ESTONIAN UNIVERSITY OF LIFE SCIENCES
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ANALYSIS OF CLINICAL ENDOCRINE CASES IN CATS WITH FOCUS ON DIABETES AND HYPERTHYROIDISM

KASSIDE KLIINILISTE ENDOKRIINSETE JUHTUMIDE ANALÜÜS, KESKENDUSES DIABEEDILE JA HÜPERTÜROIDISMILE

Final Thesis
Curriculum in Veterinary Medicine

Supervisor: Toomas Tiirats

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The aim of this paper is to determine whether there are any differences in signalment, diagnostics and treatment for the two main feline endocrinopathies: diabetes mellitus (DM) and hyperthyroidism (HT) in 2 different clinics. 1 is located in Normandy, France, and 1 is in Tartumaa, Estonia.

This is a retrospective case study comprising of 46 cases; 14 cases of DM (7 in each clinic) and 32 cases of HT (4 in France and 28 in Estonia). While studying the patients' files, the date of diagnosis for each endocrinopathy was determined and the following parameters were selected: age, breed, gender, diagnostic and treatment methods. Weight and whether or not diabetic remission was achieved was also assessed in DM cases; laboratory test results were analyzed for HT cases.

Exactly 30% of these cases are DM cases. Male neutered Domestic Shorthair cats of 10-11 years of age are the typical patient, here. Moreover, the average patient was 4.8kg at the time of diagnosis. Polydipsia (PD) and/or polyuria (PU) was observed by owners in 71.4% of cases, followed by lethargy (in 50% of cases).

The main observation here is the same rate of remission despite using 2 different types of insulin: lente insulin in France and glargine insulin in Estonia.

As for HT, which represents 70% of our cases, the patient is on average 13.7 years and comes in for weight loss, vomiting and inappetence. All patients are treated medically with methimazole.

As regards signalment, the cases of this study generally support the statements found in literature. The main difference in DM were remission rates according to the insulin used. In HT, dynamic function tests and treatment plans other than medical seem to exist only in theory, i.e. in literature.

Keywords: endocrinology, diabetes mellitus, hyperthyroidism, insulin, treatments

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Selle töö eesmärk on analüüsida kahe erineva kliiniku baasil (Prantsusmaal Normandias ja Eestis Tartumaal) erinevusi kahe peamise kasside endokrinopaatia: suhkurtõve (DM) ja hüpertüreoidismi (HT) haigustunnustes, diagnostikas ja ravis..

See on retrospektiivne juhtumiuuring, mis hõlmab 46 haigusjuhtu: 14 DM juhtu (igas kliinikus 7) ja HT 32 juhtu (4 Prantsusmaal ja 28 Eestis). Patsientide haiguslugude uurimisel määrati iga endokrinopaatia diagnoosimise kuupäev ja koguti järgmised parameetrid: vanus, tõug, sugu, diagnostika- ja ravimeetodid. DM juhtudel hinnati ka kehakaalu ja seda, kas saavutati diabeetiline remissioon või mitte; analüüsiti HT juhtude laboratoorsete analüüside tulemusi.

Täpselt 30% neist juhtudest on DM juhtumid. Tüüpilised patsiendid olid 10–11-aastased isased steriliseeritud lühikarvalised kodukassid. Keskmine patsient kaalus haiguse diagnoosimise hetkel 4,8 kg. Polüdipsiat (PD) ja/või polüuuriat (PU) täheldasid omanikud 71,4% juhtudest, millele järgnes letargia (50% juhtudest).

Peamine tähelepanek DM juures on sama remissiooni määr vaatamata 2 erinevat tüüpi insuliini kasutamisele: lente insuliin Prantsusmaal ja glargiininsuliin Eestis.

HT haigusjuhud moodustasid 70% kõigist käsitletud juhtudest. Keskmine patsient oli 13,7-aastane, kellel täheldati kaalulangust, oksendamist ja isutust. Kõiki patsiente raviti meditkamentoosselt metimasooliga.

Käsitletud juhtude haigustunnuste spetsiifika toetab üldiselt kirjanduses leiduvaid väiteid. Peamine erinevus oli DM remissioonimäärades vastavalt kasutatud insuliinile. HT puhul selgus, et praktikas ei kasutata kirjanduses soovitatud funktsionaalseid teste ja spetsiifilisi raviplaane. Piirdutakse valdavalt medikamentoosse raviga.

Märksõnad: endokrinoloogia, suhkurtõbi, hüpertüreoidism, insuliin, ravi

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LIST OF ABBREVIATIONS AND TERMS

ALP	alkaline phosphatase
ALT	alanine transaminase
AST	aspartate aminotransferase
BPA	bisphenol A
CI	confidence interval
DM	diabetes mellitus type 2
Exenatide ER	Exenatide extended release
EMÜ	Eesti Maaülikool
GIT	gastro-intestinal tract
GLP-1	glucagon-like peptide-1
HT	hyperthyroidism
IAPP	islet amyloid polypeptide
IGTT	intravenous glucose tolerance test
IU	international units
ME	metabolizable energy
Nadir	the lowest concentration measured of a specific element or parameter
NTI	non-thyroidal illness
PBDE	polybrominated diphenyl ethers
PCV	packed cell volume
PU/PD	polyuria/polydipsia
PZI	protamine zinc insulin
RBC	red blood cells

RV	reference value
T3	triiodothyronine
T4	thyroxine
TRH	thyroid releasing hormone
TSH	thyroid stimulating hormone
tT4	total thyroxine
WNL	within normal limits

INTRODUCTION

Feline hyperthyroidism and diabetes mellitus are the two most commonly diagnosed endocrine disorders in cats. The incidence of both diseases is increasing, presumably because of the increasing presence of risk factors, but the reason is not always known (Gottlieb and Rand, 2018; Vaske *et al*., 2014).

In feline diabetes, we know that obesity plays an important role in increasing the risk of developing the disease and that is one risk factor that can be controlled. The disease can then be managed through diet and medical treatment (Nelson and Reusch 2014). Different insulins can be given to cats: porcine lente insulin, glargine and detemir, which all have different advantages and disadvantages. There are also different rates of remission reported and our study will show a contrasting result (Gottlieb and Rand, 2018).

Both diseases typically affect older cats and this is especially the case with feline hyperthyroidism. Advanced age also means that the patients are more likely to develop or have developed concurrent diseases, which is why one should always assess liver and kidney parameters and understand where changed values can arise (Mooney and Peterson, 2012; Nelson and Reusch, 2014)

Clinical signs such as polyuria, polydipsia, weight loss, vomiting and lethargy can present in both illnesses and are those reported by owners (Broussard *et al.*, 1995; Rand, 2012). Knowing what is prompting owners to seek veterinary care allows us to understand which changes they are able to detect and allows us to better communicate with them.

In this paper, we will discuss both diseases in the literature review the clinical signs, risk factors, diagnostic tools, treatment options and challenges these disorders cause. We will then analyze cases of these feline endocrinopathies from two clinics: one based in France and one in Estonia.

1. LITERATURE REVIEW

1.1. Feline diabetes mellitus

DM is one of the 2 most common endocrine diseases amongst felines and it is described as a persistent hyperglycemia. Type 2 diabetes mellitus is by far the most represented type of diabetes, accounting for 85-95% of diabetic cats (Rand, 2012). Here, DM results from both impaired insulin secretion, insulin resistance and amyloid deposition in the pancreatic islets. This type was previously referred to as adult-onset diabetes mellitus (Lutz and Rand, 1995; Henson and O'Brien, 2006).

Pancreatic adenocarcinoma and pancreatitis causing beta cell loss and endocrinopathies such as hyperthyroidism and hyperadrenocorticism causing insulin resistance represent other types of diabetes. Type 1 diabetes mellitus is immune-mediated and has only been described in a few cases (Gilor *et al.*, 2016) . Gestational diabetes cases have not been reported in cats. (Rand *et al.*, 2004; Nelson and Reusch, 2014). These types of diabetes will not be discussed further in this literature review.

From now on, the abbreviation DM is used to denote type 2 diabetes mellitus unless otherwise stated.

The prevalence is very different from study to study and can range from 0.25-1% of felines. It is believed to be more and more diagnosed due to the increasing occurrence of cat obesity and physical inactivity, which are predisposing factors (Rand *et al.*, 2004). The typical patient is 10-13 years old and male. Burmese, Domestic Shorthairs and Longhairs, Main Coons, Siamese and Russian Blues are the most representative breeds (Rand, 2012).

1.1.1. Aetiology

Insulin resistance has both genetic and acquired aspects and they both play a part in DM. Insulin resistance is defined as decreased insulin sensitivity, which is how responsive a body's cells are to glucose. If there is insulin resistance, glucose levels do not lower appropriately for a given amount of insulin (Nelson and Reusch, 2014).

Prolonged hyperglycemia will suppress insulin secretion from beta cells and this is known as glucose toxicity. This can be reversible at first, but beta cells can undergo irreversible changes if glycemic control continues to fail. This is why glycemic control is important for diabetic remission (Rand, 2012).

Amyloid deposition may be a cause for the loss of beta cell function. The islet amyloid polypeptide (IAPP), a.k.a. amylin is the hormone producing islet amyloid. However, cats have

an amyloidogenic amino acid structure of amylin, which may lead to amyloid depositions in the islets (Nelson and Reusch, 2014).

Other factors may be involved in this disease; acromegaly is a disorder that causes marked insulin resistance and the use of diabetogenic drugs such as glucocorticoids and progestins may cause glucose intolerance. Severe pancreatitis may lead to pancreatic islet damage and to beta cell loss, but this is a rare occurrence in cats. It is reported as a frequent co-morbidity but not usually a cause of DM (Nelson and Reusch, 2014).

1.1.2. Risk factors

As for acquired insulin resistance, both environmental and genetic causes are suspected. It may be a combination of several of the following factors: obesity, physical inactivity, medical treatments, co-morbidities, stress, genetic predisposition and male gender (Henson and O'Brien, 2006).

Obesity is presented as the main risk factor for DM in cats. According to Appleton *et al.* (2001), obese cats are 3.9 times more at risk of developing the disease than cats of optimal weight. Moreover, an average weight gain of 1.9 kg in healthy cats was accompanied by a 50% decrease in insulin sensitivity. Their study also demonstrated that male cats tend to have a lower insulin sensitivity than females and tend to gain more weight. This can explain why male cats are at higher risk of DM.

