in every 35 patients in the group. As for the steroidal anti-inflammatory treated individuals, diabetes cumulative incidence was 16.20 cases of diabetes in 1000 cats or 1 in every 61 cases. Diabetes incidence in cats that never received any of these substances was significantly lower, of 1 case to every 165 patients or 6.05 per 1000 cats. Representation of 52.3% of diabetic patients receiving insulin antagonists indicates a clear impact in the incidence of diabetes mellitus and the need to include data regarding their administration in the anamnesis of diabetic cats. Predisposing and favoring factors underlying pathologic sustained hyperglycemia had a major influence on the clinical evolution, remission degree and survival rate, all described in *Chapter VI.3.*



Results regarding the *"Pathophysiology study of feline diabetes mellitus in relation to underlying causes"* provide vital information, guiding the approach of each case in relation to clinical signs and complications related to diabetes. Clinical status evaluation of 65 cats included anamnesis, previous diagnosis and adjacent treatments.

Subclinical diabetes was identified in 6 (9.2%) individuals, presented in an early-stage of the disease, identified either as a result of routine or other purposes consults. The clinical state was observed in 12 patients (18.4%) and clinical panel ranged from obvious signs of marked PU/PD, polyphagia alternated with a capricious appetite and weight loss, constipation and frequent episodes of vomiting. Complicated diabetes was observed in a number of 38 (58.46%) patients, present in an advanced stage of the disease. The comatose phase was observed in 9 (13.8%) patients, presented for examination in a critical phase, with hepatic lipidosis, severe metabolic acidosis and varying degrees of organ failure.

Also in subchapter VI.3 are presented the most important persistent hyperglycemia secondary pathophysiological conditions such as peripheral neuropathy, found in 8% patients and cataracts, seen only in 1.5% of feline diabetes patients. Coronary atherosclerosis and diabetic nephropathy, complications of diabetes characteristic to human pathophysiology, are still unproven in feline diabetics. Yet, heart disease and varying degrees of renal insufficiency were associated with 9.2% (n=6) of feline diabetes mellitus cases.

A major importance has been granted to feline hypersomatotropism/acromegaly, as the disease is associated in a proportion of 100% with diabetes mellitus. Acromegaly (hypersomatotropism), led to the installation of insulin resistant diabetes of 3% (n=2) evaluated cases. For one of the acromegalic patients, immunohistochemical labeling of protein p53, an important marker of carcinogenesis, showed an intense positive signal in the nuclei of tissue samples collected from the pituitary gland, liver lobes and the left submandibular gland. Data reported in the case study brought feline endocrinopathies closer to human pathophysiology, by showing an increased risk of developing different forms of cancers. Due to major involvement of hypersomatotropism in the incidence of feline diabetes, and limitations encountered in the diagnosis, research has been directed towards the validation of an enzyme-linked immuno-assay for growth factors determination.



Chapter V focuses on *"Research on the diagnosis of feline diabetes mellitus and potential diabetogenic endocrinopathies"*, divided into two sections. In the first subchapter, V.1., *"Screening diabetic cats for hypersomatotropism: performance of an enzyme-linked immunosorbent assay for insulin-like growth factor 1"* research were focused on the validation for feline diagnosis of a quantitative test designed to determine human IGF-1. Analytical performance protocol included the recovery of the compound after dilution, linearity testing, determination of intra and inter-test coefficient of variation, the effect of hyperlipidemia, hyperhemoglobinemia and hyperbilirubinemia on the stability of basal concentration of IGF-1 in plasma/serum and detection limit.

Average recovery of IGF-1 from the high and low concentrations mixed pools was 101.1 $\pm$ 13.9SD % (mean SD $\pm$) (serum) and 93.7% $\pm$ 6.4SD% (plasma). The linearity of serial dilutions of both serum and plasma has demonstrated a correlation coefficient (R^2) of 0.96 (serum) and 0.96 (plasma). Intra-assay coefficient of variation was 9.5 $\pm$ 1.65% (serum) and 7.16% 13.6 $\pm$ (plasma), while the average inter-assay coefficient of variation was 11.4 $\pm$ 4.3% (serum) and 7.6 $\pm$ 6.37% (plasma). Lipids, haemoglobin and bilirubin caused minimal alterations in the concentration of IGF-1 in the serum (8.54 $\pm$ 8.60%, 4.02 $\pm$ 8.98%, respectively 7.09 $\pm$ 8.59%), all considered unimportant. Analysis delays and storage at room temperature showed no major alterations after 24 and 48 hours in plasma samples, although a marked increase in IGF-1 after 48 hours was observed in serum samples ($p = 0.003$) (comparing impaired concentration of IGF-1 in serum samples, the reference value at 0 hours, with the 24 hours: 10.14 $\pm$ 16.34 SD %, and 48 hours: 54.32 $\pm$ 18.36 SD%). Delayed analysis and storage at room temperature showed no significant changes in plasma samples at 24 and 48 hours ($p = 0.23$) (concentration alterations of IGF-1 in plasma samples compared to 0 hours, 24 hours: 0.11 $\pm$ 10.53SD %, at 48 hours: 9.16 $\pm$ 9.87SD %). The detection limit was calculated to be 71.34 ng / ml.