Insulin resistance acquired with weight gain can be reversible if we implement weight management, which is positive. Biourge *et al.* (1997) put healthy cats on an *ad libitum* diet and tested their glucose and insulin concentrations via an intravenous glucose tolerance test (IVGTT). These were both increased compared to their baseline after weight gain. However, once weight loss was achieved after several weeks, the IVGTT results were similar to those at baseline.

Current diets of domesticated cats may also be in their disadvantage. Indeed, they have evolved as strict carnivores and feral cats typically have a high-protein low-carbohydrate diet. However, commercial diets contain moderate to high amounts of carbohydrates (>50% of calories) and this change in diet has developed fairly recently, i.e. 2-3 decades ago. This increased load of carbohydrates may lead to obesity and increases beta cell activity. Thus, there is increased insulin, which leads to hyperinsulinemia, beta cell failure and eventually type 2 DM (Biourge *et al.*, 1997).

Farrow *et al.* (2013) conducted a study with 3 groups (n=8) each having a specific diet for 5 weeks. The cats were fed a diet high in protein (46% of metabolizable energy [ME]) in one group, high in fat in another (47%) and high in carbohydrate in the last group (47%). Glucose was measured in all cats and cats fed the high-carbohydrate diet reached a 10–31% higher peak and mean glucose compared with the other individuals. Conclusively, cats being at risk of developing DM would benefit from a high-protein, moderate-fat, and low carbohydrate diet. One should also keep in mind the overall energy intake when switching to such a diet, so as to prevent weight gain (Farrow *et al.*, 2002).

The source of carbohydrate is also of importance. In a study conducted by Appleton *et al.* (2004), 16 overweight cats were divided into 2 groups and fed an *ad libitum* diet with wither rice as the source of carbohydrate or sorghum/corn. In the first group, cats tended to ingest more energy and gained more weight. Moreover, their glucose and insulin levels were higher than those fed the sorghum/corn diet, leading one to conclude that rice is an inferior source of carbohydrate and foods containing a high-glycemic index will lead to higher energy intake due to reduced satiety.

Another important factor in a diet for a diabetic patient is chromium. This trace element is needed for the metabolism of lipid and glucose metabolism and helps in improving insulin sensitivity. Although the daily recommended intake for chromium in cats is not defined, it is hypothesized that at least some diets offer an amount too low and that most cats would benefit from supplementation (Rand *et al.*, 2004).

All this being said, obesity and suboptimal diets do not necessarily lead to DM. There must be a beta cell dysfunction leading to impaired glucose tolerance for the disease to develop. As explained previously, amylin may play a role in developing DM and it was found that levels of this hormone are elevated in cats with insulin resistance, namely obese cats. (Nelson and Reusch, 2014).

Inherited susceptibility to DM is also supported and domestic long- and short-hair cats are more often affected. In Australia, New Zealand and the UK, Burmese cats are overrepresented by approximately 4 times than other domestic cats (Rand *et al.*, 2004).

1.1.3. Diagnosis

1.1.3.1. Signalment and clinical features

The main clinical signs of DM are PU, PD and weight loss. These develop when hyperglycemia reaches a concentration that results in glycosuria. PU/PD is reported in 80% of cats and weight

loss in 70%. These signs are similar to those found in hyperthyroidism. However, change in appetite can be either increased or decreased. It is increased in 20% of cats only but can be decreased at the time of diagnosis due to dehydration, ketonemia, electrolyte imbalance and/or other concurrent diseases (Rand, 2012; Nelson and Reusch, 2014).

Typically, cats are 10-13 years old when diagnosed and are often overweight (40%). In about 50% of cats, especially those with longer-standing diabetes, a diffuse peripheral neuropathy is reported. Owners may also notice an unsteady gait, hindlimb weakness and possibly a plantigrade stance (Rand, 2012).

1.1.3.2. Laboratory and clinical diagnosis

A blood glucose concentration of ≥ 14-16 mmol/l should already cause signs of polyuria and polydipsia and a concentration of ≥ 20 mmol/l is considered to be a marked hyperglycemia. It can be challenging to measure blood glucose in cats in clinics, as both acute stress and transient illness may cause elevated values. Blood glucose concentrations can be as high as 10 mmol/l if the patient is struggling, yet these may resolve in 3 to 4 hours. (Gottlieb and Rand, 2018).

Link and Rand (2008) has also stated that one should be careful when using fructosamine concentrations. Using these measurements doesn't allow to differentiate between stress hyperglycemia and DM in cats with blood glucose concentrations < 20 mmol/l. This is why using fructosamine concentrations may cause DM to be underdiagnosed.

Upon laboratory analysis, one may also find a mild anemia as well as a stress leukogram. Elevated liver enzymes, hypertriglyceridemia and hypercholesteremia are all possible findings (Rand, 2012).

Ketones and lipids can be measured to assess ketosis and hyperlipidemia. The best measurement is plasma or urine beta-hydroxybutyrate concentration, as this is the main ketone present in ketoacidosis. Acetate and acetone can be measured with urine test strips but this can delay a ketonuria diagnosis, as these ketones are not the major players (Rand, 2012; Nelson and Reusch, 2014). **Table 1** shows the common laboratory findings in patients diagnosed with DM.

Table 1. Typical findings in hematology in feline diabetic patients. Adapted from Behrend *et al.* (2018).

neutrophils	↑
lymphocytes	↓

monocytes	↑
eosinophils	↓
cholesterol	↑
triglycerides	↑
ALP	WNL or ↑
blood glucose concentration	↑

↑ indicates elevated values; ↓ indicates decreased values. WNL: within normal limits.

Glucosuria together with hyperglycemia is considered to be diagnostic (Rand, 2012; Gottlieb and Rand, 2018).

1.1.4. Treatment

Previously, treatment focused on managing clinical signs. Today, the main focus when considering a diabetic cat is to achieve "diabetic remission", which is euglycemia without the use of insulin or other hypoglycemic medicament. Of course, this is possible for cats whose cause of DM is correctable. For cats who present with long-term DM and/or who suffer from uncorrectable causes of DM (such as end-stage pancreatitis), the goal is to control clinical signs. This is why knowing the type of diabetes in a patient is important when considering treatment (Behrend *et al.*, 2018).

Therapy started early, close monitoring and a suitable diet are all criteria for achieving diabetic remission. However, this goal is only achievable if there remain functional beta cells (Rand, 2012; Behrend *et al.*, 2018).

Different insulin options are available, such as porcine lente insulin, glargine and detemir. Based on the drug chosen, a different protocol will be followed (Behrend *et al.*, 2018).

The only available registered insulin for veterinary use is the porcine lente insulin 40 IU/ml, which is a medium acting insulin. This is known as Caninsulin or Vetinsulin. The typical duration of action in cats is 8-10 hours and the anticipated glucose nadir is 2-8 hours post-injection. Cats administered lente insulin are typically left hyperglycemic for 4-8 hours every 24 hours. This hyperglycemia is enough to continue to cause beta cell destruction and makes diabetic remission difficult. Blood glucose can be 20 mmol/l or higher pre-injection, while one should aim for 4-11 mmol/l (Rand, 2012; Sparkes *et al.* 2015).

Protamine zinc insulin (PZI) 100 IU/ml is a longer acting insulin also licensed for veterinary use.. Glargine and detemir are longer-acting insulins that have been used more recently in cats and they have shown higher remission rates (Marshall *et al.*, 2009).

Both glargine and detemir are designed for a once-daily administration and no clinical differences were observed between cats treated with either drug. The reason glargine is the insulin of choice today is that more research was conducted on it and the pharmacodynamics and kinetics are better known. However, data collected from Roomp and Rand (2012) shows that detemir requires a 30% lower maximal dose and the duration of action is longer. There is also less variability between individuals and within individuals themselves. Given this data, detemir would be the insulin of choice.

An initial dose of 0.5 IU/kg of either lente insulin, glargine or PZI is administered for newly diagnosed cats. The initial dose is of 0.25 IU/kg for detemir. Regardless of the choice of insulin, a twice-daily administration is more likely to reduce the exposure of beta cells to hyperglycemia (Rand, 2012).

Cats are initially treated for 3 days, then go through the following 4 phases: the increasing phase, the consistent dosing phase, the decreasing phase and finally, remission. Specific protocols are put in place according to the type of insulin used. Relevant information for detailed protocols is available in the product information leaflets accessible on the official website of the European Medicines Agency (www.ema.europa.eu) or on the websites of national authorities such as the French Agency for Veterinary Medicinal Products – *Agence Nationale du Médicament Vétérinaire* – (www.ircp.anmv.anses.fr).

A recent study published by Gilor *et al.* (2021) suggests an ultra-long acting recombinant insulin as an alternative treatment. This insulin is to be given once weekly, which can be an attractive feature for many owners. The ease of administration may ultimately be beneficial for the cats. More clinical trials are needed for this drug, though, and protocols must be put in place for a safe introduction (Gilor *et al.*, 2021).

The cats' glucose concentrations should be measured every 2-4 hours during the day and the insulin dose should be reduced if these become low. Depending on the type of insulin used, either nadir or nadir and pre-insulin glucose concentrations are used (Rand, 2012; Gottlieb and Rand, 2018).

As mentioned previously, there are variations in glucose-lowering effects between different cats and within one same individual. These variations can depend on the type of insulin used, the rate and percentage of its absorption from the injection site and the specific insulin sensitivity of one individual. Another challenge is the administration itself of the drug. Very small doses are required for cats and using 100 IU 0.3 ml syringes make precise dosing difficult.

If the insulin can be diluted (such as detemir), this can help resolve the dosing issue (Rand, 2012; Behrend *et al.*, 2018).

Oral hypoglycemic agents can sometimes be used in the treatment scheme and work in different ways. They can either stimulate beta cells to secrete insulin, increase insulin sensitivity or reduce glucose absorption from the gastrointestinal tract (e.g. acarbose). According to Rand (2012), the use of these drugs alone is not recommended.

However, the use of acarbose, an alpha-glucosidase inhibitor, can be beneficial to cats following a typical weight loss program diet, i.e. one to two meals with a high-carbohydrate content. Acarbose is then administered with the feed. If cats consume multiple small meals throughout the day, the drug will have minimal effect Rand (2012).

Finally, another approach to feline DM treatment involves the use of glucagon-like peptide-1 (GLP-1) analogs. These incretin hormones are implicated in glucagon secretion regulation and appetite suppression, thereby reducing energy intake and reducing weight. This is important in overweight patients, as discussed previously. Incretin hormones also have the capacity to increase sensitivity to glucose and insulin synthesis. Gilor *et al.* (2016) discuss the potential of GLP-1 analogs to be used in feline DM. While it is agreed that insulin is needed to manage overt DM and control hyperglycemia, chronic administration of GLP-1 analogs may also extend the period of diabetic remission by preserving and even increasing beta cell mass.

Exenatide extended-release (ER) is a very long-acting GLP-1 receptor agonist that could be administered once a month subcutaneously. No significant side effects were noted and the drug was deemed safe, even at supraphysiologic concentrations. Gilor *et al.* (2016) believe that such therapies have the potential to replace twice-daily insulin injections. This could mean a dramatic improvement on the quality of life of both the cats and owners.

1.1.5. Monitoring

Close monitoring of the disease includes home blood glucose measurements, regular visits to the clinic, dietary management, observation in water drunk and urine output, as well as bodyweight tracking (Rand, 2012; Bloom and Rand 2014).

Dietary management implies choosing the right type of diet, feeding frequency and maintaining a healthy weight. A low- or even ultra-low-carbohydrate lowers the need for beta cells to secrete insulin, which has a sparing effect. It is also recommended for weight loss, if needed.

As for feeding frequency, it is recommended that cats are fed twice daily, i.e. once before each insulin injection (Bloom and Rand, 2014).

When monitoring the cat's response to treatment and/or when adjusting insulin dosages, home glucose measurement is more accurate. This is because cats are less likely to be stressed or struggle during measurement (and confound the results due to stress-related hyperglycemia) and because they are more likely to follow their normal diet at home rather than at the clinic (Rand, 2012).

Rand (2012) recommends that cats under long-acting insulins such as glargine or detemir should have their glucose concentrations measured before the administration of insulin and at the nadir point. For intermediate-acting insulins, only the blood nadir needs to be identified. Glucose meters calibrated for feline blood should be prioritized as those intended for human use tend to underestimate blood glucose concentrations by 20-40% (Bloom and Rand, 2014).

1.1.6. Prevention

No studies have been conducted in cats with persistent mild to moderate hyperglycemia. However, there may be a great advantage to monitoring the blood glucose curve of these cats at risk of developing more severe hyperglycemia. If dealt with early, the disorder could be managed by diet and weight loss alone. It has been shown that persistent mild and moderate hyperglycemia may also have adverse effects in humans and it may cause microvascular and retinal damage. According to Rand (2012), these discoveries have led to a lowering of the blood glucose threshold when identifying DM in humans, which may prove beneficial to cats as well.

1.1.7. Prognosis

The prognosis depends largely if remission has been achieved. Gottlieb and Rand (2018) stated that 25-30% of diabetic cats in remission will relapse and that the majority of cats in remission do not have normal beta-cell function. In a study conducted by Marshall *et al.*, (2009) on newly diagnosed cats, those treated with glargine had a higher rate of remission than those treated with PZI insulin or lente insulin. By day 112, 100% of the cats treated with glargine had achieved remission compared with 38% of those treated with PZI insulin and 25% with lente insulin.

The underlying cause of DM and/or concurrent diseases also affects prognosis. Chronic kidney disease is a common occurrence in older cats and may negatively affect survival time. Complications may also occur due to the treatment of DM itself; overadministration of insulin may result in iatrogenic hypoglycemia (Gottlieb and Rand, 2018).

1.2. Feline hyperthyroidism

HT or thyrotoxicosis is an endocrinopathy resulting from an excessive amount of active thyroid hormones release from thyroid follicular cells: triiodothyronine (T3) and/or thyroxine (T4). This disorder was first described in cats in the late 1970s and is now recognized as the most common feline endocrine disorder (Mooney and Peterson, 2012).

It is difficult to speak of prevalence for this disease, as it varies according to the geographical area, the populations tested and the study design used. In Germany for example, the prevalence can reach 12.3% in a population of cats older than 8 years old (Köhler *et al*. 2016). In a study conducted by de Wet *et al.* (2009), the prevalence of HT within a population of cats over 10 years old reached 3.93%.

1.2.1. Aetiology

Benign adenomatous hyperplasia constitutes 98% of cases. 70% of those cases are bilateral and 30% have one lobe affected. Thyroid carcinoma is a much rarer occurrence and represents 2% of hyperthyroid cats only (Mooney and Peterson, 2012; Vaske *et al.*, 2014).

In felines, the disease resembles toxic nodular goiter in humans, rather than Graves' disease, which is more diffuse (Mooney and Peterson, 2012; Vaske *et al.*, 2014). What exactly causes this hyperplasia remains unclear. Mutations in the TSH (thyroid stimulating hormone) receptor and/or alterations of G proteins have been identified and may play a role.

1.2.2. Risk factors

Identifying specific risk factors is important in understanding, preventing and treating feline HT. This has been attempted but it has proven difficult due to the complexity of this multifactorial disease. The increased prevalence might at least partly be due to increasing age of domestic cats due to better care and increased awareness of the disease, both amongst veterinarians and owners (Peterson, 2020).

Proving a causal relationship between risk factors and feline HT according to the Bradford Hill criteria requires a specific study design where cats need to be studied throughout their whole lives (longitudinal studies) and this is difficult to put in place. Moreover, it sometimes remains unclear whether a factor is a cause or an effect (van Hoek *et al.*, 2015).

Non pure-breed, males, increasing age, the use of cat litter and a diet consisting of a majority of canned food were all considered possible risk factors (Wakeling *et al*., 2009; Mooney and Peterson, 2012).

Canned food and HT are associated due to the BPA found in the container of the wet food, especially in pop-top cans. BPA is thought to be an endocrine disruptor in humans but the exposure to it and its effect in feline HT has not been proven. The low-dose exposure to BPA molecules from these canned foods does not explain the development of HT, especially when it occurs in adult cats. However, exposure during gestation and development could cause thyroid illness (Wakeling *et al*., 2009; van Hoek *et al.*, 2015).

Polybrominated diphenyl ethers (PBDEs) and flavonoids have also been found in canned food for cats and are suspected to play a role in HT but no studies can substantiate this claim today. According to van Hoek *et al*. (2015), certain studies met only 3 of the 9 Bradford Hill criteria when analyzing the correlation between canned foods and feline HT.

The hydroxylated metabolites of PBDEs and the natural thyroid hormones T4 and T3 have structural similarities, which is why PBDEs are thought to be endocrine disruptors. These compounds are emitted from electrical equipment such as computers, televisions as well as textiles and furniture and they can settle in dust. The fact that cats groom themselves and that they have been kept more and more indoors would explain their tendency to ingest these particles (Jones *et al.*, 2019).

As for iodine, it is unclear whether an increased, decreased or simply a fluctuating intake contributes to the illness. Moreover, iodine recommendations have changed over the past decades. This means that it is difficult to regulate iodine concentrations in cat food and it also makes retrospective studies more challenging. Dietary selenium poses a similar conundrum: both selenium deficiency and increased intake may play a part (van Hoek *et al*. 2015).

1.2.3. Diagnosis

1.2.3.1. Signalment and clinical features

According to Mooney and Peterson (2012), the average age of onset of hyperthyroidism is 12-13 years, so some owners might attribute certain clinical signs as part of the ageing process. This point is important, because it may make the owner delay in seeking veterinary attention.

Common clinical signs include weight loss, sometimes concomitant with polyphagia; tachycardia, polyuria and polydipsia. Systolic murmurs, arrhythmias, behavioral changes such as hyperactivity and irritability may also be observed. Other associated signs are intermittent vomiting and diarrhea as well as a palpable goiter (Mooney and Peterson, 2012)

That being said, approximately 10 % of cats may present with “apathetic hyperthyroidism”, which translates to a decreased appetite and lethargy (Varske *et al.*, 2014).

Because of a higher metabolic rate, weight loss (mild or severe), mild elevation of body temperature and heat intolerance are signs to be aware of (Mooney and Peterson, 2012). Coat changes can sometimes be observed and include matted fur and/or alopecia (patchy or bilateral), which may be due to either failure to groom or excessive grooming. The latter can be explained by heat intolerance (Carney *et al*., 2016)

1.2.3.2. Laboratory and clinical diagnostics

Specific thyroid tests are required to confirm the diagnosis of HT. However, routine biochemistry and hematology can further support the diagnosis and prove useful when assessing the severity of the disease. This may help to give a more accurate prognosis as well as in the investigation of possible concurrent diseases (Vaske *et al.* 2014; Carney *et al*., 2016). **Table 2** shows the common findings in hematologic and biochemical abnormalities.

Table 2. Most common present hematologic and biochemical abnormalities in diagnosed cats with feline HT. Content adapted from Mooney and Peterson (2012) and Vaske *et al.* (2014).

PCV	↑ 40-50% of cats
RBC	↑
neutrophils	↑
lymphocytes	↓
eosinophils	↓
monocytes	↑
ALT	↑ (typically mild)
ALP	↑ (typically mild)
AST	↑ (typically mild)
blood phosphorus concentration	↑
blood glucose concentration	↑ (mild)

↑ indicates elevated values; ↓ indicates decreased values.

Oxygen consumption increases in HT and it is thought to cause an increase in erythropoietin, which in turn causes erythrocyte changes. Different explanations can be given to changes in liver values: hepatic hypoxia, malnutrition, direct toxic effects of thyroid hormones and congestive cardiac failure. These may return to normal if and when HT is managed. Liver markers are typically mild in HT. Therefore, it is wise to suspect a concurrent disease when the

patient presents with elevated liver values and only mildly elevated serum thyroid concentrations (Mooney and Peterson, 2012).

Urinalysis can be used to differentiate between hyperthyroidism and diabetes mellitus, especially if the owners report polyuria and polydipsia. Urea and creatine can be used to assess renal function. As previously mentioned, older cats are at higher risk of hyperthyroidism. Their age also means that they are naturally at a higher risk of having a decline in renal function (Mooney and Peterson, 2012).