ROC analysis showed an area inside the curve of 0.99 for serum. Also, the analysis revealed a high diagnosis accuracy for the determination of IGF-1 in serum samples with a diagnostic limit 997 ng/ml (ELISA) when used to confirm acromegaly in diabetic cats [sensitivity, 100%; specificity, 88.1%]. For plasma, area inside the curve was lower, 0.93. Diagnosis limit for plasma IGF-1 was determined at 1013 ng/ml [Sensitivity 100% specificity, 72.2%].



The aim of the research consisted of validating an ELISA test for the measurement of IGF-1 in diabetic cats and particularly an alternative to RIA test, solely considered valid at the moment. Determination of IGF-1 has a relevant clinical significance in feline medicine, as acromegaly is a relatively common cause of feline diabetes, the diagnosis being hampered by the limited availability and high costs of RIA test and involvement of radioactive substances. By emphasizing the high concentration of GH and/or IGF-1 and the possibility of hypersomatotropism, it is advisable to confirm the diagnosis with the aid of imaging methods to demonstrate the increased volume of the pituitary gland, which makes the diagnostic protocol more expensive. Thus, any means of reducing the costs of diagnosis, including replacing RIA with the ELISA test can be considered useful by veterinarians.

Feline serum and plasma IGF-1 determination by ELISA system holds high accuracy and precision. Recovery of IGF-1 in the dilutions ranged roughly between 80% and 120%, with an average 101% in serum and 94% in plasma, which are considered to be within normal limits. Average intra- and inter-assay coefficient of variation was less than 15%, within the safe limits. This study has demonstrated an area under the curve value of 0.99 for serum samples and 0.93 in plasma samples, demonstrating the excellent diagnostic accuracy. Hypersomatotropism screening was recommended based on a relatively high prevalence in diabetic cats, on the variable phenotype and often subtle in cats suffering from this endocrinopathy.

With a high commercial availability, validated ELISA test can be easily used in veterinary medical laboratories, in experimental studies and research projects.

The results obtained in the research regarding the etiopathogenesis of diabetes mellitus revealed the association of this disease with other pathologies, which usually entail an insidious development, imposing major difficulties in controlling and restoration of normal glucose level. The establishment of diabetes diagnosis involves a thorough assessment, depending on the nature of primary and secondary pathologies, requiring additional serum biochemistry and imaging investigations, so that individualized therapeutic protocol can be approached. For this purpose research developed in Chapter V.2 focused on the development of a differential diagnosis panel, with high clinical applicability, which holds the ability to spot all primary and secondary diseases associated with pathological sustained hyperglycemia.



In chapter V.2. an *"Enhanced differential diagnosis system for feline diabetes mellitus"* was developed. The Decision Support System is purposed to assist, guide and confirm clinicians resolutions for a certain diagnosis. The program was implemented by analyzing the medical records of 29 diabetes diagnosed cats, by using MATLAB software (Version 2013), represented by an interactive environment with a complex language. Basic structure of the Decision Support System consists of information provided by the literature, patient data and sets of possible situations that could be encountered in the clinical environment, all organized in a stepwise manner, followed by data interference and generating the final conclusion. A discrimination of the entire panel of diseases in feline pathology was performed by starting the diagnostic scheme from the PU/PD syndrome. All forms of diagnosis generated in cascade, only after the completion of a logical set of rules, with a low error degree.

The set of diagnoses which can be generated by the Decision Support System consists of: a) primary uncomplicated diabetes; b) diabetes induced or associated with endocrinopathies like: (b.1) hypersomatotropism, (b.2) hyperthyroidism, (b.3) hyperadrenocorticism (b.4) diabetogenic medications (iatrogenic); c) diabetes induced/associated with organ failure (c.1) chronic/acute renal failure (c.2) heart failure; d) keto-acidotic diabetes; e) pancreatitis. d) Fanconi syndrome. The system has been successfully applied in all 29 cases, resulting in the following diagnoses/no. : (a) - 8 (b.1) - 2 (b.4) - 9 (c.1) - 3 (c.2) - 3 (d) – 4. For diseases not diagnosed in the 29 patients a series of simulations were performed, guided by data from the literature and showing the same high accuracy results.