1.2.3.3. Specific thyroid function tests

For confirmation of HT, we need to demonstrate an increase in production of thyroid hormones or an increase of thyroidal radioisotope uptake. The former will be the first step in ruling in or out HT. Elevated circulating concentrations of total T4 (tT4) and total T3 are clear indicators for hyperthyroidism and are extremely specific. Approximately 90% of cats will show elevated serum T4 concentrations (Peterson, 2006).

That being said, tT4 has limitations. TT4 values normally fluctuate during the day in cats and it may fall within the reference range when tested. Cats with concurrent non-thyroidal illnesses (NTIs) may have their circulating total T3 and T4 suppressed, which may also cause hyperthyroid cats to present with serum tT3 and tT4 concentrations within the reference range (Mooney and Peterson, 2012; Vaske *et al.* 2014).This is why it is prudent to renew testing in cats whose values are within normal limits but who present with an anamnesis, clinical signs and laboratory changes corresponding to feline HT.

If the clinician is presented with such a case, measurement of free T4 is recommended. Indeed, cats with tT4 values within the upper range of the reference interval and elevated free T4 are considered hyperthyroid. However, this free T4 measurement is not useful if we already have tT4 concentrations exceeding the upper limit; hyperthyroid cats presenting with elevated tT4 values will always present with elevated free T4 values as well. Testing for free T4 in that case will therefore not provide the clinician with more information (Vaske *et al.*, 2014).

The clinician may resort to dynamic thyroid tests, especially if the aforementioned case, when a diagnosis remains unclear. These dynamic tests, however, present their own challenges because of either poor availability, strong dependence on owner compliance and/or suboptimal adaptability to feline hormones. T3 suppression tests, TRH (thyroid releasing hormone) stimulation tests and TSH response tests aim to assess the integrity of the negative feedback

exerted by the hypothalamus-pituitary-thyroid gland axis (Peterson *et al.*, 2015; Vaske *et al.* 2014).

TSH concentration measurement in humans is a commonly used test to rule out hyperthyroidism. No feline-specific assays are available for TSH measurement so canine TSH assays are used. However, this only detects about 35% of the recombinant feline TSH which makes it more likely to over-interpret low values. That being said, if the value exceeds the limit of detection of the assay, this test may prove useful in ruling out hyperthyroidism (Peterson *et al.*, 2015; Vaske *et al.* 2014).

Thyroid scintigraphy, using radioactive iodine or technetium-99m, can also be performed. Thyroid activity is then assessed by visualizing the thyroid to salivary gland radionuclide uptake ratio. This method can be used if the thyroid tests remain inconclusive. It is also a way to detect the presence of metastasis in case of malignant thyroid tumors. However, thyroid scintigraphy is an expensive diagnostic tool and not all clinics have access to the necessary equipment (Broome, 2006; Vaske *et al.*, 2014). Above-mentioned diagnostic tests are not usually required and may not be feasible for the owner (Mooney and Peterson, 2012).

In conclusion, most hyperthyroid cats with tT4 values within the reference range can be confirmed as having the disease with repeated measurements of tT4 or by adding free T4 measurement. The identification of concurrent illnesses is necessary to understand if suppression of tT4 is present.

1.2.4. Treatment

The aims of treatment are to remove or destroy thyroid tissue functioning abnormally, to inhibit the release and/or synthesis of the hormone or to improve the adverse effects of excess thyroid hormones. This can be done via medical, dietary, radioactive iodine, or surgical treatments (Kintzer, 1994; Peterson, 2006).

Medical treatment is not curative but it is the most available option, both in terms of accessibility, skills required and cost. Methimazole and carbimazole are the two main drugs used in long-term medical management. They both suppress thyroid hormone production and can be given prior to surgery and for chronic management. Carbimazole is converted to methimazole after administration, hence its being considered a “pro-drug” (Mooney and Peterson, 2012). For product leaflet information for both methimazole and carbimazole, please refer to the list of references. **Figure 1** provides a dosage regiment for oral methimazole.

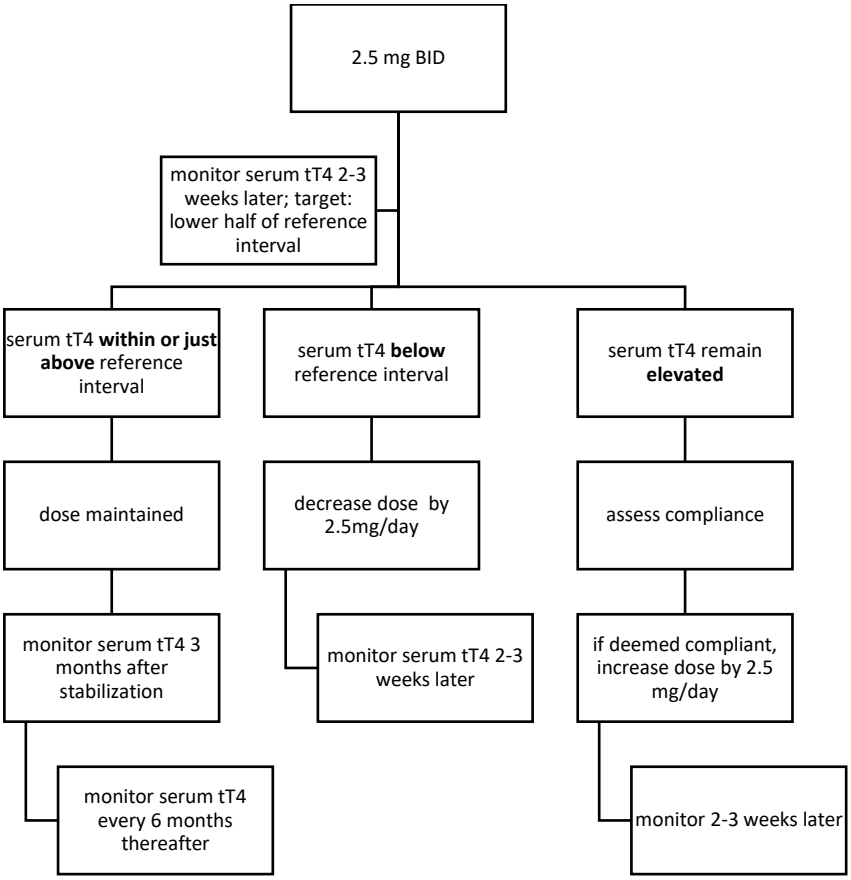


Figure 1. Methimazole dosage regimen. Scheme created according to the protocol described by Vaske *et al.* (2014).

Both carbimazole and methimazole can be reformulated so as to be used for transdermal administration. This can be indicated in case of uncooperative cats and/or in case of a concurrent gastrointestinal disease affecting the absorption of the drug when taken orally. According to Vaske *et al*. (2014), transdermal methimazole has a lesser bioavailability and lesser overall efficacy. However, even though oral administration is more effective in the beginning of treatment, transdermal administration was seen to be effective 1 month after initiation of treatment. Indeed, T4 concentrations were similar after this period of time.

Hill's y/d® diet offers another non-curative treatment and is restricted in iodine. Different studies have been made to assess the efficacy of the treatment but there is still doubt as to whether normalization of T4 can be achieved in highly hyperthyroid cats (Mooney and Peterson, 2012; Vaske *et al.* 2014). This treatment method also presents disadvantages: the impossibility to implement it in a multicat household and the necessity of strict dietary compliance. Indeed, when opting for this treatment method, cats can only be given this diet, which may be problematic in cats with a more selective pallet.

Thyroidectomy and radioactive therapy are two curative treatment possibilities. The former has decreased in popularity due to the availability, the skill required for the procedure and the emergence of medical treatments. The other important drawback is the risk of postoperative complications, namely hypocalcemia – due to damage or removal to the parathyroid glands – Horner's syndrome and laryngeal damage (Vaske *et al.* 2014). Given the advanced age of most hyperthyroid cats, general anesthesia required by this surgery may be challenging or even impossible. However, this remains a viable option if radioactive iodine is not available. It is also an effective and fast method (Kinzer, 1994; Mooney and Peterson, 2012).

Radioiodine therapy is considered to be the treatment of choice for most cats (Kinzer, 1994; Mooney and Peterson, 2012). Radioactive iodine ^{131}I can concentrate within the thyroid gland and this ultimately allows the destruction of any surrounding hyperfunctioning thyroid tissue. It is also considered a good treatment modality for cats diagnosed with thyroid carcinoma, as it can destroy malignant thyroid tissue. In a study conducted on 524 hyperthyroid cats having received this treatment (Peterson and Becker, 1995), 94.2% of these cats became euthyroid after a single dose. This suggests that the treatment is efficient, safe and quick. This type of therapy is cost-efficient but nonetheless costly. It also requires the patients to be hospitalized during treatment and to be housed separately 7-10 days post-treatment, as they emit radioactivity during that time (Vaske *et al.* 2014).

The choice of treatment ultimately depends on the availability of treatment, owner and cat compliance and lifestyle, disease severity, treatment cost and the age of the patient. One should keep in mind that feline HT is a progressive disease and that non-curative treatments do not remove nor destroy the thyroid tumor. This means that there is a potential for the tumor to become malignant. However, offering long-term medical treatment makes sense for geriatric cats who are not expected to live long enough for a tumor to grow and who are present too high a risk for anesthesia (Carney *et al.*, 2016; Peterson, 2020).

Peterson (2020) suggests that curative treatments should be considered for healthy cats – with uncomplicated HT – who are expected to live for longer than 2 or 3 years post-treatment. This option may even be less of a financial burden for the owner. Even though these treatments are less frequently offered, they may be more beneficial for both the owner and the cat in terms of quality of life.

The different advantages and disadvantages of the treatments for feline HT that have been described are summarized in Table 3.

Table 3. Advantages and disadvantages of different treatments for feline hyperthyroidism. Adapted from Mooney and Peterson, 2012 and Carney *et al.* 2016.

treatment	persistent/ recurrent HT	convenience for owner	hospitalization	side effects	availability	cost
medication (per os or transdermal)	common (relapse 100% when off medication and depends on cat/owner compliance)	poor: twice daily administration and regular monitoring required	none	possible: lethargy, facial pruritus, GIT disturbance (less with transdermal); more rare are blood dyscrasias and hepatopathies	excellent	can be significant over the years
dietary therapy	seemingly good (studies lacking)	simple to implement but the only food that can be given inconvenient in multicat households	none	none reported (consider with cats with renal insufficiency)	excellent	can be significant over the years
radioactive iodine	rare	special precautions to be taken after treatment to avoid radiation exposure	2-4 weeks	minimal	limited; requires special license and equipment/facility	high but cost-effective
surgical thyroidectomy	rare if both thyroid glands are removed	prior treatment to achieve euthyroidism is recommender; treatment of iatrogenic hypothyroidism possible	1 day or more, if complications occur	risk of hypoparathyroidism	skilled surgeon required	intermediate

1.2.5. Prognosis

The prognosis depends largely on the method of treatment. According to Mooney and Peterson (2012), the majority of cats treated with radioiodine have an expected survival time of 1-3 years. Other studies have shown a median survival time of 4 years with radioiodine treatment, compared with 2 years with methimazole treatment, for example. One should be reminded that these patients are typically middle-aged to geriatric and therefore will more easily develop diseases typically related to advanced age, such as renal disease.

2. AIMS OF THE STUDY

The aim is to compare feline endocrinopathies between different clinics and current literature. This entails looking at possible differences in prevalence, risk factors, predispositions, as well as differences in diagnostics and treatment. The response to treatment is also evaluated for DM. Analyzing the data allows the reader to know what is the current approach in clinics in different parts of Europe, and how it relates to the most recent literature.

3. MATERIALS AND METHODOLOGY

3.1. Cases – animals and clinics

46 cases were used in this study and all were collected from 1 small animal clinic in France and 1 small animal clinic in Estonia. The French clinic is located in Les Pieux, Normandy, whereas the Estonian clinic is located in Tartu. This is the University of Life Sciences 'clinic.

In both clinics, a traineeship was completed by the author of this paper. A final diagnosis of either diabetes mellitus or hyperthyroidism was made from 29-06-2018 to 09-09-2022 and the most relevant were selected. That means that cases where a diagnosis was unclear and/or where there was no follow-up of the patient were not used in this study. The latter can be due to the owner moving away or the patient dying of other causes, for example.

All relevant cases within the same time frame were taken in each clinic. Because of this, an uneven number of cases are taken in each clinic. 4 cases of feline hyperthyroidism were used in the French clinic and 28 were used in the Estonian clinic. This makes for few cases, but a retrospective study can nevertheless be done. As for diabetes mellitus, the same number of cases was collected for each clinic.

3.2. Statistical analysis

The following parameters were used in this study: breed, age, gender, status of sterilization, clinical signs, liver enzymes, kidney parameters, diagnostic tools and treatment used. These data were collected from two different databases: Provet in the Estonian clinic and Bourgelat in the French clinic. These were then put into an Excel file. Using this software, we were then able to obtain percentages, averages and means, as well as calculate standard deviation. Epitools was used to calculate confidence intervals. Data was compared between different clinics as well as data found in literature.

4. RESULTS

4.1. General Overview

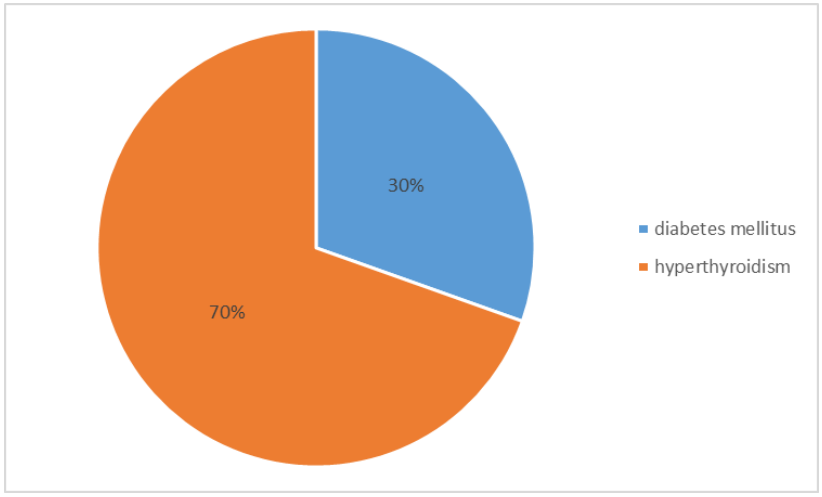


Figure 2. Distribution of feline endocrinopathies in all 46 cases used in the study.

Within the same time frame, only one third of all these cases concern DM. HT represents the vast majority of them, i.e. 70%. HT has been described as the most common feline endocrinopathy and this is also reflected in this study.

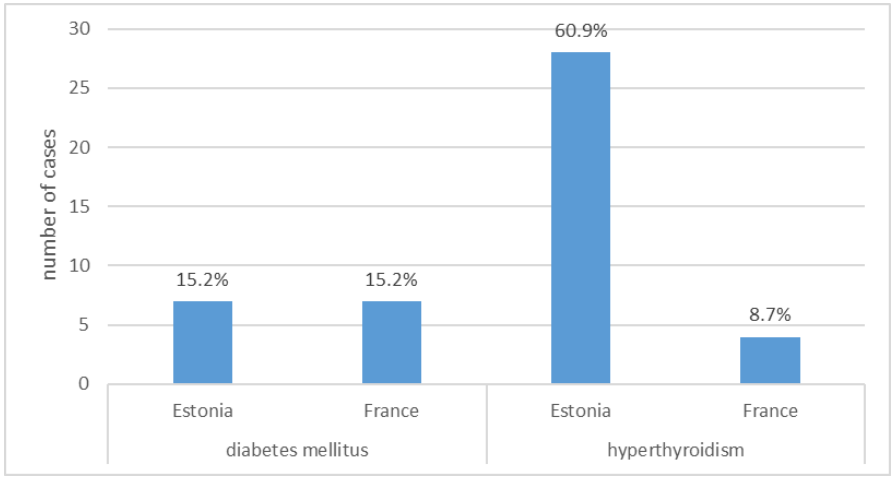


Figure 3. Distribution of feline endocrinopathies in each clinic.

There is an exact number of cases of DM for both countries. However, EMÜ's clinic had 28 cases of HT, which is 7 times more than the HT cases collected in France. This is the only group that stands out, as DM cases and HT cases in France are all under 10 cases.

All cats but one are Domestic Shorthair. Indeed, there was one case of DM with a Main Coon in the French clinic.

Only 4 amongst the 46 cats were not neutered. For DM cases, 1 entire female cat case was collected in France and 1 entire male in Estonia. For HT, both 1 entire female and 1 entire male were present in Estonia.

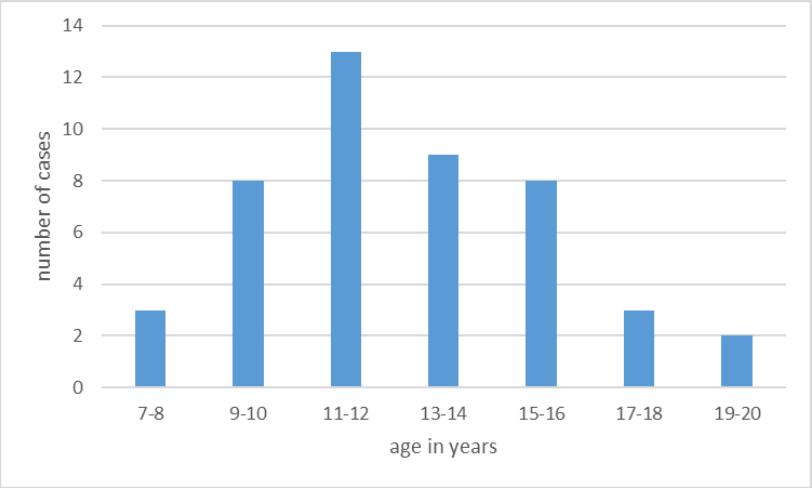
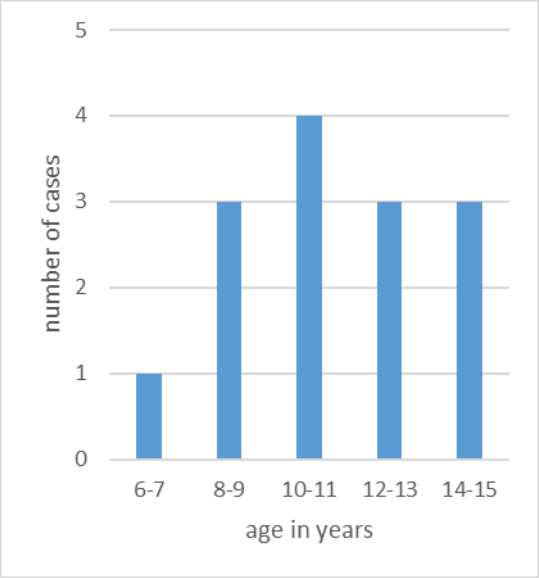


Figure 4. Age at the time of a diagnosis of either endocrinopathies.

The youngest patient is 7 years of age, whereas the oldest is 20 years old. Most cats are diagnosed with either DM or HT at 11-12 years old.

4.2. Diabetes Mellitus



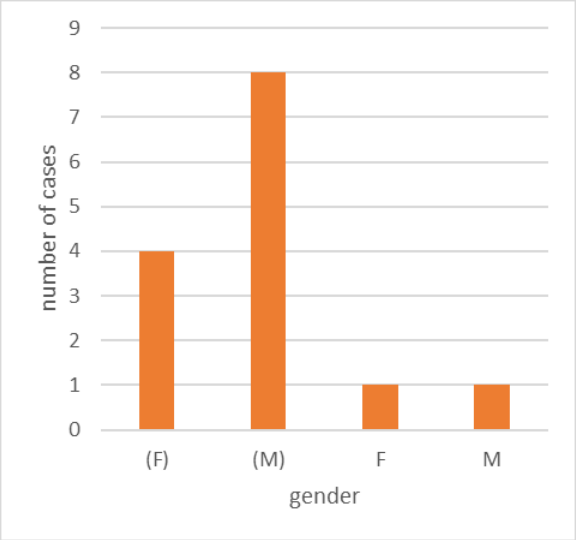


Figure 5. Age and gender of patients diagnosed with DM in the 14 selected cases. (F): spayed female; (M): neutered male; F: entire female; M: entire male.