The goal of Decision Support System development was to focus in a logical manner all expert's knowledge in feline diabetes mellitus and to maximize the reliability of clinical decisions. The developed system supports accurate diagnosis and appropriate treatment in patients with complex conditions, which sometimes are difficult to detect on a first clinical examination. The high novelty degree of the built Decision Support System is evidenced by its ability to direct clinical and laboratory steps in the differential diagnosis, comprising all diabetogenic endocrinopathies and probable diseases associated with pathological hyperglycemia.



The panel of *"Research regarding the therapy of feline diabetes mellitus "* is presented in Chapter VI, divided into three sections. The first subchapter VI.1 regards the *"Management of the therapeutical protocol in feline diabetes mellitus and associated complications"* addresses both diabetic patients that were in a stable clinical condition and also those diagnosed in a critical state.

For subclinical, clinical and stabilized patients, insulin therapy was based on intermediate and slow-acting analogues, starting with the lowest effective dose of 0.25/kg/administration twice daily. The ideal evolution of the glucose-insulin dynamics had an action peak at 6-8h, a nadir in the range of 100-170 mg/dL and a period of activity developed on 10-12h post-administration. For the complicated forms of the disease, therapy was focused on regular fast-acting insulin, administered up until the resolution of ketonuria.

The therapy of keto-acidotic diabetes was based on adjusting the blood pH by IV supplementation of bicarbonate solution, for which the dosage was calculated according to the plasma bicarbonate level (<12 mEq/L) or the concentrations of total venous carbon dioxide (<12 mmol/l) [HCO_3^- (mEq) = body weight(kg) $\times$ 0.4 $\times$ (12-determined bicarbonate) $\times$ 0.5]

Hyperosmolarity correction [$Osmolarity = (2 \times natriemie_{mEq/l}) + (Gl_{mg/dl}/18) + (urea_{mg/dl}/2.8)$] (> 350 mOsm/kg) required saline solutions 0.9% administered gradually, over a period of 48 hours.. The specific treatment of hepatic lipidosis was mainly aimed at seizing the lipid mobilization by starting the assisted enteral feeding, with 5 kcal/kg/24h on the first day of treatment, increasing to 50 kcal/kg/24h on the ninth day. Drug therapy targeted L-carnitine (250-500 mg/kg/day) and stimulants of glutathione secretion (S-adenosylmethionine - 20 mg/kg/day and N-acetylcysteine - 70mg/kg). Fluid therapy was based strictly on the administration of saline solutions 0.9% supplemented with K. No lactate liquids (worsen hepatic lipidosis), with glucidic compounds (enhance fat accumulation in the liver) or dextrose (inhibits oxidation of fatty acids) were administered. Hypokalaemia (<3.5mEq/L) [$mg = (mEq \times atomic\ weight)/valence$] was rectified according serum potassium level. For the severe form, doses of 0.22 mEq/L to 1mEq/kg/h were administered until the potassium level returned normal.

The current panel for the therapy and monitoring of diabetes mellitus involves high costs and allocation of long periods of time in order to establish insulin requirements. To this purpose, two predictive methods for estimating insulin requirements have been developed.



The study developed in *Chapter VI. 2* reveals the "*Neural based prediction development for case oriented glucose control in feline diabetes mellitus therapy*".

The approach uses artificial neural network models, constructed on data obtained from monitoring a group of white Wistar rats, with type I diabetes, artificially induced by intraperitoneal injection of 50 mg/kg of streptozotocin, a β cell selective toxic substance. This type of model, currently under development, has been adapted and validated using data recorded during clinical and therapeutic management of insulin dependent cats.

Artificial neural networks have been projected using the organization and functioning characteristic to the human nervous system, containing a number of highly interconnected simple units called neurons. These structures can be viewed as parallel and distributed information processing and can be considered an adequate solution to model complex biological systems. A neural network learns to represent as many features of the environment from which it receives information, the learning process being represented by the formation of new synapses and/or modifying the existing ones, a process by which the network parameters are adapted continuously as a result of stimulations it receives from the environment. Thus, the construction of a neural network is based on neuron layers. In the presented model the connections between the neurons of the same layer are called „lateral, from the previous layer "backward" and the next layer "forward". Neural networks which only admit forward connections achieve static information transferred between inputs and outputs and are called "forward" transmitting networks or feed-forward neural networks.

Two types of *feed-forward networks* called *Multi-Layer Perceptron* and *Radial Basis Function* were considered. The information obtained from diabetic rats was analyzed and filtered to remove data with high variations. The group was characterized by an average behavior, and for each individual calculations were performed for *least error squares difference from the mean*. This identified the individuals whose conduct did not fit the average of the group. Obtained values were statistically analyzed and eventual data not in the average and dispersion criteria were eliminated.