As said in the literature review, the typical patient is male and 11-13 years old (Rand, 2012). All but 2 of the 14 patients are neutered. Neutered males represent twice as many cases as neutered females. This corrolates with what is seen in the study.

Most patients are 10-11 years old, which is close to what is found in literature. The rest of the patients' age ranges from 6-15 years of age.

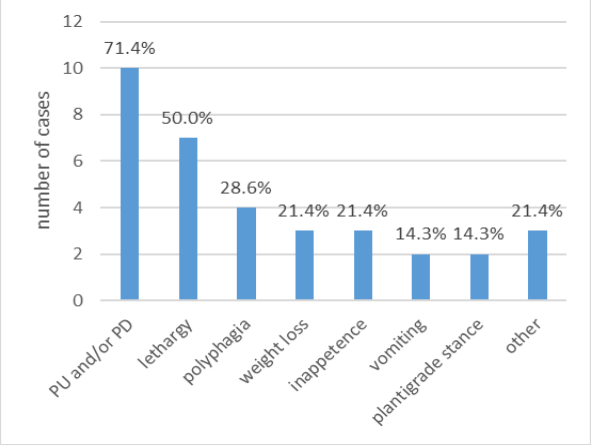


Figure 6. Clinical signs reported by owners during the clinical visit at the time of a DM diagnosis.

According to Nelson and Reusch (2014), the main clinical signs are PU, PD and weight loss. In this study, PU/PD is the most often reported clinical sign, accounting for 71.4% of cases, which is comparable to the 80% found in literature. Weight loss, however, was found in 21.4% of our cases, which differs from the 70% reported by Nelson and Reusch (2014).

These authors also reported a 20% increase in appetite, which is less than the 28.6% found in this study. Cats presenting with a plantigrade stance in this study (14.3%) are also less common than the 50% reported by Rand (2012).

Other main complaints were hematuria and weight gain. One cat also presented to the clinic with a previous diagnosis of pancreatitis.

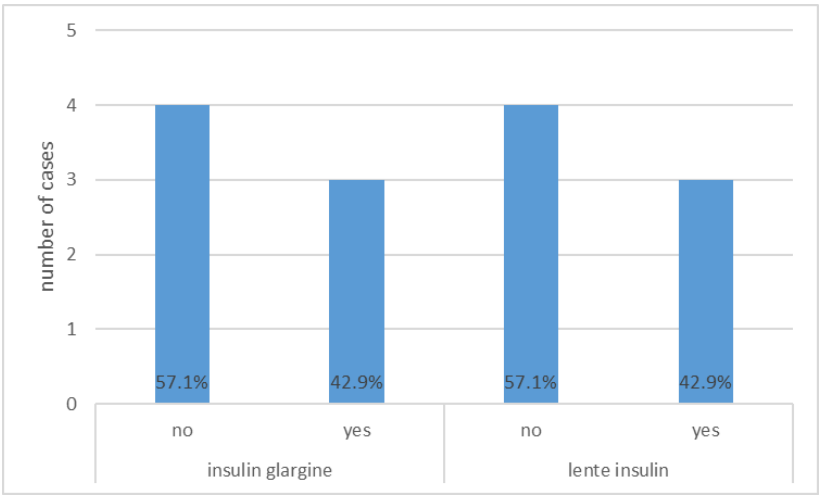


Figure 7. Type of insulin used in both clinics and the response observed. "No" indicates that the patient did not achieve remission and "yes" indicates that it has (95% CI: 25.1% - 84.2%).

In the French clinic, all 7 cats were started on lente insulin but only 3 went into diabetic remission. 2 of those cats were switched to insulin glargine after 1 month and 1.5 year respectively. Neither of these underwent remission.

In the Estonian clinic, all 7 cats were treated with insulin glargine but diabetic remission was observed in only 3 of those cases.

It was previously stated that glargine and detemir have shown higher remission rates (Rand, 2012; Linari et al., 2022). However, in this study, the patients treated with glargine insulin did not show higher remission rates than the ones treated with lente insulin. In both clinics, the same amount of patients showed diabetic remission.

Table 4 suggests that glargine insulin would offer feline patients with a higher probability to achieve remission. The proportion even reaches 100% by day 112 with glargine insulin, whereas only 25% of cats undergo remission with lente insulin. With the latter insulin, this number is unchanging after day 42 and 112.

Table 4. Proportion of cats going into remission from start of treatment with either lente insulin or glargine. Table adapted from Marshall *et al.* (2009).

	lente	**glargine**
% cats going into remission by day 42	25	75

% cats going into remission by day 112	25	100

These data are different from those collected in our study, where there is so significant different between insulins.

Table 5. Mean, average, minimum and maximum weight of patients in each clinic and in all DM cases. Standard deviations are shown for both countries and in both clinics combined as well.

	Estonia	**France**	**overall**
mean (median) weight, in kg	4.27 (4)	5.18 (5.7)	4.8 (5.1)
standard deviation	0.91	1.38	1.23
minimum, maximum weight, in kg	3.38, 5.5	2.47, 6.65	2.47, 6.65

The patients in the French clinic tended to be heavier than those in the Estonian clinic. The range is also much wider. However, this is not taking into account their build and overall conformation. Indeed, one of the cats in the French clinic is a Main Coon, weighing 5.85 kg, which is within the weight average of an adult Main Coon (Freeman *et al.*, 2013). Cats in the French clinic were on average 0.91kg heavier than the other clinic.

14 cats in this study were diagnosed with DM and at the time of diagnosis, the average weight was of 4.8kg and half of the patients were over 5.1kg.

4.3. Hyperthyroidism

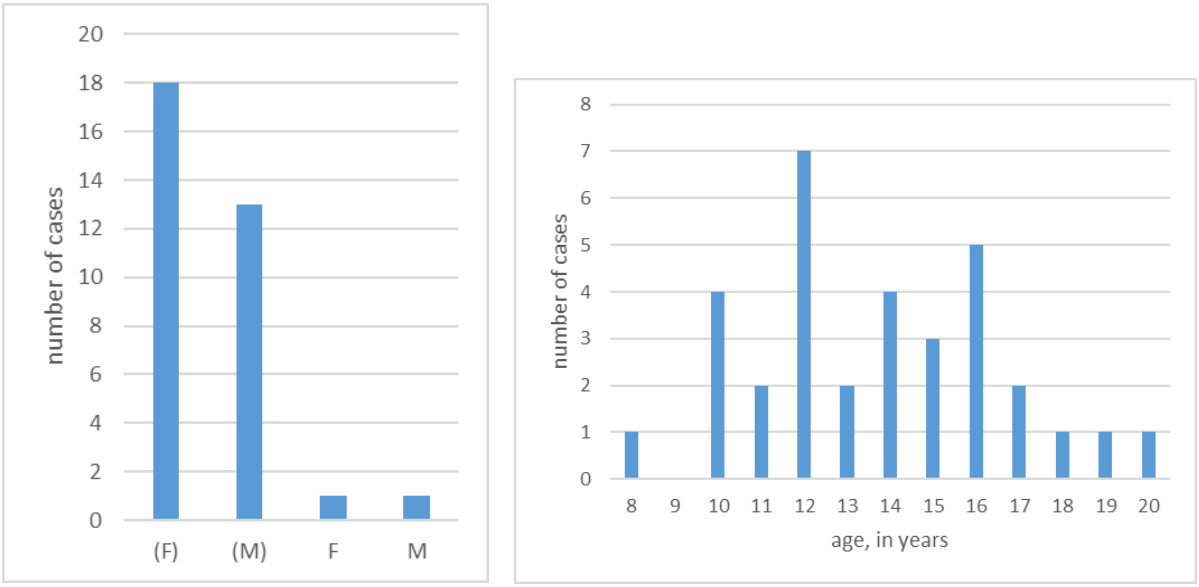


Figure 8. Distribution of gender and age in cats diagnosed with hyperthyroidism in both clinics in this study. (F): spayed female; (M): neutered male; F: entire female; M: entire male.

The 2 neutered cats are patients of the Estonian clinic. All other patients are neutered. There is a comparable incidence of hyperthyroidism amongst males and females. This correlates with the fact that no mention of clear breed predisposition was found in literature.

Table 6. Mean, median, minimum and maximum age of patients at the time of diagnosis in different clinics. Standard deviations are shown for both countries and in both clinics combined as well.

	Estonia	**France**	**overall**
mean (median) age, in years	13.8 (14)	12.8 (12)	13.7
standard deviation	2.9	2.4	2.9
minimum, maximum age, in years	8, 20	11, 16	8, 20

According to Mooney and Peterson (2012), 12-13 years is the average age of onset this disease in cats. The same average was calculated in both clinics, with 12.8 years in France and 13.8 years in Estonia.

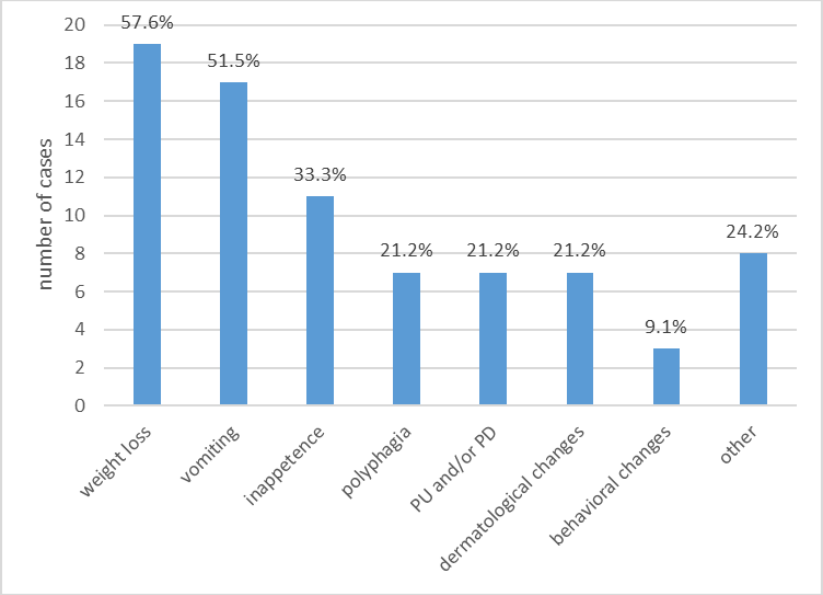


Figure 9. Clinical signs reported by owners during the clinical visit at the time of a HT diagnosis

The clinical signs shown in this figure are the main complaints reported by owners. Weight loss is the most common clinical sign observed, followed by vomiting and inappetence.