Neural architecture was a simplistic one, with a single hidden layer and a maximum of 12 neurons, without the inclusion of saturated neurons. In the first step, the neural networks were trained using the glucose measurements determined from the diabetic Wistar rats. The next step consisted in the validation of models on diabetic felines. To estimate the glucose-insulin dynamics,



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various doses and types of insulin were administered. These included slow-acting insulin glargine, intermediate-acting isophane insulin, followed by a mixed type.

Data considered for the registration of glucose-insulin dynamics included the dosage and type of insulin, quantity of consumed food and glycemic alterations on every 60 minutes, for a period of 24 hours, for each individual, registering a total working time of 432h. Insulin was administered twice daily, on every 12 hours and food was provided ad-libitum in order to mimic feline insulin therapy and feeding behavior. For each type of insulin and for each individual, the registered data was scaled by dividing the determined glucose level to the first baseline glucose, this way the data became adimensional and numerical relevant characteristics were calculated.

Once trained, it was observed that both neural networks could be used for short and medium term prediction of blood glucose evolution after insulin input. Multiple tests were conducted on a group of 46 diabetic cats and neural network predictions were compared with actual data recorded from each patient. Using the normalization criterion of mean square error, with a threshold equal to 0.01, it resulted that for 84.78% of patients, the blood glucose predictions were correct, with a predictions confidence level of 91.63% for both models.

Both *Multi-Layer Perceptron* and the *Radial Basis Function* have shown good performance as predictors of post-insulin glucose dynamics, for each type of insulin.

Glucose predictions in diabetic cats are important for the optimization of exogenous insulin input, so that hypoglycemia or hyperglycemia episodes can be avoided. Feline diabetes mellitus develops due to a relative insulin deficiency, most cases being able to resume through adequate glycemic control. Insulin therapy in feline diabetes mellitus imposes major decision difficulties due to the interference of interfering factors such as caloric intake, variable exercise, stress factors, associated diseases and/or adjacent medications, which frequently induce major changes in insulin requirements. The research suggests various modeling techniques addressed mainly in human medicine, which attempt to learn as many proprieties as possible of the glucose-insulin biological system and generate a high accuracy behavioral model.



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"A new approach in designing high performance *in silico* mathematical model for the predictions of blood glucose dynamics" was motivated by the need for an algorithm which can predict post-insulin glycemia alterations at any given dose in the subcutaneous compartment. Subchapter VI.3 follows the development of a mathematical model based protocol for insulin administration.

The model includes two major important parameters, glucose effectiveness (S_G) and insulin sensitivity (S_I). Glucose effectiveness is defined as the ability of glucose to promote its own uptake in the presence of an increased blood glucose level, while insulin sensitivity is the ability of insulin to enhance glucose effectiveness. The *in silico* predictive model requires adaptation for each new patient taken in to observation. A total of three newly diagnosed insulin dependent clinically stable cats, in which the insulin treatment protocol was initiated, were included in the trial for continuous glucose monitoring and data analysis. The glucose-insulin system can be divided into three subsystems, such as insulin, glucose and the interaction between glucose and insulin. Insulin subsystem describes insulin absorption from deposits formed in the subcutaneous compartment. Glucose subsystem describes postprandial glucose uptake.

The adapted method tries to predict insulin dynamics through the rate of blood glucose disappearance. Glucose-insulin dynamics prediction requires a multitude of nonlinear data and correlation with a multiparametric model. Performance of glucose effectiveness (S_G) and insulin sensitivity (S_I) were estimated from a basic model reported in the literature and on the basis of glucose-insulin dynamics observed in a group of insulin-dependent Wistar rats. Basic parameters had the following limits: $S_G = (1.4 \pm 0.3) \times 10^{-2}/\text{min}$, $S_I = (0.58 \pm 0.16) \times 10^{-4} \text{ LMU}^{-1}\text{min}^{-1}$. Empirical parameters establishment entails real deficiencies in the accuracy of generated predictions.

The proposed approach generated a mathematical model able to predict glycemia alterations based on the insulin dose, providing adequate control and minimizing the risk of hypoglycemia in the studied cases.



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Chapter VII presents the *"General conclusions"* and recommendations of the thesis for various clinical and paraclinical maneuvers for feline diabetes. Data presented in the paper holds a high novelty degree, with the possibility of extension to both feline and human diabetology. Final resolutions characterised by an increased clinical applicability, address researchers, veterinary clinicians and veterinary medical students. Data validity is supported by the research development on a large number of patients, correlation of the information provided by feline patients with those obtained from laboratory subjects and testing the accuracy of results through computer systems and mathematical algorithms.

The research objectives address the topics on diabetes mellitus currently approached by literature, providing interpretative results, with an unlimited degree of development.