Other common signs mentioned by Mooney and Peterson (2012) such as polyphagia, PU/PD, and behavioral changes were found in this study and were found to be amongst the main reasons why owners saught veterinary care.

11 owners reported inappetence, which represents 33% of cases. This is more than the 10% of cats presenting with „apathic hyperthyroidism“, stated in literature.

Polyphagia was reported only 7 times. Excessive urination and/or drinking was also reported 7 times.

Other clinical signs prompting owners to book an appointment include diarrhea, seizures and hindleg weakness.

Table 7. Mean, median, minimum and maximum values of selected liver and kidney parameters. Percentage of cases showing an increase or decrease in these parameters.

parameter	**reference values (RV)**	**number of cases**	**mean, (median)**	**min., max.**	**% cases above RV**	**% cases under RV**

ALT	12-130 U/L	31	183.5 (150)	43, 677	61.3	0
ALP	14-111 U/L	31	124.3 (106)	34, 334	45.2	0
AST	0-48 U/L	23	69.1 (60)	29, 256	82.6	0
SDMA	0-14 µg/dL	14	10.3 (10)	6, 21	14.3	0
urea	5.7-12.9 mmol/L	31	10.6 (9.4)	4, 23	19.4	6.5
creatinine	71-212 µmol/L	31	100.7 (87)	24, 282	3.2	29

These liver enzymes as well as urea and creatinine are one of the most consistently measured parameters in these patients, after thyroid function tests.

ALT and AST are often above the reference value and are often more than mildly elevated, as opposed to what is stated in literature. Elevated levels of urea are seen in 19.4% of cases and this indicates kidney injury. Low creatinine, as we see in 29% of cases, can be due to loss of muscle mass, chronic kidney disease, or malnutrition.

In terms of specific thyroid function tests, tT4 was measured for each case in this study. T3 suppression tests, TRH stimulation tests, TSH response tests and fT4 were not measured in this study. Repeated measurements of tT4 were taken in cases where there was doubt, i.e. the patient showed all clinical signs consistent with HT but had values within the reference range or only slightly elevated.

All patients in this study received a medical treatment, i.e. methimazole.

5. DISCUSSION

5.1. Diabetes mellitus

With the adult domestic cat typically weighing 4-5kg (Mattern and McLennan, 2000), weight is a suspicious factor in this study. Even though we do not have body condition scoring for most patients in this study, we can say that half of the patients are above 5.1kg, which is higher than the reference.

This brings us to believe that being overweight may have played a role for these patients. The clinic in Les Pieux is considerably smaller than the one in Tartu, which suggests that 7 cats in the former may represent a higher incidence rate than in the latter.

Diabetic remission is the goal that should be achieved when treating these patients. The diabetic remission was the same in both clinics, despite the average weight of cats in Les Pieux being higher by nearly 1kg. Once treatment is started and once a cat diagnosed with DM has been started on a weight management program, how important is the starting weight in terms of remission rates?

It is worth conducting a study of how aware owners are of the consequences that obesity may have on their feline pets. Not only can it be a risk factor but it may also present a complication during treatment. It is worth knowing how familiar owners are with feline endocrinopathies in general and if being more informed may urge some to seek veterinary attention sooner.

The fact that most owners reported PU and/or PD suggests a certain level of observational skills on their part.

An important observation to be made in this study is the choice of insulin in different clinics and the equal rates of remission with different insulins. The study does not show the same results as the literature review, where 100% of cats eventually achieved remission with insulin glargine. Here, the choice of insulin does not seem to affect diabetic remission, which leads us to question why.

Possible obstacles to the non-achievement of diabetic remission are treatment protocols, owner and patient compliance, status of the patient at the time of diagnosis (how far the disease has progressed and how many functioning beta cells are present) and monitoring.

The choice of treatment refers not only to the type of insulin used but to the entire protocol. Weight management is part of this. The administration of insulin itself may also be problematic

for some owners. Indeed, it was mentioned that precise dosing is challenging and using an insulin that can be diluted, such as detemir, could resolve this. It would be worth knowing exactly how owners administer insulin to their pets at home; both in the time of administration and the manner of administration. The latter refers to both the precise dosage and the route, i.e. subcutaneous. It is also important to make sure that owners monitor their pets correctly and that it is done consistently.

As for other medical treatments, GLP-1 analogs were not found in treatment protocols in this study. It may be beneficial to implement this in the future for cats suffering from DM, provided there is access to this drug in France and Estonia. This may help improve remission rates. This drug is to be administered along with insulin and it would represent an additional subcutaneous injection as well as an additional cost. However, both owners and cats may be reluctant to the idea of another daily injection and owners may find the additional cost cumbersome.

As regards prevention of DM in cats, it would be beneficial to conduct a study with cats suffering from persistent mild to moderate hyperglycemia. Lowering the threshold of blood glucose may help in identifying patients at risk. It may also allow the disease to be managed by diet and weight loss, thus making insulin administration unrequired, at least for a given amount of time.

5.2. Hyperthyroidism

The question of awareness is also in question here. Indeed, the overall average of the patients' age in our study is higher than what is reported in literature. Moreover, 13 years could already be considered as high for a domestic cat. Either the disease manifests itself late in the cat's life, and/or owners delay in seeking veterinary care. The latter may be due to different reasons, such as a lack of observations or a lack of knowledge. Some owners may not be aware of what is normal in their pet's behavior and what changes should be worrisome.

Another finding in this study was the high number of cases of HT in the clinic in Estonia. As previously said, the clinic of EMÜ is larger than the one in Les Pieux, therefore it makes sense that the number of cases should be higher. However, local differences may also play a role. While the risk factors for feline HT remain unclearly and uncertainly identified, the environment seems to play a role. Exactly how different is the home environment of a cat in France and in Estonia? Would there be large differences in incidence rates within one same country? These questions would require an in-depth study in different clinics within both

countries. Owners could be asked to participate in a survey search in order to identify possible risk factors as well.

Conducting a study researching the presence of the risk factors (BPA, PBDEs, and iodine levels in food) mentioned in the literature review would most likely be difficult and tedious. However, obtaining incidence rates in 2 different countries and studying the suspected risk factors may help determine why this disease is so often diagnosed.

It is also worth investigating how well and how often owners are informed on the different treatment options available. If these options were presented but refused, it is important to know why; whether it is a question of availability (staff and/or facilities), financial cost or adverse health effects. Some of the younger patients in our study might benefit or have benefited from radioactive therapy or thyroidectomy.

Understanding why these curative options are not taken may help remove obstacles. If there is a higher demand than we realize, this may allow for better supply.

In terms of laboratory diagnostics, the parameters shown in Table. 4 were the most consistently measured values. Both ALT and AST were elevated in the majority of cases (61.3% and 82.6% respectively) and sometimes more than twice the highest value. This shows that no matter what the cause of liver damage – be it hepatic hypoxia, malnutrition or toxicosis due to thyroid hormones – it is worth systematically investigating when suspecting HT.

These high liver values may be due to concurrent diseases or a direct cause of HT or both. This could also explain the choice of choosing medical treatment, as these would make for high-risk patients for both surgery and radioactive iodine with an extended hospital stay. These values and a high age average leads us to believe that the endocrine disorder has been ongoing for a while. Delayed veterinary care may be explained by lack of exterior signs, lack of observation or because signs such as lethargy and weight loss are simply attributed to old age.

A 2-month practical was done in Borrisoleigh, Ireland from January to March 2023. This mixed-practice clinic is located in a rural area, employs 3 veterinarians and has one consultation room. I hoped to be able to collect cases from this clinic for this study but this proved impossible. During the practice, no cases of feline endocrinopathy was seen and the veterinarians could not recall having had one during their work at the clinic (which extended to over 10 years for one of them).

However, there were cases of canine endocrinopathies, which begs the question why. In my opinion, cats may not be quite as valued as dogs, at least in certain areas. This may lead to potential endocrine disorders going unnoticed and/or untreated amongst cats. Many of these cats are also exclusively outdoors, which makes any changes difficult to observe.

5.3. Limitations of this study

There are several limitations in this study, one of them being the small sample size. It is not large enough to be fully representative of the population for either country. Moreover, the clinics' size and location within the country is different. One clinic is located in a more rural area and is of smaller size with a subsequently smaller clientele and the other is located in a more urban area and of a much larger size.

Obtaining reliable incidence rates for each clinics was not possible because some patients would be examined only once and not have a follow-up. There were patients that were not seen before nor after in that same clinic. Therefore, it is not wise to use such cases to calculate incidence rate in a specific area.

Different data was present in different cases. The clinic of EMÜ uses more parameters while analyzing blood and urine, which can be useful when identifying concurrent diseases. Moreover, this clinic uses much more detailed reports with a fuller anamnesis. This can only be better in terms of patient follow-up and monitoring, especially in clinics where it is common for a patient to be treated by different veterinarians.

CONCLUSIONS

Diabetes mellitus

- No breed predisposition could be noted, due to the patients being all domestic shorthair cats, save for one.
- Male cats show a higher incidence rate.
- No correlation could be made between neutered and non-neutered animals because only one patient was in each clinic.
- Cats are more at risk at 10 years of age and over.
- Weight may play a role in developing the disease and may be an important risk factor.
- PU and/or PD and lethargy are the main clinical signs that prompt owners to seek veterinary care.
- The remission rates between intermediate-acting lente insulin and longer-acting insulin glargine did not differ.
- I believe we could consider lowering the threshold of the reference range for hyperglycemia in order to detect cats with mild or early onset DM. This would improve chances of remission. Overweight adult cats, even without evidence of DM should be more closely monitored. This would not only be beneficial to the patient but would benefit the owner as well, both in terms of time and finance.

Hyperthyroidism

- No breed predisposition could be observed.
- No gender predisposition could be observed.
- The average age was higher than the one reported in literature.
- Weight loss and vomiting are the most common clinical signs observed by owners. Inappetence is seen more frequently than polyphagia. Owners report PU and/or PD, like in DM.
- tT4 is the specific thyroid test of choice. Dynamic function tests were never used.
- Amongst medical and curative options, only medical treatment was used in all cases.

- Other treatments could and should be considered. Radioactive iodine, for example, could be a viable option for cats that are otherwise healthy. We do not know what owners might be willing to accept unless there are more open discussions about different options available.

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REFERENCES

Appleton, D.J., Rand, J.S. and Sunvold, G.D., 2001. Insulin sensitivity decreases with obesity, and lean cats with low insulin sensitivity are at greatest risk of glucose intolerance with weight gain. *Journal of Feline Medicine & Surgery*, *3*(4), pp.211-228.

Appleton, D.J., Rand, J.S., Priest, J., Sunvold, G.D. and Vickers, J.R., 2004. Dietary carbohydrate source affects glucose concentrations, insulin secretion, and food intake in overweight cats. *Nutrition Research*, *24*(6), pp.447-467.

Behrend, E., Holford, A., Lathan, P., Rucinsky, R. and Schulman, R., 2018. 2018 AAHA diabetes management guidelines for dogs and cats. *J Am Anim Hosp Assoc*, *54*(1), pp.1-21.

Biourge, V., Nelson, R.W., Feldman, E.C., Willits, N.H., Morris, J.G. and Rogers, Q.R., 1997. Effect of weight gain and subsequent weight loss on glucose tolerance and insulin response in healthy cats. *Journal of Veterinary Internal Medicine*, *11*(2), pp.86-91.

Bloom, C.A. and Rand, J., 2014. Feline diabetes mellitus: clinical use of long-acting glargine and detemir. *Journal of Feline Medicine and Surgery*, *16*(3), pp.205-215.

Broome, M.R., 2006. Thyroid scintigraphy in hyperthyroidism. *Clinical techniques in small animal practice*, *21*(1), pp.10-16.

Broussard, J.D., Peterson, M.E. and Fox, P.R., 1995. Changes in clinical and laboratory findings in cats with hyperthyroidism from 1983 to 1993. *Journal of the American Veterinary Medical Association*, *206*(3), pp.302-305.

Carney, H.C., Ward, C.R., Bailey, S.J., Bruyette, D., Dennis, S., Ferguson, D., Hinc, A. and Rucinsky, A.R., 2016. 2016 AAFP guidelines for the management of feline hyperthyroidism. *Journal of feline medicine and surgery*, *18*(5), pp.400-416.

De Wet, C.S., Mooney, C.T., Thompson, P.N. and Schoeman, J.P., 2009. Prevalence of and risk factors for feline hyperthyroidism in Hong Kong. *Journal of Feline Medicine and Surgery*, *11*(4), pp.315-321.

Farrow, H.A., Rand, J.S. and Sunvold, G.D., 2002. Diets high in protein are associated with lower postprandial glucose and insulin concentrations than diets high in either fat or carbohydrate in normal cats. *Journal of Veterinary Internal Medicine*, *16*, p.360.

Farrow, H.A., Rand, J.S., Morton, J.M., O'Leary, C.A. and Sunvold, G.D., 2013. Effect of dietary carbohydrate, fat, and protein on postprandial glycemia and energy intake in cats. *Journal of veterinary internal medicine*, *27*(5), pp.1121-1135.

Freeman, L.M., Rush, J.E., Meurs, K.M., Bulmer, B.J. and Cunningham, S.M., 2013. Body size and metabolic differences in Maine Coon cats with and without hypertrophic cardiomyopathy. *Journal of feline medicine and surgery*, *15*(2), pp.74-80

Gilor, C., Niessen, S.J.M., Furrow, E. and DiBartola, S.P., 2016. What's in a name? Classification of diabetes mellitus in veterinary medicine and why it matters. *Journal of veterinary internal medicine*, *30*(4), pp.927-940.

Gilor, C., Rudinsky, A.J. and Hall, M.J., 2016. New approaches to feline diabetes mellitus: Glucagon-like peptide-1 analogs. *Journal of feline medicine and surgery*, *18*(9), pp.733-743.

Gilor, C., Hulsebosch, S.E., Pires, J., Bannasch, M.J., Lancaster, T., Delpero, A., Ragupathy, R., Murikipudi, S. and Zion, T., 2021. An ultra-long-acting recombinant insulin for the treatment of diabetes mellitus in cats. *Journal of Veterinary Internal Medicine*, *35*(5), pp.2123-2130.

Gottlieb, S. and Rand, J., 2018. Managing feline diabetes: current perspectives. *Veterinary Medicine: Research and Reports*, *9*, p.33.

Henson, M.S. and O'Brien, T.D., 2006. Feline models of type 2 diabetes mellitus. *ILAR journal*, *47*(3), pp.234-242.

Jones, B., Engdahl, J.N. and Weiss, J., 2019. Are persistent organic pollutants important in the etiology of feline hyperthyroidism? A review. *Acta veterinaria scandinavica*, *61*(1), pp.1-6.

Kintzer, P.P., 1994. Considerations in the treatment of feline hyperthyroidism. *Veterinary Clinics of North America: Small Animal Practice*, *24*(3), pp.577-585.

Köhler, I., Ballhausen, B.D., Stockhaus, C., Hartmann, K. and Wehner, A., 2016. Prevalence of and risk factors for feline hyperthyroidism among a clinic population in Southern Germany. *Tierärztliche Prax. Kleintiere*, *44*, pp.149-157.

Linari, G., Fleeman, L., Gilor, C., Giacomelli, L. and Fracassi, F., 2022. Insulin glargine 300 U/ml for the treatment of feline diabetes mellitus. *Journal of Feline Medicine and Surgery*, *24*(2), pp.168-176.

Link, K.R. and Rand, J.S., 2008. Changes in blood glucose concentration are associated with relatively rapid changes in circulating fructosamine concentrations in cats. *Journal of feline medicine and surgery*, *10*(6), pp.583-592.

Lutz, T.A. and Rand, J.S., 1995. Pathogenesis of feline diabetes mellitus. *Veterinary Clinics of North America: Small Animal Practice*, *25*(3), pp.527-552.

Marshall, R.D., Rand, J.S. and Morton, J.M., 2009. Treatment of newly diagnosed diabetic cats with glargine insulin improves glycaemic control and results in higher probability of remission than protamine zinc and lente insulins. *Journal of feline medicine and surgery*, *11*(8), pp.683-691.

Mattern, M.Y. and McLennan, D.A., 2000. Phylogeny and speciation of felids. *Cladistics*, *16*(2), pp.232-253.

Mooney, C. T., & Peterson, M. E. (2012). Feline hyperthyroidism. In *BSAVA manual of canine and feline endocrinology* (pp. 92-110). BSAVA Library.

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*(3), pp.T1-T9.

Peterson, M.E. and Becker, D.V., 1995. Radioiodine treatment of 524 cats with hyperthyroidism. *Journal of the American Veterinary Medical Association*, *207*(11), pp.1422-1428.

Peterson, M.E., 2006. Diagnostic tests for hyperthyroidism in cats. *Clinical techniques in small animal practice*, *21*(1), pp.2-9.

Peterson, M.E., Guterl, J.N., Nichols, R. and Rishniw, M., 2015. Evaluation of serum thyroid-stimulating hormone concentration as a diagnostic test for hyperthyroidism in cats. *Journal of veterinary internal medicine*, *29*(5), pp.1327-1334.

Peterson, M.E., 2020. Hyperthyroidism in cats: considering the impact of treatment modality on quality of life for cats and their owners. *Veterinary Clinics: Small Animal Practice*, *50*(5), pp.1065-1084.

Product information: Caninsulin (2015).
http://www.ircp.anmv.anses.fr/rcp.aspx?NomMedicament=caninsulin, 01.12.2022.

Product information: Lantus (2021). https://www.ema.europa.eu/en/documents/product-information/lantus-epar-product-information_en.pdf, 01.12.2022.

Product information: Levemir (2021). https://www.ema.europa.eu/en/documents/product-information/levemir-epar-product-information_en.pdf, 01.12.2022.

Product information: Thiafeline (2020). http://www.ircp.anmv.anses.fr/rcp.aspx?NomMedicament=thiafeline+2%2c5+mg+comprimes+pellicules+pour+chats, 01.12.2022.

Product information: Vidalta (2022). http://www.ircp.anmv.anses.fr/rcp.aspx?NomMedicament=vidalta+10+mg+comprimes+a+liberation+prolongee+pour+chats, 01.12.2022.

Rand, J.S., Fleeman, L.M., Farrow, H.A., Appleton, D.J. and Lederer, R., 2004. Canine and feline diabetes mellitus: nature or nurture?. *The Journal of nutrition*, *134*(8), pp.2072S-2080S.

Rand, J., 2012. Feline diabetes mellitus. In *BSAVA manual of canine and feline endocrinology* (pp. 133-147). BSAVA Library.

Roomp, K. and Rand, J., 2012. Evaluation of detemir in diabetic cats managed with a protocol for intensive blood glucose control. *Journal of feline medicine and surgery*, *14*(8), pp.566-572.

Sparkes, A.H., Cannon, M., Church, D., Fleeman, L., Harvey, A., Hoenig, M., Peterson, M.E., Reusch, C.E., Taylor, S. and Rosenberg, D., 2015. ISFM consensus guidelines on the practical management of diabetes mellitus in cats. *Journal of feline medicine and surgery*, *17*(3), pp.235-250.

van Hoek, I., Hesta, M. and Biourge, V., 2015. A critical review of food-associated factors proposed in the etiology of feline hyperthyroidism. *Journal of Feline Medicine and Surgery*, *17*(10), pp.837-847.

Vaske, H.H., Schermerhorn, T., Armbrust, L. and Grauer, G.F., 2014. Diagnosis and management of feline hyperthyroidism: current perspectives. *Veterinary Medicine: Research and Reports*, *5*, p.85.

Wakeling, J., Everard, A., Brodbelt, D., Elliott, J. and Syme, H., 2009. Risk factors for feline hyperthyroidism in the UK. *Journal of small animal practice*, *50*(8), pp.406-414.

APPENDICES

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